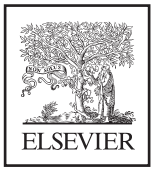
# COSMETIC SCIENCE AND TECHNOLOGY: THEORETICAL PRINCIPLES AND APPLICATIONS

Kazutami Sakamoto
Robert Y. Lochhead
Howard I. Maibach
Yuji Yamashita




elsevier.com

Elsevier
Radarweg 29, PO Box 211, 1000 AE Amsterdam, Netherlands
The Boulevard, Langford Lane, Kidlington, Oxford OX5 1GB, United Kingdom
50 Hampshire Street, 5th Floor, Cambridge, MA 02139, United States

Copyright © 2017 Elsevier Inc. All rights reserved.

No part of this publication may be reproduced or transmitted in any form or by any means, electronic or mechanical, including photocopying, recording, or any information storage and retrieval system, without permission in writing from the publisher. Details on how to seek permission, further information about the Publisher's permissions policies and our arrangements with organizations such as the Copyright Clearance Center and the Copyright Licensing Agency, can be found at our website: www.elsevier.com/permissions.

This book and the individual contributions contained in it are protected under copyright by the Publisher (other than as may be noted herein).

**Notices**
Knowledge and best practice in this field are constantly changing. As new research and experience broaden our understanding, changes in research methods, professional practices, or medical treatment may become necessary.

Practitioners and researchers must always rely on their own experience and knowledge in evaluating and using any information, methods, compounds, or experiments described herein. In using such information or methods they should be mindful of their own safety and the safety of others, including parties for whom they have a professional responsibility.

To the fullest extent of the law, neither the Publisher nor the authors, contributors, or editors, assume any liability for any injury and/or damage to persons or property as a matter of products liability, negligence or otherwise, or from any use or operation of any methods, products, instructions, or ideas contained in the material herein.

**Library of Congress Cataloging-in-Publication Data**
A catalog record for this book is available from the Library of Congress

**British Library Cataloguing-in-Publication Data**
A catalogue record for this book is available from the British Library

ISBN: 978-0-12-802005-0

For information on all Elsevier publications visit our website at https://www.elsevier.com/books-and-journals




*Publisher:* John Fedor
*Acquisition Editor:* Kostas KI Marinakis
*Editorial Project Manager:* Sarah Watson
*Production Project Manager:* Maria Bernard
*Cover Designer:* Victoria Pearson Esser

Typeset by TNQ Books and Journals

# List of Contributors


**T. Abe** Tohoku University, Sendai, Japan

**H. Ando** Okayama University of Science, Okayama, Japan

**M. Ardigò** San Gallicano Dermatological Institute, Rome, Italy

**E. Berardesca** San Gallicano Dermatological Institute, IRCCS, Rome, Italy

**H. Fukui** FUKUI Professional Engineer Office, Yokohama, Japan

**M.J. García-Celma** Faculty of Pharmacy and Food Sciences, University of Barcelona (UB) and Biomedical Research Networking Center: Bioengineering, Biomaterials and Nanomedicine (CIBER-BBN), Barcelona, Spain

**A. Ghofranian** University of California, San Francisco, CA, United States

**D. Gräbner** University of Bayreuth, Bayreuth, Germany

**J. Grice** The University of Queensland, Woolloongabba, QLD, Australia

**F. Harada** Lion Corporation, Odawara, Kanagawa, Japan

**I.N. Haridass** The University of Queensland, Woolloongabba, QLD, Australia

**M. Hatao** Shiseido Global Innovation Center, Yokohama, Japan

**I. Hatta** Nagoya Industrial Science Research Institute, Nagoya, Japan

**M. Hayase** Kao Corporation, Odawara, Japan

**S. Herman** Diffusion LLC, Totowa, NJ, United States

**T. Himeno** KOSÉ Corporation, Tokyo, Japan

**T. Hirao** Chiba Institute of Science, Choshi, Japan

**H. Hoffmann** University of Bayreuth, Bayreuth, Germany

**J. Hosoi** Shiseido Global Innovation Center, Yokohama, Japan

**P. Huber** ZHAW Zurich University of Applied Sciences, Wädenswil, Switzerland

**O. Ifuku** Maruzen Pharmaceuticals Co., Ltd., Fukuyama, Hiroshima, Japan

**S. Inoue** Cosmetic Health Science, Gifu Pharmaceutical University, Gifu, Japan

**T. Iwata** Procter & Gamble, Singapore Innovation Center, Singapore, Singapore

**T Joseph Lin** T Joseph Lin Associates, Pacific Palisades, CA, United States

**F. Kanda** Shiseido Global Innovation Center, Yokohama, Japan

**K. Kikuchi** Department of Dermatology, Tohoku University Graduate School of Medicine, Sendai, Japan

**J. Kishimoto** Shiseido Global Innovation Center, Yokohama, Kanagawa, Japan

**T. Kitano** OHNO & PARTNERS, Tokyo, Japan

**H. Kojima** National Institute of Health Sciences (NIHS), Tokyo, Japan

**Y. Konno** KOSÉ Corporation, Tokyo, Japan

**J. Koyama** Shiseido Global Innovation Center, Yokohama, Japan

**V.R. Leite-Silva** Universidade Federal de São Paulo, UNIFESP-Diadema SP, Brasil

**B. Lindman** Lund University, Lund, Sweden

**R.Y. Lochhead** The University of Southern Mississipi, Hattiesburg, MS, United States

**P.S. Lopes** Universidade Federal de São Paulo, UNIFESP-Diadema SP, Brasil

**A.C.H.R. Machado** Universidade Federal de São Paulo, UNIFESP-Diadema SP, Brasil

**H.I. Maibach** University of California, San Francisco, CA, United States

**H. Masaki** Tokyo University of Technology, Hachioji, Tokyo, Japan

**M. Masuda** Consultant, Ninomiya, Kanagawa, Japan

**M. Minamino** BelleVienus Co., Ltd., Osaka, Japan

**R. Miyahara** Shiseido Global Innovation Center, Yokohama, Japan

**M. Miyake** Lion Corporation, Tokyo, Japan

**S. Nafisi** Central Tehran Branch, IAU, Tehran, Iran; University of California, San Francisco, CA, United States

**N. Naito** KOSÉ Corporation, Tokyo, Japan

**Y. Nakama** Kishi Kasei Co., Ltd, Kanagawa, Japan

**N. Nakamura** KISHI KASEI CO., LTD., Yokohama, Japan

**Y. Nakazawa** Shiseido Global Innovation Center, Yokohama, Kanagawa, Japan

**J. Nikitakis** Personal Care Products Council, Washington, DC, United States

**Y. Nonomura** Yamagata University Graduate School of Science and Engineering, Yonezawa, Japan

**F. Nozaki** Linberg Co., Ltd., Tokyo, Japan

**T. Nylander** Lund University, Lund, Sweden; Mid Sweden University, Sundsvall, Sweden; Nanyang Technological University, Singapore, Singapore

**N. Oguchi-Fujiwara** Shiseido Global Innovation Center, Yokohama, Japan

**E. Oshimura** Ajinomoto Co., Inc., Tokyo, Japan

**T. Ozawa** Society of Cosmetic Chemists of Japan, Yokohama, Japan

**C.P. Raffier** The University of Queensland, Woolloongabba, QLD, Australia

**M. Roberts** The University of Queensland, Woolloongabba, QLD, Australia

**C.M. Rocafort** BASF Corporation, Florham Park, NJ, United States

**T. Sakai** Material Science Research Laboratories, Kao Corporation, Wakayama-shi, Wakayama, Japan

**K. Sakamoto** Tokyo University of Science, Chiba, Japan

**J. Sanzone** Estee Lauder Companies, Inc., New York, NY, United States

**C. Solans** Institute of Advanced Chemistry of Catalonia, Spanish Council for Scientific Research (IQAC-CSIC) and Biomedical Research Networking Center: Bioengineering, Biomaterials and Nanomedicine (CIBER-BBN), Barcelona, Spain

**T. Suzuki** Cosmos Technical Center Co., Ltd., Tokyo, Japan

**H. Tagami** Emeritus professor of Tohoku University, Sendai, Japan

**M. Takahashi** Takahashi Cosmetic Consulting, Tokyo, Japan

**K. Tsujii** Hokkaido University (retired), Wakayama, Japan

**Y. Uchida** University of California, San Francisco, CA, United States; Department of Veterans Affairs Medical Center, San Francisco, CA, United States; Northern California Institute for Research and Education, San Francisco, CA, United States

**K. Watanabe** Shiseido Global Innovation Center, Yokohama, Japan

**Y. Yamashita** Chiba Institute of Science, Choshi, Japan

**J. Yang** Beauty Hi-tech Innovation Co., Ltd., Kobe, Japan

# Biography

## *Kazutami Sakamoto, PhD*

Kazutami Sakamoto is a former professor of the Faculty of Pharmacy at Chiba Institute of Science and currently a guest professor of the Department of Pure and Applied Chemistry, Faculty of Science and Technology, at Tokyo University of Science. He graduated from the master's program of Applied Chemistry, School of Engineering at Tohoku University in 1971 after finishing an undergraduate program at the same university. He received his PhD from the Faculty of Science at Tohoku University in 1980. In 1971, Dr. Sakamoto joined the Central Research Laboratories of Ajinomoto Co., Inc. as a research chemist and spent most of his professional carrier with the company until 2003. During his time with Ajinomoto, Dr. Sakamoto worked on the development of the Ajinomoto's functional chemical products especially cosmetic ingredients. He also conducted basic research in the area of colloid and interfacial chemistry and skin science. In 2003, he retired from Ajinomoto and joined Shiseido Research Center as a Resident Special Technical Advisor, where he spent three years consulting on the creation and promotion of Shiseido's new R&D projects. He then worked for Seiwa Kasei Co. LTD. as a director of R&D. Along with his industrial career, Dr. Sakamoto has been active in research and education at various universities including Yokohama National University, Shinsyu University, and Tokyo University of Science as an adjunct professor. After retiring from industry in 2008, he has been expanding his academic activities.

Dr. Sakamoto has done extensive research on the physicochemical properties of amino acid–based chiral molecules, especially of their self-assembled conditions, since the late 1970s. His explorations of chiral self-assemblies included micelles, lyotropic liquid crystals, which were pioneering studies in the 1970s. The discovery of lyotropic cholesteric liquid crystal formed by acylamino acid as a chiral surfactant is a good example of this work. His curiosity regarding the structure and functions of chiral assembly led Dr. Sakamoto to create chiral mesoporous silica as a solid matter, which was templated from chiral lyotropic liquid crystal formed by acylamino acid as a soft matter. His study "Self-organization of Amino Acid–Based Chiral Surfactants: Evaluation of Organized Structures and Interactions with Biological System" received an award from the Japan Oil Chemists' Society in 2005. In the past 10 years, he has actively participated in many international conferences as an invited speaker. Dr. Sakamoto was a chairman of the Division of Colloid and Surface Chemistry of the Chemical Society of Japan for 2007–08.

## *Robert Y. Lochhead, PhD, FRSC*

A long-time leader in polymers for cosmetics, Dr. Lochhead is currently Professor and Director Emeritus of Polymer Science at the University of Southern Mississippi. He served as a professor at the School of Polymers and High Performance Materials at the University of Southern Mississippi, and he was director of that school for almost 2 decades. His students have won best annual national/international paper awards for 18 of the 26 years that he spent in academia. Prior to joining academia, the first 25 years of his career were spent in industrial research that ranged from polymer and silicone synthesis to colloid and surface science for cosmetics and personal care products and to the management of the rheology applications segment of a large hydrophilic polymer research group. Dr. Lochhead is the author of more than 100 scientific papers and reviews and a named inventor on 25 patents.

His inventions have enabled new and better technologies that benefit society and the environment. These include:

- Camouflage "makeup" that protects personnel from the ballistic thermal fronts of explosions
- Stimulus-responsive polymer–surfactant systems for personal care and home care (the stimulus-responsive coacervate formation that underpins the mechanism of conditioning shampoos has been named "the Lochhead Effect")

- The concept of polymeric emulsifiers and the first polymeric emulsifier, which enabled:
  - skin lotions for sensitive skin and sports sunscreens;
  - the now common stimulus-responsive alcohol sanitizing gels;
  - sprays that stay active on plants even when it rains, thereby lowering the frequency of use and reducing runoff of pesticides and herbicides;
  - waterborne water seal coating compositions that essentially eliminate the volatile organic compound emissions of earlier oil-based water seal formulations
- Bioadhesive polymers for the lubrication of mucous membranes and drug delivery
- Compositions for the repair of retinal tears
- Hypochlorite-resistant waterborne rheology modifiers that enabled automatic dishwashing gels
- Novel, ecologically beneficial dispersants for oil spills
- Polymers for textile and carpet printing that essentially replaced kerosene emulsions and the pollution that often went along with the use of these emulsions

Dr. Lochhead has received many awards for his contributions and these include:

- The Maison G. DeNavarre medal from the Society of Cosmetic Chemists
- The Chemical Pioneer Award from the American Institute of Chemists
- The Education Award from the Society of Plastics Engineers

Dr. Lochhead serves on the International Nomenclature of Cosmetic Ingredients committee and he has served twice as the President of the Society of Cosmetic Chemists and President of the International Association of Formulation Chemists.

## *Howard I. Maibach, MD, PhD*

Dr. Howard Maibach is an expert in contact and occupational dermatitis and sees patients at the Environmental Dermatosis Clinic, which is part of the Dermatology Clinic. His specialties are dermatotoxicology, or skin exposure toxicity; allergies and skin disorders; and dermatopharmacology or the study of medications for skin disorders. Dr. Maibach has been on the editorial board of more than 30 scientific journals and is a member of 19 professional societies, including the American Academy of Dermatology, San Francisco Dermatological Society, and the Internal Commission on Occupation Health. He is a professor in the Department of Dermatology at UCSF.

Dr. Maibach has written and lectured extensively on dermatotoxicology (the toxicity to man from skin exposure) and dermatopharmacology (the treatment of skin diseases). His current research programs include defining the chemical-biological faces of irritant dermatitis and the study of percutaneous penetration.

When Dr. Maibach is not in the lab conducting research or in the classroom teaching, he is seeing patients at the Environmental Dermatoses Clinic (of the Dermatology Clinic), mostly providing second opinions on allergic contact dermatitis.

Dr. Maibach has been on the editorial boards of over 30 scientific journals and is a member of 19 professional societies, including the American Academy of Dermatology, San Francisco Dermatological Society, and the International Commission on Occupational Health.

Clinical Specialties.

- Dermatopharmacology
- Allergic Contact Dermatitis

Research Interests.

- Dermatotoxicology
- Dermatopathology
- Percutaneous Penetration

# *Yuji Yamashita, PhD*

Yuji Yamashita received his MS and BS from Yokohama National University, Japan, and his PhD in natural science from the University of Bayreuth, Germany, in 2005. After several years of research work on thermotropic liquid crystals at Chisso Petrochemical Co., Japan, he began to study dermatology, especially transdermal drug delivery systems, as a postdoc at St. Marianna University, Japan. In October 2011, Dr. Yamashita became an assistant professor at Chiba Institute of Science, teaching and researching cosmetic science; he was promoted to junior associate professor in 2014. His area of expertise is surfactant science such as phase behavior and self-assembly, which is related to formulation technology. His current research topics include establishment of a novel parameter to replace the HLB number, emulsion stability under microgravity, micro-calorimetric study on the structural transitions of self-organized matters, and alpha-gel formulation, of which "establishment of a novel parameter to replace the HLB number" received an award in November 2016 from the Society of Cosmetic Chemists of Japan.

# Foreword

*Kazutami Sakamoto*
**Tokyo University of Science, Chiba, Japan**

If you picked up this book, you likely have an interest in cosmetics and you may find yourself struggling to find your specific area of interest in this field, which involves a number of disciplines including natural sciences, technologies, and even social sciences. Cosmetics is an exceptional field where cutting-edge sciences and technologies are quickly applied into innovative products deeply integrated with social, cultural, and traditional lifestyles. This book is structured in four sections to introduce the world of cosmetics by integrating scientific and technological aspects: **General Views of Cosmetic Science and Technology, Fundamental Resources for Cosmetics, Physicochemical Aspects and Formulations, and Physiological and Dermatological Aspects.**

We provide the essence needed to learn what cosmetics are, from both scientific and technological perspectives with interwoven contents in relation to beauty and care. You may be a scientist seeking updated knowledge in cosmetic science and looking for the most advanced and practical information, or perhaps you are a nonscientist looking for reliable and easily accessible introductory information with a robust scientific basis in cosmetics. This book aims to fulfill such needs by providing well-integrated content written by the leading scientists in the field. It provides basic scientific aspects that are integrated into cosmetics in the areas of material development, physicochemical aspects of formulations, and dermatological concerns.

I am grateful to all the contributors that made this book possible by offering their expertise on the basis and application of cosmetic science and technologies. My heart-filled thanks go to the coeditors; without them it would have been impossible to bring this endeavor to fruition. Dr. Howard I. Maibach opened my eyes not only to the world of science but also connected me with a new network of people. When I arrived in San Francisco in late August 1983, I had no practical communication skills in English and he so kindly offered to help me in every aspect of living and working in the United States. Since then, Howard has always been my mentor. Dr. Robert Y. Lochhead, with whom I became acquainted through a colleague at Ajinomoto USA Inc., kindly accepted a scientist from Ajinomoto to study at his lab in the mid-1990s. Since then we have become close friends. Bob has been kind enough to visit and encourage my students at Chiba Institute of Science (CIS) in Japan, after I opened my own lab for cosmetic science in 2012. My relationship with Dr. Yuji Yamashita started at the beginning of the 21st century. I was a guest professor at Prof. Hironobu Kunieda's lab at the time and Yuji was a graduate student, and I have supervised for his master's degree thesis. When I started my new career at CIS in 2010, Yuji was a postdoctoral scientist at the St. Marianna University School of Medicine in Japan after finishing his PhD at Bayreuth University in Germany under Professor Heinz Hoffman and had several years of experience in industry. I invited Yuji to join me to establish our lab, and Yuji now leads the lab after my retirement from CIS.

I feel life is always filled with unexpected encounters with people and opportunities, which grow into an interwoven network. In this sense, this book is a great outcome of my long journey. I hope readers will enjoy this book and find an opportunity to explore the world of cosmetic science and technology, and go further with their own journeys.

My first thanks goes to Emeritus Professor Hiroyuki Ohshima of Tokyo University of Science (TUS) and Dr. Kostas Marinakis of Elsevier B.V. Registered Office who brought this project to me. One day in early 2013, Prof. Ohshima found me on the platform of Kashiwa Station, which many people use to commute to TUS. Since we were both members of the Division of Colloid and Surface Chemistry at Chemical Society Japan, he knew my background of working in industry and academia. He proposed this project when it was still just a concept brought from Kostas. At the meeting with Kostas in New Orleans at the Spring ACS meeting in April 2013, Kostas inspired me to reveal the scientific treasures hidden deep inside the cosmetic companies and the secret resources of cosmetic products that bring dreams to consumers. My journey started with these two encounters. Howard and Bob guided me with their expertise on how to explore science and technology even further, and with Yuji's patient support our

journey has finally reached its goal. We hope this book opens doors to our readers and helps them start their own expeditions.

I am also indebted to Sarah J. Watson, editorial manager of Physical Science and Maria J. Bernard, project manager of Science and Technology Books at Elsevier for their editorial assistance and patience, and to my son Izumi Sakamoto for his contribution of translating many chapters originally written in Japanese to English while preserving the cultural flavors to the universal language just as cosmetics itself has a nature of commonality and demographic diversity.

In closing, I offer my profound thanks…

To my teachers, many friends who have enriched my life in more ways I can express.

To my family who stood by me and supported me in the many years I lived in the United States and after resettling in Japan. I give special thanks to my wife Mariko for all the love and dedication to our family.

**Kazutami Sakamoto**
November 28, 2016

# Preface

During the past quarter of a century, the reach of cosmetic companies has become global and our understanding of the underlying scientific principles has sharpened and expanded. We now have a better understanding of structure—property relations down to ingredient molecular levels and physical interactions; our understanding of the biochemistry, biology, and morphology of skin and hair has advanced significantly, even as formulated compositions have become increasingly constrained by regulation. Cosmetic science is now entering an era of increased ecological awareness that will probably persist for the next quarter of a century as more of the world's burgeoning population becomes able to enjoy the benefits of personal care products. Nevertheless, despite worldwide domination by a few multinational corporations, there are still regional variations that result from cultural preferences and regulatory differences, and these offer new challenges to the formulators of today and tomorrow.

At this juncture, there is a need to review the state of the art, to mentor the next generation of cosmetic scientists, and to establish a starting point for the forthcoming era of cosmetic science. The purpose of this book is to address that need. It constitutes a comprehensive review, with contributions from some of the world's leading cosmetic scientists. The need to condense our knowledge into a document was brought home to me poignantly when I sought guidance on a technical point from a colleague, only to find out that he had died 2 weeks earlier and his advice was silenced forever.

I am grateful to Dr. Kazu Sakamoto for inviting me to participate as a co-editor and for taking the lead in this venture. I am also thankful to Dr. Yuji Yamashita for his dedicated efforts in uploading the chapters and to Dr. Howard Maibach for lending his experience and skill to the planning and implementation of the book.

During my career in cosmetic science, I have had the privilege of being mentored by many excellent scientists, too many to mention individually in this short preface, and I thank them for molding me into the professional that I have become. In particular, I wish to thank my wife, Margaret, for her encouragement and for her contributions to figures and equations in my publications.

Reader, I hope that this book will enlighten you, and I encourage you to drive our understanding of cosmetic science to a broader and deeper level.

**Robert Y. Lochhead**
August 2, 2016

CHAPTER

# 1

# General Aspects of Cosmetics in Relation to Science and Society: Social, Cultural, Science, and Marketing Aspects*

*F. Nozaki*
**Linberg Co., Ltd., Tokyo, Japan**

## 1.1 COSMETIC SCIENCE AND SOCIETY

### 1.1.1 Cultural/Social Aspects Are Vital Aspects Along With Biological Aspects in Cosmetic Science

Cosmetics are consumer goods that have become widely common in our social life, but the culture of cosmetics and makeup we enjoy today is the result of a rich and long history. As a medium that enhances our social stature, cosmetics have always been an item for comfort and well-being.

Cosmetic science is a field in applied natural science, but the ideas and theories are centered on humans living in society. Ever since the rise of humans, our ancestors played among Mother Nature's flowers, trees, water, or soil, which naturally became the first primitive makeup. As they formed social structures, the meaning and values of customary cosmetics were reviewed and reevaluated, and established beliefs and philosophy on cosmetics. Eventually cosmetic science was founded based on natural science, but the scope of this field spreads to social ethics or cultural aesthetics, and is now a field that also considers psychological aspects of the mind and emotions beyond logic.

Scientific and analytic methods are not enough to evaluate cosmetics, and human philosophy, values, aesthetics, and artistic aspects regarding cosmetics, and this field becomes meaningless as a practical study if the research is purely objective. In real life we feel unity through the feelings of personal warmth, not the cold objective and third-person visions. As Protagoras said, "Man is the measure of all things." The academic scope of cosmetic science is not only broad but is also deeply integrated into human values.

Cosmetic science cannot only focus on human beings and objects like other natural sciences since it is integrated with social well-being, sexual differences, gender norms of masculinity and femininity, and fashion. Colors and scents are objects in the scope of natural science, but the senses and emotions that these colors and scents trigger belong to a broader point of view, of what they mean to us or what values they have for society. It is not light waves that have color; it is our mind that perceives color, along with their cultural meanings and social values.

This does not only apply to color and scent as the human skin is highly sensitive and what we feel or touch has more meaning than what we see. Cosmetics must satisfy all sensual expectations. The skin is not just a barrier that protects the body from various stimulations or foreign materials in the natural world but is an interface that constantly processes information between the body and the psychologically and emotionally separated external world. Although cosmetics protect and enhance the skin, at the same time they create a social interface to embellish people's stature or to improve communication with the community. In Japanese, "Feel with the skin" means to read the atmosphere, and this expression states the true nature of the skin.

Cosmetics are daily goods that many of us use in our lives, and their quality and safety must be assured under governmental standards and provided by the entities that distribute them to the consumers, which are the

*Translated from Japanese by Izumi Sakamoto.

*Cosmetic Science and Technology: Theoretical Principles and Applications*
http://dx.doi.org/10.1016/B978-0-12-802005-0.00001-X



Copyright © 2017 Elsevier Inc. All rights reserved.

manufacturers that produce and sell these products. Cosmetic science is a foundation to assure the consumers of such safety and functionality, but this field must be flexible and conscious about changes in economy, social demands, consumer preferences, and values. Cosmetics must continue to satisfy their users by flexibly changing to comply with trends and changes.

### 1.1.2 Science-Technology-Society Balance and Generalist Perceptions for Corporate Operation

Since prehistoric times humans have enjoyed using familiar resources provided by Mother Nature as makeup. They enjoyed the colors of flowers, savored their scents, then discovered the stickiness of clay, the blackness of ochre and coal, or the striking presence of white clay and were overwhelmed by the power of hues. As they innocently played among nature, they appreciated all the phenomena around them with curiosity and with all their five senses. In their playfulness they found that their skin felt refreshing after they played in water, and they mimicked animals playing in mud and found that their skin became even more revived. During cold seasons they realized that the oils from foods that stayed on their hands and skin were rather comfortable. They found materials from natural environments, painted their skin with inspiration, played in water and mud, and as this spread among their community it became a custom in society, creating the origin of the culture of cosmetics. This playful act of makeup was passed down through generations as customs in their community or social traditions as cosmetic culture.

As human beings, people seek society and culture, better economics and politics, and scientific technology. To borrow the words of Lincoln, we seek life "of the people, by the people, for the people." In order to achieve to these desires, cosmetic engineers must build their foundation with natural science, point their heads toward humanities and social sciences, and keep a mindset to learn from these three fields (Fig. 1.1). Science and technology can evolve only when we keep our minds open and are disciplined to seek information within overlooked messages from every moment of unbroken history to find prologues for the next generation. Hippocrates's words "Art is long, life is short" is an aphorism to encourage learners to keep their motivation because "medical skills take a long time to master even though a man's life is so short," and this discipline can be applied to the scientific technologies of cosmetics. We all exist in a space and time, or interface where this moment is just a transition to tomorrow.

All cosmetic scientists and engineers today must acknowledge the universal nature of science through their specific target of cosmetics to link wisdom and action. They should not be preoccupied by individual studies but should always read the demands from the times and society, and stand beside the consumers for awareness on science-based social conscience to help create a safe and sound society for all citizens to enjoy and appreciate.

In today's society, corporate operation requires an optimal balance of science-technology-society (STS) as a technique to adjust the highly subdivided demands of science and society. This means that the art of cosmetic manufacturing must be combined with all knowledge of relating scientific fields to connect the dots of overlapping technological services that utilize cosmetics in society into an overlapping surface and bring them into fruition. Using interface science syntax, the key to technology management is activating the liaison area of both fields (Fig. 1.2).

Like a reed with a flexible and strong core, cosmetic engineers must have cosmetic techniques and knowledge in cosmetology to answer to the society, and also have a generalist mind with STS balance to utilize their skills and knowledge in various sites.

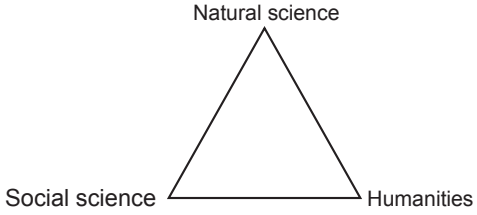



**FIGURE 1.1** Three disciplines of science.




**FIGURE 1.2** Science-technology-society balance.

# 1.2 THE ESTABLISHMENT OF HUMANS AND SOCIETY

## 1.2.1 Cosmetics: True Nonverbal Communication

"The human being is only a reed, the most feeble in nature; but this is a thinking reed" are the words of Blaise Pascal. As animals, our species needed to overcome our biological weaknesses. Struggling to obtain air, water, and food, humans (and prehumans) were in direct competition with wildlife. They realized their weaknesses and chose to live in communities to thrive through harsh natural environments and learned to control fire to protect their habitats overnight to create a veil of security between them and wildlife, successfully maintaining space for their community to survive.

Biologically, the human species is known as *Homo sapiens*, a species of animals that emerged as an African anthropoid. Their erect bipedalism narrowed their birth canals, and they adapted to this change by taking off their furs and being born as premature naked apes.[1] The brain size of a newborn is only a quarter of that of an adult, and although it triples over their first three years, the infancy of *H. sapiens* is long and needs long parenting. We are destined as neotenies or pedomorphic beings, and need a long period to mature. As neotenies, our bodies have plasticity where they can flexibly adjust depending on experience even after maturity. In other words, a human life is life of long youth and late maturity.

Infants can support their body weight and lie on their backs even before they can see. Their faces are interfaces with the outer world, and they express their emotions with expressions and voices of laughs and cries. Eventually they realize that they are being seen, and the face shifts to a social interface for interpersonal communication. "The eyes are the mirror of the soul." "Eyes speak more than words." These expressions show that facial expressions can deliver more information than words as a form of nonverbal communication and are the center of body language.

Infants show the most innocent form of sympathy and imitation by crying when other infants cry, and as they start to see, they read their mother's expression to make their own. Biological *H. sapiens* learn emotions, expressions of anger, joy, sadness, and happiness, and learn words to become individual human beings. As they communicate with their surrounding world they grow into persons with sympathy and discipline. Although humans invented and equipped themselves with language, they never let go of the communication with their facial expressions.

According to Mehrabian's rule, nonverbal information, such as the intonation and loudness of words, facial expressions, and movements of the hands and body, account for 93% of communication and merely 7% are transmitted through words. Borrowing Marshall McLuhan's words, "the medium is the message," cosmetics are a practice to enhance nonverbal communication as a medium with a message to embellish our stature.

## 1.2.2 Makeup: An Invention From the Playful Human Nature

While working together to gather food and distributing them voluntarily, or through their sympathy nurtured by raising premature children as a community, humans created their basis of society. Children mature as individual social citizens only through the blessings of nature, society, and culture (Fig. 1.3). Humans lived with Mother Nature, made the groundings of securing life necessities in society, and then fostered culture for a more civilized life. They found more than joy and delight in the playfulness of cosmetics, and cosmetics became a culture.

We created our own environment and learned to live our lives while expressing our sensitive and versatile souls within an invisible wall of social structure that divides us from other wildlife of Mother Nature. Society is a vessel for the public, and culture is the product of human activity created by people living in society striving for a better life.

In their social life, humans passed down the tradition of cosmetics along with traditions of life necessities of food, clothing, and shelter as a relic of cultural change that still continues to this day. Only when human evolution of both

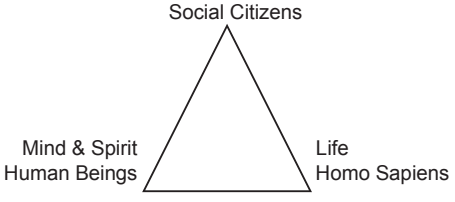



**FIGURE 1.3** Three aspects of human beings.

morphological shape and the brain were combined, were they were able to create society and culture. The body structure of *H. sapiens* evolved into an optimal form for bipedalism, and although they were weak as animals, their brains developed so they could flexibly handle any situation that eventually allowed them to create the basis of modern civilization as humans.

When the human body stood upright humans' throats became longer and lower, humans gained the ability for clear vocals. The brain developed and language was invented, and they controlled their vocals to pronounce words and created verbal communication. Furless and naked-born humans fully utilized their brain to discover and invent every single aspect that leads to today, and developed all societies and cultures on this planet.

The universe is a term that defines the entirety of all matter, phenomena, and events, whereas space is literally the space, or the unlimited space known as outer space where matter exists and events occur. Cosmos is an antonym of chaos, and is a concept of space as an entirety of the complex system of order, and microcosmos points to human beings. As microcosmos a human being is an insignificant weak being in the macrocosmos and the entirety of their existence on Gaia is merely the result of a larger order of macrocosmos.

On the other hand, H. sapiens is our biological name that means "wise man," and they are the existence that displays multiple talents on Mother Earth as human beings. Although the human brain is relatively large, it accounts for less than 3% of the body mass but consumes 25% of our entire metabolism. Human beings are social persons who control the balance of individuality and autonomy and give diversity to society.

There have been many attempts to describe the diversity and social/cultural nature of humans using biological taxonomy. *Homo ludens*, or "playing man," expresses the somewhat fundamental nature of survival, that our actions are only based on playing just like animals. Pure joy and innocent happiness is not the only reason for our actions, but this concept explains that all of our culture results from this motivation. *Homo technicus*, or "technical man," and *Homo socius*, or "social man," define the foundations of modern civilization, and the practice of economic-minded *Homo economicus* and political *Homo politics* operate modern society.

*H. sapiens* were not just intellects. In their culture they implemented multilateral playful elements. Humans first satiated hunger as animals but learned to dine and enjoy accompanied meals, and found new ways to cook delicious foods, and even invented gastronomy as a playful concept of a cosmos in the stomach. Painting skin was a recreational game that evolved into cosmetics as a shared ritual or a custom and a social tradition. As a communication medium, the culture of cosmetics, cosmesis, and cosmetology is supported by the beauty of cosmos (system and order).

In *Homo ludens*, Johan Huizinga states, "Play is older than culture, for culture, however inadequately defined, always presupposes human society, and animals have not waited for man to teach them their playing. We can safely assert, even, that human civilization has added no essential feature to the general idea of play."[2] The formation of society itself is possibly the result of which was originally playing and frolicking in groups. No matter how wise the *H. sapiens* were, it is doubtful that communities emerged for a strictly logical goal. Presumably their custom of eating meals together was established simply because they enjoyed sharing their happiness during the meals. Not only the act of consuming, but the joys and happiness from the taste of good food or their satisfaction of easing hunger were the origin of meals, and nutrition and health are merely explanations of scientific knowledge used by generations far after. Perhaps human beings are equipped with an instinct where they feel joy in actions that are actually logical. No matter what the action is, it seems that the origin of all social habits are based on joyful feelings from playing. The fun of not only collecting but cooking the collected foods, the excitement of discovering foods that taste better when cooked together, or the rules that made communication better when eating together may have led to the social manners or cultures of eating meals together.

Cosmetics also followed the same path of dining. Cosmetics started with playing and enjoying the act of decorating their bodies, but eventually spread throughout the community and created the culture of cosmetics. The meaning of cosmetics as a form of expression that leads to acceptance, or the presence and power of communication of cosmetics led to the happiness of being accepted, emotional support, or relief. And today science is revealing the effects that cosmetics bring to the body and mind.

Both dining and cosmetics differ depending on countries and cultures, and in current-day globalization they now influence each other, opening the door to a new era. Japanese cuisine is accepted in Western cultures, and Western recipes are beginning to use Japanese ingredients. In the world of art, there is already a history where Japanese *Ukiyoe* influenced Western Europe art, and likely Western European art influenced traditional Japanese art. Globalization is a two-way process where all sides accept their differences and form a new balance, and is an active phenomenon of cultural interfaces.

## 1.3 SOCIETY AND THE FOUNDATION OF COSMETIC CULTURE

In order to understand how the culture of cosmetics was implemented as a part of society, let's look into a rather unique case of the cosmetics in Japan. Many *haniwa* (archeological remains of clay images) decorated with red makeup have been discovered from the late 3rd century to the late 6th century, before the nation was unified. In *Gishi-Wajinden* ("Records of Wei: An Account of the Wa," the oldest record mentioning Japan), it was written that in China, people wear white makeup whereas in Japan (or *Wa*) men wear red makeup and have black tattoos. For ancient people, makeup may have been a religious and sacred symbol from their awe for animistic spirits in their life in harsh natural environments.

During the middle of the 6th century, Buddhism was imported from China, and white makeup spread among the men and women in the Japanese royal court, becoming the origin of Japanese makeup. Later in the Sengoku period (the Japanese civil war era in mid-15th to early 17th century), makeup spread from the nobility to the new ruling class of *Bushi* (Japanese feudal lords and warriors, also known as *Samurai*). The *Busho* (Bushi commanders) went to war risking their lives, and prepared to show their dignity with their final makeup if they were to lose and be decapitated and gibbeted. Cosmetics was a way to show determination by purifying the body, easing the spirits, and decorating their souls with bravery, and expressing the Bushi's pride, their prominence in society, and self-support.

In general, the history of cosmetics started with body painting and evolved to partial makeup, mostly on the face. Humans realized the power of facial expressions in communication, and facial makeup became an important medium and tool for intimate social and interpersonal communication. Originally cosmetics were not meant for splendor or glamorous consuming. And it was definitely not for self-satisfaction by boasting or showing off. Self-decoration was recreation to enhance joy and taste for beauty, and cosmetics is a method to lift our own spirits. Wearing clothes, accessories, makeup—all are forms of social fashion that sharpen the body and soul to express ourselves and support our minds for a better character to humbly reach out to one another, and give us direction for wise judgment.

## 1.4 THE CULTURE OF COSMETICS AND ESTABLISHMENT OF COSMETIC PHILOSOPHY: A CASE STUDY IN JAPAN

### 1.4.1 The Evolution of Japanese Cosmetic Culture Through Fusion of Western Cultures and Japanese Traditions of *Wa*

Written around 1000 BCE during the Heian Era, Sei Shonagon wrote in her essay *Makura No Soshi* (*The Pillow Book*) that "Washing my hair, putting on my makeup, and wearing perfumed clothes" are things that lift the spirit. In an era when people could not wash their hair often, she describes that the refreshment of washing her hair, putting on makeup, and wearing clothes perfumed with the aroma of incense filled her with joy and excitement with delight. Even in the old imperial days, makeup, sanitation, and aroma were all combined with clothing, and old archives document that fashion was for enjoying its joy and feelings. The foundation of the heart of cosmetics is playfulness and emotions of joy and happiness.

Cosmetics spread to common people after their society became peaceful and affluent. In Japan, this was after the days of disorder of the civil war era, and when the Edo period (early 17th to mid-19th century) brought peace for over 200 years for townsfolk culture to flourish.

Humans have tried to understand the meaning of cosmetics as a tool to make their lives happier and healthier and a medium for communication through philosophy and logic of health and beauty. In Japan, cosmetics spread to common people in the Edo period 200−300 years ago. The science of cosmetics started in Japan in the Meiji period, around 150 years ago when the country studied from Western nations as a state and promoted scientific development.

When the Meiji period started in 1868 and Japan started to modernize, the government announced that even traditional customs would be altered if they did not meet the new era, and cosmetic methods were subject to this new restriction. The government did not show attachment to the tradition of some Japanese *Wa* makeup such as *Ohaguro*, which is makeup of dyeing teeth in black, and *Kaki-Mayu-Kesho*, which is shaving eyebrows and drawing them in the upper forehead, and these were politically discontinued to Westernize the state. The emperor cut his hair to a Western style, and the empress took off her tooth blackening. The calendar was changed to the Western standard solar calendar, and these great changes led to current-day Japan.

No matter how traditional the customary makeup was, the focus was what impression it gave to the developed Western states, and the strong message of cosmetics as a nonverbal communication tool was once again reevaluated. This episode illustrates again that the foundation of cosmetic culture is not only self-assertion but is a balance with manners and kindness to our surroundings. Japan is a rare case where political decisions of a country changed the nature of the heart and culture of cosmetics. Following this era, Japan has Westernized its cosmetic culture while mixing it with the culture of *Wa*.

Japan has a long custom of bathing and had an established cosmetic culture where people bathed in public baths and washed their bodies with *Nuka-Bukuro*, bags with rice bran. In 1865, 6 years before he excavated the archaeological site of Troy, Heinrich Schliemann visited Japan and wrote that "The Japanese are undoubtedly the most sanitary citizens in the world. No matter how poor they are, they visit public baths at least once a day."[3]

## 1.4.2 Sanitary Care and Philosophy Through the *Yojo-Kun*

All manners and customs, no matter what they are, tend to go too far and flow toward an easier path once they are fixed in society. There always comes a time to rethink the meaning of tradition and view the way it should be. In the Edo period, two books were written to guide the ways of cosmetics in a simple and easy manner for the common people. These books, *Yojo-Kun* (Lectures on Health Preservation)[4] and *Miyako-Fuzoku Kewai-Den* (Customs of Grooming in the Capital),[5] were guides for intellectual health and cosmetics. From the Meiji period to this day, these books are the origin of the customs of health and cosmetics in Japan.

In 1713, Ekiken Kaibara wrote *Yojo-Kun* at 84 years old. This book is a *Kun* (guidance) of *Yojo*, meaning to nourish vitality or to pay attention to details for health, and is a health guidance that does not rely on medical advice. *Miyako-Fuzoku Kewai-Den* was published 100 years later, in 1813, and was a guiding text for cosmetics for women. In *Yojo-Kun*, the term *Eisei*, or hygiene, is repeatedly used. Kaibara teaches that *Eisei* is to preserve life and vitality, and is accomplished by acknowledging a two-layered interface of the inside and outside of the body, and the body and mind. As a warning against relying on medicine, he states that "There is a path to hygiene, but there is no medicine for long life. Vitality can be nourished, but there is no medicine to lengthen life that we are not born with." On the other hand, he also demonstrates specific practices, such as in the chapter of "Hygiene Practices for the Morning" he proposes to "brush your teeth, wash your eyes, clean your nostrils, and rinse your mouth." *Yojo* is advice for practicing prevention through careful habits in daily life over curing with medicine.

*Yojo-Kun* teaches that the enrichment of the soul and enrichment of the body are connected by the unity of body and soul as an enrichment of humanity, and that habits in daily life are essential. The grounds of these teaching are the ethics and mindsets to appreciate connection with nature of heaven and earth and the connection to one's parents, and not to neglect "the body, hair, and skin" passed down from the parents. The ethics perceive that self-care of the body and maintaining healthy skin and hair lead to filial piety, or devotion to parents. While having awe for the evil from the outside, Kaibara teaches to repress the inner explosion of desires and act with humbleness, and his teaching is a theory of daily preparation and modesty to make life more certain. This teaching is an inclusive path to ethics where a mindset to proactively have awe will essentially lead to positivity, making inclusive balance of individuality and autonomy, and is a perspective of the intrinsic nature of mortal humans who live among nature.

The body and soul, selflessness and selfishness should be balanced "like looking into a deep valley, like stepping on thin ice," not by avoiding but with bold challenging, and Kaibara's words relate to the skills of modern-day risk management. Since this guidance of *Yojo* and *Eisei* existed in the Edo period, the ideas of hygiene and sanitary imported from Western nations in the Meiji period were easily accepted, and Japan became a sanitary environment.

## 1.4.3 The Philosophy of Grooming Through *Miyako-Fuzoku Kewai-Den*

*Miyako-Fuzoku*, in the title *Miyako-Fuzoku Kewai-Den*, refers to the traditional Japanese *Wa* cosmetic culture in its origins, but also strongly refers to the newest sophisticated fashion in the city. "Since the women of the city wear makeup that best suits their face and wear clothes that best suits their style, ugly women also appear beautiful" are the first words of this book, explaining that the city is not especially filled with beautiful women, and states with hope that a relative balance of fashion can overcome their natural appearance.

This book emphasizes that the roots of cosmetics are from conscious grooming, and specifically states that no matter how well-mannered and no matter how good the makeup is, all is undone if any grooming is lacked. In this book such ideas on grooming are introduced: "If the nose hair is long, the ear hair is shaggy or full of earwax, if the teeth are not finely cleaned, or have bad breath or crumbs are on the tongue, if the nails on the hand or feet are long or has

dirt, and if there is even a spot on the tip of the nails, you will be ridiculed and laughed at if seen by somebody who looks at the details." "If this grooming is rushed, it could not be thorough so grooming must be a habit."

The roots of habitual grooming are the mindset of preparing for the future. They are a perspective for looking at what the body and mind should be as a member of society. Where *Yojo* is preparation for life, cosmetics are preparation to enhance stature, which connects nature and society by realizing health and beauty. Cosmetics are an independent act of fashion, but its balance and sense of fashion with clothing that share the sense of beauty still continues to this day.

These ideas connect to modern-day society and do not contradict our perception of health and life, and this can be backed up by the World Health Organization's definition of health and quality of life (QOL). Based on the definition of health as "a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity," QOL is an "individual's' perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns." In other words, QOL is the balance of health perceived socially and the objective view of the individual as a member of society.[6]

## 1.5 PROGRESS OF SCIENTIFIC TECHNOLOGY AND HISTORY OF THE COSMETICS INDUSTRY IN JAPAN[7,8,9]

The nature and perception of health and beauty in Japan was established from the Edo period, but cosmetic science was established much after. After the Meiji period, when the society valued hygiene, cosmetics were scientifically studied, and in 1900 the first regulations on cosmetics restricted toxic pigments.

Even from today's common knowledge, suspicious substances that are considered toxic have a long history in cosmetic use. In ancient times, red makeup was made from red ochre, with iron oxide as the main component, but in later years more vivid and beautiful mercury and lead compounds such as vermilion or minium were used. Vermilion is composed of mercury sulfide, while minium is a slightly yellow pigment composed of lead (II, IV) oxide. The only nontoxic pigment among these is iron oxide, and the history of makeup coloring was a history of toxic substances. During the Sui and Tang dynasty eras, white makeup methods were imported from China to Japan through cultural interchange, and from the Nara to Heian period white makeup became common in Kyoto (the capital of Japan during the Heian period). Decorating the face white became the basic style of *Wa* makeup in this period and was inherited down until the Meiji period. Although rice powder was occasionally used for white makeup, the main ingredients were again mercury and lead compounds, namely mercury (I) chloride and basic lead carbonate (white lead). The scientific term for pigments in Japanese is *Ganryo*, which literally means "face material," and up to the Meiji Period it meant colorings that do not dissolve in water and are used on the face or as cosmetic powders. *Funshoku* originally meant the act to decorate the face with these powders, but its definition has changed to "to hide something," and is now used only for negative meanings, such as *Funshoku Kessai*, which means "accounting fraud." This is just one example of how cosmetics is deeply integrated to the society and culture.

Although the restriction order of toxic pigments in 1900 banned all mercury and lead compounds for pigments as a general rule, there were exceptions with white lead, which was permitted on the market until 1935. Even though there were cases of lead poisoning since the Meiji period, the application touch and vivid appearance made them popular and the new safety standards could not immediately ban this traditionally used material. Thanks to the development and public acceptance of nonlead white powders, after 35 years a common understanding that safety is the number one priority in cosmetics was finally established. Along with hygiene studies, cosmetic science has contributed to safety and hygiene, but furthermore the target of cosmetics is the highly reactive and the forefront tissue of the immune system, the skin. The skin protects the body as a sensitive defensive barrier by showing alarm signals. We must all remember that safety issues will always exist as long as cosmetics exist, and that cosmetics will always have potential for new issues.

Cosmetic science and the cosmetic industry of Japan were established and they evolved based on governmental policies of the Meiji government to promote chemical technology. Cosmetics and perfumery were among the industries that were promoted by the state, and matched the policy of importing Western cultures and scientific technology. Published in 1872, *Kaibustu-Sousetsu* (Review of the Works of Development) states, "chemistry is an occupation to strengthen and enrich the state … and one must study chemistry if they hope to succeed in economics," and introduces production methods of soap translated from Western books. The first known example of technical publication with cosmetics as a large topic is the *Kagaku Kougei Houkan* (Anthology of Chemical Craftwork) published in 1896, and in the chapter on cosmetics they were introduced as chemical craftwork. In 1897 the first technical book on cosmetics *Kesho-hin Seizou-hou* (Production Methods of Cosmetics) was published, and the historically known Katsu

Kaishu wrote the title calligraphy. This shows the importance of cosmetic science as a leading technology of that age. *Kosho-hin Seizo-hou* (Production Methods of Perfumery) was published in 1899, and the concept of today's skin care and hair care was categorized as *Kesho-hin/Hifu Setsuyo-hin/Mohatsu Setsuyo-hin* (Cosmetics/Skin Nourishing Items/Hair Nourishing Items). In 1943, the Ministry of Agriculture and Commerce also published *Koryo Oyobi Kosho-hin* (Perfumery and Cosmetics) as a governmental report of two years of research in Germany.

In the Meiji period, under the governmental policy five domestic exhibitions were held in Tokyo, Osaka, and Kyoto from 1877 to 1903, and there are records that lipstick, fragrant oils, perfumes, soap, and skin toners were exhibited. The Taisho government followed the Meiji government's promotion of these new industries. In the 1914 Tokyo Taisho Exhibition and the 1922 Peace Commemoration Tokyo Exhibition held in Ueno Park, cosmetics were the main exhibition of the chemical industry pavilion, while cosmetic manufacturers opened many pavilions and records show they contributed to the success of the exhibitions. These exhibitions are the foundation of the cosmetics and perfumery industry in Japan, which withstood World War I, the Great Kanto Earthquake, and World War II, and evolved to this day. This brief history in Japan shows how science and technology contributed to economic development and created a virtuous circle that led to further development, and as engineers we must keep in mind what our standpoint is to create and keep this circle.

## 1.6 SCIENCE, TECHNOLOGY, AND SOCIAL DEMANDS

### 1.6.1 Corporate Responsibilities for Accountability in Science and Technology

Science and technology played their first role in the world of cosmetics in Japan not by creating something new but to stall cosmetics by prohibiting toxins as a country. The beautiful colors in cosmetics had a history of toxic materials in their substances such as red and white pigments. Today, consumers directly seek information on safety and effectiveness.

Engineers today must possess the skills of the technology of cosmetics as well as provide information on the technology used in cosmetics. Information on technology is important for corporate marketing and for society, but the responsibility of technology does not end by just providing information. To the common audience, science is difficult to understand. Engineers have the responsibility to put efforts into scientific education. Providing information on technology is a service of marketing that is based on the premise that the people understand them correctly so the consumers can purchase their products happily. Safety is also a concern, and we live in an age where nature alarms us that the environment does not guarantee safety. This is also an age where information is flooded on effectiveness, or on managing healthy skin, including suspicious information.

Ultraviolet (UV) rays induce skin aging and can increase the risk of skin cancer; although this information is scientifically correct, it must be carefully handled. Biological aging cannot be avoided, and not everybody will have skin cancer. This issue relates closely to other factors such as exposure to UV rays, the melanin content in the skin, and ethical differences. A one-sided statement with an implicit basis that UV is evil is not proper education. This statement could even be a fraud to fake science and manipulate someone to the wrong path. There are already so many people who today misguidedly fear UV rays. Even though there may have not been any ill intent, sun-care products exaggerate the danger of UV to boost their sales, and these marketing techniques of implanting fear use scientific-looking rhetoric but are actually indecent pseudoscience. Such marketing techniques take advantage of the vulnerability to threats and weaker competence of people who care for their skin stronger.

If Caucasians move to a region with strong sunrays, it is only natural that the risk of skin cancer increases. However, if Japanese or Indians move to a northern area of Europe with weak sunlight, the weaker UV rays contrarily can lead to vitamin D deficiency, and it is evident that the risk of rickets in children increases. If a healthy Japanese person living in Japan has excessive fear of UV rays and excessively avoids sunrays, this can even be a potential cause of rickets in children. Human beings have adapted to their habitat by adjusting the melanin content in their skin depending on the UV rays, and after long years this resulted in racial skin color differences. This is a result of the people living in each region adapting to their natural environmental factor of sunlight as organisms over a long period. However, modern technology has allowed us to move from the Northern Hemisphere to the Southern Hemisphere within a day. It is evident that if the northern midwinter environment suddenly changes to a midsummer environment with strong UV rays, our bodies are unable to adapt.

Just as we appreciate the warmth of fire during cold winters, we long for sunlight. And like fire, UV rays are vital to our lives but we will get burned if we are too close. UV light is not the only villain, and knowing how to keep some distance from the inconvenient conditions created by modern civilization is vital to our lives. "Beware of fire" does

not deny fire but warns us to handle with care. We must understand the standpoint of the speaker and the situation of the words as prior information in order to judge if the scientific information is used as fraudulent rhetoric. Discussions between experts can be based on implicit common understanding, but the knowledge between the consumers will have a strong asymmetry, and even from good intent, words from experts could lead to unexpected misunderstandings and actions. We must recognize that communication has risk in itself.

In modern society science may have become another religion, where words in scientific vocabulary are sometimes trusted without doubt. As engineers and scientists, we must consciously understand our social responsibility and step toward the listeners and help them understand, and not participate with those who claim to be scientific with ill intent. Development of a healthy cosmetics industry can only be achieved by science and technology that keeps distance from pseudoscientific rhetoric and supports correct marketing.

### 1.6.2 Binding Corporations, Consumers, and Society With Maternal Communication

Corporations, consumers, and society—if there is no information gap and equal communication is possible, the communication between these three stakeholders will be a win-win-win relationship. The oval pattern shown in Fig. 1.4 is a visualization of the basics of this ideal economic interchange. In this modern world the rights of the consumers are expanding but their information is still limited. We must keep in mind that there is an information gap between the consumers and communicate as if a mother would to her child with maternal communication.

Maternal communication can be shown by an egg-shaped pattern. The information illiterate consumers are shown is a small circle and the corporates are shown in a large circle, and the society forms an egg shape in the background. This also resembles a birds-eye view of a mother holding her child (Fig. 1.5). In a society with highly advanced information communication technology, corporations must use maternal communication to lean toward the consumers and talk gently to maintain the win-win-win relationship. Overcoming the risk of a communication gap is also a demand from our society and times.

Cosmetics are distributed among society through corporate economical activities, but if the consumer needs and science and technology of the corporate seeds are healthy, the products will keep their sales and the market will continue. The cosmetics industry is a fashion to follow the clients' changing needs, and this change itself has value. The vision and evaluation of beauty changes to make a new context in the world and continues to create social value.

### 1.6.3 Soft Science to Read the Changes of Trends

Fashion is not possible to explain in logic, but is a lifestyle of feeling, a way to feel sympathy by conversation from the senses, a world of nonverbal instinct languages. The story of color, the story of smell, and the story of touch all

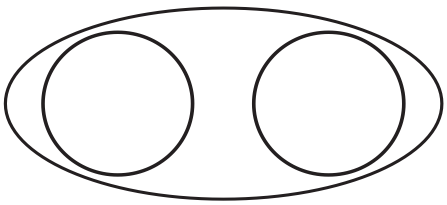


**FIGURE 1.4** Win-win-win relationship of stakeholders.

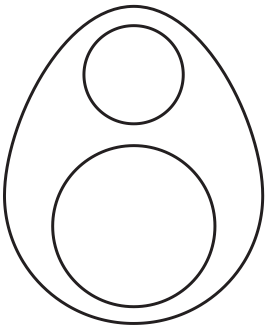


**FIGURE 1.5** Maternal communication.

become one to make a unified world of liking and taste. So what story does cosmetics tell? As the center of nonverbal communication, facial skin, facial muscles, eyebrows and eyes, the mouth, the nose, and hair speak their own facial language. The fingers and nails are also important storytellers in body language. Cosmetics support the expressive language of the face and hands, supplement to enhance our stature, and create emotions of happiness and joy to support our souls. This is not of logic and is connected by playfulness at the very roots.

No matter how beautiful and gorgeous something may look, the richness of the soul can be mentally saturated. Like how the most delicious-looking foods may not be appetizing when we are full, the heart also gets filled. When it feels enough, or too much, it loses its appeal in the fashion trend. To be tired is one thing, but does not mean that we start to dislike it. This is exactly like the playfulness of children, and it simply means that their likings partially change, as well as the priorities, but the circulating desire of fun is always there.

The technology of cosmetics has the responsibility to keep adapting to these constant changes. To understand the changes correctly, the core of our judgment should be flexible cores based on the universal indicators natural science. Both society and people can perceive the same thing differently depending on the situation, and this reality of changing meanings and values must be observed impartially with a mind of flexible science that can predict the future, as a soft science.

## 1.7 SCIENCE, TECHNOLOGY, AND MARKETING

### 1.7.1 Research and Development and Marketing as the Core of Corporate Management

For engineers who work in corporate research and development (R&D), marketing is not something of a different world or an entirely separate division but is the basis of R&D and the core of corporate management. The role of corporate engineers is to develop products that sell; products that sell are products that satisfy consumers. As consumer goods, sales of cosmetics mean that customer satisfaction is ongoing and the company can exist. The ultimate evaluation of products is judged by the customers. Good products are products that are preferred by consumers, and this also means that they will sell for a long period in large volumes.

The marketing division is the core of management that should not be separated from R&D when operating a business. Healthy management combines natural science and humanities where the knowledge of both fields must supplement each other, and management that separates these two fields must be avoided. The logic of interface science can be applied to organization management.

If the goals and visions of the company are shared throughout the organization, the company can be managed by letting the experts handle the details in each field. The role of engineers and researchers is not to be closed in their world of science but aggressively bound at their interface with marketing to utilize their scientific expertise. Science-based cosmetics is to have a foundation of technology, but also means to build on this foundation beyond functionality and sensory evaluation to evaluate cultural and social values, and the primary success of science and technology is achieved when they join hands with marketing.

To reach this goal the world of science and technology must understand and act in the ways of marketing. The definition of marketing is market activities that act on and create the market. Even if cosmetics are widely accepted in society, developing products that are not chosen by the customers is a waste of science and technology. Peter Drucker explains, “the purpose of business is to create and keep a customer” and “the aim of marketing is to know and understand the customer so well that the product or service fits him and sells itself.” In other words, he emphasizes that we should not try to sell products but develop products that would sell themselves. This also means that we must fully understand the customer. These definitions undoubtedly show the responsibility of science and technology and motivate engineers.

### 1.7.2 The 4Ps and Best Timing of Science, Technology, and Marketing

We must know what the mission of science and technology is in the context of marketing. E. J. McCarthy proposed the marketing mix concept, and in this concept he states that the basic challenge of technology is to control the 4Ps, which stand for product, price, place, and promotion. The product and price are directly related to development and are factors where technology has a strong influence. Price and promotion are direct market activities, but cosmetics are in a market of an ever-changing fashion where there are strong trends and changes, and small repeating trends and changes.

Changes in socioeconomic environments and overall cultural environmental changes are changes that lead to the strong trends in the cosmetics market. High-priced cosmetics are sold as high-end products and are accepted as luxuries, and then they spread to create a larger market. Using an analogy of small streams becoming large rivers, this market spread from top to bottom is known as the trickle-down effect and was believed to be a principle in economics. However, in our current abundant market, the change itself is changing. High-quality and affordable products are first adopted, and as if they go upstream, high-priced products change their features, showing a bottom-up effect. Nowadays it is common to see adult fashion influenced by younger fashion. In the ever-changing cosmetics market, the role of R&D is to be undercover to anticipate the market change in advance and be prepared.

The most important aspect of marketing in a dynamic market is to know and not miss the best timing. The best timing does not only mean that the launch is not delayed, but a product launch too early can also waste the technology. Marketing decisions must be made in advance of the best timing, and the R&D and marketing can have a head start and cooperate to meet the best timing only if the corporation is structured so R&D has the prototypes tested and ready.

Being ready is to prepare by predicting the future, and having enough time to prepare for the future. Preparing is to quickly read the changes in the market for indications and meet the changes. In order to answer to the marketing demands of "now," the organization's structure must always have a mindset of being able to synchronize with the project of tomorrow and the day after, and conversation with future projects initiate the cooperation of R&D and marketing. Science and technology is an operation that requires the mindset of soft science to always be one step ahead.

Product releases are based on operations of research, development, and manufacturing, and they need support from relating technological follow-up services. Technological follow-up services are operations that support operations such as legal handling of regulations on safety and health for quality control, public announcement united with marketing, and customer care after the product launch.

Products are distributed in the economic chain after they are launched, and cosmetic technology contributes to this economic chain. There are many economic activities prior to launch from product development to manufacturing. In other words, there are nonmaterial costs for R&D, as well as costs for purchasing materials and equipment. These prior costs, production costs, and engineering costs strongly influence the final price when the product prices are designed to meet consumer demands. R&D is a procedure prior to marketing, so it is vital that the marketing policies are utilized in this procedure. Good products do not always deserve a high price. Products can only be widely distributed in society when the acceptable cost limit is well managed.

Even if an appropriate price is set, market expansion will always have a risk. The best way to handle such risks is to think, try, and improve based on experience while moving forward and expanding. Assuming that the ultimate target of the market size is 100, the first step is a trial based on a market size of 10 to test the hypothesis, and after finding and solving the problems, the risks of expanding should be eliminated in a market size of 30 to reach the ultimate goal, a risk management strategy of market expansion called 10-30-100.

Cosmetics are products where emotional and mental value have more weight than scientific functionality. The customers are not just consumers, but are cosmetic users who love the process and effects of using cosmetics. Cosmetics are a medium and tool for social communication. We must be consistent with customer-focused marketing to put our values in customers first. From a scientific point of view, customer-focused marketing is continuing to create customer satisfaction, make sales easier for the company, and contribute to developing products that sell themselves. Food products have already reached a stage of cooking and gastronomy beyond hunger and the science of nutrition.

The future of the science and technology of cosmetics relies on knowledge of understanding things rather than objects to propose a unique selling proposition as new differentiating cosmetics. In the United States, the campaign by the industry group CTFA (Cosmetic Toiletry and Fragrance Association) and governmental Food and Drug Administration of "Look Good, Feel Better" has already helped cancer patients. I hope the next generation of cosmetic engineers and researchers reading this book will have a mindset to understand things and be generalists with a flexible core based on science, and embrace the ideas of soft science with a sensitive and rich perspective.

Time is money. Slow and steady,
We are tomorrow's past. Pass on today to tomorrow,
The future is the past in preparation. And be prepared.

## References

1. Morris D. *The naked ape: a zoologist's study of the human animal*. London: Jonathan Cape; 1967. Trans. Hidaka, Toshitaka. Tokyo: Kadokawa Bunko, 1969.
2. Huizinga J. *Homo Ludens; a study of the play-element in culture*. Boston: Beacon Press; 1955. Trans. Takahashi, Hideo. Tokyo: Chuko Bunko, 1973.
3. Schliemann H. *Le Chine et le Japon au temps present (China and Japan in the present age)*. 1867. Trans. Ishii, Kazuko. Tokyo: Kodansha Gakujutu Bunko, 1998.
4. Kaibara E. In: Ishikawa K, editor. *Yojo-kun (Lectures on health preservation)*. Tokyo: Iwanami Bunko; 1713. 1961.
5. Sayama H. In: Takahashi M, editor. *Miyako-Fuzoku Kewai-Den (Customs of grooming in the capital)*. Tokyo: Toyo Bunko Heibonsha; 1813. 1982.
6. Nozaki F. Keshohin no Rekishi — Eisei Kara QOL he — (The history of cosmetics: from hygiene to QOL.). *Yakushi Gakkaishi* 2013;**48-1**.
7. Takahashi M. *Kesho Monogatari. (Story of cosmetics)*. Tokyo: Yuzankaku Shuppan; 1997.
8. Nozaki F, editor. *Keshohinn Kogyo 120 Nenn No Ayumi (The evolution of 120 years of the cosmetics industry.)*. Tokyo: Nihon Keshohin Kougyo Rengoukai; 1995.
9. Nozaki F. "Customer Service." Anata no Iryou ha Annzenn Ka? — Igoushu kara Manabu Risk Management. (Is your medical safe? Learning risk management from other industries). In: *Kikikanri Kenkyuukai — Medical Risk Management Bunkakai*. Tokyo: Nanzan-Do; 2011.

CHAPTER

# 2

# Global Cosmetic R&D Trends Unveiled From Past IFSCC Award-Winning Papers

M. Minamino[1], F. Kanda[2]

[1]BelleVienus Co., Ltd., Osaka, Japan; [2]Shiseido Global Innovation Center, Yokohama, Japan

## 2.1 INTRODUCTION

Research and development (R&D), whose final goal is to provide the best possible new benefits and values to our consumers, evolves continually absorbing new technologies based on new perspectives. Diverse formulations ranging from skin care, makeup to hair care products exist along with studies to ensure their safety and efficacy, all of which fall under such R&D activities. Numerous technological innovations gave birth to new cosmetic products creating new trends. Meanwhile, in the real-life market, even products based on conventional technologies could enjoy hot sales depending on when and how they were strategically launched. Therefore, taking a look back at cosmetic technologies of the past serves to not only provide us with tips to tackle unmet demands but also to revisit conventional technologies from which new utility values might be exploited. In view of this, we have attempted to analyze past award-winning papers presented at IFSCC Congresses and Conferences where topnotch cosmetic findings are shared annually, hopefully to gain an overview of cosmetic innovations during the last five decades.

## 2.2 THE INTERNATIONAL FEDERATION OF SOCIETIES OF COSMETIC CHEMISTS

Established back in 1959 by national cosmetic societies worldwide, the International Federation of Societies of Cosmetic Chemists (IFSCC) is an international academic Federation currently comprised of 47 national societies embraced within its umbrella, with total members counting over 15,000 individuals. As by far the most important of the various activities conducted by the IFSCC, all of which are related to the advancement of technologies to ensure the development of safe and efficacious cosmetics and affiliated products, congresses on even years and conferences on odd years are held to which cosmetic scientists from all over the world gather to present and share their latest scientific findings. At each of these events, awards serving different purposes are granted to outstanding papers.

The IFSCC award for the most meritorious podium paper was first introduced at the 6th IFSCC Congress held in Barcelona, Spain, back in 1970. An honorary mention(s) could be announced when there was an excellent runner-up paper(s) of equivalent quality to the award winner. Since the 17th IFSCC Congress in Yokohama in 1992, a poster award was additionally introduced to credit the best poster paper. As it turned out that the majority of IFSCC awards were granted to downstream studies closely linked to the final products, the award structure was reformed as from the 23rd IFSCC Congress in Orlando in 2004 to also credit upstream research studies, which are equally important. This gave birth to the "IFSCC Basic Research Award" and "IFSCC Applied Research Award" of perfectly equal value. In 2003 in South Korea, the IFSCC Conference Award (now renamed as the Johann Wiechers Award) was granted for the first time to credit an outstanding author at a conference as well. The IFSCC Conference Poster Award was introduced in 2013 at the 22nd IFSCC Conference in Rio de Janeiro. There are other awards intended for the youngsters and authors from the host society, but these will not be mentioned in this chapter.

*Cosmetic Science and Technology: Theoretical Principles and Applications*
http://dx.doi.org/10.1016/B978-0-12-802005-0.00002-1



Copyright © 2017 Elsevier Inc. All rights reserved.

All papers eligible for the IFSCC Awards are strictly judged by an award committee consisting of qualified and experienced cosmetic scientists selected as defined in the IFSCC Operations Manual, and the criteria are "Novelty and originality of the experimental approach," "The impact of the experimental findings for the cosmetic industry at large," and "The extent to which the results provide an answer to as yet unresolved scientific matters." How skillfully the presentation was given, and how the presenter dealt with questions from the floor, will also be taken into consideration.

## 2.3 TRACING THE HISTORY OF ARTICLES PRESENTED AT IFSCC CONGRESSES/CONFERENCES

At each IFSCC Conference/Congress, topics on various cosmetic disciplines are presented. Using the KOSMET database that contains all papers presented at IFSCC Conferences/Congresses since 1968, we took a look at the frequency with which "controlled terms" appeared in the papers presented between 2002 and 2014, and found out as depicted in Fig. 2.1 that the majority of topics were related to either "Raw Materials" or "Skin/Dermatology." In terms of research fields, there were many papers related to "Analysis" and "Biophysics" covering pharmacokinetic studies such as percutaneous absorption, followed by "Physicochemistry" represented by rheology, and "Biology" including physiology.

Articles related to "Raw Materials" and "Skin/Dermatology" have appeared constantly and consistently (Fig. 2.2).

Turning now to research fields (Fig. 2.3), whilst "Biophysics" and "Analysis" count constant articles from 2004 onward, "Biology" articles scarcely present in 2002 and 2004 begin to gain ground from 2006. On the other hand, "Physicochemical" articles begin to decline since 2004.

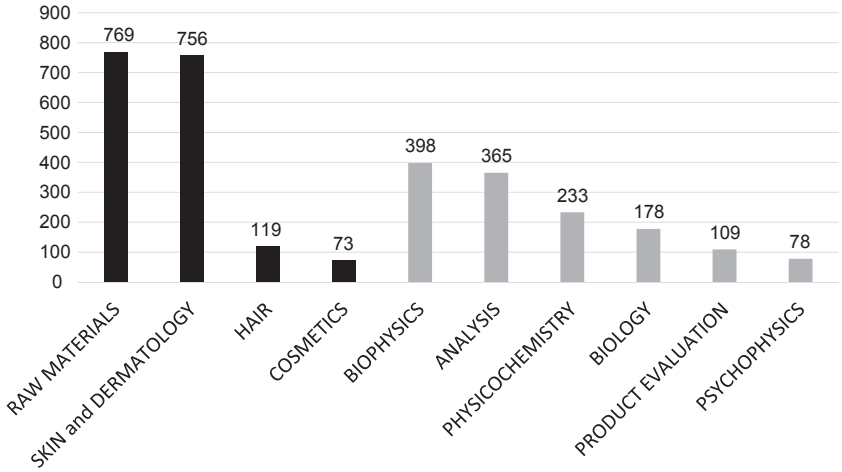



**FIGURE 2.1** Papers presented at IFSCC Conferences/Congresses (2002–2014). Occurrence rate of KOSMET-controlled terms (SH).

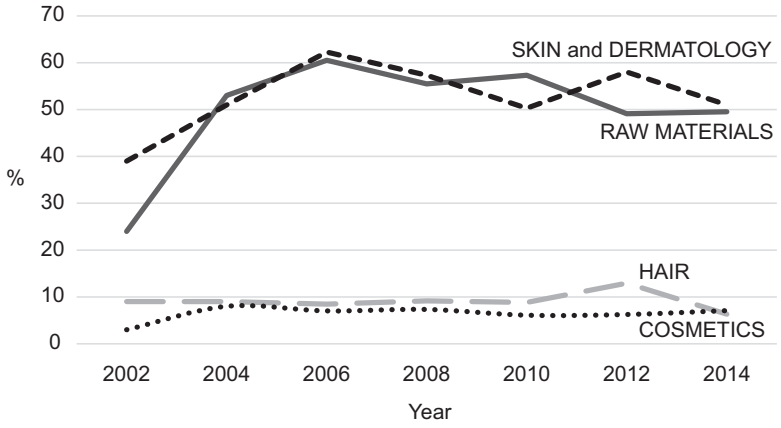



**FIGURE 2.2** Trends in articles presented at IFSCC Congresses. Occurrence rate of KOSMET-controlled terms (SH).

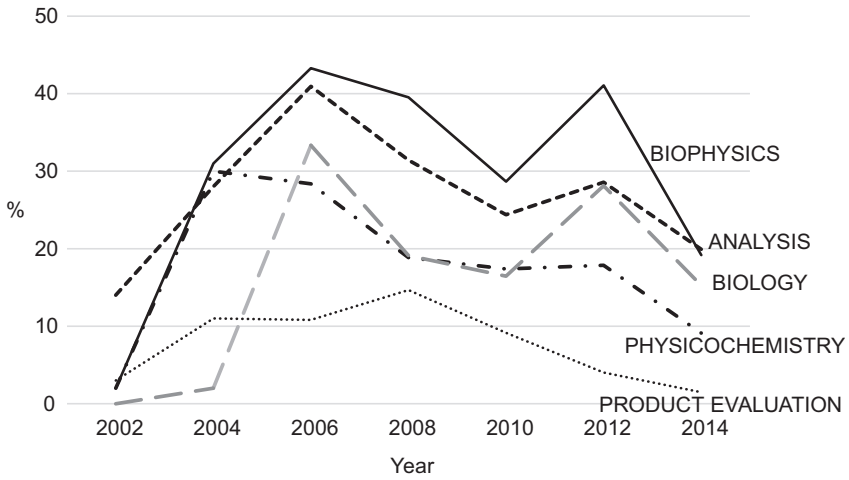



FIGURE 2.3 Trends in research fields of articles presented at IFSCC Congresses. Occurrence rate of KOSMET-controlled terms (SH).

## 2.4 TRENDS INTERPRETED FROM AWARD-WINNING PAPERS

### 2.4.1 An Overview of Award-Winning Papers

Ever since the first IFSCC Award was granted at the 9th IFSCC Congress in Boston back in 1970, during the 46 years up until the most recent IFSCC Congress in Orlando, USA (2016), a total of 80 papers as summarized in Table 2.1 have been presented with an award for their outstanding contribution to the cosmetic industry.

Looking at award-winning papers by societies to which the first authors belong, the majority of them are from Japan, France, Germany, and the United States, i.e., major IFSCC societies with large memberships (Fig. 2.4).

Out of the 80 papers, 40 were on skin biology (almost one-half), and 19 on formulation, constituting almost a quarter of the fraction pie. The rest can be categorized into development of new ingredients, hair-related studies, and psychological aspects of cosmetics (Fig. 2.5). The 40 papers on skin biology consist of 27 basic dermatological papers and 13 evaluative studies such as skin measurement.

### 2.4.2 Skin Biology

When the 40 papers on skin biology were broken down into the organs that they are targeting, it is apparent as shown in Table 2.2 that a vast majority of 22 papers were on the epidermis. Located as the outermost layer of the skin where cosmetics come into direct contact, not surprisingly, the epidermis was considered an accessible research target by many researchers over a long period of time (Fig. 2.6).

#### *2.4.2.1 Moisture in the Stratum Corneum*

An attempt to measure moisture content in the skin has been reported at the IFSCC Congress in London (Paper no. 5:1974, Table 2.1), where it was rewarded with an "honorary mention." The principle of this method is "low-frequency impedance," employed in on-site tools to measure skin moisture at shop fronts. This method makes use of the changes seen in the electric resistance (impedance) of the stratum corneum once it comes into contact with water, and hence offers a means of measuring moisture in the stratum corneum in vivo. Prior to the introduction of this method, cosmetics have been made available for three facial skin types, i.e., for "oily," "normal," and "dry" skin, depending on the sebum content of the consumer's skin, and recommended accordingly. In 1984, a paper reported at the IFSCC Congress suggested the fourth type of skin, a "hybrid skin" that is dry but abundant in sebum content, the finding of which was possible through measuring moisture in the stratum corneum via the impedance method. The paper received an honorary mention for this work (Paper no. 20:1984, Table 2.1).

Thereafter, the presence of "ceramides" within the stratum corneum was revealed, making it clear that the barrier function of the stratum corneum played a crucial role in maintaining healthy skin. As a reference for the barrier function of the stratum corneum, transepidermal water loss that measures the moisture transpired through the skin, came to be used.

**TABLE 2.1** IFSCC Award Winning Papers (1970–2016)

| Paper No | Congress/ Conference | | Award | First Author | Country | Title |
|---|---|---|---|---|---|---|
| | Year | Venue | | | | |
| 1 | 1970 | 6th Congress | Barcelona | Best Paper | G. Aubin | France | Inhibition de la Sebogenese par Blocage Metabolique Specifique (Inhibition of the Sebogenesis by Specific Metabolic Blockage) |
| 2 | 1972 | 7th Congress | Hamburg | Best Paper | K.D. Bingham | UK | Male Pattern Baldness and the Metabolism of Androgens by Human Scalp Skin |
| 3 | 1974 | 8th Congress | London | Best Paper | A.C. Brown | UK | Hair Breakage: the Scanning Electron Microscope as a Diagnostic Tool |
| 4 | 1974 | 8th Congress | London | Honorable Mention | T.J. Lin | Taiwan | Effects of Phase Inversion and Surfactant Location on the formation of O/W Emulsions |
| 5 | 1974 | 8th Congress | London | Honorable Mention | E.J. Clar | France | Skin Impedance and Moisturization |
| 6 | 1976 | 9th Congress | Boston | Best Paper | Y. Kumano | Japan | Studies and Practices of Water-in-Oil Emulsions Stabilized with Amino Acids or their Salts |
| 7 | 1976 | 9th Congress | Boston | Honorable Mention | H.W. Kreysel | Germany | Das Bindegewebe der Menschlichen Haut unter dem Einfluss von UV-light (Connective Tissue of Human Skin under the influence of Ultra Violet Light) |
| 8 | 1976 | 9th Congress | Boston | Honorable Mention | P.T. Pugliese | USA | The Measurement of Enzyme Kinetics on the Intact Skin - A New Method to Study the Biological Effects of Cosmetics on the Epidermis |
| 9 | 1978 | 10th Congress | Sydney | Best Paper | A. Meybeck | France | Etude par R.P.E. des Radicaux Libres Formes par Action de la Lumiere Ultra Violette sur les Proteins de la Peau (ESR Study of the Free Radicals formed by action of Ultra Violet Light on Skin Proteins) |
| 10 | 1978 | 10th Congress | Sydney | Honorable Mention | T.J. Lin | USA | Low-Surfactant Emulsification |
| 11 | 1978 | 10th Congress | Sydney | Honorable Mention | R.M. Handjani-Vila | France | Dispersions de Phases Lamellaires de Lipides Non Ioniques en Cosmetique. |

**TABLE 2.1** IFSCC Award Winning Papers (1970–2016)—cont'd

| Paper No | Congress/ Conference | | Award | First Author | Country | Title |
|---|---|---|---|---|---|---|
| | Year | Venue | | | | |
| | | | | | | (Dispersions of Lamellar Phases of non-ionic Lipids in Cosmetic Products) |
| 12 | 1980 | 11th Congress | Venice | Best Paper | J.G. Dominguez | Spain | The Inhibitory Effect of Some Amphoteric Surfactants on the Alkylsulfates Irritation Potential |
| 13 | 1980 | 11th Congress | Venice | Honorable Mention | M. Yamaguchi | Japan | Antimicrobial Activity of Butyl P-Hydroxybenzoate in Relationship to its Solubilization Behaviors by Nonionic Surfactants |
| 14 | 1980 | 11th Congress | Venice | Honorable Mention | A.K. Reng | Germany | Manufacture of Cosmetics and Tolletaries with Low Energy and Optimal Agitation |
| 15 | 1982 | 12th Congress | Paris | Best Paper | T. Suzuki | Japan | Secondary Droplet Emulsion; Contribution of Liquid Crystal Formation to Physicochemical Properties and Skin Moisturizing Effect of Cosmetic Emulsion |
| 16 | 1982 | 12th Congress | Paris | Honorable Mention | J. Scandel | France | Shampoos and their Aesthetic Effects |
| 17 | 1982 | 12th Congress | Paris | Honorable Mention | U. Zeidler | Germany | In vitro Test for the Skin Compatiblity of Surfactants |
| 18 | 1984 | 13th Congress | Buenos Aires | Best Paper | L. Aubert | Monaco | An in vivo Assessment of the Biomechanical Properties of Human Skin Modifications under the Influence of Cosmetic Products |
| 19 | 1984 | 13th Congress | Buenos Aires | Honorable Mention | J.L. Parra | Spain | Uso de Microemulsiones Para Vehiculizar Reactivos Nucleofilicos de Potencial Applicacion en Formulaciones Cosmeticas |
| 20 | 1984 | 13th Congress | Buenos Aires | Honorable Mention | H. Kumagai | Japan | Development of a Scientific Method for Classification of Facial Skin Types |
| 21 | 1986 | 14th Congress | Barcelona | Best Paper | A. Kimura | Japan | Development of New Type Colored Nacreous Pigment |

*Continued*

**TABLE 2.1** IFSCC Award Winning Papers (1970–2016)—cont'd

| Paper No | Congress/ Conference | | Award | First Author | Country | Title |
|---|---|---|---|---|---|---|
| | Year | Venue | | | | |
| 22 | 1986 | 14th Congress | Barcelona | Honorable Mention | M. Courtois | France | Study of the Recoiling Process of Hair with the Replica Technique |
| 23 | 1986 | 14th Congress | Barcelona | Honorable Mention | N. Nakamura | Japan | Blurring of Wrinkles through Control of Optical Properties |
| 24 | 1988 | 15th Congress | London | Best Paper | F. Kanda | Japan | Elucidating Body Malodor to Develop a Novel Body Odor Quencher |
| 25 | 1988 | 15th Congress | London | Honorable Mention | F. Comelles | Spain | Application of Ternary Systems in Specific Cosmetic Formulations |
| 26 | 1990 | 16th Congress | New York | Best Podium Paper | K. Yamazaki | Japan | Development of a New W/O Type Nail Enamel |
| 27 | 1990 | 16th Congress | New York | Honorable Mention | J.C. Garson | France | Study of Lipid and Non-Lipid Structure in Human Stratum Corneum by X-Ray Diffraction |
| 28 | 1990 | 16th Congress | New York | Poster Award | T. Cavalletti | Italy | Lipoaminoacids are Powerful Scabengers of Free Radicals |
| 29 | 1992 | 17th Congress | Yokohama | Best Podium Paper | T. Sakamoto | Japan | Measurement Method of Efficacy of Anti Dandruff Cosmetics and Development of the New Active Commercial Product |
| 30 | 1992 | 17th Congress | Yokohama | Honorable Mention | T. Suzuki | Japan | Multilamellar Emulsion of Stratum Corneum Lipid—Formation Mechanism and its Skin Care Effects |
| 31 | 1992 | 17th Congress | Yokohama | Honorable Mention | K. Ohno | Japan | Development of Photochromic Titanium Dioxide and Its Application to Make-up Foundation |
| 32 | 1992 | 17th Congress | Yokohama | Poster Award | D.C. Salter | UK | Moisturization Processes in Living Human Skin studied by Magnetic Resonance Imaging Microscopy |
| 33 | 1992 | 17th Congress | Yokohama | Poster Award | S. Akazaki | Japan | A Relevant Study Correlating the Actual Observed Physical Properties and a Cosmetic-Users Subjective Evaluations |
| 34 | 1994 | 18th Congress | Venice | Best Podium Paper | C. Kan | Japan | Psychoneuro-immunological Benefits of Cosmetics |

**TABLE 2.1** IFSCC Award Winning Papers (1970–2016)—cont'd

| Paper No | Congress/ Conference | | Award | First Author | Country | Title |
|---|---|---|---|---|---|---|
| | Year | Venue | | | | |
| 35 | 1994 | 18th Congress | Venice | Honorable Mention | C. Colin | France | Non Invasive Methods of Evaluation of Oxiditive Stress Induced by Low Doses of Ultra Violet in Humans |
| 36 | 1994 | 18th Congress | Venice | Poster Award | A.V. Rowllings | USA | Seasonal Influences on Stratum Corneum Ceramide 1 Linoleate Content and the Influence of Topical Essential Fatty Acids |
| 37 | 1996 | 19th Congress | Sydney | Best Podium Paper | G.E. Westgate | UK | A New Model of Hair Growth Regulation |
| 38 | 1996 | 19th Congress | Sydney | Honorary Mention | K. Nishikata | Japan | Optical Propertoes of stratum corneum and Development of Natural Looking Make-up |
| 39 | 1996 | 19th Congress | Sydney | Poster Award | H. Hosokawa | Japan | Development of Water-Based Nail Enamel |
| 40 | 1998 | 20th Congress | Cannes | Best Podium Paper | Y. Nishimori | Japan | A New Approach for the Inprovement of Photoaged Skin Through Collagen Fiber Bundle Reconstruction Mechanism |
| 41 | 1998 | 20th Congress | Cannes | Best Podium Paper | B. Querleux | France | Brain Activation in Response to a Tactile Stimulation: functional Magnetic Resonance Imaging (fMRI)versus Cognitive Analysis |
| 42 | 1998 | 20th Congress | Cannes | Poster Award | G.S. Payonk | USA | In vivo 3D Topographical Skin Profiling Device |
| 43 | 2000 | 21st Congress | Berlin | Best Podium Paper | S. Amano | Japan | Basement Membrane Damage, a Sign of Skin Early Aging, and Laminin 5, a Key Player in Basement Membrane Care |
| 44 | 2000 | 21st Congress | Berlin | Honorary Mention | L. Declercq | Belgium | Influence of Age and Ultraviolet A Exposure upon Energy Metabolism of Human Skin: an in vivo Study by $^{31}$P Nuclear Magnetic Resonance Spectroscopy |
| 45 | 2000 | 21st Congress | Berlin | Honorary Mention | F. Leroy | France | Historical Structure of Human Nails as Synchroton X-ray Microdiffraction |

*Continued*

**TABLE 2.1** IFSCC Award Winning Papers (1970–2016)—cont'd

| Paper No | Congress/ Conference | | Award | First Author | Country | Title |
|---|---|---|---|---|---|---|
| | Year | Venue | | | | |
| 46 | 2000 | 21st Congress | Berlin | Poster Award | K. Kaneko | Japan | Super-Rapid Drying "Dip-in-Water" Nail Enamel |
| 47 | 2002 | 22nd Congress | Edinburgh | Best Podium Paper | E. Kawai | Japan | Can Inorganic Powders Provide any Biological Benefit in Stratum Corneum while residing on the Skin Surface |
| 48 | 2002 | 22nd Congress | Edinburgh | Honorary Mention | M.R. Green | UK | The human periorbital wrinkle: Immunohistology and computer modelling suggest key roles for directional collagen Fibers, and Mechanical Force in Wrinkle Maintenance |
| 49 | 2002 | 22nd Congress | Edinburgh | Poster Award | J.A. Bouwstra | Netherland | Visualizing Water Uptake in the Stratum Corneum Using Cryo-SEM |
| 50 | 2003 | 17th Conference | Seoul | Conference Award | J.W. Wiechers | Netherland | Formulating for Efficacy |
| 51 | 2004 | 23rd Congress | Orlando | Basic Research Award | K. Tanaka | Japan | Continuous Three-Dimensional Examination of Interior Hair Structure |
| 52 | 2004 | 23rd Congress | Orlando | Applied Research Award | M. Rohr | Germany | Compatibility Testing of Coloured Cosmetics - A New Tool of Objective Testing Near-Infrared-Remission-Spectroscopy (NIR-RS) |
| 53 | 2004 | 23rd Congress | Orlando | Poster Award | T. Doering | Germany | Cutaneous Restructuration by Phytohormones: From DNA Chip Analysis to Morphological Alteration |
| 54 | 2005 | 18th Conference | Firenze | Conference Award | K. Yagi | Japan | Optical Rejuvenating Makeup Using an Innovative Shape-controlled Hybrid Powder |
| 55 | 2006 | 24th Congress | Osaka | Basic Research Award | J.A. Bouwstra | Netherland | A Novel Stratum Corneum Substitute Mimics the Barrier Properties of Dry and Normal Skin: A Convenient and Efficient Approach for Screening of Active Ingredients |

**TABLE 2.1** IFSCC Award Winning Papers (1970–2016)—cont'd

| Paper No | Congress/ Conference | | Award | First Author | Country | Title |
|---|---|---|---|---|---|---|
| | Year | Venue | | | | |
| 56 | 2006 | 24th Congress | Osaka | Basic Research Award Honorary Mention | C. Katagiri | Japan | Identification of a Regulatory Molecule in Keratinocyte Denucleation and Its Relevance to Barrier Disruption |
| 57 | 2006 | 24th Congress | Osaka | Applied Research Award | J. Peguet-Navarro | France | Differential Toxicity on Monocytes and Monocyte-derived Dendritic Cells: a New Tool to Differentiate Allergens from Irritants? |
| 58 | 2006 | 24th Congress | Osaka | Poster Award | T. Iida | Japan | How Can We Improve the Appearance of Conspicuous Facial Pores? |
| 59 | 2007 | 19th Conference | Amsterdam | Conference Award | A. Puig | Spain | A New Decorin-like Tetrapeptide for Optimal Organisation of Collagen Fibres |
| 60 | 2008 | 25th Congress | Barcelona | Basic Research Award | S. Kuroda | Japan | Epidermal Tight Junction:The Master Skin Barier Regulator |
| 61 | 2008 | 25th Congress | Barcelona | Applied Research Award | T. Osawa | Japan | Development of a Water-Resistant/ Detergent-WashablePowder Coated with Stimuli-Responsive Polymer and Its Application to Sun-Care Products |
| 62 | 2008 | 25th Congress | Barcelona | Poster Award | E. Schulze zur Wiesche | Germany | Specific Repair of Aging Hair Keratin |
| 63 | 2009 | 20th Conference | Melbourne | Conference Award | K. Shimizu | Japan | A Proposal on a New Anti-Aging / Anti-Wrinkling Story Blocking Epidermal-Dermal Crosstalk by Strengthening the Intracellular Reactive Oxygen Species Scavenging Capability |
| 64 | 2010 | 26th Congress | Buenos Aires | Basic Research Award | T. Hibino | Japan | Characterization and Regulatory Mechanism of Bleomycin Hydrolase as a Natural Moisturizing Factor (NMF) Generating Enzyme in Human Epidermis |
| 65 | 2010 | 26th Congress | Buenos Aires | Applied Research Award | T. Ikeda | Japan | No More Smeary Coffee Cups! A Novel, Long-Lasting, Non-Smear Lipstick Utilizing a |

*Continued*

**TABLE 2.1** IFSCC Award Winning Papers (1970–2016)—cont'd

| Paper No | Congress/ Conference | | Award | First Author | Country | Title |
|---|---|---|---|---|---|---|
| | Year | Venue | | | | |
| 66 | 2010 | 26th Congress | Buenos Aires | Poster Award | A. Matsuo | Japan | Phase Separation Mechanism is Totally Devoid of Secondary Stain<br>A Novel Self-Assembled Structure for Transparent, Reversibly Deformable Oil Gels and Its Application to Cosmetics |
| 67 | 2011 | 21st Conference | Bangkok | Conference Award | Y. Matsunaga | Japan | Development of Self-Dissolving Microneedles Consisting of Hyaluronic Acid as an Anti-Wrinkle Treatment |
| 68 | 2012 | 27th Congress | Johannesburg | Basic Research Award | T. Yamashita | Japan | Non-Invasive In Situ Assessment of Structural Alternation of Human Dermis Caused by Photo-Aging Using a Novel Collagen Specific Imaging Technique |
| 69 | 2012 | 27th Congress | Johannesburg | Applied Research Award | G. Hillebrand | USA | Validation of a Web-Based Imaging System for 'At-Home' Facial Skin Analysis |
| 70 | 2012 | 27th Congress | Johannesburg | Poster Award | T. Motokawa | Japan | Identification and Mechanisms of Adrenomedullin as a Novel Melanocyte-Activating Factor |
| 71 | 2013 | 22nd Conference | Rio de Janeiro | Conference Award* | M. Egawa | Japan | Visualization of Water Distribution in Facial Skin Using Novel High-Sensitivity Imaging Systems and Application to Cosmetics Evaluation<br>Development of a camera system that clearly reveals the moisture distribution in the face! |
| 72 | 2013 | 22nd Conference | Rio de Janeiro | Conference Poster Award | S. Iriyama | Japan | The Role of Heparan Sulfate at the Dermal-Epidermal Junction in Hyperpigmentation |
| 73 | 2014 | 28th Congress | Paris | Basic Research Award | H. Goto | Japan | Antimicrobial Peptide Human Beta Defensin-3(hBD-3) as a Key Factor for Acne Flare-up during the Premenstrual Stage |

TABLE 2.1 IFSCC Award Winning Papers (1970–2016)—cont'd

| Paper No | Congress/ Conference | | Award | First Author | Country | Title |
|---|---|---|---|---|---|---|
| | Year | Venue | | | | |
| 74 | 2014 | 28th Congress | Paris | Applied Research Award | A. Léopoldès de Vendômois | France | New Strategy for the Protection of Consumers: a Functional Film Limiting Exposition to Fragrance Allergens |
| 75 | 2014 | 28th Congress | Paris | Poster Award | T. Ezure | Japan | Novel Approach to Anti-aging Facial Skin Care through Reconstruction of "Dermal Anchring Structures" to Improve Facial Morphology |
| 76 | 2015 | 23rd Conference | Zurich | Conference Award* | A. Sakata | Japan | Breakthrough in Improving the Skin Sagging with Focusing on the Subcutaneous Tissue Structure, Retinacula Cutis |
| 77 | 2015 | 23rd Conference | Zurich | Conference Poster Award | I. Meyer | Germany | AhR Antagonists: Potent Cosmetic Actives to Protect Against Air Pollution Induced Premature Aging |
| 78 | 2016 | 29th Congress | Orlando | Basic Research Award | M. Nomura | Japan | Translating the human hair surface state into sound |
| 79 | 2016 | 29th Congress | Orlando | Applied Research Award | R. Voegeli | Swiss | The presence of essential and non-essential stratum corneum proteases: the vital need for protease inhibitors |
| 80 | 2016 | 29th Congress | Orlando | Poster Award | T. Ezure | Japan | The sweat gland as a breakthrough target for anti-aging skin care - Discovery of novel skin aging mechanism: "dermal cavitation" |

* *Johann Wiechers Award*

With the advent of new dermatological findings in the 1990s, methods were developed to measure moisture in human skin both simply and noninvasively, and a paper presented in 1992, in which magnetic resonance imaging (MRI) microscopy was utilized to measure skin moisture, received the award (Paper no. 32:1992, Table 2.1). It marked the beginning of utilizing "visual" means for skin measurements.

Later on Bouwstra et al. reported the "morphological" change of moisture in the stratum corneum through visually capturing water distribution in the stratum corneum using cryo- scanning electron microscopy (SEM) (Paper no. 49:2002, Table 2.1).

Later in 2013, Egawa et al. succeeded in visualizing moisture content in the stratum corneum using a near-infrared (NIR) camera, making it possible to see facial moisture at one glance (Paper no. 71:2013, Table 2.1).

In recent years, the advent of technologies for "visualization" has opened up the door for two-dimensional skin measurement, allowing skin conditions to be studied with utmost and unprecedented details.

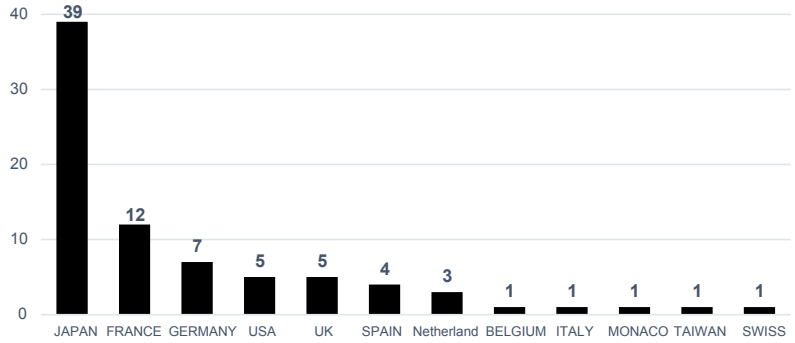



FIGURE 2.4 IFSCC Awards by societies.

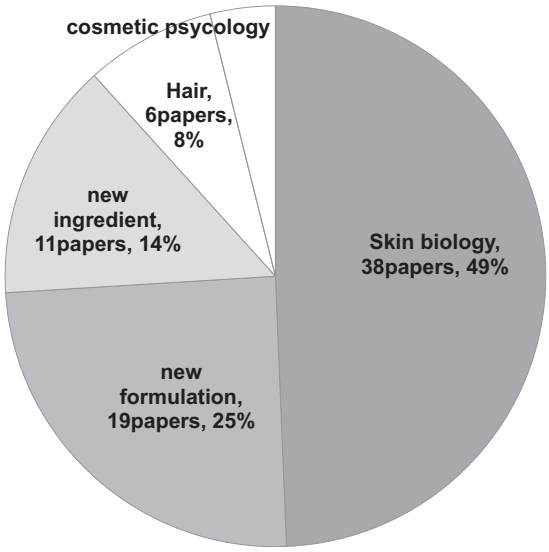



FIGURE 2.5 IFSCC Awards by theme.

TABLE 2.2 38 Skin Biology Papers

| | |
|---|---|
| Epidermis | 21 |
| Basal membrane | 2 |
| Dermis | 5 |
| Dermis-epidermis | 1 |
| Subcutaneous tissue | 1 |
| Scalp | 3 |
| Safety | 3 |
| Acne | 1 |
| Nail | 1 |
| Total | 38 |

FIGURE 2.6 Map of award-winning papers related to skin biology.

#### 2.4.2.2 *Epidermal Barrier Function (Natural Moisturizing Factor and Intercellular Lipids)*

Studies on epidermal barrier function had already opened up dating back prior to 1970 when the first IFSCC Award was conferred, and they still continue to be worked on as an important area of interest to our industry. Natural moisturizing factor (NMF) and intercellular lipids that are generated through the course of keratinization of the dermis have been studied vigorously as a key area of interest in dermatology in the 1980s. For example, ever since H.W. Spier et al. revealed the composition of NMF in 1956,[1] studies in the 1980s have shown that amino acids constituting NMF are enzymatic degradants of filaggrin[2] and that there is a correlation between moisture in the stratum corneum and amino acids/PCA contents.[3] Furthermore, with regard to intercellular lipids, their presence[4] and composition[5,6] were revealed in the 1980s, followed by findings on their moisture-retaining role in the stratum corneum[7,8] and that dry skin or skin with atopic dermatitis tends to be low in ceramide content.[9]

Not surprisingly, studies related to NMF and/or intercellular lipids began to appear at IFSCC scenes as well in the 1990s. "Study of Lipid and Non-Lipid Structure in Human Stratum Corneum by X-ray Diffraction" (Paper no. 27: 1990, Table 2.1) and "Seasonal Influences on Stratum Corneum Ceramide one Linoleate Contents and the Influence of Topical Essential Fatty Acids" (Paper no. 36:1994, Table 2.1) received an honorary mention and the poster award in 1990 and 1994, respectively. Following the year that intercellular lipids were reported to be effective in improving skin roughness, a paper describing the development of a multilamellar emulsion formulation containing synthetic ceramides and its efficacy, received an honorary mention (Paper no. 30:1992, Table 2.1).

The arrival of the 2000s shifted research interests into the structure of the epidermis and differentiation. A study (Paper no. 56:2006, Table 2.1) unveiling that nucleated cells appear within the stratum corneum as a consequence of serpin b3, a protein that is known to generate in parallel with rough skin, inhibiting the degradation of horny cell nuclei, won an honorary mention in 2006. In 2008, an award-winning paper (Paper no. 60:2008, Table 2.1) showed that a tight junction structure is playing a role in controlling the calcium ion concentration in the epidermis, in turn affecting the production of NMF, and hence necessary for the formation of healthy stratum corneum. It also states that as the function of tight junction deteriorates, the secretion of ceramides varies as compared to normal conditions. A paper describing the finding of an enzyme BH that produces NMF from filaggrin, and uncovering the low abundance of this enzyme in dry skin and skin with atopic dermatitis, received the IFSCC Award in 2010 (Paper no. 64:2010, Table 2.1). The millennium opened up a mainstream trend in studies attempting to unveil the mechanisms leading to the formation of healthy stratum corneum.

#### 2.4.2.3 *Antiaging Studies From Dermal Perspectives*

Antiaging research kicked off in the 1970s with studies related to ultraviolet (UV) rays and how they can damage skin. At the IFSCC scene, studies on the observation of UV-damaged skin (Paper no. 7:1976, Table 2.1), an electron spin resonance (ESR) method through which free radicals generated by UV irradiation can be measured (Paper no. 9: 1978, Table 2.1), and a noninvasive means of measuring oxidative stress (Paper no. 35:1994, Table 2.1) have been honored through awards.

Awards granted later on went to the development of an active ingredient that reassembles UV-damaged collagen fiber bundles (Paper no. 40:1998, Table 2.1), a report verifying that cells protect themselves from UV-A damage through storing ATP (Paper no. 44:2000, Table 2.1), and a study confirming that the structure of the basement membrane is affected through UV damage (Paper no. 43:2000, Table 2.1).

With respect to wrinkles, an award went to a paper reporting the improvement of crow's feet (Paper no. 48:2002, Table 2.1). Apart from reports on improvement of wrinkles, evaluation methods that could measure wrinkles in vivo, and to visualize UV-damaged collagen bundles, won awards in 1998 (42) and 2012 (69), respectively.

More recently, studies on "flabbiness" are gaining attention. In 2014, a study showing the relationship between flabbiness and an anchoring structure protruding downward from the dermal layer (Paper no. 75:2014, Table 2.1), and in 2015, a study focusing on subcutaneous tissues, came out, both of which won an award (Paper no. 76: 2015, Table 2.1).

In Orlando (2016), the poster award went to a paper in which a newly developed microcomputed tomography method made it possible to identify a "dermal cavitation" localized in the deep dermal layer at the bottom of the eccrine sweat glands of aged skin (Paper no. 80:2016, Table 2.1). It was revealed that dermal cavitation significantly decreased the dermal elasticity, which promoted sagging. Hence, it was considered that sweat glands, previously considered as simple appendages, are a new mechanism-based target for antiaging cosmetics.

As briefly described herein, studies on antiaging lead off with the detection of oxidative damages, shifting toward observing the influences of UV and damages to the skin, and understanding more about wrinkles and flabbiness.

## 2.4.3 Formulation Technologies and New Materials

Out of the award-winning papers on formulation technology, seven of them are related to emulsification, all of which appeared during the decade between 1974 and 1984. There were also seven award-winning papers since 1986 related to novel powders applied to foundation, deodorant, and sunscreen formulations (Fig. 2.7). New functional formulations created through new emulsification technologies and development of novel powders will be touched on.

### *2.4.3.1 Studies on Emulsification Technologies*

The history of how emulsification technologies evolved over the years is in parallel with how new surfactants and emulsifying methods came to be developed. Prior to 1960, most emulsifiers were surfactants of natural origin such as soap, beeswax, and lanolin. Hence, creams with confined textures, e.g., either dewy-textured oil-in-water (O/W) type vanishing creams with little oil, or rich-textured water-in-oil (W/O) cold creams with abundant oil, both of which make use of fatty acid soaps, have been mainstream items. The 1960s saw the development of nonionic surfactants such as polyoxyethylene sorbitan esters and polyoxyethylene fatty acid esters with emphasis on their superior surface activities. However, due to the emergence of problems related to skin irritation, safety-conscious surfactants (e.g., sucrose fatty acid esters and polyoxyethylene hardened castor oil) came out in the 1970s, encouraging studies on new emulsifying methods.

Dispersion methods in which microparticles are created through imparting mechanical energy to the oil and water phase were frequently used as means of emulsification. The process requires the addition of surfactants, and several indices have been suggested in order to form emulsions of high stability. For example, whether a given emulsion ends up as an O/W type or a W/O is governed by the "Bancroft rule," where it is known that there is a tendency of it becoming an O/W when a hydrophilic surfactant is used, whereas a W/O is likelier to be formed through the usage of a hydrophobic surfactant.[10] As studies progressed, it was revealed later on that the phase in which the surfactant was dissolved as micelles constitutes the continuous phase.[11,12] An index for selecting the choice of surfactant as suggested by Griffin was hydrophilic-lipophilic balance (HLB).[13,14] Surfactants with adequate hydrophilic-lipophilic balance are selected, predicted through the "required HLB" of the oil phase to be emulsified.

Under such background, the first emulsification paper to have received an IFSCC Award was the 1974 report by T.J. Lin et al. (the author of Chapter 45). They had already verified that a finer O/W emulsion can be achieved when surfactants are predissolved in the oil phase prior to emulsification as compared to when they are first dissolved in the water phase, even with an identical formulation.[15] The award-winning paper focused on the mechanism of this finding, in which it was clarified that when the water phase is added to the oil phase in which hydrophilic surfactant is predissolved, at first the water phase is solubilized in the oil phase to form an W/O emulsion, but by further adding the water phase, the hydrophilic surfactant in the oil phase migrates into the water phase, causing phase inversion, finally to form an O/W emulsion in which extremely fine oil droplets are dispersed in the water phase (Paper no. 4:1974, Table 2.1). Based on this knowledge, phase inversion emulsification was established later on.[16]

T.J. Lin went on further to demonstrate that by adequately controlling the amount of water phase to be added to the oil phase in which the surfactant is dissolved, a fine particle O/W emulsion can readily be formed with low concentration of surfactant regardless of its HLB. This work was rewarded with another IFSCC Award four years later (Paper no. 10:1978, Table 2.1).

The second emulsification technology to receive the IFSCC Award was the "amino acid gel-emulsification method" developed by Y. Kumano et al. (Paper no. 6:1978, Table 2.1). This method showed that when amino acids or their salts are added to the surfactant, a gel is formed, and when the water phase is added to the oil phase containing this gel, a stable W/O emulsion can be obtained even in the absence of a thickener for stabilization. With the advent of this technology, it became feasible to provide formerly unstable W/O emulsions as nonsticky creams with high-moisturizing capability. In the same year, liposomes whose utility had already been recognized in drugs were applied to cosmetics where a report describing the benefits of lamellar dispersions of neutral lipids to the skin won an IFSCC Award (Paper no. 11:1978, Table 2.1).

In 1982, a study on the preparation of a secondary particle emulsion with high stability and good texture, along with its structure elucidation, received the award (Paper no. 15:1982, Table 2.1). This study was presented by T. Suzuki (the author of Chapter 35). In these days back in the 1980s it was already widely recognized that by adding higher alcohols to an O/W emulsion formulation the viscosity of the system increased due to a liquid crystal involved gel network (refer to Chapter 30), and droplet coalescence could be hindered through the formation of liquid crystal, enhancing the overall stability. Given this, Suzuki et al. foreseeing the importance of liquid crystals formed within the emulsion, found out that under certain conditions, an aggregate of emulsion particles associated

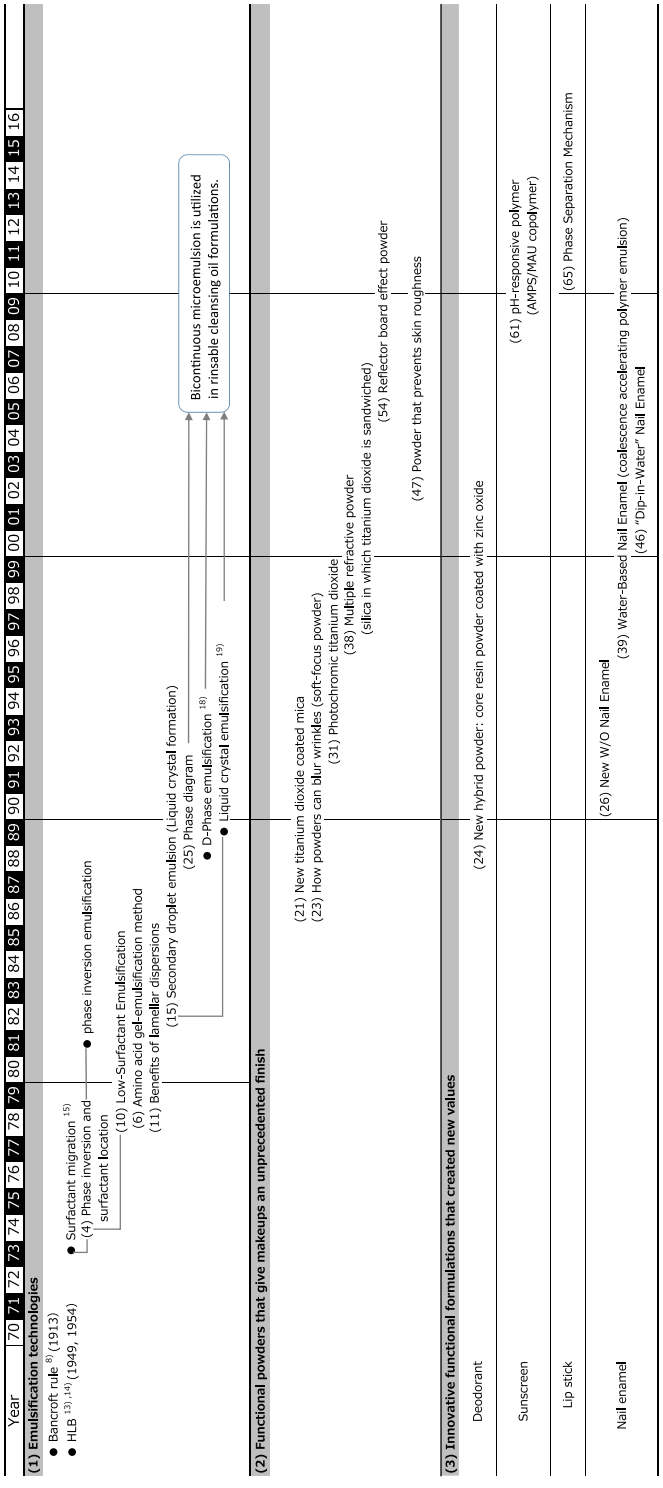



FIGURE 2.7 Map of award-winning papers related to formulation technologies and new materials.

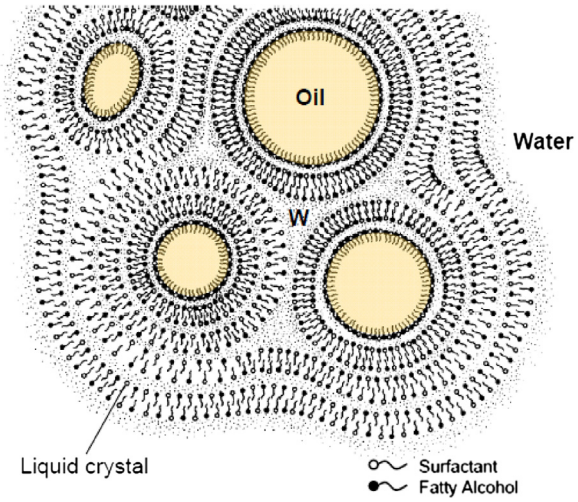



FIGURE 2.8 Schematic model of an O/W emulsion stabilized with a lamellar liquid crystalline phase.[17]

with liquid crystals is formed within an O/W emulsion containing nonionic surfactants and higher alcohols. They named this aggregate "secondary particles." After looking into the configuration of this aggregate, they speculated that "secondary particle" is a structure consisting of a closed lamellar liquid crystal comprised of nonionic surfactant/higher alcohol/water in which emulsified particles are encased (Fig. 2.8).[17] They showed that emulsion particles are stabilized through the formation of liquid crystals in the continuous phase of the emulsion, and that applying such secondary particle emulsion to the skin, enhances moisture content in the stratum corneum as compared to conventional O/W emulsions.

In 1988, F. Comelles et al. used a phase diagram to investigate the physicochemical aspects of a transparent gel formed by a ternary system of water/hydrocarbon (mineral oil)/surfactant (oleth 3 and oleth 3-phosphate), and received an IFSCC Award through an attempt to apply the finding to a cosmetic formulation (Paper no. 25: 1988, Table 2.1). In this study, it was shown that adding octyl methoxycinnamate, a UV-absorbing polar oil, enlarged the area in the phase diagram where a transparent phase can be obtained. In this transparent phase, the presence of regions pertaining to three liquid crystal structures, namely Cubic L.C., Hexagonal, and Lamellar L.C., was confirmed. By further adding water to the transparent phase, the status shifts from Hexagonal to Isotropic L.C. cubic to form an Isotropic micellar solution. The utility of formulation development utilizing the transparent gel composition of ternary system was hence demonstrated. Contrary to conventional formulation that relies on HLB, this breakthrough formulatory approach was significant as it would eventually lead to "liquid crystal emulsification" that can produce stable emulsions of fine particles without resorting to strong agitation power.

No studies on emulsification have received an IFSCC Award since 1988. Nonetheless, studies on emulsification kept on evolving, giving birth to newly established methods that could produce fine O/W emulsions without strictly adjusting HLB, such as D-phase emulsification[18] and liquid crystal emulsification.[19] In recent years, these methods making use of D-phase, liquid crystal, or bicontinuous microemulsion phase to readily produce fine emulsions that are applied to practical formulation development. The bicontinuous microemulsion structure is currently utilized in many of the rinsable cleansing oil formulations.

The fact that award-winning papers on emulsification are centered around the 1970s–1980s probably indicates that there were many drawbacks to formulations that simply depended on HLB back then, and hence new technologies were being sought to complement the situation. More recently, an arsenal of diverse surfactants, e.g., amino acid–based, monoglycerides, phospholipids, silicone or fluorine-based, polymer-based emulsifiers have been developed, making cosmetics with new textures and functions available relatively easily. Hence, awards have not gone to emulsification technologies. However, there will always be demands to control immiscible interfaces in developing cosmetics with new added values, where new emulsification technologies utilizing, for example, functional polymers and Pickering emulsion rather than surfactants, will become necessary.

### *2.4.3.2 Functional Powders That Give Makeup an Unprecedented Finish*

Generally, powder-based makeup cosmetics such as foundations and eye colors create their color and texture through powders such as inorganic and pearlescent pigments and oil parts in which they are dispersed. Dyes are

used at times for eye colors. Color pigments such as iron oxides and powders with covering property such as titanium dioxide are used in foundations to entirely cover the facial skin with inorganic pigments to improve skin texture and to adjust the feel through combining platy powders, such as mica or talc, and spherical powders, such as silica or nylon. In the past, titanium dioxide, mica, and talc all of natural sources were pulverized and formulated, which led to drawbacks such as the availability of limited makeup shades, unnaturally white finish from application of foundations, and uncomfortable skin textures. To overcome such drawbacks, efforts to develop composite or hybrid powders intensified in the 1980s.

The first IFSCC Award-winning paper on composite powder was a report by A. Kimura et al. in which they developed a unique new titanium dioxide—coated mica that could emit color on its own in the absence of colored inorganic pigments (Paper no. 21:1986, Table 2.1). The history of pearlescent pigments began with natural "argentine" dating back to the 17th century. Out of the many synthetic pearlescent pigments with stable quality that became available in the 20th century, "titanium dioxide—coated mica" developed in the 1960s is still considered as today's mainstream item. This item consists of mica with fine particles whose surface is coated with a thin film of titanium dioxide (a white pigment). A unique optical characteristic as a result of multiple reflections and interference of light happening within the thin film gives rise to deep pearl-like gloss. A. Kimura et al. looked into solving the problem of conventional pearlescent pigments where different skin complexions to which they are applied could change the appearance of their color. They succeeded in blackening the surface of the coated titanium dioxide black through reduction firing, thereby developing a pearlescent pigment that always emits vivid colors regardless of the skin complexion to which it is applied. By controlling the thickness of the three layers of the titanium dioxide coat, i.e., titanium dioxide/reduced titanium dioxide/titanium dioxide, interference colors from silver to gold, red, purple, blue, green, etc. could be obtained. As it is inert and superior in terms of safety, light and heat resisting properties, the material is still utilized in a wealth of makeup products.

In the same year, a report by N. Nakamura et al. received an honorary mention for their work on how powders can blur wrinkles (Paper no. 23:1986, Table 2.1). In this study, a mixture of powders and oil parts typically formulated in makeup cosmetics were used to observe their optical characteristics in relation to the degree with which the contour of visual disorders (wrinkles, age spots, etc.) can be blurred. They found that the combination of powder and oil parts that reduces straight transmitted light and increases diffused transmitted light could blur visual disorders, and that spherical silica can enhance this effect. They newly developed a diffuse reflective composite powder in which talc particles are coated with acrylic polymers. Furthermore, the term "soft-focus" was used for the first time in this report describing how wrinkles can be blurred. Later on, various spherical powders, e.g., nylon, silica, polymethyl methacrylate and silicone resin, etc. were employed as powders to impart the "soft-focus" effect, depending on the desired texture. Composite powders consisting of platy powders such as mica on which spherical powders are evenly adhered became available and utilized for the development of foundations with enhanced texture and functionality.

A report on "photochromic titanium dioxide" developed by K. Ohno et al. received an honorary mention in 1992 (Paper no. 31:1992, Table 2.1). They developed a functional powder, namely photochromic powder, that would look dark under strong light due to reflectance reduction of visible light but would revert to its original color in the dark, in an attempt to offer a solution to a long-standing complaint by the consumers, i.e., "my makeup looks natural indoors, but looks unnaturally white outdoors under the sun." The developed photochromic powder is a sintered pigment as a result of firing a mixture of titanium dioxide and iron oxide in which a portion of Ti atoms is substituted by Fe atoms, i.e., iron-doped titanium dioxide. This powder undergoes "decreased luminosity" under UV-A light of 360—380 nm but reverts to its original state in the dark. Hence, foundations formulated with this powder give a natural makeup even under sunlight.

Studies in the quest for developing foundations giving superior "natural makeup" went on. In 1996, K. Nishikata et al. developed a natural-looking makeup focusing on the optical characteristics of the stratum corneum, for which they won an IFSCC Award (Paper no. 38:1996, Table 2.1). First, the optical properties of the skin of 36 subjects with diverse ethnicities were quantified. Consequently, they discovered the importance of not concealing translucent stratum corneum in order to make the skin look natural. This led them to develop a new composite powder that does not interfere with the optical properties of the stratum corneum. It was named "multiple beads" and consisted of silica in which titanium dioxide with high refractive index is sandwiched.

The advent of these composite powders dedicated to specific functionalities greatly contributed in reducing "unnatural looking makeups" that were believed to occur as trade-off issues arising from conventional concepts of concealing shortcomings related to the skin.

With the arrival of the 21st century, IFSCC Awards went to composite powders with new purposes, e.g., a powder that prevents skin roughness (Paper no. 47:2002, Table 2.1), and a "reflector board effect powder" that optically corrects sagging skin due to aging (Paper no. 54:2005, Table 2.1). The "reflector board effect powder" is the

outcome of a technology in which crystals of barium sulfate that function as reflector boards are formed upright on a red pearl pigment. This is a unique powder that was born inspired by a reflector board used for photographing and filming. Foundations formulated with this powder could improve sagging face line, making the applicant look a lot younger than her actual age.

On the other hand, the development of a powder that prevents skin roughness began from finding out that an enzyme called "urokinase" exists on the skin surface that produces "plasmin," an enzyme that is known to be responsible for roughening skin. Through screening for a powder that can effectively counteract urokinase, zinc oxide was found to inhibit the activities of urokinase whilst talc and silica can adsorb urokinase. A foundation formulation containing a composite powder of talc and zinc oxide, and zinc oxide coated with silica, was prepared to investigate its skin care effect (Paper no. 47:2002, Table 2.1). The breakthrough was brought about by focusing on the skin care effect through the removal of the contributor to skin roughness, rather than conventional composite powders that were designed merely to arm them with optical functionalities.

#### *2.4.3.3 Innovative Functional Formulations That Created New Values*

So far we have gone through award-winning papers on skin biology, emulsification technologies, and functional powders for makeup cosmetics. In this section, we will touch on award-winning papers related to development of formulations with new functions from new perspectives. Development of cosmetics in recent years is being strongly driven toward what the consumers want, and innovative attempts to fulfill such demands have received IFSCC Awards. The common features shared here are that they all commence by investigating what the current issues are, then seek solutions for such issues, and finally incorporate the solutions into workable formulations.

##### 2.4.3.3.1 A Deodorant That Works in an Instant

In the 1980s, the main mechanisms through which deodorant products intended to combat body odors worked were the usage of antiperspirants that prevent perspiration from the sweat glands, antimicrobials that inhibit the activities of residential bacteria from degrading odorless sweat and sebum-derived substances into odorous compounds, and masking offensive body odors using citrus and floral fragrances. However, their efficacy was insufficient to live up to the expectations of the consumers. The report by F. Kanda et al. in which they developed an innovative deodorizer that not only prevents body odors as did conventional products but could also instantly quench body odors once formed, won them an IFSCC Award in 1988 (Paper no. 24:1988, Table 2.1).

After pinpointing "short chain fatty acids" as major contributors to offensive body odors, the authors studied further to look into why some people smelled more intensely than others with only faint odors.[20] They eventually ascertained that short chain fatty acids were also present in people with faint odors, but as odorless metallic salts and not as the free odorous form that was abundantly found in smelly people. This led the authors to believe that the malodors of free short chain fatty acids could be quenched by converting them into odorless metallic salts and found out that zinc oxide could effectively pursue this objective. However, zinc oxide can easily aggregate within a formulation and would cause aerosol sprays to clog. To overcome this issue, a new hybrid powder (Fig. 2.9) was developed in which a spherical synthetic resin core powder is evenly coated with a monolayer of fine zinc oxide particles. This gave birth to a consumer-friendly formulation with exceptionally high deodorizing capabilities.

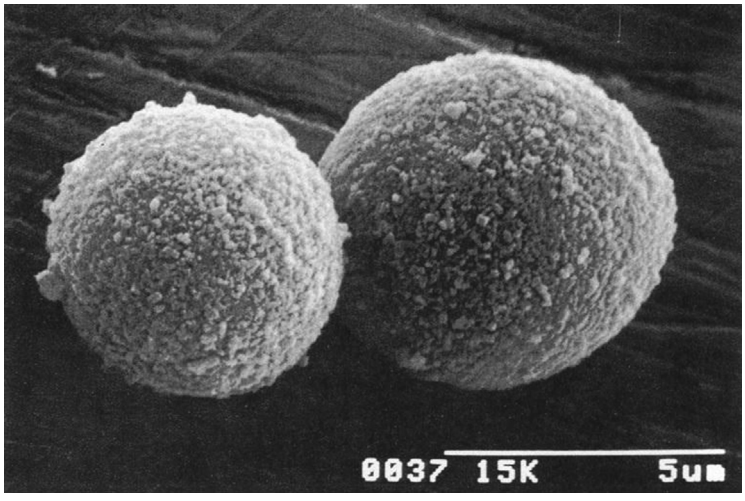



**FIGURE 2.9** Electron micrograph of "hybrid powder."

#### 2.4.3.3.2 A Sunscreen That is Highly Water Resistant but Easy to Remove

Despite their availability since the dawn of the 19th century, there wasn't a major demand for sunscreens, given that there was a global trend in favor of a suntanned skin as looking healthy and beautiful. However, influenced by many reports that came out in the 1980s revealing the downsides of what UV does to the skin, the World Health Organization in 2002 released a document that called out to "refrain from sunbathing" as exposing the skin to sunlight UV can trigger skin cancer.[21] This made the world realize the significance of sunscreens in protecting the skin from UV, in order to maintain the skin and body in a healthy state. Hence, from the 1980s onward, various sunscreen agents blossomed, encouraging effective sunscreen formulations to be studied actively.

In its infancy, most sunscreens were formulated with powders that block UV (UV-scattering agents) such as titanium dioxide and zinc oxide, but with the advent of UV absorbers that absorb UV rays, today's sunscreens contain both UV-scattering agents and UV absorbers. With the high-rising demand for sunscreens in the 1980s and onward, products offering higher protection from UV with better textures and usability have been developed. Major long-standing issues of sunscreens include unnatural makeup attributed to the UV-protective agents, skin trouble invoked by UV absorbers, and smeared makeup that deteriorates UV protectability. In order to cope with unnatural makeup attributed to UV-protective agents, attempts to micronize UV-scattering agents or to develop composite powders have been carried out. As for improving the stability of UV absorbers, development has been focused on achieving UV absorbers invoking minimal skin trouble, sufficiently absorbing UV rays over a wide range of wavelengths and allowing stable formulation. In order to prevent UV-protective properties from declining, various formulation technologies have been considered to micronize UV-scattering agents to keep them from aggregating in the formulation, and to enhance water resistance (Chapter 40). Along this historical trend of formulation development, many sunscreen papers on both material and/or formulation design have appeared on the IFSCC platform, but strangely enough with no award winners up until 2008.

The award-winning paper in 2008 was a study by T. Osawa et al. (Paper no. 61:2008, Table 2.1), the objective of which was to find a way of improving the difficulties in removing sunscreens that have been formulated with inorganic UV-protective powder whose surface is coated with hydrophobic compounds such as fatty acids to enhance its water resistance. In an attempt to design a new coated powder with high water resistance but miscible with soap, they took notice of the fact that whilst the pH of water and sweat are acidic to neutral, the pH of soap water is alkaline, and went on to develop a pH-responsive polymer (AMPS/MAU copolymer) that is immiscible with acidic to neutral water but miscible only with alkaline water. Formulated with a special powder (Fig. 2.10), i.e., titanium dioxide coated with this polymer, they were able to develop a groundbreaking W/O-type sunscreen with high water resistance that could be rinsed off easily using normal soap bars.

#### 2.4.3.3.3 Long-Lasting Glossy Lipstick

Studies on lipsticks of a generation ago were mostly about their product quality, e.g., dispersion of pigments and colorants, formation of crystals due to waxes, prevention of sweating, etc., but nowadays, research interests have shifted to how functions that consumers are longing for can be achieved.

Lipstick is a makeup item that is strongly influenced by fashion trends. Whilst a "matte" finish was preferred in the past, the recent trend is in demand for "gloss" and "moisture." Lipsticks possessing both characters are designed to achieve the former, i.e., "gloss" through the use of oils with high refractive index, and the latter, i.e., "moisture," through adequately dissolving the oils in the water/oil emulsion. However, lipsticks imparted with sufficient "gloss" and "moisture" as described herein can easily stain cups and do not last long either. Applying a long-lasting lipstick that does not stain cups produced via conventional technology that resorts to the usage of film-forming agents and volatile oils would result in taut and dry lips lacking gloss.

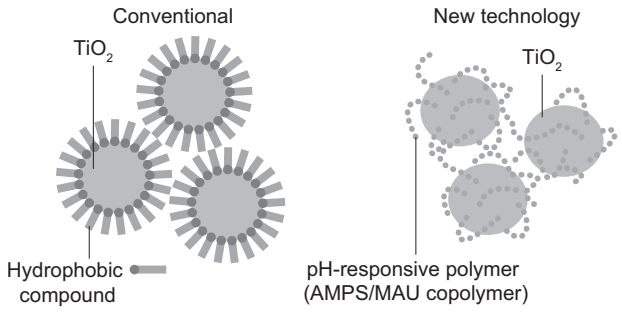



FIGURE 2.10 A new solution for a highly water resistant sunscreen that can easily be rinsed off with normal soap bars.

In an attempt to resolve the trade-off between "gloss/moisture" and "not staining cups," T. Ikeda et al. succeeded in developing a lipstick that when applied to the lips separates into two immiscible oil layers, one in direct contact with the lips containing the color agents, and a clear layer on top of it. This innovation won them an IFSCC Award in 2010 (Paper no. 65:2010, Table 2.1).

The formulation of this revolutionary lipstick is comprised of the phase that comes into close contact with the lips (adhesion phase), the oils at the outmost (separation phase) separated from the adhesion phase, and volatile oils (compatibilizing agent) to keep the two phases homogeneous within the formulation. Once the lipstick is applied to the lips, the volatile oils vaporize, causing phase transition to form liquid crystals through which the formulation separates into two phases (Fig. 2.11). The separation phase is clear and prevents the colored adhesion phase from coming into direct contact with cups. Hence it does not smear cups and lasts long on the lips while maintaining gloss and moisture.

#### 2.4.3.3.4 Nail Enamels

Three "nail enamel" papers have received the IFSCC Award so far. Nail enamel formulations of today date back to the early 1930s and consist of film-forming agent (nitrocellulose), solvent, oil, pigment, pearl pigment, and gelling agent. When applied to the nails, the solvent evaporates and dries as the film-forming agent solidifies. Until the 1980s, studies have focused on ease of application, drying speed, gloss of the coat, longevity of the coat, and stability toward separation. However, nail enamels back in this era were used in repeated sequences with removers for their removal, and this was pointed out to cause "onychoschisis," a disorder of the nail.

The first award went to a W/O-type nail enamel formulation containing "water," a component that had never found its place in a nail enamel before, the objective of which was to minimize nail problems related to dehydration and delipidation (Paper no. 26:1990, Table 2.1).

Later on in 1996, in an attempt to develop aqueous nail enamels that made use of a polymer emulsion to replace nitrocellulose, the film-forming agent, a "coalescence-accelerating polymer emulsion" was obtained through a special method of synthesis. Aqueous nail enamels utilizing this polymer emulsion were not only very gentle to the nail but also excellent in terms of coating ability and usability. An IFSCC Award went to this study (Paper no. 39:1996, Table 2.1).

As described herein, the two award-winning papers in the 1990s were on the developments intended to prevent inconveniences resulting from application of nail enamels, i.e., dehydration and delipidation of the nail. In the year 2000, an IFSCC Award went to a paper that attempted to improve the usability of the nail enamel formulation. In order to resolve the inconvenience of nail enamels in which one had to wait for a few minutes for the solvent to evaporate and dry, the authors developed a formulation that did not resort to the evaporation of the solvent but rather to quickly remove the solvent through dipping the fingers into water after applying the nail enamel, leading to a formulation that would dry in 45 s. This was accomplished through screening a water-soluble solvent that could dissolve the film-forming agent that is insoluble in water. It was a unique study that was attained through changing the mindset (Paper no. 46:2000, Table 2.1).

### 2.4.4 Studies on Hair and Scalp

So far eight reports related to "hair of scalp" have received IFSCC Awards. They can be classified into three categories: "hair loss," "visualization of hair damage," and "development of formulation based on basic research studies concerning scalp and damaged hair" (Fig. 2.12).

The first award on hair of scalp went to a study on "hair loss" that looked into the relationship between "male pattern baldness" and "metabolism of androgens" in which it was clarified that 5α−reductase activity is increased in bald skin when compared to hairy skin from the same subject (Paper no. 2:1972, Table 2.1). Ever since this report appeared, materials that inhibit 5α−reductase activity have been screened and utilized in commercial products intended to improve hair loss affected by androgens. More than 20 years later, the second award related to hair loss was granted to a study on a new model for controlling hair growth. In this study, an in vitro test model was used to investigate how cytokines and their receptors are involved in hair growth, in which it was discovered that various cytokines were involved at the various stages during hair growth (Paper no. 37:1996, Table 2.1). Since the advent of this study, the expression of cytokines became used as a means for screening active agents.

The first award on visualization of hair damage went to a report in which damaged hair was observed using SEM, now practiced routinely (3: 1994). Since then, SEM was used to observe hair damage for a long period of time until in 2004 when a new method was reported that could continuously observe the process of bleaching or dyeing at the

**FIGURE 2.11** A schematic describing the phase separation mechanism of the long-lasting glossy lipstick.




**FIGURE 2.12** Map of Award winning papers related to hair and scalp.

interior of the hair via optical coherence tomography (OCT), for which an IFSCC Award was granted (Paper no. 51: 2004, Table 2.1).

With regard to basic research and formulation development, an IFSCC Award was given in 1982 to the development of a shampoo that focused on its esthetic effect toward hair. In this study, sensorial assessments were carried out on consumers who had used various shampoo formulations, in which it was shown that "supple hair" and "soft hair" were significantly correlated to the overall preference of shampoo (16: 1982).

In 1986, a paper that observed the secreted scalp lipids after shampooing using a newly developed replica technique won an IFSCC Award. The paper states that the continuous use of shampoo leads to the reduction in the level of greasiness (Paper no. 22:1986, Table 2.1).

The 1992 Award went to a study on dandruff and a formulation designed for its prevention. Up until then, it was known that dandruff generates through decomposition of scalp lipids via skin bacterial flora, and hence antimicrobials were used worldwide as means of preventing dandruff. The study clarified that other than dandruff generated from scalp lipids through decomposition, dandruff can also generate through dryness. A certain antioxidant component was effective as a new antidandruff agent that works on both types of dandruff (Paper no. 29:1992, Table 2.1).

In an attempt to reproduce damaged hair, E. Schulze et al. developed an automatic test device that can impose daily stress from shampooing and blow drying. Through this device, they studied how "aging hair keratin" can specifically be repaired and won an IFSCC Award (Paper no. 62:2008, Table 2.1).

A very unique paper appeared in Orlando that attempted to translate the status of hair surface through converting its friction into electronic signals, then to sound, and finally into "music," offering brand new evaluation perspective on top of the already available visual, tactile, and olfactory sensory inputs (Paper no. 78 :2016, Table 2.1). Backed by state-of-the-art acoustics, this paper went on to win the Basic Research Award. The paper wrapped up that the logic could possibly be applied to skin care procedures as well.

## 2.5 CONCLUSION

Ever since it started in 1970, the custom to reward meritorious papers presented at IFSCC Congresses/Conferences with IFSCC Awards has carried on (for 46 years). As described in detail in Section 2.2, the types of awards given at IFSCC events have grown over time, currently with six different awards (3 Conference awards and 3 Congress awards), not counting the honorary mentions nor swards for the younger generation and the developing societies. An overall number of 80 IFSCC Awards have honored the best papers presented in the history of IFSCC thus far. We are well aware that despite them being the best papers, there is no way that a mere 80 papers can accurately represent the global trends in cosmetic R&D over a span of almost half a century. Neither are we convinced that the technologies covered in these 80 papers have all led to commercial success. However, as we try to unveil the historical background behind the award-winning papers, it becomes apparent that each era had its unmet technical issues that challenged the scientists back then whose relentless efforts in quest for solutions eventually paid off through breakthrough findings. It makes us realize once again that only those who tackled the issues with an open mind devoid of preconceptions came up with unique ideas that led to the elucidation of a skin mechanism that nobody had ever imagined or resolving a trade-off issue in formulation that everyone took it for granted that a solution would not exist. As mentioned earlier, whilst this chapter does not offer a comprehensive coverage of trends in cosmetic R&D, all scientists whose studies are described here have contributed considerably to the advancement of modern cosmetic technologies, and hence there is a lot to learn from them in terms of their attitudes and perspectives toward cosmetic R&D.

## Acknowledgments

The authors would like to thank Ms. Kyoko Ueno of the Japan Association for International Chemical Information (JAICI) and Professor Kazutami Sakamoto of Tokyo University of Science for conducting search using KOSMET, Ms. Mary Lynn Halland, the Secretary General of IFSCC, and Ms. Gem Bektas, the Secretary General of SCS for gathering many of the award-winning papers for us, and Dr. Andrea Weber of Dr. Babor GmbH & Co. KG for translating a German award-winning paper into English.

## References

1. Spier HW, Pasher G. Analytical and functional physiology of the skin surface. *Hautarzt* 1956;**7**:55–60.
2. Horii I, Kawasaki K, Koyama J, Nakayama Y, Nakajima K, Okazaki K, Seiji M. Histidine-rich protein as a possible origin of free amino acids of stratum corneum. *J. Dermatol* 1983;**10**:25–33.

3. Horii I, Nakayama Y, Obata M, Tagami H. Stratum corneum hydration and amino acid content in xerotic skin. *Br J Dermatol* 1989;**121**:587–92.
4. Lampe MA, Williams ML, Elias PM. Human epidermal lipids: characterization and modulations during differentiation. *J Lipid Res* 1983;**24**: 131–40.
5. Wertz PW, Miethke MC, Long SA, Strauss JS, Downing DT. The composition of the ceramides from human stratum corneum and from comedones. *J Invest Dermatol* 1985;**84**:410–2.
6. Long SA, Wertz PW, Strauss JS, Downing DT. Human stratum corneum polar lipids and desquamation. *Arch Dermatol Res* 1985;**277**:284–7.
7. Imokawa G, Hattori M. A possible function of structural lipids in the water-holding properties of the stratum corneum. *J Invest Dermatol* 1985; **84**:282–4.
8. Imokawa G, Kuno H, Kawai M. Stratum corneum lipids serve as a bound-water modulator. *J Invest Dermatol* 1991;**96**:845–51.
9. Imokawa G, Abe A, Jin K, Higaki Y, Kawashima M, Hidano A. Decreased level of ceramides in stratum corneum of atopic dermatitis: an etiologic factor in atopic dry skin? *J. Invest. Dermatol* 1991;**96**:523–6.
10. Bancroft WD. Theory of emulsification. *J Phys Chem* 1913;**17**:501–19.
11. Harusawa F, Saito T, Nakajima H, Fukushima S. Partition isotherms of nonionic surfactants in the water-cyclohexane system and the type of emulsion produced. *J Colloid Interface Sci* 1980;**74**:435–40.
12. Harusawa F, Nakajima H, Tanaka M. The Hydrophile-Lipophile Balance of Mixed Nonionic Surfactants. *J Soc Cosmet Chem* 1982;**33**:115–29.
13. Griffin WC. Classification of Surface-Active Agents by "HLB". *J Soc Cosmet Chem* 1949;**1**:311–26.
14. Griffin WC. Calculation of HLB Values of Non-ionic Surfactants. *J Soc Cosmet Chem* 1954;**5**:249–56.
15. Lin TJ, Kurihara H, Ohta H. Effect of Surfactant Migration on the Stability of Emulsions. *J Soc Cosmet Chem* 1973;**24**:797–814.
16. Sagitani H. Making homogeneous and fine droplet O/W emulsions using nonionic surfactants. *J Am Oil Chem Sci* 1981;**58**:738–43.
17. Suzuki T, Tsutsumi H, Ishida A. Secondary droplet emulsion; Effects of liquid crystal formation in O/W emulsion. *J. Dispersion Sci. Technol* 1984;**5**:119–41.
18. Sagitani H. Formation of O/W Emulsions by Surfactant Phase Emulsification and the Solution Behavior of Nonionic Surfactant System in the Emulsification Process. *J Dispersion Sci Technol* 1988;**9**:115–29.
19. Suzuki T, Takei H, Yamazaki S. Formation of fine three-phase emulsions by the liquid crystal emulsification method with arginine β-branched monoalkyl phosphate. *J Colloid Interface Sci* 1989;**129**:491–500.
20. Kanda F, Yagi E, Fukuda M, Nakajima K, Ohta T, Nakata O. Elucidation of chemical compounds responsible for foot malodour. *Br J Dermatol* 1990;**122**:771–6.
21. WHO. *Helping people reduce their risks of skin cancer and cataract - A practical guide for using the global solar UV index, Geneva*. 22 July 2002.

CHAPTER

# 3

# Basic Physical Sciences for the Formulation of Cosmetic Products

*R.Y. Lochhead*

**The University of Southern Mississipi, Hattiesburg, MS, United States**

## 3.1 INTRODUCTION

The US Federal Food, Drug, and Cosmetic Act (FD&C Act) defines cosmetics by their intended use, as "articles intended to be rubbed, poured, sprinkled, or sprayed on, introduced into, or otherwise applied to the human body-…for cleansing, beautifying, promoting attractiveness, or altering the appearance."[1] Interestingly, soap and water are widely used for cleansing the human body, but soap is deliberately excluded from this legal definition of cosmetics. The US Food and Drug Administration (FDA) lists products included in this definition as skin moisturizers, perfumes, lipsticks, fingernail polishes, eye and facial makeup preparations, cleansing shampoos, permanent waves, hair colors, and deodorants, as well as any substance intended for use as a component of a cosmetic product.

This simple FDA definition disguises the complexities of cosmetic science, which is a melee of physical, biological, medical and psychosensory endeavors. This chapter is directed to the fundamental physical science aspects that underpin cosmetics and personal care products. Research and development on the basics of cleaning requires an elemental knowledge of surfactant science, mechanism of soil removal, adsorption at interfaces, self-assembly of micellar and liquid crystal structures, and how to manipulate the structures to attain the desired product attributes. The advancement of beauty products requires a deep-seated knowledge of the colloid and polymer science underpinnings of emulsion and dispersion products.

In this chapter, I have attempted to concisely show these underpinnings of cosmetic science in a descriptive manner without too much mathematics. This chapter should not be read in isolation. Rather it provides the physical science underpinnings for many other chapters in this book.

## 3.2 THE BASIC SCIENCES OF CLEANSING

### 3.2.1 Surfactants and Adsorption

Shampoos and body washes are the highest volume products sold in personal care. The main function of each of these products is to remove dirt, grime, and sebum from the surface of skin and hair. However, mere cleansing is not sufficient for a shampoo or body wash. Today's consumer also expects these products to cleanse, condition, facilitate cleansing, and fragrance the body with a pleasant aroma that lingers.[2] The topic of fragrance is covered by Dr. Herman in Chapter 20. This section will consider the basic sciences that underpin cleansing.

Presently, products aimed at promoting hygiene and cleanliness have been aimed at removing odors and the bacteria that cause these odors from the surface of the human body. However, the importance of the symbiotic relationships associated with the human microbiome are being realized and the beneficial effects of colonization of the skin by a diverse milieu of microorganisms is beginning to be appreciated.[3]

One aspect of personal cleanliness is the absence of a sweaty odor. The odor associated with sweat arises from the interaction of bacteria with apocrine gland secretions.[4–6] One role of cleansing products is to inhibit, kill, or remove

*Cosmetic Science and Technology: Theoretical Principles and Applications*
http://dx.doi.org/10.1016/B978-0-12-802005-0.00003-3



Copyright © 2017 Elsevier Inc. All rights reserved.

the odor and the bacteria that are responsible for the odor. Sebum glands adjacent to hair follicles emit a lipid-rich substance called *sebum*. From a cosmetic-removal point of view, sebum is the semifluid secretion of the sebaceous glands of mammals, consisting chiefly of fat, keratin, and cellular material.[7] Sebum serves to protect and lubricate the skin and hair. Sebaceous secretions favor the growth of facultative anaerobes such as *Propionibacterium acnes*.[8,9] *P. acnes* hydrolyses the triglycerides present in sebum, releasing free fatty acids onto the skin.[10,11] The released fatty acids contribute to the acidic pH of the skin surface,[12,13] which inhibits the growth of many common pathogens such as *Staphylococcus aureus* and *Streptococcus pyogenes*.[14]

Thus the presence of sebum and the symbiotic microorganisms that it supports may be beneficial to the health of the skin. However, buildup of sebum on the skin and hair is perceived by modern consumers to be "unclean" and undesirable. Additionally, particulate dust and dirt can adhere to the sebum layer and this exacerbates the feeling of lack of cleanliness. Consequently, the principal aim of today's cleansing products is to remove oils, particulate soil, and microorganisms from the surface of skin and hair, and one task of this chapter is to review the foundation of physical and chemical sciences upon which the cleansing products and methods are based.

Because sebum is an oily substance, it cannot be removed by water alone. For this reason, surface active agents (*surfactants*) are included in personal care cleaning products. The main purposes of surfactants are to lower the interfacial tension between the soil and the substrate, to emulsify and/or solubilize oily soils, and to disperse particulate matter.

In order to understand how surfactants work, it is necessary to understand why oil and water are incompatible. For example, substances like salts and sugars dissolve because the interaction of water with the constituent ions or molecules of these substances is favored over the interaction between the salt ions or sugar molecules. As the concentration of the solute increases, the tendency for the constituent molecules of the solute to escape from the solid state into solution decreases. Saturation is reached when the escaping tendency (thermodynamically this is called the chemical potential) of the solute becomes equal to the tendency for the solute to separate, or precipitate from solution. There are several different possibilities for a substance to be insoluble in water. Substances like sand, clay, and glass are insoluble in water because the molecules of sand attract each other more strongly than the molecules of water, and this attraction leads to the sand being insoluble because the interaction of water with the individual silicate groups of the sand would lead to a higher free-energy state than the mutual interaction of silica groups. The function of surfactants for such particulates is to enhance wetting and permit dispersion.

On the other hand, water insolubility of oils and waxes is caused by *hydrophobic interaction*.[15,16] The intermolecular forces between the oil molecules are weaker than the intermolecular bonds between water molecules, and the oils are *expelled* from water to minimize the water-oil interfacial area in the system. This structuring of water at the oil-water interface causes a decrease in entropy of the system, and the system resists this entropy decrease by forcing the oil to phase separate and thereby decease the area of contact between the oil and water.

In this respect, surfactants achieve their purpose by lowering surface and interfacial tensions and by solubilizing oils and waxes. The effect known as surface tension is caused by an imbalance of intermolecular forces at the gas-liquid interface. Molecules in the bulk of liquids are attracted on all sides by their neighboring molecules. However, molecules at the surface are subjected to imbalanced forces; they are attracted by the underlying liquid molecules, but there is essentially no interaction with the vapor-gas molecules on the other side of the liquid-vapor boundary. This imbalance leads to a two-dimensional force at the surface, and this is surface tension. Surface tension is usually expressed in linear dimensions (e.g., millinewtons/meter). Surface energy is expressed as work per unit area (joules/$m^2$). The dimensions of surface tension and surface energy are equivalent, and the absolute values of surface tension and surface energy are identical. For example, water has a surface energy of 0.072 J/$m^2$ and a surface tension of 0.072 N/m. The magnitude of surface tension directly correlates with the strength of the intermolecular forces. Water has hydrogen bonds, dipole−dipole interaction, and dispersion forces between its molecules, and as a consequence the surface tension of water is rather high (0.072 N/m at room temperature). In hydrocarbons only dispersion forces are present between the molecules, and the resulting surface tension is relatively low (0.020−0.030 N/m).

Surfactant molecules contain two distinct moieties: a hydrophobic segment that is expelled by water and a hydrophilic segment that interacts strongly with water. Due to this construction, surfactant molecules are designated as being amphipathic (*amphi* meaning "dual" and *pathic* from the same root as *pathos*, which can be interpreted as "suffering") because surfactant molecules "suffer" both oil and water. The hydrophilic moiety favors the aqueous phase, and the hydrophobic moiety is compatible with the oil phase. The hydrophilic moiety may be nonionic, anionic, or cationic. The hydrophilic moiety is usually a hydrocarbon, but it can also be a silicone or a fluorocarbon. For aqueous phases in the absence of oil, at very low surfactant concentrations the amphipathicity expels surfactant molecules to the surface, a process called adsorption. The driving force for surface adsorption derives from hydrophobic interaction, which rejects the hydrocarbon from the aqueous phase. The adsorbed surfactant molecules maintain intimate contact with water at the surface as a consequence of the relatively strong interactions between the hydrophilic moieties and water at the surface. These strong interactions can be polar, ionic, Lewis acid/Lewis base, and London dispersion forces. This adsorption causes the surfactant concentration at the surface to be

much higher than the surfactant concentration in the bulk of the solution. At extremely low concentrations, the adsorbed surfactant far exceeds its solution concentration and Traube's rule applies. Traube's rule states that the ratio of the surface concentration to the bulk concentration increases threefold for each $CH_2$ group of an alkyl chain.[17] The ratio between the surface adsorbed concentration and the bulk concentration of a surfactant was coined the "surface excess concentration" by Gibbs.[18] According to Traube's rule, soap with a dodecyl chain should have a surface excess concentration that is more than half a million times its concentration in the bulk solution. At extremely low concentrations, the surfactant molecules on the surface act as a two-dimensional gas. As the concentration increases, the surfactant molecules begin to interact, but they are still mobile within the plane; they behave as two-dimensional liquids. At even higher concentrations, as the surfactant saturates the surface, the hydrophobic groups orient out of the surface plane and the interactions between neighboring hydrophobic groups cause the surfactant monolayer to behave as a two-dimensional solid.[19] When sufficient surfactant molecules are adsorbed to form a monolayer, the surface properties are dominated by the hydrophobic groups of the surfactant and the surface energy becomes essentially the surface energy associated with hydrophobic group interaction.

High surface energies of pure liquids resist the expansion of a liquid surface. On the other hand, expansion of the interface is facilitated by surface adsorption of surfactants, hence the common observation that surfactant solutions readily form foams. Structuring of the foam surface by the adsorbed surfactant enhances the stability of the foam.[20]

### 3.2.2 Surfactant Micelles

Surface adsorption of surfactants is favored at low concentrations. However, above a critical concentration, designated the CMC, the chemical potential drive of molecules to form large micellar aggregates becomes favored over surface adsorption.[21] Micellar aggregates are large on a molecular scale, often comprising 50 or more molecules; for example, micelles of sodium dodecyl sulfate at the CMC contain about 100 molecules and the thickness of the headgroup layer is about 0.4 nm.[22] The micelles are configurationally stabilized by assembling hydrophobic groups in their core and hydrophilic groups at the micelle surface adjacent to the aqueous phase.[23]

Micelles have the capacity to solubilize oils within their hydrophobic cores.[24] Such solubilization forms the basis of one mechanism of detergency and soil removal from substrates. Micelles solubilize oils only when the core of the micelle is liquid, that is, when the temperature of the system is above the melting point of the hydrated solid surfactant.[25] Krafft found this phenomenon in 1895, and the critical temperature for solubilization is designated "the Krafft Point".

Micelles can assume a number of different shapes. Indeed the same surfactant can adopt different micelle shapes depending upon, for example, the concentration of surfactant, the pH of the solution, or the presence of salt ions. Micellization is essentially a phase separation of water from oil (the hydrophobic moieties of the surfactant). However, the extent of phase separation is limited by the need of the hydrophilic moieties to be in intimate contact with the aqueous phase. Tanford explains that micellar shape is a consequence of two opposing forces: the cohesion of the core due to hydrophobic interaction, which is limited by the repulsion between the hydrophilic moieties (Fig. 3.1). Thus, bulk separation is prevented and micellar phase separation is favored by the curvature imposed by the

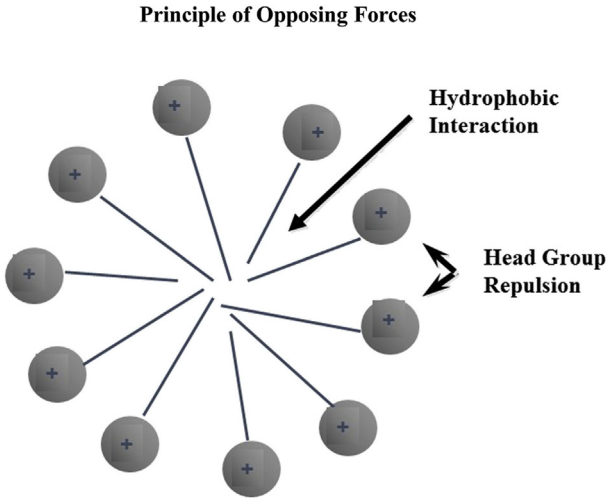



FIGURE 3.1 The formation of surfactant micelles is a thermodynamic phase separation of oil from water. The size of the separated phases is constrained by the mutual repulsion of the hydrophilic headgroups of the surfactant molecules.

repulsion between the hydrophilic moieties at the micelle surface.[26] Decreased repulsion between hydrophobic moieties or increased steric hindrance between hydrophobic core molecules causes a decrease in the curvature of the micelle structure.

The molecules must pack according to intermolecular forces, and consequently the decrease in curvature forces the micelles to transition in shape from spheres to elliptical spheroids to rods to worms to packed rods (hexagonal phase) to infinite two-dimensional layers (lamellar phase) to inverse rods and inverse spheroids. The shapes of micelles can be appreciated by consideration of the conceptual hypothesis of "packing factor."[27] (Fig. 3.2). The packing factor relates the volume of the hydrophobic molecular moiety to the volume subtended by the cross-sectional area of the hydrophilic moiety measured over the length of the surfactant molecule:

$$\text{Packing Factor} = \frac{v}{al}$$

Spherical micelles form when the packing factor has a value of 1/3 or less. When the packing factor becomes 1/2, rodlike micelles are preferred (Fig. 3.3).

As the packing factor is increased above 1/2, the rodlike micelles grow into wormlike micelles (Fig. 3.4). The ends of the micelles are in a state of higher free energy than the sides of the micelles. Therefore, at some stage the ends of the micelles merge with adjacent wormlike micelles to become branched micelles.[28] Fig. 3.4 depicts the transition from rodlike to wormlike and branched micelles of an archetypal ionic surfactant. The transition from rodlike to wormlike is brought about in this case by increasing the concentration of salt, which weakens the ionic repulsion between the ionic surfactant headgroups in the micelle. Common salt also enhances the hydrophobic interaction[29] and lowers the CMC.

Above a threshold surfactant concentration, shown as $c^*$ in the figure, the wormlike micelles overlap and as the concentration increases further, the micelles become entangled in each other.[30] Entangled micelles confer structure that can endow viscoelastic rheology on a formulation.[31–34] Shampoo and surfactant gel formulators often rely upon an entangled micelle structure to give their product the viscosity and rheology desired by consumers. Above critical

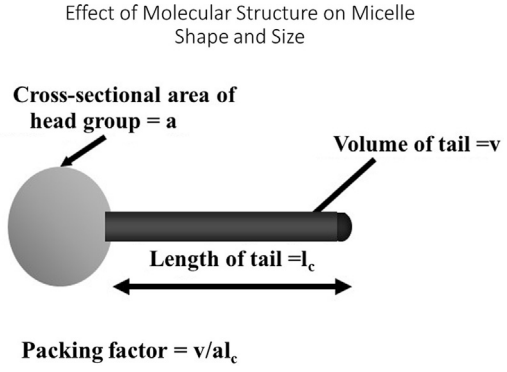



**FIGURE 3.2** The shape and size of surfactant micelles depends upon the shape of the molecules that self-assemble to make up the micelle. The shape of surfactant molecules can be described by the packing factor, which is the volume of the hydrophobic group divided by the cylinder subtended by the headgroup for the length of the tail group. As the packing factor increases, micelle curvature decreases. For example, a packing factor of 1/3 would correspond to spherical micelles and a packing factor of 1 would correspond to self-assembled planar lamellar layers.

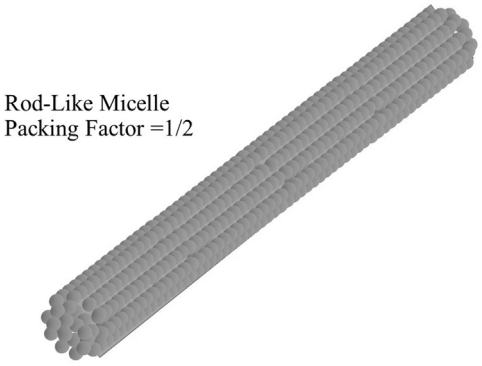



**FIGURE 3.3** Surfactant molecules with a packing factor = ½, will self-assemble into rodlike or wormlike micelles.

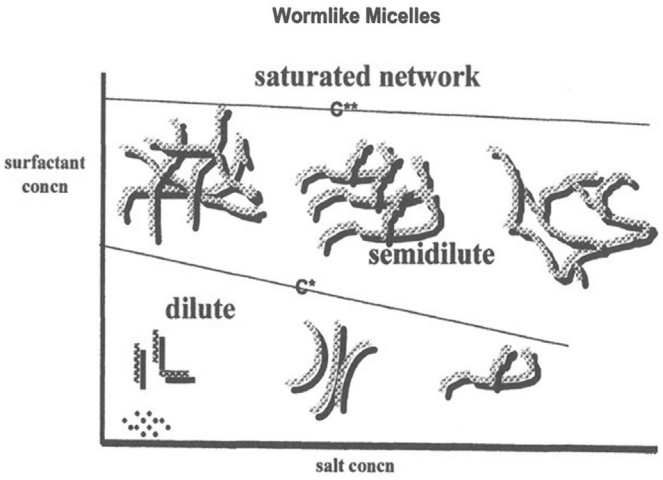



FIGURE 3.4 The addition of soluble salt ions to ionic surfactant micelles shields the repulsion between the ionic hydrophilic groups in the micelle, which results in the formation of rodlike micelles, wormlike micelles, and branched wormlike micelles. Increase in surfactant concentration beyond a critical overlap concentration results in entangled micellar networks. These "phantom" networks show characteristic monodisperse relaxation times under shear.

shear stresses the entangled micelle network loses its viscoelastic properties and the relaxation times become monodisperse.[35] Cates explained the molecular basis of this behavior as "phantom networks" caused by the micelles disassembling and reassembling as they passed through each other[36,37] like a phantom walking through a closed door. The phantom network may explain why shampoos and shower gels do not exhibit the stringy flow that is characteristic of polymer solutions. The polymer molecules cannot pass through each other, and the entanglements cause elongation of the polymer molecules under flow. Polymers are "entropy springs." As the flow is diminished, the polymer molecules snap back to their original conformation driven by the need to reduce entropy in order to minimize the system's free energy. The effective rheology will depend upon the rate at which the "phantom entanglements" can be unraveled relative to the rate of flow. The Debra number is a characteristic dimensionless number that relates the ability of a material to respond to an applied stress. In the case of phantom micellar networks, it the ratio of the time it takes for the micelles to move through each other (the relaxation time) compared to the duration of the applied stress. Longer relaxation times will be experienced as higher viscosities and higher storage modulus components of viscoelasticity. The relaxation time (exchange kinetics), and hence the viscosity, of self-assembled surfactants scales with the chain lengths of the surfactant molecules.[38–41] In other words, longer chain lengths confer greater perceived micellar viscosities under pouring conditions.

At even higher concentrations, the mutual repulsion of rodlike micelles causes them to align in arrays. The rods are hexagonally packed in the most common array, which is designated as hexagonal liquid crystal phase if the system is above its Krafft temperature (Fig. 3.5). Below the Krafft temperature the self-assembled hydrophobic moieties "freeze" and the system becomes a hexagonal, gel phase. Gel phases are useful structurants for surfactant-based formulations. Hexagonal phases are often clear ringing gels that show uniaxial flow properties. Such phases are anisotropic and they can be identified by the characteristic focal conic patterns that they display in polarized light microscopy.

Further increase in the packing factor leads to the planar bilayers of lamellar phase (Fig. 3.6). Perfect planar bilayers would have a packing factor of 1. Slight changes in such bilayers result in a rich hierarchy of lamellar phases including vesicles, liposomes[42–44], and gel phases with adjacent planes rotated in a regular pitch. Vesicle and liposome structures are characteristic of cell membranes and conditioners.[45] Lamellar phases are also useful for the stabilization of emulsions.[46–49] Lamellar gel phases are used to structure surfactant formulations to confer stable compositions with excellent shear-thinning rheologies. Lamellar phases are anisotropic and birefringent, and they can be identified by polarized light microscopy. Expanded L-$\alpha$ phases offer the possibility of gel compositions that are clear and optically isotropic, but they are liable to become unstable and they confer relatively low yield stress to compositions.[50]

Further increase in the packing factor leads to inverse hexagonal phase, inverse rodlike micelles, and inverse micelle phases, in which the continuous phase is oil, and discontinuous droplets of aqueous phase reside inside the inverse micelles. There are also four cubic phases. Discontinuous cubic phases are essentially spherical micelles packed in cubic array. Continuous cubic phases consist of precisely cubic-ordered interpenetrating networks of

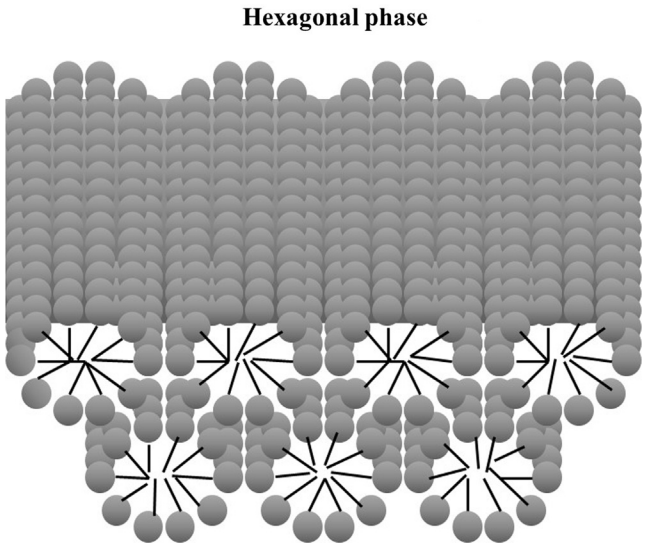



FIGURE 3.5 The rodlike micelles can pack into regular arrays. One common geometry is hexagonal packing to form hexagonal liquid crystals or gels. Hexagonal phase is a clear ringing gel.

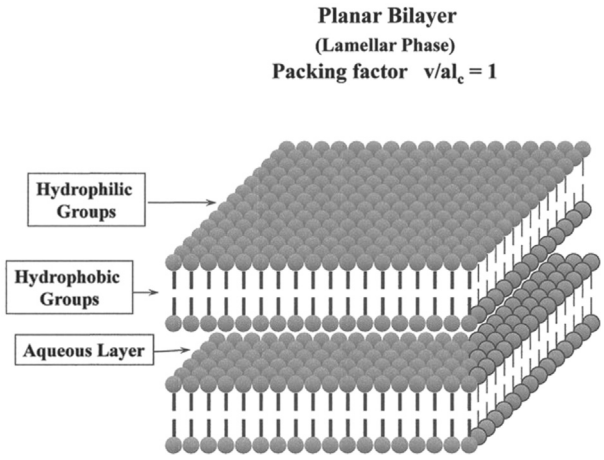



FIGURE 3.6 At packing factor = 1, stacked bilayers of lamellar phase form.

wormlike micelles. In general, formulators try to avoid these cubic phases because they can result in persistent "fish-eye" gels in a final composition. Nevertheless, nanoparticulate forms of cubic phase called "cubosomes" have been disclosed as controlled release matrices.[51–53]

Packing geometries limit the number of micellar structures available to any particular surfactant or surfactant mixture. This limitation prevents the smooth transition from spheres to rods to mesomorphic hexagonal and lamellar phases. As a consequence, two-phase and three-phase regions border the single-phase structures[54]; there is not a clean transition from spherical micelles to hexagonal phase to lamellar phase, etc (Fig. 3.7). The mixed-phase regions between pure phases can pose difficulties for the modern formulator in attempts to produce storage-stable formulations that exhibit stimuli-responsive behavior during use.

The formulator can manipulate self-assembly of surfactants to modify the physical characteristics of compositions. The transition from spheres to rodlike micelles to hexagonal phase to lamellar phase can be achieved using tactics that reduce the effective headgroup size or the mutual repulsion between headgroups in the self-assembled structures and thereby to increase the effective packing factor. For example, this can be achieved by:

- Adding soluble salts to reduce the mutual repulsion between ionic surfactant headgroups.
- Including cosurfactants with small or nonionic headgroups. Formulators use this tactic when they add alkylbetaine cosurfactants to shampoos, and when long-chain alkanols are included with cationic surfactants in conditioner formulations. Many modern shampoos are formulated at a pH of 5.5, which corresponds to the isoelectric point of

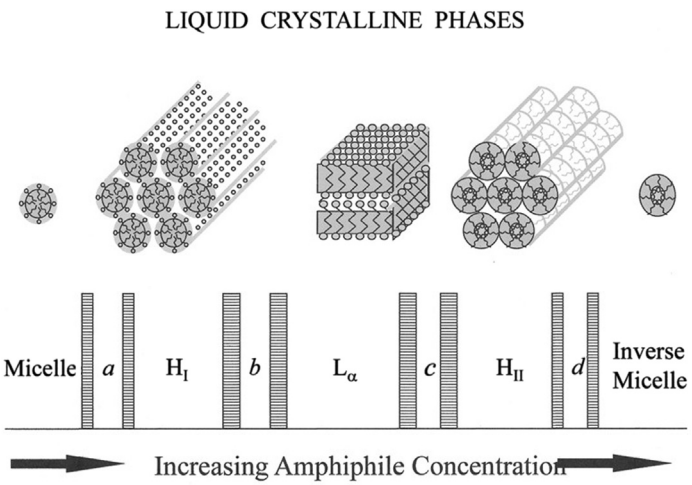



FIGURE 3.7 Increase in surfactant concentration causes micelles to transition from spheres to rods to hexagonal phase to lamellar phase to inverse hexagonal phase to inverse micelles. Two-phase composition regions usually lie in the transition zone from one phase to another.

hair. It is common to find sodium lauryl ether sulfate coformulated with cocamidopropyl betaine because this combination is mild and it is easily thickened due to the formation of rodlike and wormlike micelles. Betaines are zwitterionic, having amine groups and carboxylic groups on the same molecule. These zwitterionic surfactants display a negative charge at high-pH values due to charge domination of the carboxylate group.[55] They are positively charged at low-pH values due to the charge domination of the amine group. The isoelectric point is the pH at which the negative ionic charge of the carboxylate groups is exactly counterbalanced by the positive ionic charge of the alkyl ammonium groups. Streaming potential measurements of micellar solutions of betaines show that the isoelectric point is greater than pH 9 for C12-14 alkylbetaines. When alkylbetaines are mixed with sodium lauryl ether sulfate, the ionic attraction between the positively charged betaine headgroups and the negatively charged sulfate headgroups cause a dramatic increase in the packing factor of the mixed micelles. The isoelectric point of micellar cocamidopropyl betaine is 6.25. Therefore, at pH 5.5, cocamidopropyl betaine is slightly positively charged. This charge is just enough to confer an increase in packing factor on sodium lauryl ether sulfate micelles to ensure that the mixed micelles are wormlike, and, therefore, they exhibit a "thickened" rheology. On the other hand, cocamidoethylbetaines have an isoelectric point (IEP) of less than pH 3.5, which means that this cosurfactant is essentially negatively charged at all pH values above 3.5. It has been proposed that this low IEP is due to the formation of six-membered ring conformation that brings the carboxylate group into the direct vicinity of the amine group, thereby effectively neutralizing a proportion of its charge. Correspondingly, cocamidoethylbetaines are less efficient "thickeners" of anionic surfactant compositions.

In addition, the effective packing factor can be increased by the inclusion of surfactants with branched chain or bulky hydrophobic moieties.

Alternatively, packing factors can be decreased to maintain simple micellar compositions and to avoid the unwanted formation of higher-order structures such as cubic, hexagonal, or lamellar phases. Such a decrease in packing factors is regularly achieved by the addition of hydrotropes.[56] Hydrotropes are amphipathic molecules in which the amphipathicity is biased toward the hydrophilic content. This can be achieved by reducing the size of the hydrophobic group. For example, sodium xylene sulfonate is a frequently used hydrotrope in laundry applications.

### 3.2.3 Surfactants and Cleansing

Surfactants remove oils from the skin and hair surface by several mechanisms. There are four main mechanisms for removing oils: rollup (Fig. 3.8), emulsification (Fig. 3.9), penetration (Fig. 3.10), and solubilization.

1. Rollup of the oil droplets occurs readily for oils spread on hydrophilic surfaces. Surfactant adsorption on the substrate and on the oil surface causes an increase in the contact angle of the oil at the oil-water-substrate interface.[57,58] When the 3-phase contact angle approaches 180 degree, the resultant interfacial force holding the oil droplet to the surface is overcome by the wetting tension of the surfactant-covered oil and substrate surfaces, and the oil rolls up into a droplet that lifts off from the substrate under mild agitation. Due to the wide variation of

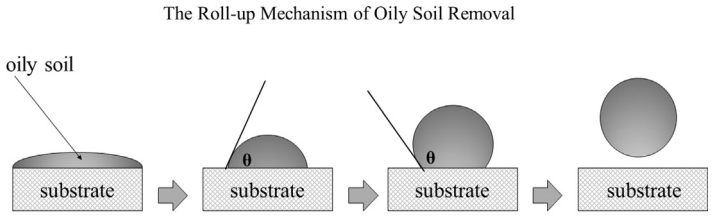



FIGURE 3.8 The rollup mechanism of detergency. Surfactant adsorption on the substrate and the oil causes mutual repulsion at the oil-substrate interface, which causes the oil to "rollup" and detach.

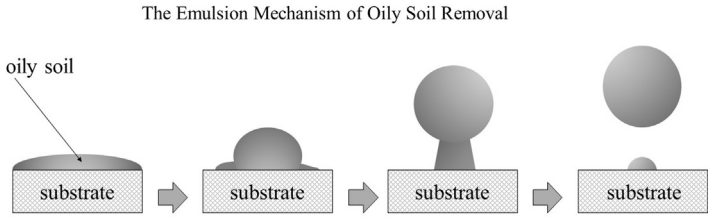



FIGURE 3.9 The emulsification mechanism of detergency. Adsorption of the surfactant on the oil phase causes the oil-water interface to expand and finger into the aqueous phase. Rayleigh–Taylor instability causes the oil fingers to break into droplets of emulsified oil, which are detached from the underlying oil layer. Given sufficient surfactant, the process repeats until the substrate is "clean."

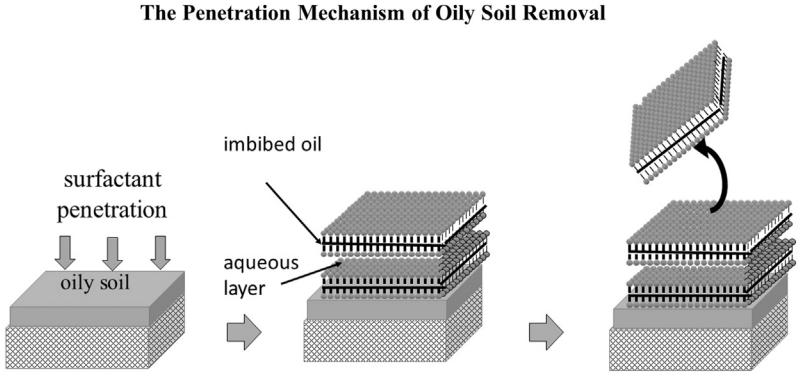



FIGURE 3.10 The penetration mechanism of detergency. Surfactant penetrates the oil and forms lamellar liquid crystalline bilayers that solubilize the oil. Repulsion between the bilayers causes them to successively slough off to form lamellar stabilized emulsion droplets.

surface energies on the skin and hair, the rollup mechanism is not necessarily predictable. Moreover, the diversity on oily soils can alter the route by which the surfactant adsorbs to the soil and the substrate. For example, the surfactant may adsorb by (1) encroachment along the surface, (2) through interaction with a previously applied permeable surface treatment, or (3) by absorption into the substrate and subsequent diffusion to the interface; this occurs, for example, in the case of bleached hair. The rate of rollup varies with the viscosity of the oily soil. Viscous or crystal-containing oils and waxes tend to rollup slowly and may require vigorous mechanical application to become dislodged from the substrate.

2. Emulsification is favored when the substrates are relatively hydrophobic and adsorption of the surfactant at the oil-water interface is facile and results in a low oil-water interfacial tension.[59] The resulting low interfacial tension favors expansion of the oil-water interface into the aqueous phase and the oil-droplet necks and emulsifies driven by Rayleigh–Taylor instability.
3. The penetration mechanism is favored by polar oils, such as sebum, or phase-separated simple coacervates at temperatures above their lower critical solution temperature. If the surfactant diffuses into the oil in sufficient concentrations, the oils can become part of a self-assembled mesomorphic phase, such as lamellar phase. Water layers are an essential part of these self-assembled surfactant systems. Repulsion between the bilayers of a resulting lamellar phase will cause the lamellar phase to swell and break off. Fresh surfactant then penetrates the newly exposed surface and the process repeats.[60] The dislodged oil becomes an emulsion stabilized by lamellar

phase.[61] The penetration mechanism is especially useful in hard water area where anionic surfactants form coacervate phases in the presence of calcium salts.[59]

4. Solubilization is the process of incorporating a water-insoluble hydrophobic substance in the internal hydrophobic core of micelles.[62] The kinetics of micellization and surfactant adsorption and exchange between micelles is important in this mechanism.[63]

## 3.2.4 Surfactants and Foam

Foaming is a cue that provides the user with evidence that the product is working to cleanse the body, but foaming is more than a consumer-perceived sensory attribute; foam does serve to float hydrophobic particles away from the substrate.[64] In general, foaming of liquids is enabled by surfactants.[65] Foams are characterized by their very low density. For example, an aqueous foam consisting of bubbles having a mean radius of 5 mm and a lamellar thickness of 10 μm will have a density of about 0.003 $g/cm^3$. Myers reports that a realistic surface area of such a foam would be 2000 $cm^2/g$.[66] This is an enormous surface area that confers advantages of soil removal, but the adsorption of surfactant from the bulk could deplete the micellar surfactant concentration and thereby diminish cleansing by emulsification, penetration, and solubilization mechanisms. In such instances the need to generate a foam while achieving excellent cleansing mandates a lower limit of surfactant concentration in the formulation.

There are three distinct processes that should be considered when trying to understand the basics of foams:

- foam initiation and formation
- foam stability
- foam drainage and rupture

### *3.2.4.1 Foam Formation*

The formation of a foam initially requires the formation of large gas voids that create enormous area of liquid-gas interface. Initially small spherical bubbles are imbibed in a creamy "kugelschaum" foam. When the volume fraction of air reaches about 0.7, the liquid faces between the bubbles distort and the foam becomes a system of air trapped in polyhedral films (polyederschaum). In a pure liquid, the interfacial area is unstable and the liquid film retracts into the bulk liquid almost as quickly as it formed. In surfactant solutions, however, surfactant adsorption serves to stabilize the interface for sufficient time to allow the foam to form. This surfactant adsorption results in a surface tension gradient that creates velocity gradient normal to the plane of the film, which creates a tension at the interface that opposes drainage of the liquid from the film. In the case of a pure liquid, there is no preferential adsorption at the interfaces, and hence no velocity gradient to oppose liquid drainage. As a result, there will be no viscous shear force opposing drainage, and the film will exhibit plug flow (resisted only by extensional viscosity), and the draining elements will tear the film apart[67] (Fig. 3.11).

On the other hand, surfactant adsorption leads to a surface tension gradient that balances the viscous forces of liquid flow, and the film becomes stable for a longer duration.

$$((d\sigma_{AL})/dy = \eta_L du/dx)_{(x=0)}$$

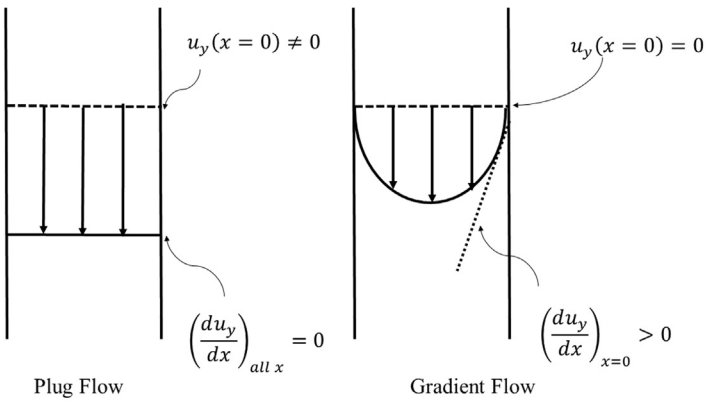



FIGURE 3.11 The importance of surface tension gradients in forming soap films. If there is no surfactant adsorption, there will be no surface tension gradient in the film. The walls will have essentially the same composition as the liquid within the film. In this case the "walls" will flow at the same rate as the liquid contained within the walls. The resulting plug flow will tear the film apart and, at best, only transient foams will be forms. Alternatively, if surfactant adsorption occurs, there will be a surface tension gradient and the walls will flow much more slowly than the liquid within the film. In the limit there will be zero shear at the walls and parabolic flow fronts will develop. This is a condition for the formation of a stable foam.

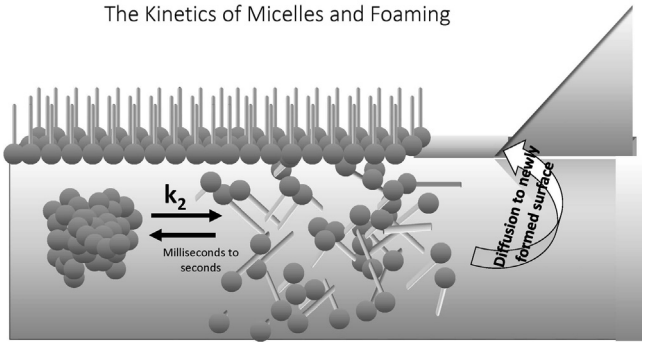



FIGURE 3.12 Stable foams are produced from micellar solutions when the processes of micelle disaggregation, diffusion, and adsorption to the surface are faster than the formation of the new liquid-gas interface. If micelle disaggregation kinetics are too slow, stable foams will not be formed.

where $(d\sigma_{AL})/dy$ is the surface tension gradient arising from surfactant adsorption, $\eta_L$ is the viscosity of the draining liquid, and $du/dx$ is the liquid velocity gradient across the film.

When the soap film is stretched, a surface tension gradient is generated in the film, which imparts "Gibbs" elasticity to the film.[68] The Gibbs elasticity equates the change in the surface tension arising either from a change in film surface area or film thickness.[69]

There is an optimal surfactant concentration for maximal Gibbs elasticity for a given surfactant system and a given soap film thickness.[70]

Stable films are formed when surface tension gradients are set up in the expanding film. These gradients are caused by the film being stretched faster than the surfactant can adsorb at the growing interface. The kinetics of transport of the surfactant to the rapidly expanding surface becomes the rate-limiting process that determines whether or not a foam will be formed. If the surfactant concentration is less than the optimum for Gibbs elasticity, the surfactant reaching the interface may be insufficient to confer film stability. In personal care products, foaming usually occurs from micellar systems. For such systems the flux of surfactant molecules to the interfaces depends upon the rate of disintegration of the micelles (Fig. 3.12) Slowly disaggregating micelles lead to a slower flux, which results in a higher overall dynamic surface tension that resembles stretching of a pure liquid, which result in low foaming.[71] For ionic micelles, such as lauryl sulfates, the mutual repulsion between headgroups enhances the tendency of the micelle to escape from the micelle. As the surfactant concentration increases, the counterion concentration also increases. The counterions are bound as a diffuse layer adjacent to the micelle surface. Increase in counterion concentration causes an increase in the concentration of the ions in the diffuse double layer, and this in turn damps the repulsion between surfactant headgroups, leading to slower disaggregating micelles and hence to lower foaming capability. As a consequence, ionic surfactants, like lauryl sulfates, should be optimally formulated for the generation of foam. Below the optimum the surfactant ions are too scarce to populate the interface effectively. Above the optimum, the kinetics of micelle disaggregation are too slow to provide sufficient ions to populate the expanding interface as the foam is formed. Due to absence of ionic repulsion, nonionic surfactants generally have slower kinetics of micelle formation and disaggregation than ionic surfactants. Anionic lauryl sulfates have relaxation times of second or fractions of seconds; alkyl PEG surfactants can have relaxation times of the order of minutes. Foaming tends to drop off precipitously above the Krafft temperature due to the enhanced stability of the crystal aggregates of the surfactant molecules.

### 3.2.4.2 *Foam Stability*

All foams are thermodynamically unstable, due to their high interfacial energy, which is dissipated upon rupture of the foam. For practical purposes, foams have been classified into two extreme types: transient foams with lifetimes of seconds and stable foams with lifetimes of minutes or hours. Champagne foam is an example of a transient foam. Shaving foam and whipped cream are examples of stable foams. A minimum concentration of surfactant is required to increase foam lifetime to confer stability on the foam lamellae. Low surface excess concentrations of surfactant result in adsorption of isolated molecules of surfactant and the adsorbed layer behaves as a two-dimensional gas. Increase in the number of surfactant molecules per unit area results in an increase in two-dimensional surface pressure.[19] This is analogous to the behavior of a gas that increases in pressure as the available volume is restricted. Higher concentrations result in a transition to an adsorbed layer in which the surfactant molecules are close enough

to mutually interact but insufficiently close to pack in a latticelike structure; the adsorbed layer behaves as a two-dimensional liquid. At even higher concentrations the adsorbed layer transitions to a "two-dimensional solid." The stability of a foam depends upon the packing characteristics of the adsorbed surfactant layer and the ability of the foam lamellae to withstand deviations in surface area that occur due to thermal or mechanical fluctuations in the foam. In many cases, the adsorbed monolayer is not uniformly dispersed but exists as a dynamic equilibrium between aggregates and surfactant monomers within the monolayer.[72,73]

Foam formation can be linked to dynamic surface pressure, but foam stability seems to depend on surface dilatational rheology.[74] Low concentrations of adsorbed surfactants result in liquid monolayers that are elastic. Expansion of the interface leads to an immediate elastic recoil that prevents the formation of a foam. At higher surface excess concentrations, the surface dilatational rheology becomes viscoelastic, and it seems that the viscous component is necessary for foam stability. Dilatational viscoelasticity has been linked to the presence of surfactant aggregates or complexes in the surface adsorbed layer.[75,76]

#### 3.2.4.3 *Foam Drainage*

During foam production the foam is predominantly in a liquid state and the volume fraction of liquid/gas is relatively high. However, this liquid state is metastable, and upon cessation of foam generation, the foam coarsens. The process of coarsening essentially entails an increase in the average bubble size and a decrease in the lamellar distance between bubbles. The pressure inside a bubble is described by the Young–Laplace equation:

$$\Delta P = \frac{2\gamma}{R}$$

where, $\Delta P$ is the excess pressure inside the bubble relative to the pressure outside the bubble; $\gamma$ is the surface tension at the liquid/air interface of the bubble.

The Young–Laplace equation shows that as the radius of a bubble decreases, the internal bubble pressure becomes greater.[77] The effect of Laplace pressure on soap bubbles is demonstrated in a video by Jubobroff.[78] As the foam relaxes back to equilibrium, the foam coarsens to reduce the average bubble internal pressure. Coarsening is the process by which the average bubble size increases. Coarsening occurs by drainage of the liquid between the fragile membranes of the bubbles, and diffusion of gas across the faces of liquid films that surround the gas bubbles.[79] Drainage of the foam can be followed by measurement of the liquid fraction that separates with time under the influence of gravity.[80] The highest volume fraction that monodisperse spherical bubbles can occupy is 0.74. Above this volume fraction departure from spherical geometry is necessary. For heterodisperse bubbles, the volume fraction attainable for spherical bubbles is higher than 0.74, but the Laplace pressure inside the smaller bubbles disfavors their stability and coarsening of the foam by removal of the smallest bubbles can be expected. Thus, when the liquid volume of a foam is small, the structure of foams is polyhedral, with Plateau borders[81] (channels) where the three faces meet. Plateau's laws state:

- Three and only three films meet at an edge at an angle of 120 degree;
- Four and only four edges (Plateau border channels) meet at a point (called a Plateau node) at the tetrahedral angle of 109.5 degree.

These rules have been used as a justification for the use of the regular pentagonal dodecahedron as the "idealized" foam bubble, but real foams are not composed of perfect pentagonal dodecahedra.

From the Young–Laplace equation it can be construed that the negative curvature of the Plateau border region causes the "nodes" of the plateau border to have a lower pressure than the less-curved lamellae. This causes the liquid in the films to be sucked into the Plateau border channels, which causes drainage and thinning of the foam lamellae.[82]

The disjoining pressure ($\Pi$) is the repulsive force that arises between the film surfaces when they are close enough to interact. If $\Pi$ is positive (repulsive), the film surfaces are held apart and film thinning is opposed. If $\Pi$ is negative (attractive), the film surfaces are driven together and film rupture occurs. Van der Waals forces between the film surfaces result in attraction. Repulsion between the film surfaces arises from ionic double-layer repulsion from ionic surfactant-adsorbed layers, and steric repulsion from long-chain molecules or hydration forces.

Drainage of aqueous foams has been extensively studied, but it is still far from being completely understood.

Early theories assumed that the walls of the lamellae were rigid and the liquid inside the lamellae showed Poiseuille flow. However, the assumption that the walls are solid may not always be valid.[83] If the dilatational modulus is greater than the surface tension, the surface behaves essentially as a solid. However, when the dilatational modulus is less than the surface tension, the film surface moves with the interlamellar liquid and the flow can be pluglike.[84]

For example, the lamellae walls are relatively fluid if the adsorbed surfactant molecules are relatively mobile (for example, for sodium lauryl ether sulfate solutions of low concentrations). In this case, drainage will be limited mainly by the nodes at the Plateau borders. This is consistent with the Fainerman–Lucassen–Reynders–Miller hypothesis that films with surface aggregates are viscoelastic. On the other hand, if the lamellae walls are relatively rigid (such as aqueous sodium lauryl ether sulfate foams stiffened by long-chain alcohols or cocobetaines) then the liquid at the walls shows classic Poiseuille flow, with zero shear at the walls and maximum flow at the center of the channel—so-called channel-dominated flow—with the flow rate varying as $1/r^3$, where "$r$" is the channel radius.

Film drainage can be slowed by increasing the viscosity of the intralamellar liquid. This can be achieved by the addition of water-soluble polymers, especially hydrophobically modified hydrophilic polymers that can interact with both sides of the lamellae and span the channel.[85,86] This approach is, however, limited to polymer molecules that can "fit" into the intralamellar spaces. Polymers that are insufficiently interactive with the walls and have a hydrodynamic volume that is greater than the lamellar spaces are unable to enter the lamellar spaces. Such polymers can microphase separate from the foam, compete for the available water, and cause the film surfaces to be driven toward each other sufficiently for the van der Waals attractive forces to force film rupture.[87,88] Film drainage can also be achieved by "plugging" the Plateau borders with, for example, phase-separated liquid crystals.[89–93]

#### 3.2.4.4 *Foam Rupture and Collapse*

A liquid of high surface tension pulls more strongly on the surrounding fluid than a liquid of lower surface tension. Therefore, if a surface tension gradient is set up in a liquid, the liquid will spontaneously flow away from the region of low surface tension. This can be demonstrated by sprinkling pepper on a clean water surface and then adding one drop of surfactant solution to the center of the surface. The pepper immediately flows to the periphery of the vessel.[94] This is an example of *Marangoni flow.*[95] Marangoni flow can lead to lamellar film stability or instability; soap films comprise minimal surfaces, that is, the tension in the surface causes the system to adopt the shape that constitutes minimum energy. However, soap films are in a condition of pseudoequilibrium since the surface energy can be lowered by collapse of the film into a smaller volume of unfoamed liquid. Fluctuations caused by air flows or convection within the film cause variations in the film thickness. If the fluctuation causes the film to be pinched, the surface area of the pinch point increases with respect to the rest of the film. This causes a transient lowering of the excess surface concentration of surfactant, which causes a momentary increase in surface energy, which in turn causes Marangoni-driven flow of liquid into the pinch point, which restores the film to its original thickness, thereby stabilizing the film against rupture. This process is called the *Gibbs– Marangoni effect*, and the surface elasticity conferred on the film to cause it to self-heal is called *Gibbs–Marangoni elasticity.*

If the Marangoni flow is faster than the surface diffusion rate of surfactant, the weak spot in the film may not be repaired, and catastrophic film failure will result.

Surfactant films devoid of liquid (so-called Newtonian black films) can be made under draft-free and convectionless conditions.

#### 3.2.4.5 *Defoaming*

If a liquid (e.g., dimethicone) having a lower surface tension is placed on a soap film, the liquid will spontaneously spread on the film due to (1) thermodynamically driven lowering of the total surface energy of the system, and (2) Marangoni-flow driven retraction of the higher energy surface. The local surface tension depression then results in the rupture of the soap film.[96,97]

Oils and hydrophobic particles induce defoaming, and, for this reason simulated sebum and simulated conditioning agents and silicones are often included in foaming tests for personal care compositions. The science of antifoaming is complex and advanced, although it is still incomplete. Detailed discussion of antifoaming is beyond the scope of this chapter. Readers who wish to learn more about defoaming are referred to the excellent book by Garrett that is devoted entirely to this subject.[98]

### 3.2.5 Surfactants Phase Diagrams and Pseudophase Diagrams

As disclosed earlier, surfactants can form a range of self-assembled structures, which translates to a range of distinct physical properties, rheologies, and sensory attributes. The construction of phase diagrams and pseudophase diagrams reveals the range of structures and guidance on the compositional location of each of the structures for a given surfactant system. Fig. 3.13 is a schematic example of a surfactant phase diagram, showing the location of the different self-assembled structures.[99–102]

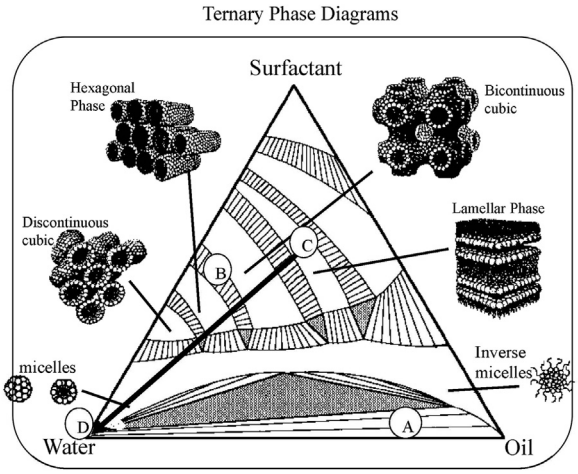



**FIGURE 3.13** A schematic ternary phase diagram for a water-oil-surfactant system. Each point on the diagram represents a unique composition. The diagram shows regions of pure self-assembled surfactant mesomorphic phases and two-phase and three-phase regions at interim compositions between the pure phases. Tie lines connect the compositions of each separated phase in the two-phase regions.

This is a ternary diagram that plots the micellar structures as a function of composition of a system comprising water, surfactant, and an oil. Each point in the diagram corresponds to a unique chemical composition of surfactant: oil:water. The diagram is constructed by determining the structure of distinct compositions and then mapping these structures on the diagram. In Fig. 3.13, almost all of the major-listed surfactant self-assembled structures are shown, approximately in equal compositional ranges. This is not usually the case, since amphipathic molecules are limited in the way they can pack together and this limits the number of self-assembled structures that are possible for a given surfactant or surfactant mixture.

The regions of pure mesomorphic phases are shown as clear areas in the diagram: micelles, inverse micelles, cubic phases, hexagonal phase, and lamellar phase. The area with "hash" lines depicts compositions that are biphasic. The lines are, in fact, tie lines. Each tie line connects the compositions of the constituent phases of all compositions that lie along the tie line. For example, tie lines in the region depicted A show that the compositions in that region are composed of mixtures of micelles and inverse micelles. Tie lines in the region denoted B show that compositions in that region consist of mixtures of hexagonal phase and bicontinuous cubic phase. Triangular areas show compositions with three coexisting phases. Consistent with the Gibbs phase rule, these compositions have no degrees of freedom.

The arrow CD shows the ideal path that would be taken as composition C is diluted with water. Note that upon dilution, such a composition would traverse through biphasic lamellar/bicontinuous cubic phase, pure bicontinuous cubic phase, biphasic bicontinuous cubic/hexagonal, then pure hexagonal phase, then biphasic hexagonal/discontinuous cubic, then pure discontinuous cubic, the biphasic discontinuous cubic/micelle, and finally to a simple micelle phase. Each of the liquid crystal phases is characterized by a distinct rheology. For example, while small micelles show Newtonian viscosity, rodlike micelle systems are typically viscoelastic. Hexagonal phase is a shear-thinning gel, and lamellar phase is a less-shear thinning gel with a distinct yield stress. Cubic liquid crystals are predominantly elastic gels with ringing gel properties.[103,104]

In real systems, the dilution pathway may not follow a straight line, due to the difficulty of mixing certain phases, which delays the approach to equilibrium. For example, cubic phase might not be molecularly dispersed upon dilution while lamellar phase may mix more readily. In this case cubic phase could persist as immutable "fish eyes," while the lamellar phase in the first biphasic mixture mixes more readily, thus altering the effective dilution path. For the case of a nonvolatile oil, the path of evaporation of a given composition would be the reverse of the dilution path. If the oil is volatile, however, and if the oil-water vapor is not an azeotrope, the path of evaporation will vary depending on the relative vapor pressures of the volatile components. In addition, polar oils can insert themselves into the surfactant layers to become part of the mesomorphic structure, or even alter the mesomorphic structure. In such a case the volatile oil may lose some of its volatility. This is an important consideration in fragranced compositions,[105] in which some of the fragrance oils are favored over others in the structured surfactant phase; this can remove fragrance notes and alter sensory perception of the fragrance.

Pseudophase diagrams serve as useful guides: (1) to the formulator who is seeking particular properties for product attributes, (2) to the process engineer, especially during scale-up or trouble shooting exercises, and (3) to the scientist who is seeking stimulus-responsive behavior by changing micelle structure during use.

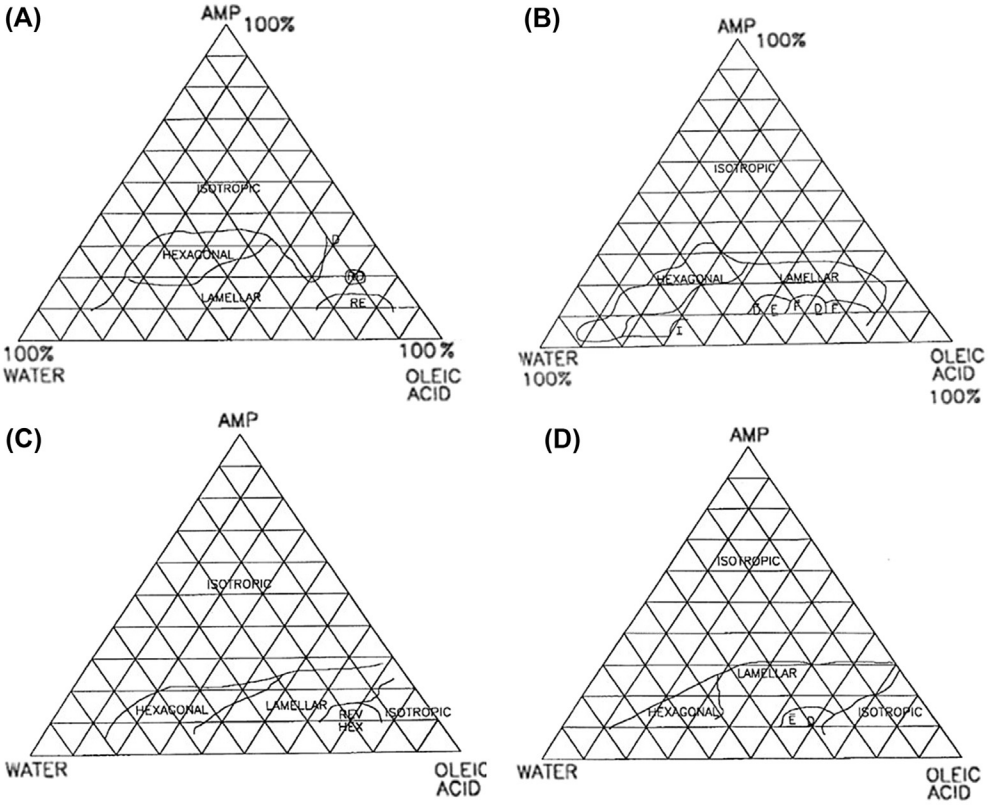



**FIGURE 3.14** The use of phase diagrams to guide formulators to optimum compositions of water, oleic acid, aminomethylpropanol neutralizer, and nonionic surfactant. In this case, the goal was to formulate a hexagonal phase gel at the lowest surfactant and oil concentrations. See text for explanation.

*Example of phase diagram use by a formulator:* For the purpose of formulating oleate cleaning gels[106] and fragrance gels,[107] it was necessary to find the formulation that would have the lowest oleic acid and neutralizer (AMP) concentrations. Fig. 3.14A is a ternary phase diagram for oleic acid soap compositions; Fig. 3.14B is a ternary phase diagram for oleic acid soap compositions with 5 wt% of a particular nonionic surfactant, Fig. 3.14C is a ternary phase diagram for oleic acid soap compositions with 5 wt% of a particular polar solvent, Fig. 3.14D is a ternary phase diagram for oleic acid soap compositions with 5 wt% of a particular nonionic surfactant and 5 wt% of a particular polar solvent.

Clearly, the composition with both the nonionic surfactant and polar solvent enables the formation of hexagonal gel with the lowest concentration of oleic acid and neutralizing agents.

*Example of phase diagram use by a process/scale-up engineer.* Sodium lauryl ether sulfate (SLES) was originally offered at 28% solids. A later process made the product at 70% solids. During shampoo manufacture, the 70% solids was diluted and the composition gelled beyond the capability of the agitator to mix on a commercial scale. Phase diagram studies showed that the 70% SLES was in a flowable lamellar phase that, upon dilution, transitioned into a viscoelastic hexagonal phase gel. Phase diagrams guided the engineers around the troublesome hexagonal phase compositions and enabled manufacture of the shampoo with the 70% SLES.

*Example of phase diagram to the scientist who is seeking stimulus-responsive behavior by changing micelle structure during use.* There was a need for a surfactant product that thickened upon dilution with water. Phase studies could show that addition of certain salts of ammonium lauryl ether sulfate would give low-viscosity compositions that, upon dilution, would be converted to the more-viscous lamellar liquid crystalline phase (Fig. 3.15).[108]

### 3.2.6 Basic Physical Principles for the Use of Polymers in Cosmetics

Polymers are used extensively in cosmetic products, almost to the point of being ubiquitous. The range of uses for polymers is diverse and, apart from packaging, polymers are used as:

- film formers in hair fixatives, nail products, mascara, and transfer-resistant makeup

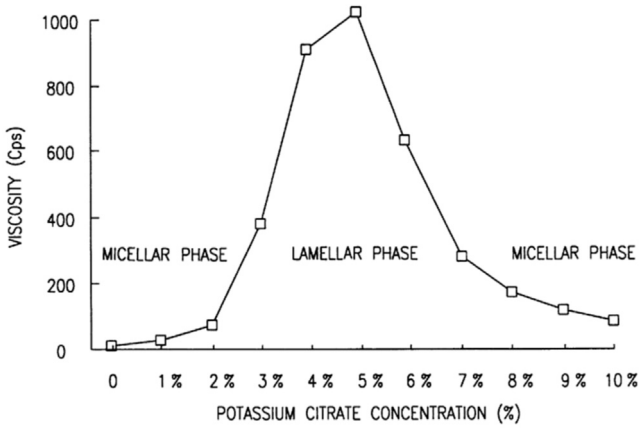



**FIGURE 3.15** Tracking phase behavior to find compositions with stimuli-responsive behavior. In this case compositions containing potassium citrate paradoxically increased their viscosity upon dilution due to a transition from micelles to lamellar phase.

- thickeners and rheology modifiers for emulsions, gels, pigmented dispersions, hair colorants, and hair relaxers
- emulsifiers that can be stimuli responsive upon application for sophisticated skin treatments and products such as sports sunscreen
- conditioners for skin and hair
- moisturizers for skin
- emollients that improve the "rub-in" characteristics of skin products
- pigment dispersers and stabilizers
- waterproofing agents
- controlled-release matrices
- foam stabilizers and destabilizers
- sensory-feel additives
- antimicrobial agents

### *3.2.6.1 Polymer Solubility and Compatibility*

In considering the use of polymeric ingredients, it is essential to understand the basis of polymer solubility and compatibility. Regular solution theory reveals two drivers for the dissolution of one substance in another:

- enthalpic interaction between the components; a negative enthalpy of interaction favors dissolution
- increase in configurational entropy due to mixing of the components according to the relationship,

$$S = k \ln \Omega,$$

where, $S$ is the entropy of the system, $\Omega$ is the statistical number of ways the solute and solvent molecules can be configurationally arranged, and $k$ is the Boltzmann constant.

As the molecular weight of the solute increases, the value of $\Omega$ decreases, and, as a result the entropic driving forces are diminished for dissolution of polymers. As a consequence, polymer solubility depends strongly on the enthalpic interaction between the polymer and the solvent.

Early attempts to theorize the solubility of polymers took the approach of "like dissolves like." Using this approach, Hildebrand reasoned that compounds with similar intermolecular forces would be completely compatible with each other at the molecular level. He defined the intermolecular forces as the *cohesive energy density* per unit volume of each of the species.[109,110] The cohesive energy density is, in fact, the internal energy of vaporization of a liquid, and it can be measured from the heat of vaporization. Hildebrand defined the *solubility parameter*, $\delta$, as the square root of the *cohesive energy density*, and he postulated that solvents would dissolve compounds with similar solubility parameters. This hypothesis worked very well for simple compounds, such as alkanes, for which the only intermolecular forces are dispersion forces. Such forces (often called van der Waals forces) are distributed uniformly in all directions around each molecule. However, Hildebrand's hypothesis proved inaccurate for the prediction of solubility of polar compounds and Lewis acids/Lewis bases. Compounds with significant dipoles or the capability of hydrogen bonding orient themselves with other molecules of solvent and solute that are present,

and these interactions result in ordering of the system. This causes a significant loss of entropy of mixing, which the enthalpic interactions must overcome if a homogeneous solution is to be formed.

Hansen overcame this shortcoming by introducing three components of the solubility parameter, namely, the dispersion component ($\delta_d$), the polar component ($\delta_p$), and the hydrogen-bonding parameter ($\delta_h$). Each of these components can be experimentally measured, and Hansen and others tabulated the values for common solvents. Hansen discovered that the solubility of compounds, including polymers, could be predicted fairly accurately.[111,112] Hoy advanced the concept by proposing comparison of compounds using the proportions of dispersion forces, dipole interaction forces, and hydrogen bond forces rather than the absolute values of these component parameters.[113]

The advantage of Hoy's approach is that it allows the solubility of each small molecule compound to be plotted on a ternary diagram (Fig. 3.16). Each solvent has unique coordinates in such a diagram. Classes of solvents are restricted to distinct regions of the ternary diagram.

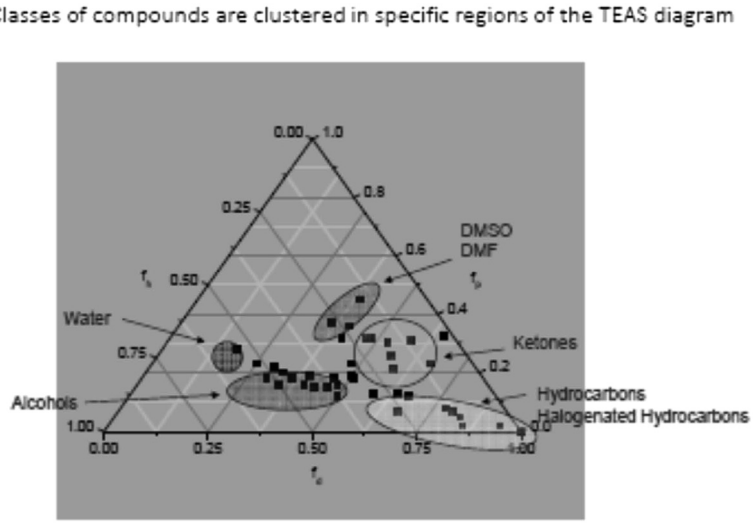



FIGURE 3.16 A TEAS solubility parameter diagram that plots the Hansen–Hoy solubility parameters for a range of solvents on a ternary diagram. Each solvent has a unique position on the triangular grid and this position is located at the point that corresponds to the relative proportions of the cohesive energy density that are due, respectively, to dispersion forces, dipole–dipole interaction, and hydrogen-bonding interaction. It is notable that solvents cluster by chemical class on a TEAS diagram.

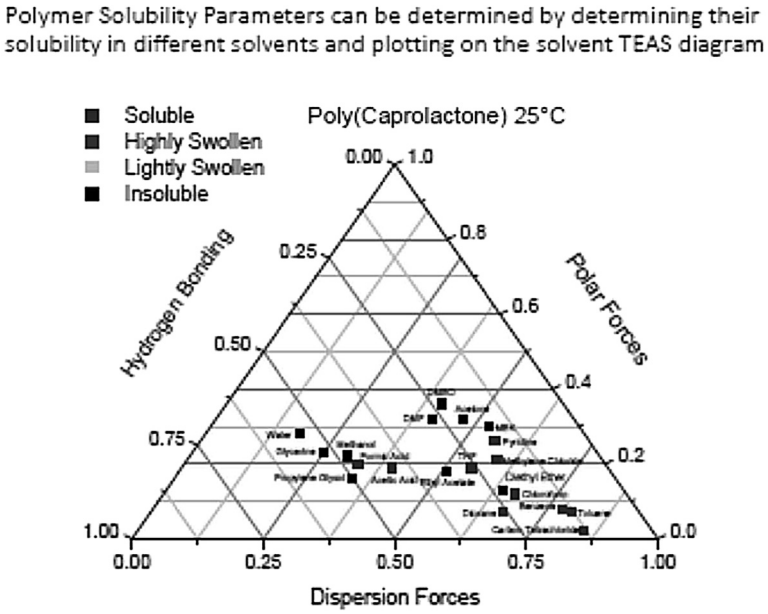



FIGURE 3.17 A TEAS diagram for polycaprolactone showing solubility, swellability, and insolubility in selected pure liquids.

The solubility boundaries of any given polymer can be plotted by observing the solubility in a range of solvents and plotting the data on a ternary diagram. This is shown below for a sample of polycaprolactone (Fig. 3.17).

Having plotted the data, a solubility boundary can be drawn around the soluble regions of the plotted points. The solubility parameter considers only the enthalpic contributions to compatibility and it ignores the entropic contributions. However, the entropic contributions manifest themselves as a shrinkage of the solubility range as the polymer molecular weight increases. Thus, as the molecular weight increased, a polymer would be predicted to have a smaller solubility range, and a lower solubility concentration in a given solvent. This is not always the case because polymer conformation can play an important role in solubility. For example, polyoxyethylene can be viewed as a polymer composed of dimethyl ether units. Dimethyl ether has a solubility limit in water of about 30% by weight, whereas polyoxyethylene is soluble in water in all proportions.[114] This fact would seem to contradict the general maxim that solubility decreases as molecular weight increases. The answer to this conundrum lies in the fact that in water at low temperatures, polyoxyethylene forms cagelike structures that shield the hydrophobic ethylene units from contact with water and enhance the interaction of the oxygen atoms in the structure with water, and clustering of the chain ends also "hides" hydrophobic groups from the water.[115] It is possible that polyoxyethylene adopts helical conformations in water.[116]

Due to configurational entropic constraints associated with high molecular mass, different polymers do not usually mix on a molecular level. The propensity for polymers to mix can be anticipated by large overlap of the solubility ranges of the given polymers (Fig. 3.18). However, caution must be exercised, since even small differences in solubility parameters can result in polymer segregation.

Flory–Huggins theory considers both enthalpic and entropic components of thermodynamic mixing in bicomponent systems. The enthalpic component is expressed by the Flory–Huggins interaction parameter, $\chi$, which is essentially the difference between the solubility parameters of the solute and solvent. The entropic component is calculated from the volume fractions of each component, but this calculation assumes homogeneous polymer molecular structure and regular thermodynamic mixing. This constrains the theory to very few real systems. For example, hydrogen bonding between the water-soluble polymers, polyacrylic acid and polyvinylpyrrolidone, provides a favorable $\chi$ interaction that enhances compatibility of these polymers, but the same hydrogen bonding causes the formation of simple coacervates that separate from aqueous solution at pH values less than 4.5 (Figs. 3.19 and 3.20).[117,118]

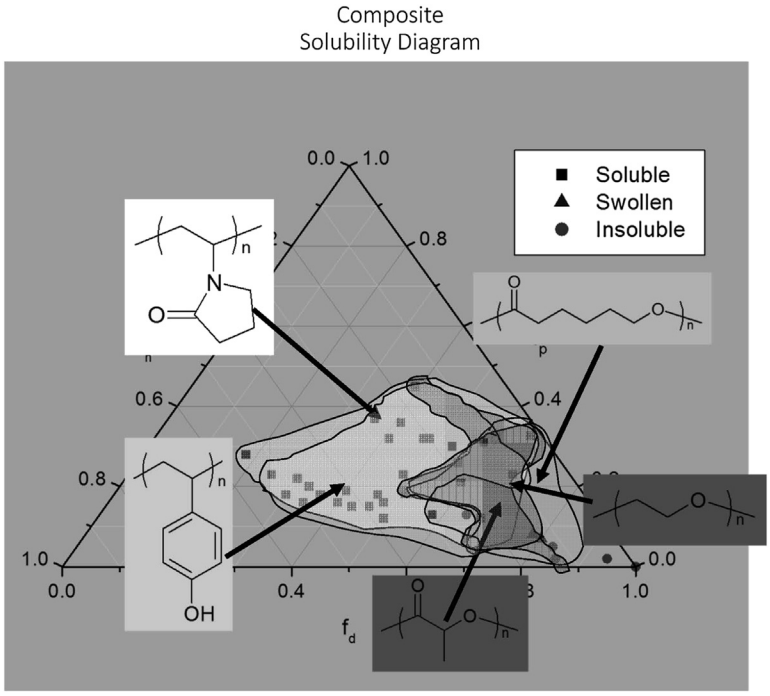



FIGURE 3.18 A composite TEAS diagram showing superimposed solubility ranges of polycaprolactone, poly(ethylene oxide), poly(lactic acid), polyvinyphenol, and polyvinyl pyrrolidone.

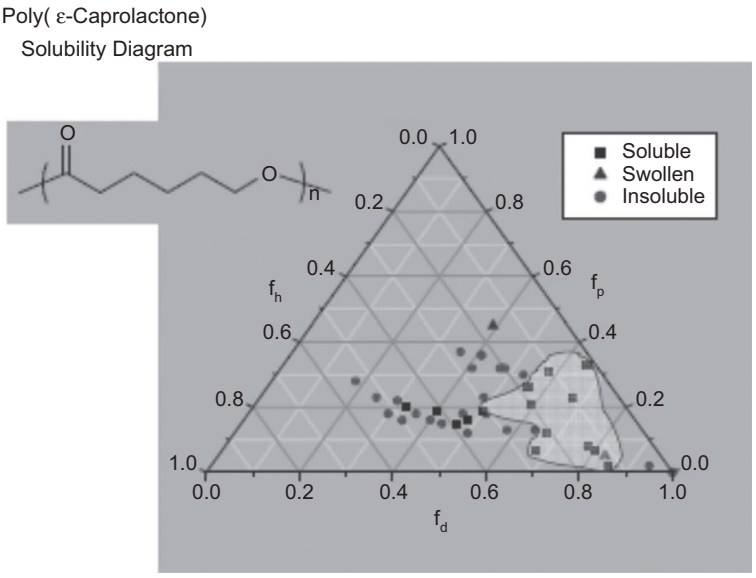



**FIGURE 3.19** A TEAS diagram showing the solubility range of polycaprolactone.

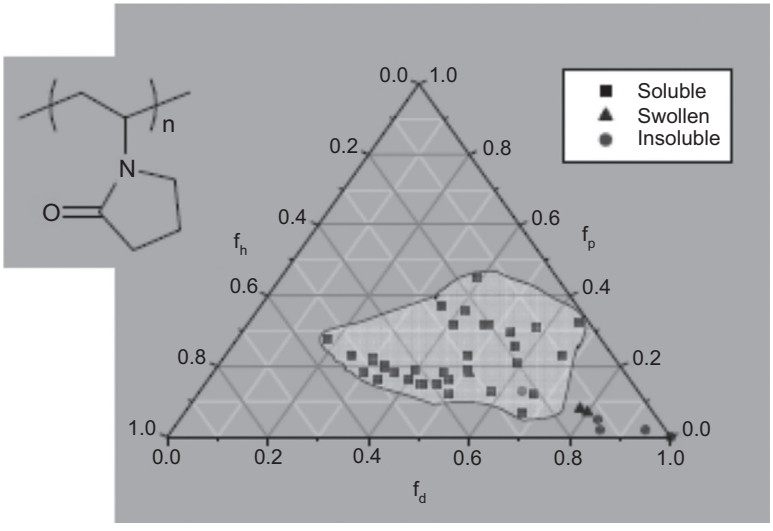



**FIGURE 3.20** A TEAS diagram showing the solubility range of polyvinylpyrrolidone.

### *3.2.6.2 Copolymers*

Polymers composed of a single repeating chemical monomer unit are known as homopolymers. Homopolymers do exist as valuable commercial products. However, it is more common to find polymers comprising two or more different monomeric repeating units on the same chain. Polymers that contain more than one monomer unit are called *copolymers*. The reason for combining different monomers within one polymer molecule is to achieve properties that are not possible from the homopolymers alone. The monomeric units are randomly distributed in the chains of random (statistical) copolymers. Random copolymers have a weighted average of the properties of the individual homopolymers. This can be illustrated by considering the properties of the early hairspray polymer PVP/VA. Poly (N-vinyl-2-pyrrolidone) (PVP) is a polar, brittle water-soluble, glassy polymer that is readily plasticized by humidity. This plasticization causes hairsprayed hair to "droop" in humid atmospheres. Poly (vinyl acetate) (PVA), in contrast, is a soft, water-insoluble, nonpolar polymer that resists removal by shampoo. By randomly copolymerizing PVP with VA, polymer chemists were able to synthesize copolymers that exhibited compromises of hardness and softness, and polarity and nonpolarity to meet the technical needs of resistance to droop and removal by shampoo that lay beyond the properties of either of the homopolymers. PVP/VA copolymers containing 70 wt% vinyl acetate

are water insoluble, ethanol-soluble hair fixatives for aerosol sprays. In contrast, PVP/VA copolymers containing 70 wt% PVP are water-soluble hair fixatives that are useful in hair gels.

Block copolymers are composed of segments of individual homopolymers joined end to end. Graft copolymers are composed of segments of one polymer attached as side chains to the backbone of another polymer. Block and graft copolymers overcome the compromise that is inherent in random copolymers. This can be illustrated by the example of block copolymers of styrene and butadiene. Polystyrene is a brittle, glassy polymer that is susceptible to cracking. Poly (1,4-butadiene) is a soft, rubbery polymer that tends to deform and creep. Random copolymers of these two monomers would exhibit properties that compromised brittleness and creep. However, block copolymers of styrene and butadiene, comprising long blocks of polystyrene and long blocks of polybutadiene, exhibit the "best" properties of both homopolymers polymers, namely, the shape retention of polystyrene and the impact resistance of polybutadiene. In this instance, the block copolymer is tougher than either homopolymer alone.

The effect of polymer conformation on solubility is dramatically illustrated by many block and graft copolymers. Block copolymers can be synthesized to display dual solubility. In these cases, the block copolymers will show two separate regions of solubility on a so-called TEAS diagram. (Named after Jean P. Teas who, in 1968, introduced the triangular graphical form to depict fractional solubility parameters.)

Today's cosmetic scientist has access to a large selection of polymers containing several monomer types in copolymers that are molecularly finely tuned to exactly deliver desired attributes.

#### *3.2.6.3 Polymer Conformation*

Regular solution theory considers the statistical thermodynamics of solute and solvent, specifically, the interactions between the components and the possible configurations that the solute and solvent molecules can be arranged relative to each other. For polymers, there is another consideration—the conformational contribution of the polymer molecule to the free energy of mixing. The conformation refers to the statistical "shapes" that are available to given polymer molecules. This is important because many of the properties of polymers are related to the size and shape of the polymers themselves. A basic understanding of the solution behavior of random coil polymers requires an appreciation of some basic concepts that are explained in the following discussion.

##### 3.2.6.3.1 End-to-end Distance

If one imagines a walk in which each step is taken at random, it is clear that a great many steps could be taken but the distance covered from start to finish would be much less than a walk taken in a straight line. In flexible polymer molecular chains, each link is joined randomly, and if one could start at the beginning of the chain and trace a path along the chain, the final distance between the two chain ends would be less than the end-to-end distance of a stretched chain. In fact, the end-to-end distance of perfectly random chain would scale as the square root of the number of links in the chain. This is a useful concept but, unfortunately, the end-to-end distance of a polymer molecule is a difficult parameter to measure. Moreover, theories that assume random-flight polymers necessarily assume unperturbed polymer chains. The conditions for an unperturbed chain are that the polymer segment−segment interactions are exactly equal to the polymer−solvent interactions. This is defined as the "theta" ($\theta$) condition. The theta condition hovers between solubility and insolubility. Increase in solvency causes expansion of the polymer hydrodynamic volume, and decrease in solvency causes collapse and phase separation of the polymer from solution. Therefore, the theta condition, which is the basis of many statistical thermodynamic theories of polymer solutions, is essentially experimentally inaccessible, since even slight fluctuations of temperature or pressure will cause a departure from theta conditions. Consequently, theta condition polymer dimensions are computed by extrapolation from experimental measurements.

##### 3.2.6.3.2 Radius of Gyration

The radius of gyration of a polymer molecule is the average distance of every link from every other link in the chain. This is equivalent to measuring the average distance of every point on the chain from the center of gravity of the whole chain. The radius of gyration is a measure of the distribution of mass in the molecule, and this parameter can be measured by light-scattering techniques.

##### 3.2.6.3.3 The Hydrodynamic Radius

Due to the constraints of the molecular chain, the "links" of polymer chains cannot usually pack tightly together. There is always some excluded volume within the chain. In a good solvent, the chain swells and imbibes many molecules of solvent. It is not unusual for a polymer molecule to swell a hundred-fold or more when immersed in a good solvent. The hydrodynamic radius is the radius of the equivalent sphere of a polymer chain plus the solvent

contained within that chain in solution. The hydrodynamic radii of polymer chains can be measured by viscosity, dynamic light scattering, and size exclusion chromatography.

#### 3.2.6.3.4 Conceptual Exercise on Polymer Dimensions

Consider a flexible chain consisting only of $-CH_2-$ units with a degree of polymerization of 20,000 (i.e., the number of $-CH_2-$ units in the chain is equal to 20,000). The length of a C—C bond is 0.15 nm. If the chain is stretched out like a taut rope, the length of the stretched chain would be $20{,}000 \times 0.15$ nm, that is, approximately 3000 nm (3 μm). *This stretched length is the contour length of the chain.*

If, however, the chain collapses to a tight ball, like a ball of string, the volume of the ball could be calculated from the known density of polyethylene (0.9 g/mL):

$$\text{Volume of ball} = \frac{20{,}000 \times 14}{0.9 \times 6 \times 10^{23}} = 520 \text{ nm}^3$$

Dividing this volume by $3/4\pi$, the radius of the polymer ball is only 5 nm.

Thus we see that a polymer chain in its completely collapsed state would occupy a sphere having a radius of only 1/500 of the contour length.

For real polymer chains, the chain is stiffened by, for example, (1) bulky groups that hindered rotation around chain backbone bonds, (2) the formation of ring structures along the backbone, (3) the formation of helical conformations, (4) intermolecular crystallization between chains, (5) interaction with a good solvent, or (6) the presence of dissociated ionic groups in the polymer molecule.

The stiffness of polymer molecules is characterized by their persistence lengths or by their "Kuhn" lengths. The persistence length is the hypothetical minimum distance one must travel along a molecule before moving at right angles to the original direction. The Kuhn length is twice the persistence length. Below the persistence length, the polymer molecule is "stiff." Beyond the Kuhn length, a polymer molecule becomes flexible. The persistence length can be measured by dielectric relaxation, viscoelastic relaxation, and ultrasonic relaxation techniques and by light scattering. The Kuhn length of stiff molecules like cellulose ethers is much longer than that for acrylic polymers. Although the cellulose ethers are stiff and their thickening properties derive from that stiffness, their molecule still become coils when they are longer than the Kuhn length.

### *3.2.6.4 Polymer Solution Viscosity and Its Relation to Polymer Molecular Dimensions*

In dilute solution in a good solvent, polymer molecules are separate isolated entities.[119] Under these conditions, the contribution of each polymer molecule to the solution viscosity will depend upon the hydrodynamic volume of the polymer in that solution. Using Einstein viscosity theory,[120] one can correlate the viscosity to the hydrodynamic volume from the measured intrinsic viscosity of the polymer. The specific viscosity is a measure of the contribution of a colloidal "solute" to the viscosity of a system that contains that solute. The contribution to the total viscosity of the suspended spheres can be found by subtracting the solvent viscosity ($\eta_o$) from the suspension viscosity ($\eta$) and then dividing by the solvent viscosity. This contribution is termed "the specific viscosity."

$$\text{Specific viscosity, } \eta_{sp} = \frac{\eta - \eta_o}{\eta_o}$$

Einstein theory postulated that uniform spheres suspended in a liquid should increase the viscosity of a liquid by 2.5 times the volume fraction of the spheres.

$$\eta_{sp} = 2.5 \frac{\text{Volume occupied by all the spheres}}{\text{Total volume of the system}} = 2.5 \frac{N_B V_\eta}{V}$$

where, $N_B$ is the number of spherical particles in the system, $V_\eta$ is the hydrodynamic volume of each sphere, and $V$ is the total volume of the system.

Assuming that each sphere is a polymer molecule, Mark, Houwink, and Sakurada derived an expression that related the specific viscosity to the molecular weight of a polymer:

$$\eta_{sp} = KM^a$$

Huggins later showed that the measured specific viscosity also included a term from the hydrodynamic frictional interaction of the polymer molecules. This overestimation was removed by extrapolating the viscosity measurements to infinite dilution (zero polymer concentration), assuming that in this limit, the distance between polymer molecules was too

large to allow interparticle perturbation through hydrodynamic interactions with intervening solvent molecules.[121] The specific viscosity at infinite dilution is termed the "intrinsic viscosity" and it is designated by the symbol $[\eta]$.

The intrinsic viscosity can be related to the polymer molecular weight by the Mark–Houwink–Sakurada equation:[122]

$$[\eta] = KM^a,$$

where $[\eta]$ is the intrinsic viscosity, $M$ is polymer molecular weight, $K$ is parameter that is related to the degree of swelling of polymer in the solvent, and $a$ is a parameter related to the draining characteristics of the solvent in the polymer coil. For a random coil polymer, the value of $a$ ranges between 0.5, for a nonfree draining coil, to 1.0 for a free-draining coil.

Although the intrinsic viscosity is measured by viscometry, the dimensions of intrinsic viscosity are volume per unit weight. *Note that the intrinsic viscosity will vary with temperature, pressure, and solvent composition.*

The hydrodynamic volumes, intrinsic viscosities, and molecular weights of dissolved polymers in dilute solution are related by the Flory–Fox equation:

$$[\eta] = \frac{\psi\left(r^2\right)^{\frac{3}{2}}}{M}$$

where, $[\eta]$ is intrinsic viscosity, $M$ is average molecular weight, $\psi$ is the Flory constant, and $r$ is the chain end-to-end distance.

Many polymers have branched rather than linear chains. The increase in molecular volume with molecular weight is less with branched than with linear polymers. This change is reflected in the $K$ and $a$ values. The ultimate branched polymers are dendrimers, for which the molecules are regularly branched, treelike structures that emanate from a core and show regular repeating branch points. Dendrimers can have Mark–Houwink–Sakurada $a$ values as low as 0.2.[123] The Zimm branching factor ($g'$) is one way of expressing the degree to which a molecule has deviated from a linear molecule.

$$g' = \frac{\text{radius of gyration of the branched polymer molecule}}{\text{radius of gyration of a linear polymer molecule of same molecular mass}}$$

The $g'$ can be experimentally computed from the ratio of intrinsic viscosities at constant molecular weight.

Dendrimers are classified by a specialized nomenclature; each unit between the branch points is called a *generation*.[124] The first generation consists of the initial monomer units added to the core, the second generation is then built on this first generation, and so on. Perfect dendrimers exhibit a spherical architecture, and with each succeeding generation, the area at the surface of the sphere grows more than the volume of the sphere. This creates excess free volume at the surface of the dendrimer molecule. Fourth or fifth generations have sufficient excess free volume to allow succeeding generation segments to "fold back" into the sphere, and this causes the intrinsic volume to show a maximum at about the fourth generation.[125]

Perfect dendrimers are synthesized by laborious methods by which each generation is added stepwise; this limits the economic feasibility of dendrimers. Therefore, it is more common to approximate dendrimer structures by preparing hyperbranched polymers by polymerizing multibranched functional units in one step by a one-pot synthesis.[126–129]

### 3.2.6.5 Polymer Molecular Mass Distribution

Some natural macromolecules, such as proteins, have molecules that are all the same size. The statistical distribution of molecular mass in such molecules is termed *monodisperse*. In contrast, synthetic polymers are *polydisperse*, i.e., the molecular masses are distributed over a range of molecular masses. The properties of polymeric materials are influenced by molecular weight distribution; low-molecular-weight fractions confer good processability but give poor mechanical properties. On the other hand, polymer distributions biased toward high molecular weights favor high viscosities and can be tough to process. Emerging "living polymerization" methods can now provide synthetic polymers having molecular mass distributions that approach monodispersity.

Dissolution processes can affect the final molecular weight distribution. Polymer dissolution is essentially a two-step process. In the first step, the solvent diffuses into the polymer to make a swollen polymer gel. In the second step, the swollen gel breaks up and the polymer molecules are distributed throughout the solution. Polymer chains are rather fragile and excessive shear during this second step can cause breakage of the chains and broadening of the distribution. There are exceptions to this two-step process; some polyelectrolytes are driven by counterion dissolution and ionic repulsion to flow directly into water upon contact.

### 3.2.6.6 Polymer Semidilute Solutions

In thermodynamically good solvents, polymer coils expand significantly, even to the point at which solvent constitutes most of the space within the hydrodynamic equivalent sphere. This degree of swell allows polymer molecules to mutually pervade each other's spaces and to become entangled in each other. Such entanglement can occur only above a threshold polymer concentration: *the critical entanglement concentration*. In dilute solutions, polymer molecules are isolated in solution. Increase in the polymer concentration eventually leads to a threshold concentration at which the polymer molecules just touch each other; this concentration is designated the critical overlap concentration.[130] Since the intrinsic viscosity is essentially the volume occupied by a swollen polymer in solution, the critical overlap concentration ($c^*$) should ideally be the exact reciprocal value of the intrinsic viscosity. The dimensionless product of the intrinsic viscosity and the concentration, $[\eta]c$ is referred to as the Berry number, *Be*.[131] The significance of the Berry number arises from the fact that for a solution to have chain entanglements, *Be* should be greater than 1. A *Be* value of 1 represents the threshold between dilute solutions (with isolated molecules) and semidilute solutions in which the molecules mutually overlap. Further increase in polymer concentration results in the onset of entanglement between polymer chains, and ideally the overall concentration of polymer segments in solution becomes equal to the polymer segment concentration inside each swollen polymer chain. The onset of entanglement hypothetically begins when the overlap region between adjacent molecules is equal in dimension to the Kuhn length. Knowledge of these critical concentrations is essential to formulators of personal care products. For example, polymer films form only above the critical entanglement concentration. However, sprays break up into droplets best if the concentration is below the critical overlap concentration. When entangled polymers are subjected to extensional flow, the entanglements behave as temporary cross-links. Extensional flow causes the polymer segments between entanglements to stretch beyond their most probable length. This in turn causes the chain segments to behave as entropy springs that are driven to recover their original distances between entanglements. The entangled polymer network causes the liquid to jet instead of breaking up into spray droplets upon emerging from the liquid nozzle. In extreme circumstances, the energy of entropic recoil can give rise to small droplets that could flow through human respiratory pathways and become embedded in the lungs of spray users. Ideally, then, hairsprays should be formulated below the polymer critical overlap concentration but should reach the critical entanglement concentration upon reaching the hair in order to form fixative films between hair fibers. Determination of $c^*$ allows the formulator to target this narrow concentration window.

Measurement of the critical overlap concentration is relatively straightforward. One measures the viscosities of the given polymer in solution, $\eta$, over a range of polymer concentrations, $c$. The specific reduced viscosity at each polymer concentration can then be calculated from:

$$\text{Reduced Specific viscosity, } \eta_{sp} = \frac{\eta - \eta_o}{\eta_o c}$$

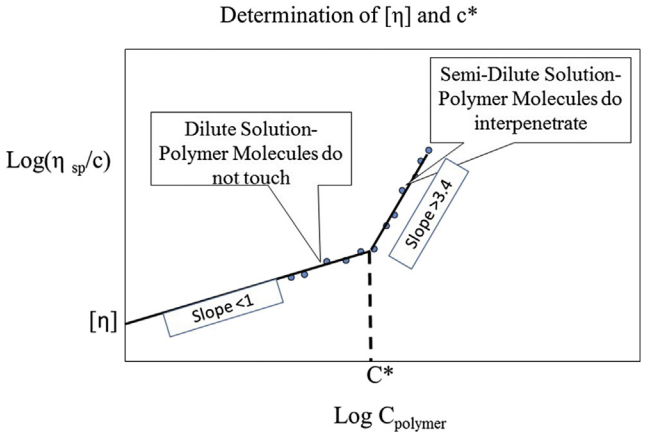



**FIGURE 3.21** The critical overlap parameter ($c^*$) can be determined by plotting the log of the reduced specific volume against the log of polymer concentration (see text). $c^*$ is the point at which there is a discontinuity of the curve. Below $c^*$ the slope should be 1 or less and above $c^*$ the slope should be equal to or greater than 3.4. Extrapolation to zero concentration of the dilute solution value gives the intrinsic viscosity. The product of intrinsic viscosity and concentration is termed the Berry number. For noninteracting polymers, the Berry number should be 1 at $c^*$. This provides a check on the value of $c^*$ that is determined solely by visual examination of the plot.

In dilute solution, $\eta_{sp}/c$ has been shown to be exactly proportional to concentration or less. In semidilute solutions, the viscosity shows a power law dependence, scaling with concentration exponent of 3.4 or higher.[132] A plot of log ($\eta_{sp}/c$) against log (polymer concentration) will be a line of slope 1 or less below $c^*$ and a slope of 3.4 or higher above $c^*$ (Fig. 3.21). The junction point between these lines is the critical overlap concentration. The value of $c^*$ can be checked by determining the concentration at which the Berry number, $[\eta]c$, becomes equal to 1. The underlying assumption of the Berry hypothesis is that the chains entangle without interactive contact. If there is an attractive interaction between the chains the experimentally determined $c^*$ will occur at a lower concentration than the Berry hypothesis, and if the polymer molecule segments mutually repel, $c^*$ will be a higher concentration than that predicted by $[\eta]c = 1$.

Ideally, determination of $c^*$ should be conducted in the complete solvent medium that is formulated in the desired product.

#### 3.2.6.7 Polymer/Disperion Rheology Basics

The rheology of cosmetic products is important in delivering the product correctly to the substrate, and sensory signaling of the products' attributes. Polymers and particulate thickeners are used extensively in personal care products to confer desired rheological characteristics. Ideal rheologies can be described as:

- *Newtonian:* Newtonian fluids are named after Sir Isaac Newton who postulated a differential form for the relation between shear stress and shear strain rate. Essentially, a Newtonian fluid is one in which the rate of flow is directly proportional to the stress applied to the liquid.
- *Pseudoplastic* fluids are liquids that show a decreased viscosity as the shear stress increases. The term *pseudoplastic* is synonymous with *shear thinning*. Shear thinning is desirable in products that are rich and viscous in the container but easily spread on the surfaces of the human body. Polymers function in such fluids to build structures under quiescent conditions that break down and flow upon application of shear, but recover their structure upon the cessation of shear. Cellulose ethers, such as hydroxyethylcellulose, are examples of polymers that provide pseudoplastic rheology to aqueous-based compositions. Dilatant fluids show increased viscosity as the shear stress is increased on the fluid.
- *Dilatant* fluids: Dilatancy can result from the following:
  - Orientation and structuring of rod- or platelike components. This occurs with wrinkle-hiding makeup when the mica plate concentration is high. Rapid application of such makeup causes the composition to crack on the surface of skin.
  - Hydroclustering in which small groups of particles form "chains" when shear is applied to a suspension containing the particles.[133] Dispersions containing high concentrations of corn starch show hydroclustering. Stirred slowly, the particles move past each other and the material behaves like a low-viscous fluid. However, if the surface is impacted sharply, the material behaves transiently like a solid.
  - Deformation of spherical particles or globules, which allows an increase in linear dimensions, that in turn allows the particles to become part of a transient ordered structure. This can occur in formulations with high concentrations of microbeads.
  - Extensional elongation of entangled polymer molecules. In general polymeric systems are viscoelastic. They recover elastically like solids under rapidly applied impacts, but they creep and deform like liquid under the application of slow, steady stresses. If the concentration of entangled linear polymers is high, the solution will show stringy flow under slow extensional shear but will snap under rapid extension. Silly putty shows extensional dilatancy. Extensionally dilatant systems tend to form liquid jets rather than droplets upon exiting spray nozzles.
  - Disaggregation of tight aggregates to yield assemblies of solvated small particles. In high-concentration compositions of fumed silica, the silica particles can disaggregate under shear to yield structured assemblies. Such compositions pour easily from the container, but they resist spreading when rubbed firmly on skin. Despite their apparently low viscosity, disaggregating dilatant systems can be impossible to spray.
- *Yield stress* fluids (Ellis fluids, Bingham body fluids, Herschel–Bulkley fluids). These are systems that are sufficiently structured in the quiescent state to essentially behave as solids. However, the system flows when the applied shear stress exceeds a critical value, termed the "yield stress." The effect of yield stress can be demonstrated by comparing whipped cream and honey. Upon stirring, honey gives more resistance to flow and, therefore, seems to be more viscous. However, if the two are left standing, honey flattens and flows but whipped cream keeps its shape. This is because whipped cream is a *yield stress fluid* that behaves as a solid below the critical

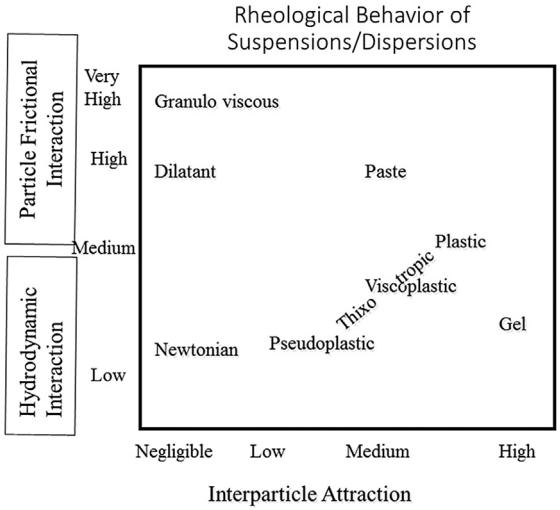



FIGURE 3.22 The rheology of dispersion depends upon the balance of hydrodynamic forces and attractive forces between the dispersed particles. This figure is a schematic map that shows the relative positions of different rheologies exhibited by dispersions.

yield stress, but honey is merely a viscous liquid that inevitably flows under an applied stress. Yield stress fluids are needed in formulations that need to stably suspend particles or droplets of immiscible liquid but yet flow easily during application. Carbomers, smectite clays, alginates, and xanthan gum, are examples of ingredients that can be used to form yield stress fluids. Simple yield stress fluids recover their yield stress instantaneously upon cessation of shearing.[134,135] Thixotropic yield stress fluids require relatively long times to recover after shearing.[136–138]

- Thixotropic fluids are sometimes described as "avalanche" fluids. Like snow in an avalanche, the structure is stable until it is critically disturbed. The critical disturbance causes a cascading loss of structure and an accelerating rate of shear driven by a constant stress (which in the case of an avalanche is the force of gravity on the snow mass).[139]
- In particulate dispersions the rheology is determined by a combination of the hydrodynamic and enthalpic interactions of the particles. A schematic summary map of the range of rheological characteristics is shown in Fig. 3.22.[140]

## 3.2.7 Basics of Dispersions

A dispersion consists of a finely divided particulate material suspended in an immiscible liquid. Emulsions are a special case of dispersions in which the dispersed phase is also a liquid. Dispersions and emulsions are not thermodynamically stable. They are pseudo stable, and the expectation for cosmetic products is that the discontinuous particulate phase can be maintained in stable suspension for several years.

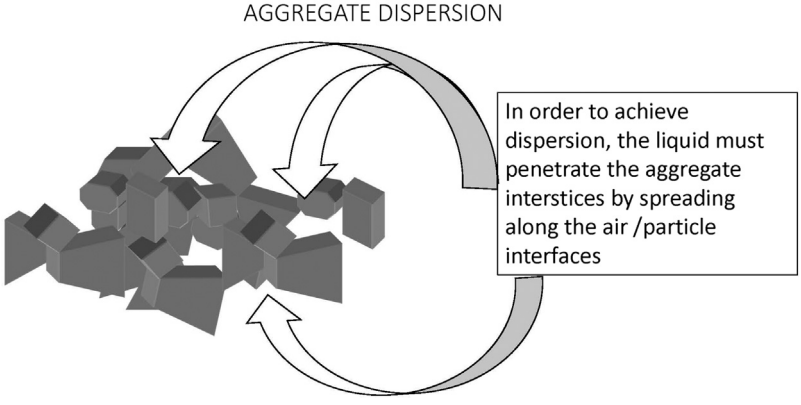



FIGURE 3.23 Spreading wetting of the capillary interstices in aggregates is necessary to achieve disaggregation and dispersion of the primary particles.

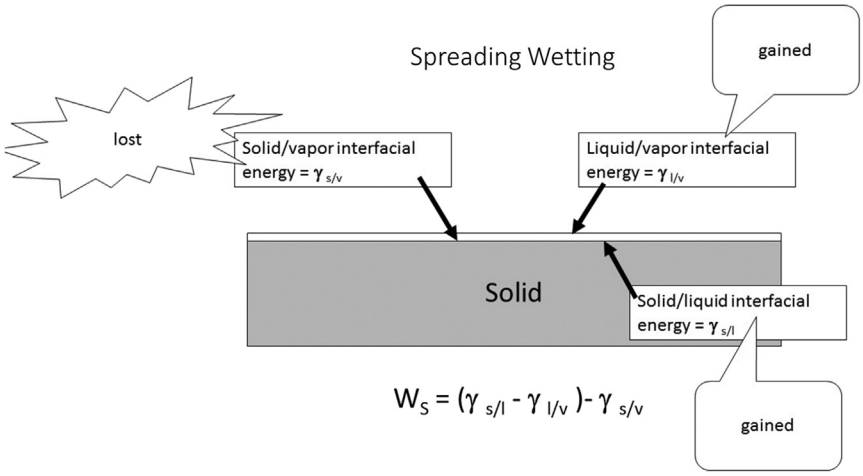



**FIGURE 3.24** When a liquid wets a solid surface by spreading, the liquid-vapor interface is lost and liquid-solid and liquid-vapor interfaces form. The work of spreading is the difference in free energies of the surfaces formed over the surface lost. The condition for spontaneous wetting is that this free energy difference should be negative.

Dispersion of finely divided solids in liquids cannot usually be achieved by mechanical mixing alone. The liquid must first thermodynamically wet the surface and interstices to penetrate the interparticle interstices and cause disintegration of the dry powder aggregates into their fundamental particles that are then uniformly distributed throughout the liquid by mechanical mixing (Fig. 3.23).

When a liquid spreads spontaneously on a solid surface, the solid−air interface is replaced by a liquid−air interface and a liquid−solid interface. Each of these interfaces has surface energies associated with them. Spontaneous creation of new surfaces requires that the total free energy of the surface(s) that are created should be less than the total free energy of the initial surfaces. This means that the work of spreading has to be negative for spontaneous spreading of a liquid on a solid surface (Fig. 3.24):

$$W_S = \left(\gamma_{s/l} - \gamma_{l/v}\right) - \gamma_{s/v}$$

where, $W_S$ is the work of spreading, $\gamma_{s/l}$ is the free energy of the solid/liquid interface, $\gamma_{l/v}$ is the free energy of the liquid−vapor interface, and $\gamma_{s/v}$ is the free energy of the solid−vapor interface.

In order to break up an aggregate, the liquid must do more than just spread; it must be forced into the pores of the aggregate. The pressure required to force a liquid into a capillary of radius, $r$, is:

$$P = -\left(2\gamma_{s/v} - \gamma_{s/l}\right)/r$$

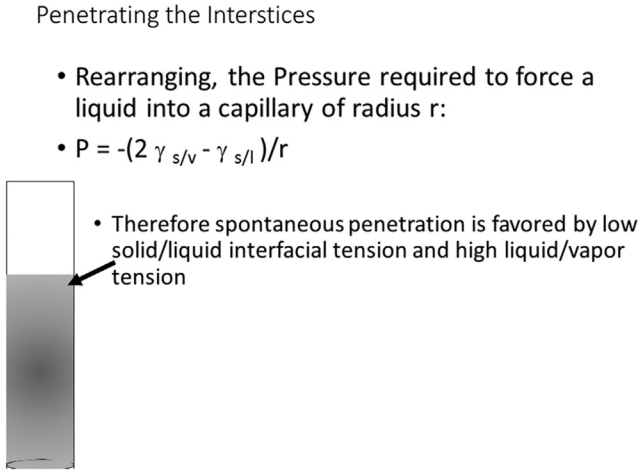



**FIGURE 3.25** Penetration of a liquid into a capillary pore is favored by high liquid-vapor tension and low solid-liquid tension (low contact angle).

Therefore spontaneous penetration is favored by low solid−liquid interfacial tension and high liquid−vapor tension, and small pore radius (Fig. 3.25) Most surfactants lower both surface tension and interfacial tension. Therefore, disaggregation depends on the use of specifically adsorbing surfactants that preferentially wet the solid−liquid interface rather than adsorb at the liquid−air interface. Since surfactants adsorb at all interfaces, specific adsorption at the solid−liquid interface ideally requires the choice of surfactants that adsorb by dipole−dipole interaction, Lewis acid−Lewis base interaction, or opposite charge attraction. The chosen surfactant should also be used sparingly to ensure adsorption at the desired interface only.

The rate of penetration of a cylindrical pore can be predicted from the Bell−Cameron−Lucas−Washburn equation:[141−143]

$$l^2 = \frac{Kt\gamma_{l/v}\cos\theta}{2\eta}$$

where, $l$ is the length penetrated in time $t$. $K$ is the capillary constant. The rate of penetration is increased by higher surface tension, lower contact angle, and lower solution viscosity.

### 3.2.7.1 *Electrical Charges Associated With Surfaces and Barriers to Aggregation*

When immersed in aqueous solution, all surfaces interact with the hydrogen ions or hydroxyl ions of the water and also with other ions in solution. These ions can adsorb (Fig. 3.26) or desorb, and an electrical potential is conferred on the surface. Adsorbed cations confer a positive charge to the surface, and adsorbed anions confer a negative charge to the surface. Soluble counterions are driven by chemical potential to diffuse away from the surface but are held in the vicinity by electrochemical potential attraction induced by the oppositely charged adsorbed ions. As a result, the counterions reside in a diffuse layer proximate to the surface. This arrangement of ions at the interface is often termed "the diffuse double layer." This balance between chemical and electrochemical potential determines the position of distribution of counterions proximate to the surface. The balance between chemical and electrochemical potential is a Gibbs−Donnan equilibrium.[144]

If the pH is raised by adding more hydroxyl ions, the chemical potential drive is decreased and the distribution of counterions favors more electroneutralization of the surface potential, and if excess base is added, the surface charge will reverse in sign, from positive to negative. If acid is added, the surface will become positively charged.

Every surface has a characteristic point of zero charge at a certain pH (Fig. 3.27). Above this pH value the surface will have a negative potential, and below the pH of zero charge the surface will have a positive potential.

Dispersion stability relies upon net repulsive forces between the dispersed particles. Attractive forces between the particles can arise from induced dipole-induced dipole (London or van der Waals force) interactions, dipole-induced

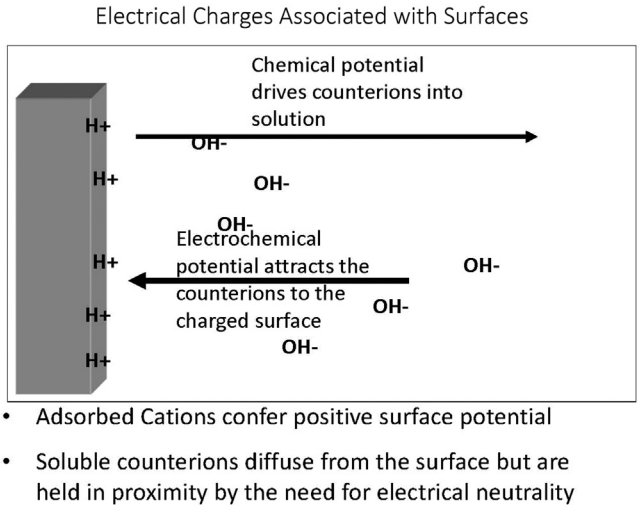



FIGURE 3.26 In the presence of soluble ions, a Donnan equilibrium is set up at solid surfaces. The extent of the diffuse layer of counterions depends on the relative values of chemical potential of escape of the counterions into solution and electrochemical potential that attracts counterions to the changed surface. Increase in dissolved salt concentration lowers the chemical potential of escape and effectively decreases to the extent of the diffuse layer.

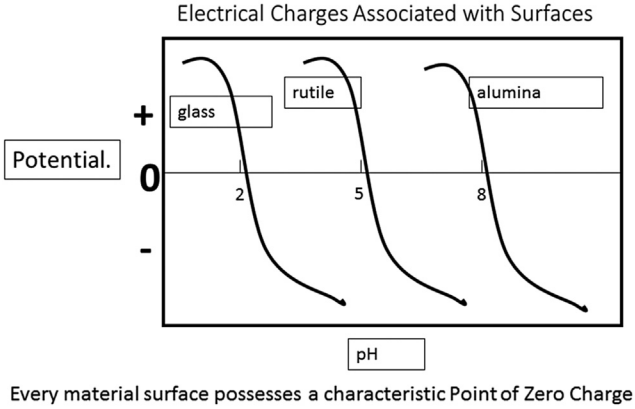



**FIGURE 3.27** Every surface has a unique overall point if zero charge. Below the pH of zero charge the surface is positively charged, and above the point of zero charge the surface is negatively charged.

dipole, or dipole−dipole (Debye) interactions, opposite charge interaction, or hydrophobic interaction. Solvation acts against interparticle attraction. While van der Waals forces are usually assumed to be weak between molecules, their additive effects can render them strong and long range for interparticle interaction. For example, for a colloidal particle, each atom or molecule of one particle attracts every atom in every adjacent particle. Each particle has $10^6$−$10^{10}$ atoms. The net effect of adding a myriad of possible atomic interactions is a generation of long-range attraction (5−10 nm) between particles that is of considerable strength.

Electrical colloidal stability of particles can be provided by:

- anionic, cationic, nonionic surfactants
- incorporation of ionic moieties ionic monomers
  - For example copolymerization of latex with ionic monomers
- interfacially adsorbed polyelectrolytes

#### 3.2.7.1.1 Stabilization of Dispersions by the Electrical Double Layer; DLVO Theory

Derjaguin, Landau, Verwey, and Overbeek (DLVO) theory[145−147] explains the stability of colloidal suspensions in terms of the balance of attractive van der Waals forces and electrostatic repulsive forces (Fig. 3.28). Dispersed particles exhibit Brownian motion, which can cause the particles to collide. At very close distances between the particles, attractive forces dominate, and if the particles approach these close distances, they will aggregate. However, DLVO theory shows that at more intermediate distances, as the diffuse double layers overlap there is an energy barrier between the particles. If the Brownian motion between the particles cannot overcome the energy barrier, the particles remain suspended.

DLVO theory explains why colloidal suspensions flocculate and aggregate upon addition of salt to the aqueous phase. Addition of salt increases the ionic strength of the solution surrounding the particles. This decreases the

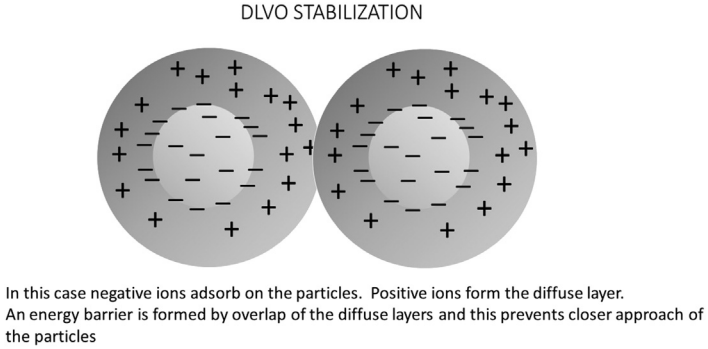



**FIGURE 3.28** Colloid particles can be prevented from aggregating by repulsion between the ionic diffuse double layers.

chemical potential (escaping tendency) of the counterions, and as a consequence the diffuse double layer shrinks as the position of Donnan equilibrium is changed to favor electrochemical potential attraction between the particles and the counterions. Shrinkage of the diffuse layer causes the intervening energy barrier to be lowered. If the barrier is lowered below the force of the van der Waals attraction between the particles, the particles are driven to aggregate.

#### 3.2.7.1.2 Steric Stabilization of Dispersions by Adsorbed Polymer

Dispersions can be sterically stabilized by adsorbed layers of soluble polymer.[148,149] In this case the adsorbed polymers form a configurational entropic barrier to overcome the forces of van der Waals attraction between the particles. Steric stabilization depends upon the polymers being anchored strongly to the particle surface in a layer that essentially covers the entire surface. As particles encounter each other, overlap of the polymer layers on the respective particles causes an increase in local polymer concentration, which restricts the range of available polymer segment configurations, which lowers the system entropy. The resulting entropy barrier prevents flocculation. This entropic barrier is effective only at concentrations below the critical overlap concentration because the intermolecular and intramolecular polymer segments become self-similar in an entangled polymer system above $c^*$. As a consequence, the driving force to separate the particles could be lost. For this reason, steric stabilizers are typically low molecular weight polymers that would have an elevated $c^*$. Many nonionic surfactants work by steric stabilization exerted by soluble PEG units.

Steric stabilization has several advantages over charge stabilization:

- Insensitivity to dissolved salts
- Applicable in nonaqueous solvents
- Effective over particle concentrations from very low to high
- Flocculation on demand and reversibility of flocculation by changing the "goodness" of the solvent (see polymer solubility theory, Section 2.6.1)

Adsorbed polyelectrolytes can give rise to electrosteric stabilization, which simultaneously confers both steric and DLVO stabilization.[150]

Nonadsorbing polymers can also stabilize particulate suspensions by a process termed "depletion stabilization."[151] In this case, the particles are held apart by the uniformity of polymer concentration and osmotic competition between the dissolved polymer and the suspended colloid. Essentially, the attractive forces acting between a particle and its surrounding polymer molecules are greater than the forces of the attraction between neighboring particles.[152,153]. Depletion stabilization is illustrated in Fig. 3.29A–D.

Depletion stabilization can be effective in the semidilute regime and it is favored by rodlike polymer molecules.[154]

On the other hand, high-molecular-weight polymers can osmotically compete for the available solvent, and they tend to give rise to depletion flocculation rather than stabilization.[155,156]

### 3.2.7.2 *Coalescence*

At high packing fraction of particles, the barriers eventually fail and aggregation occurs. If the particles are soft (viscoelastic), coalescence may occur. The process of coalescence has been extensively studied by scientists attempting to understand the process of film formation from latex paints and the coalescence of liquid droplets.[157] For monodisperse spherical particles above a volume fraction of 0.74, the spheres cannot hold spherical geometry and simultaneously fill the available volume. Just like foams, above this volume ratio, the particle faces flatten and the system becomes polyhedral. Sharp corners develop and the curvature at the corners causes the Laplace pressure to be higher at the corners than on the rest of the surface ($\Delta P = 2\gamma/r$) (Fig. 3.30). Additionally, if the particle is being stabilized by surfactant, the curvature of the interface causes an inhomogeneous distribution of the adsorbed surfactant layer and this leads to instability. The system pulls itself to its lowest energy state at the "corners" by coalescing to reduce the surface area.

Additionally, if the liquid medium between the particles evaporates, then the last vestiges of solvent in the drying front will create capillary pressure that will contribute to particle deformation if the particles can lose shape by viscous flow or creep.[158–160] The forces that promote particle deformation comprise:[161,162]

- van der Waals, $F_{vw}$
- gravity, $F_G$
- surface tension, $F_S$
- capillary forces $F_C$

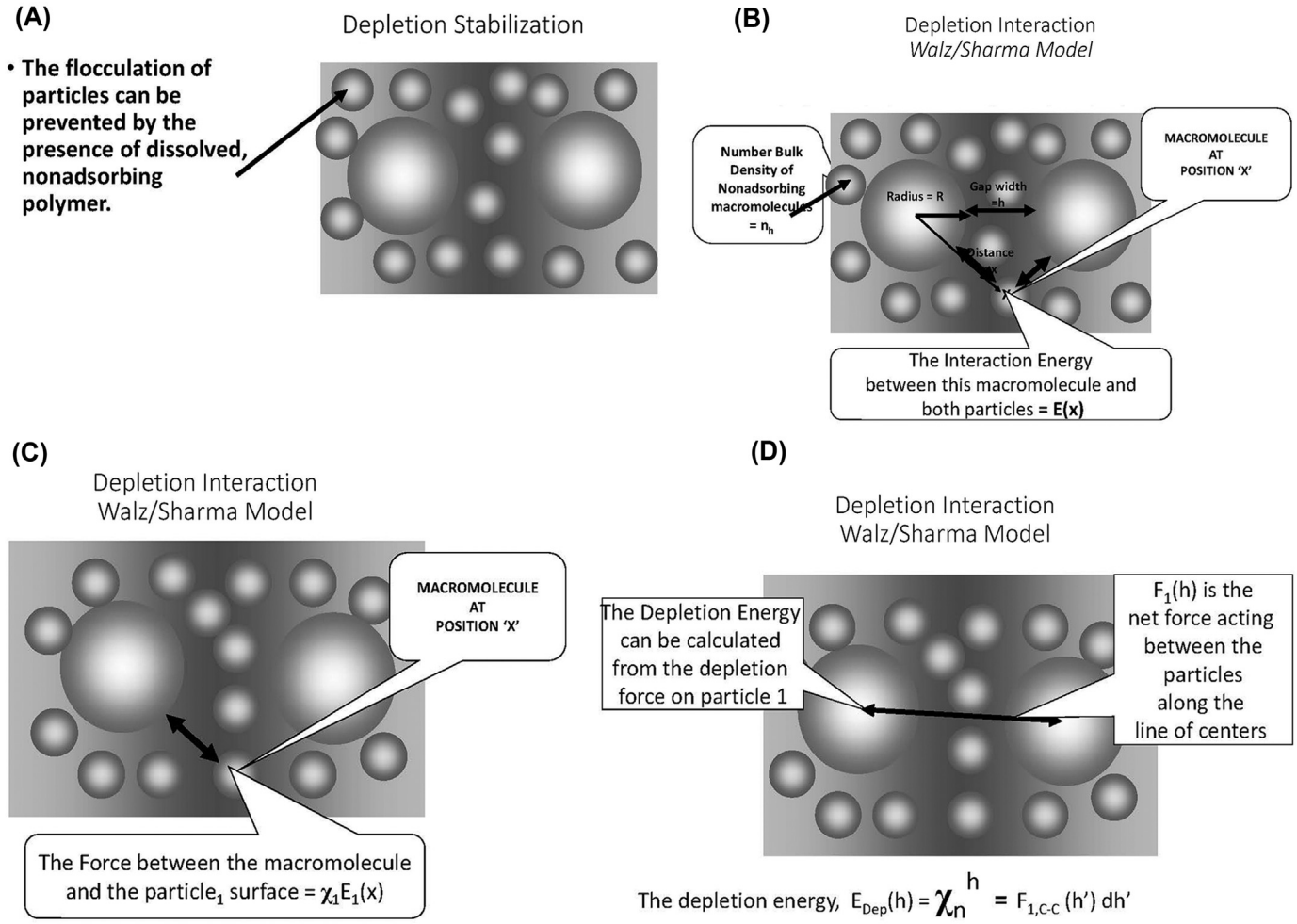



**FIGURE 3.29** (A–D): The sum of the interactions between dispersed particles and nonadsorbing dissolved polymer can result in colloidal stability of the dispersed particles (see text).

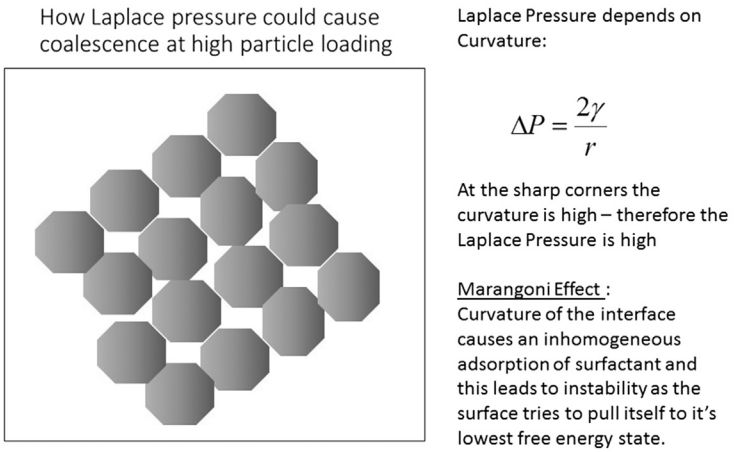



FIGURE 3.30 At high volume fractions (for example, above 0.74 for monodisperse spherical particles), the spheres can no longer retain spherical symmetry; they become polyhedral. The corners of the polyhedral have higher curvature that the rest of the particle and Laplace pressure at the corners can drive the onset of coalescence.

Forces that resist particle deformation include:

- electrostatic repulsion, $F_{EL}$
- elastic resistance to flow, $F_R$

Adsorbed polyelectrolyte layers suppress the interdiffusion[163] of polymers that is necessary for latex coalescence but unneutralized carboxyl groups enhance the rate of interdiffusion,[164] presumably due to intermolecular dipole–dipole interaction and hydrogen bonding.

### 3.2.8 Basics of Emulsions

Emulsions are dispersions of one liquid in a second immiscible liquid. Oil-in-water (o/w) emulsions consist of oil droplets dispersed in water, and water-in-oil (w/o) emulsions consist of water droplets in oil. The factors in emulsion stability are similar to those of dispersions: DLVO and polymeric stabilization. In addition, for personal care and household emulsions, stabilization by lyotropic liquid crystals and amphipathic microgels are important, especially when stimuli-responsiveness is desired to cause rapid coalescence as compositions are applied to substrates.

There are two main types of instability for emulsions: (1) creaming or sedimentation, in which the emulsion droplets remain intact but they float or sediment under the influence of gravity; and (2) coalescence in which the liquids separate as distinct liquid layers. Flocculation and creaming often precede coalescence.

Emulsions are formed by perturbing the interface between the two liquids. This sets up a series of sinusoidal oscillations at the interface. If the less-dense phase is accelerated into the denser phase, the oscillations will be damped and the system will remain as two bulk-separated liquids. If the denser phase is accelerated into the less-dense phase, the oscillations will grow into surface projections, which will finger into the less-dense phase and break into droplets by Rayleigh–Taylor instability,[165] and a transient emulsion will form. Lowering of the interfacial tension will favor emulsion formation. Surfactants are added to the emulsion system to achieve this purpose. The surfactant concentration is normally greater than the CMC. Therefore, like foams, the kinetics of demicellization and diffusion of surfactant to the interface must be faster than the rate of formation of the interface. First, the available monomers adsorb onto the freshly created interface. Then, additional monomers must be provided by the breakup of micelles. Especially when the free monomer concentration is low, as indicated by a low CMC, the micellar breakup time is a rate-limiting step in the supply of monomers.[71] The importance of micelle kinetics can be shown by a simple, yet elegant experiment. For some nonionic surfactants, the micelle kinetics are too slow to allow emulsion formation by shaking a vessel containing the surfactant, water, and oil. If, however, oil is slowly injected into an aqueous solution of the same surfactant, emulsions can be formed because the interfaces expand sufficiently slowly to allow micelle disaggregation and diffusion of the surfactant to the expanding surface in sufficient quantities to adsorb and adequately lower the interfacial tension.

Once the emulsion is formed, it must be stabilized against creaming, sedimentation, and coalescence. It must be stated at this point that emulsions are not thermodynamically stable systems. The best we can do is to delay instability for the shelf life of an emulsion product.

- Stabilization against coalescence can be achieved by DLVO electrical repulsion or by steric stabilization. DLVO stabilization applies usually to oil in water (O/W) emulsions with low loadings of oil droplets. Steric stabilization can be achieved by adsorption of nonionic surfactant to the oil/water interface. In this case, emulsion stability is achieved only if the interface is completely covered by a self-assembled adsorbed surfactant layer. This condition severely limits the number of possible emulsifier systems that will provide stability, and some empirical rules have been developed to guide the search for appropriate emulsifier systems. Griffin developed a system that attempted to balance the hydrophilic and hydrophobic components of nonionic surfactants to find a perfect match for the oil being emulsified.[166,167] This system, called the hydrophilic-lipophilic balance (HLB) system is a semiempirical procedure for selecting an appropriate emulsifier or blend of emulsifiers to prepare an emulsion. The concepts upon which it is based are:
  - an emulsifier molecule contains both hydrophobic and hydrophilic groups
  - the ratio of hydrophilic to hydrophobic should affect emulsification
  - for any particular type of emulsion, there is an optimum HLB for stability
- Griffin reasoned that surfactants have an HLB value, oils and waxes have an HLB requirement, and the HLB value should be matched with the HLB requirement to achieve emulsification. Griffin calculated the HLB value of nonionic surfactants to be proportional to the ethoxy content of the surfactant. In fact, he set the HLB scale to range from 0 to 20, with a value of 20 representing 100% ethoxy content.

The selection of emulsifiers based on HLB is outlined in Fig. 3.31, which is reproduced from one of Griffin's early publications.[168]

Practical Emulsions

| HLB Range | Water dispersibility | Suitable Application |
|---|---|---|
| • 1-4 | nil | |
| • 3-6 | poor | w/o emulsifier |
| • 6-8 | milky dispersion(agitated) | wetting agent |
| • 8-10 | stable milky dispersion | wetting agent, o/w emulsifier |
| • 10-13 | translucent to clear | o/w/emulsifier |
| • 13 | clear solution | o/w emulsifier, solubilizing agent |

**FIGURE 3.31** The performance of emulsifiers depends upon the hydrophilic:lipophilic balance. High HLB emulsifiers are useful for oil-water emulsions. Low HLB emulsifiers are useful for water-oil emulsions.

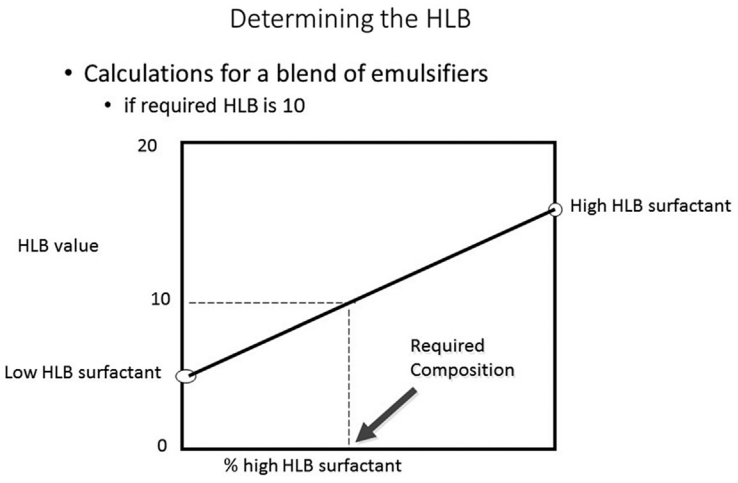



**FIGURE 3.32** The desired HLB can be achieved by mixing high HLB and low HLB emulsifiers proportionately.

Determining the HLB Experimentally

- HLB KIT

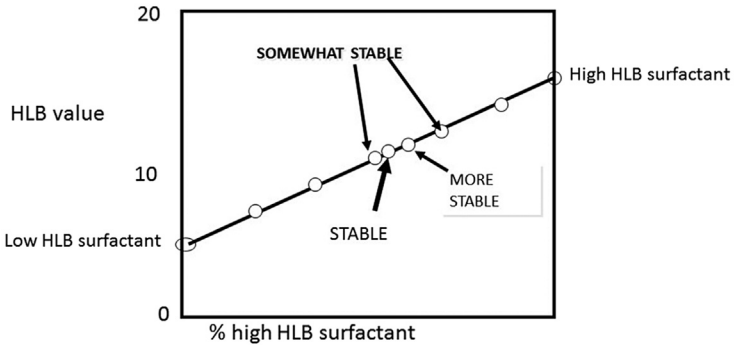



**FIGURE 3.33** The HLB for best emulsification can be found by interpolation.

The HLB Requirement of Oils

| Class | Required HLB |
|---|---|
| Vegetable oil | 6 |
| Silicone Oils | 5-10 |
| Petroleum Oils | 10 |
| Emollient Oils | 12 |
| Fatty Acids and Alcohols | 14-15 |

**FIGURE 3.34** Typical HLB values of oils by class.

As a rule of thumb, it is better to use a mixture of high HLB and a low HLB emulsifier rather than a pure emulsifier of intermediate HLB. The HLB system is purely additive, and the HLB of the mixture is readily calculated from the relative proportions of each surfactant in the mixture (Fig. 3.32).

Selection of an emulsifier system can be determined experimentally by mixing high- and low-HLB emulsifiers, testing their ability to emulsify the desired oil/water composition, and interpolating the ratios of surfactants until the best emulsifier is found (Fig. 3.33).

A useful rule of thumb in using mixed emulsifiers is to use Bancroft's rule that a surfactant that preferentially partitions into water favors the formation of O/W emulsions and that a surfactant that preferentially partitions into oil favors the formation of water-in-oil (W/O) emulsion. An extension of this rule states that the emulsifier should be placed in the phase in which it is most soluble. Therefore, in mixed emulsifier system it is advisable to dissolve the high-HLB surfactant in the water phase and the low-HLB surfactant in the oil phase and then combine the two phases to make an emulsion. This method apparently gives a good chance of the high- and low-HLB emulsifiers to combine in an appropriate ratio at the interface as it forms.

The HLB requirements of different oil classes are shown in Fig. 3.34.

Aqueous solutions of nonionic emulsifiers often show a cloud point when they are heated above a critical temperature. The cloud point corresponds to a phase inversion that results from spinodal decomposition that renders the nonionic surfactant more hydrophobic. Shinoda reasoned that this phase behavior of nonionic surfactants was akin to the phase inversion observed in some emulsions as the temperature was raised above a critical point, with the difference that the emulsion was formed by macroscopic mixing whereas the nonionic surfactant separated microscopically at the cloud point. Shinoda then reasoned that such microscopic separation would result in emulsion stability, and he recommended the formation of emulsions by mixing at temperatures above the phase inversion temperature then cooling through the phase inversion temperature.[169] Today most commercial emulsions are manufactured by Shinoda's method of phase inversion. The phase inversion of an emulsion can be determined by conductance or by viscosity measurement. The conductivity increases and the viscosity goes through a maximum as an emulsion is cooled through the phase inversion temperature.

#### 3.2.8.1 Emulsion Stability

Emulsion droplets are mutually attracted by van der Waals forces similarly to the colloidal dispersions discussed previously. However, unlike particles that merely aggregate, emulsions undergo irreversible coalescence if the droplets approach each other sufficiently closely to fall into the primary potential energy minimum. Von Smoluchowski expressed as spontaneous coalescence upon encroaching the "sphere of action" distance around each droplet.[170]

As discussed earlier, lowering the O/W interfacial tension is useful in forming emulsions but this is not sufficient to provide emulsion stability for the shelf life of a product. Likewise, decreasing the rate of droplet diffusion by merely increasing the viscosity of the continuous phase merely slows Brownian motion and delays the inevitable onset of coalescence. Emulsion stability is achieved by providing sufficient repulsion between the droplets. This can be done for "dilute" emulsions by DLVO electrical repulsion. However, a physical barrier around the droplets is more effective.[171]

Such a barrier can be formed by "wrapping" lamellar phase around the droplets,[172,173] and this form of stabilization is common in personal care products. Lamellar liquid crystal exhibits a yield stress that arises from the mutual repulsion between the surfactant layers, and this yield stress is postulated to provide the barrier to coalescence. However, for such lamellar-stabilized emulsions, the oil phase coalesces at high oil loading. This leads to the following questions:

- Does the Laplace pressure inside the droplets exceed the modulus of the stabilizing layer?
- Is there insufficient stabilizing phase to cover the entire interface?
- Does the oil penetrate the lamellar layer?
  - Soften it?
  - Modify the repulsion between adjacent lamellae?
    - Thereby lower the yield stress of the barrier

There is still a challenge in exactly correlating interfacial rheology with bulk stability of emulsions due to the heterogeneity of the adsorbed films.[174]

Amphipathic block copolymers have been advanced as steric stabilizers for emulsions.[175] In a tightly adsorbed layer, polymers and nonionic surfactants are spatially constrained and this could cause the soluble segments to expand as brushes into the continuous phase, thereby enhancing stability against coalescence.[176]

Insufficient barriers are revealed when emulsions freeze. It is common for the aqueous phase to freeze and the oil phase to remain liquid. Freezing of the aqueous phase essentially concentrates the oil droplets into a smaller volume, thereby increasing the local loading, which can lead to barrier failure and coalescence.

#### 3.2.8.2 Ostwald Ripening

Ostwald ripening[177] is an insidious process by which smaller droplets disappear and larger droplets grow by the process of the oil molecules diffusing through the continuous phase from the small droplets. The driver for this activity is the fact that the Laplace pressure inside smaller drops is higher than the pressures inside larger drops. The resulting higher energy of the smaller droplets becomes the driving force for oil molecules to escape from them and merge with larger droplets. Ostwald ripening cannot be stopped by anticoalescence barriers. The escape of the oil can sometimes be halted by intentionally including a slightly more soluble oil in the continuous phase as a sacrificial solute to "damp" the escaping tendency of the oil from the droplets.

#### 3.2.8.3 Prevention of Creaming and Sedimentation

In real emulsions, the barriers around droplets can prevent coalescence but they rarely prevent creaming or sedimentation. Individual droplets will separate at a rate consistent with Stokes' law:

$$V = \left[d^2(\Delta\rho)g\right]/18\eta$$

where $V$ is the velocity of flotation or sedimentation, $d$ is the drop diameter, $\Delta\rho$ is the density difference between the two fluids, $g$ is the acceleration due to gravity, and $\eta$ is the viscosity of the fluid of the external phase.

In real emulsions however, hydrodynamic interactions between the droplets cause deviations from Stokes' law.

Polyelectrolyte microgel thickeners are useful to maintain homogeneous dispersion of the barrier-stabilized oil droplets. For example, cross-linked poly(acrylic acid) thickeners are useful to build yield stress in the continuous phase and thereby to hold the droplets securely in place. These molecules when neutralized osmotically swell[178–180] a thousand-fold to fill the entire volume of the aqueous phase. The microgels pack in solution to form a

microstructure that resembles packed microsponges with water channels between.[181,182] This microarchitecture provides yield stress materials with shear-thinning properties.

Hydrophobically modified microgel thickeners can be primary emulsifiers in their own right. The emulsification mechanism is entrapment within hydrophobic domains within the packed microgel architecture.[183,184] This mechanism of emulsification enables these emulsifiers to stably emulsify essentially any oil, and to release the oil upon receiving a stimulus of perspiration ions, which disturb the polyelectrolyte Donnan equilibrium and cause catastrophic collapse of the microgels and release of emulsified oil to the skin.[185,186] Since this emulsification mechanism needs no, or little, added emulsifier, these microgel emulsifiers are useful in, for example, waterproof sports sunscreens and lotions for sensitive skin.[86,187,188]

### 3.2.9 Conclusions

This chapter surveyed some of the important physical science fundamentals for the design and use of cosmetics and personal care products. Familiarity with these concepts is useful in formulating products, in scale-up, and in troubleshooting the sources of product problems and failures. A firm understanding of the basics helps the researcher and the marketer to know what is and what is not feasible at the outset of new product design.

## References


1. FD&C Act, CFR21., SEC 201(i), 21 U.S.C. United States Code, 2010 Edition title 21-food and drugs, Chapter 9-Federal Food, Drug, and Cosmetic Act Subchapter II — DEFINITIONS From the U.S. Government Printing Office, www.gpo.gov, https://www.gpo.gov/fdsys/pkg/USCODE-2010-title21/html/USCODE-2010-title21-chap9-subchapII.htm.
2. Lochhead RY. Shampoo and conditioner science. In: Evans T, Randall Wickett R, editors. *Practical modern hair science*. Allured Press Business Media; 2012 [Chapter 3].
3. Grice EA, Segre JA. The skin microbiome. *Nat Rev Microbiol* 2011;**9**(4):244–53. PMC. Web. 6 June 2016.
4. Emter R, Natsch A. The sequential action of a dipeptidase and a β-lyase is required for the release of the human body odorant 3-methyl-3-sulfanylhexan-1-ol from a secreted Cys-Gly-(S) conjugate by *Corynebacteria*. *J Biol Chem* 2008;**283**:20645–52.
5. Decreau RA, Marson CM, Smith KE, Behan JM. Production of malodorous steroids from androsta-5,16-dienes and androsta-4,16-dienes by *Corynebacteria* and other human axillary bacteria. *J Steroid Biochem Mol Biol* 2003;**87**:327–36.
6. Martin A, et al. A functional ABCC11 allele is essential in the biochemical formation of human axillary odor. *J Invest Dermatol* 2010;**130**:529–40.
7. The American Heritage® Science Dictionary. Retrieved June 06, 2016 from: Dictionary.com websitehttp://www.dictionary.com/browse/sebum.
8. Marples M. *The ecology of the human skin*. 1965. Bannerstone House, Springfield, Illinois: Charles C Thomas.
9. Leeming JP, Holland KT, Cunliffe WJ. The microbial ecology of pilosebaceous units isolated from human skin. *J Gen Microbiol* 1984;**130**:803–7.
10. Marples RR, Downing DT, Kligman AM. Control of free fatty acids in human surface lipids by *Corynebacterium acnes*. *J Invest Dermatol* 1971;**56**:127–31.
11. Ingham E, Holland KT, Gowland G, Cunliffe WJ. Partial purification and characterization of lipase (EC 3.1.1.3) fromPropionibacterium acnes. *J Gen Microbiol* 1981;**124**:393–401.
12. Roth RR, James WD. Microbial ecology of the skin. *Annu Rev Microbiol* 1988;**42**:441–64.
13. Elias PM. The skin barrier as an innate immune element. *Semin Immunopathol* 2007;**29**:3–14.
14. Aly R, Shirley C, Cunico B, Maibach HI. Effect of prolonged occlusion on the microbial flora, pH, carbon dioxide and transepidermal water loss on human skin. *J Invest Dermatol* 1978;**71**:378–81.
15. Tanford C. *The hydrophobic effect: formation of micelles and biological membranes*. New Jersey: Wiley Interscience; 1980 [Chapter 1].
16. Frank HS, Evans MW. Free volume and entropy in condensed systems: iii. Entropy in binary liquid mixtures; partial molal entropy in dilute solutions; structure and thermodynamics in aqueous electrolytes. *J Chem Phys* 1945;**13**:507–33.
17. Traube J. Ueber die Capillaritätsconstanten organischer Stoffe in wässerigen Lösungen. *Justus Liebigs Ann Chem* 1891;**265**:27–55.
18. Willard Gibbs J. *American mathematician and physicist*. Yale College; 1839-1903.
19. Langmuir I. The constitution and fundamental properties of solids and liquids, II. Liquids. *J Amer Chem Soc* 1917;**39**:1848–906.
20. Mysels KJ. *Soap films: studies of their thinning*. Oxford: Pergamon Press; 1959.
21. McBain JW. Colloidal electrolytes: soap solutions and their constitution. *J Amer Chem Soc* 1920;**42**:426–60.
22. Tanford C. *The hydrophobic effect: formation of micelles and biological membranes*. New Jersey: Wiley Interscience; 1980. p. 85.
23. Hartley GS. *Aqueous solutions of paraffin-chain salts*. Paris: Hermann & Cie; 1936.
24. Shinoda K, Kunieda H, Arai T, Saijo H. Principles of attaining very large solubilization (microemulsion): inclusive understanding of the solubilization of oil and water in aqueous and hydrocarbon media. *J Phys Chem* 1984;**88**(21):5126–9.
25. Shinoda K, Yamaguchi N, Carlsson A. Physical meaning of the krafft point: observation of melting phenomenon of hydrated solid surfactant at the krafft point. *J Phys Chem* 1989;**93**:7216–8.
26. Tanford C. *The hydrophobic effect: formation of micelles and biological membranes*. New Jersey: Wiley Interscience; 1980. p. 57.
27. Israelachvili JN, Mitchell DJ, Ninham BW. Theory of self-assembly of hydrocarbon amphiphiles into micelles and bilayers. *Faraday Trans 2, J Chem Soc* 1976;**72**:1525–68.
28. Candau S, Khatory A, Lequeux F, Kern F. Rheological behaviour of wormlike micelles: effect of salt content. *J de Physique IV* 1993;**03**(C1):197–209.

29. Cacace MG, Landau EM, Ramsden JJ. The Hofmeister series: salt and solvent effects on interfacial phenomena. *Quart Rev Biophys* 1997;**30**: 241–77.
30. Buhler E, Munch JP, Candau SJ. Dynamical properties of wormlike micelles: a light scattering study. *J Phys II Fr* 1995;**5**:765–87.
31. Berret JF, Appell J, Porte G. Linear rheology of entangled wormlike micelles. *Langmuir* 1993;**9**(11):2851–4.
32. Rehage H, Hoffmann H. Rheological properties of viscoelastic surfactant systems. *J Phys Chem* 1988;**92**:4712–9.
33. Hoffmann H. Viscoelastic surfactant solutions. In: Herb CA, Prud'homme RK, editors. *Structure and flow in surfactant solutions. ACS symposium series*, vol. 578. American Chemical Society; 1994.
34. Hassan PA, Candau SJ, Kern F, Manohar C. Rheology of wormlike micelles with varying hydrophobicity of the counterion. *Langmuir* 1998;**14**: 6025–9.
35. Berret JF. Transient rheology of wormlike micelles. *Langmuir* 1997;**13**:2227–34.
36. Spenley NA, Cates ME, McLeish TCB. Nonlinear rheology of wormlike micelles. *Phys Rev Lett* 1993;**71**:939–42.
37. Cates ME. Theoretical modeling of viscoelastic phases, structure and flow in surfactant solutions. In: Herb CA, Prud'homme RK, editors. *ACS symposium series*, vol. 578. American Chemical Society; 1994.
38. Cates ME. Reptation of living polymers; dynamics of entangled polymers in the presence of chain-scission reactions. *Macromolecules* 1987;**20**: 2289–96.
39. Baker CA, Saul D, Tiddy GJT, Wheeler BA, Willis WE. Phase structure, nuclear magnetic resonance and rheological properties of viscoelastic sodium dodecyl sulfate and trimethylammonium bromide mixtures. *J Chem Soc Faraday Trans I* 1974;**70**:154–62.
40. Raghavan SR, Fritz G, Kaler EW. Wormlke micelles formed by synergistic self assembly in mixtures of anionic and cationic surfactants. *Langmuir* 2002;**18**:3797–803.
41. Oelschlager C, Wilenbacher N. Mixed wormlike micelles of cationic surfactant; effect of the cosurfactant chain length on the bending elasticity and rheological properties. In: Holmberg K, editor. *Surfaces & colloid chemistry*, vol. 2. Chichester: Wiley; 2002. p. 371–82.
42. Bangham AD, Horne RW. Negative staining of phospholipids and their structural modification by surface-active agents as observed in the electron microscope. *J Mol Biol* 1964;**8**(5):660–8.
43. Horne RW, Bangham AD, Whittaker VP. Negatively stained lipoprotein membranes. *Nature* 1963;**200**:1340 (4913).
44. Bangham AD, Horne RW, Glauert AM, Dingle JT, Lucy JA. Action of saponin on biological cell membranes. *Nature* 1962;**196**:952–5.
45. Cooke MJ, Pham T-A, Murray AM. *Conditioning shampoo comprising an aqueous conditioning gel phase in the form of vesicles*. Oct 6, 2011. U.S. Patent Application US20110243870 A1.
46. Friberg S. Liquid crystalline phases in emulsions. *J Colloid Interface Sci* October 1971;**37**(2):291–5.
47. Friberg SE, *Emulsion stability, emulsions — a fundamental and practical approach*. *NATO ASI series*, vol. 363. p. 1–24.
48. Friberg SE, Concepcion. Solans. Surfactant association structures and the stability of emulsions and foams. *Langmuir* 1986;**2**(2):121–6.
49. Friberg SE. Micelles, microemulsions, liquid crystals, and the structure of stratum corneum lipids. *J Soc Cosmet Chem* 1990;(41):155–71.
50. Hawkins J, Herve PJ, Murphy R, Hough L. *Structured suspending systems*. November 3, 2011. United States Patent Application 20110268683.
51. Garg G, Saraf S, Saraf S. Cubosomes: an overview. *Biol Pharm Bull* 2007 Feb;**30**(2):350–3.
52. Sherif S, Bendas ER, Badawy S. The design and evaluation of novel encapsulation technique for topical application of alpha lipoic acid. *J Adv Pharm Res* 2013;**4**(1):13–22.
53. Lynch ML, Spicer PT. *Functionalized cubic liquid crystalline phase materials and methods for their preparation and use*. December 2, 2003. United States Patent 6,656,385.
54. Ekwall P, Mandell L, Fontell K. Some observations on binary and ternary aerosol OT systems. *J Colloid Interface Sci* June 1970;**33**(2):215–35.
55. Kleinen J, Venzmer J. Streaming potential measurements to understand the rheological properties of surfactant formulations containing anionic and zwitterionic surfactant. *J Cosmet Sci* 2016;**67**:59–70.
56. Friberg SE, Lochhead RY, Blute I, Waernheim T. Hydrotropes —performance chemicals. *J Dispers Sci Tech* 2004;**25**(3):243.
57. Adam NK, Soc J. *Dye Colour* 1937;**53**:122.
58. Carroll BJ. Equilibrium conformations of liquid drops on thin cylinders under forces of capillarity. A theory for the roll-up process. *Langmuir* 1986;**2**:248–50.
59. Miller CA, Ramey KH. Solubilization-emulsification mechanisms of detergency. *Colloids Surfaces A; Physicochem Eng Aspects* 1993;**74**:169–215.
60. Lawrence SAC. The mechanism of detergence. *Nature* 1959;**183**:1491.
61. Stevenson DG. In: Durham K, editor. *Surface activity and detergency*. London: MacMillan; 1961 [Chapter 6].
62. Carroll BJ. The kinetics of solubilization of nonpolar oils by nonionic surfactant solutions. *J Colloid Interface Sci* 1981;**79**:126–35.
63. Oh SG, Shah DO. The effect of micellar lifetime on the rate of solubilization and detergency in sodium dodecyl sulfate solutions. *J Am Oil Chemists' Soc* 1993;**70**:673–8.
64. Ata S, Ahmed N, Jameson GJ. Collection of hydrophobic particles in the froth phase. *Int J Min Process* 2002;**64**:101–22.
65. Pugh RJ. Foams and foaming. In: Holmberg K, editor. *Handbook of applied colloid and surface chemistry*. New York: John Wiley & Sons; 2001.
66. Myers D. Physical properties of surfactants used in cosmetics. In: Rieger MM, Rhein LD, editors. *Surfactants in cosmetics*. New York, Basel: Marcel Dekker, Inc.; 1997 [Chapter 2].
67. Garrett PR. *The science of defoaming*. CRC Press; 2014. p. 5 [Chapter 1].
68. Gibbs JW. *The scientific papers*, vol. 1. New York: Dover; 1961. Originally from the collected works of J.W. Gibbs, Longmans Green, New York, vol. 1, 1928.
69. Lucassen J. Dynamic properties of free liquid films and foams. In: Lucassen-Reynders EH, editor. *Anionic surfactants, physical chemistry of surfactant action. Surfactant sci. series*, vol. 11. New York: Marcel Dekker; 1981. p. 217 [Chapter 6].
70. Garrett PR. *The science of defoaming*. CRC Press; 2014. p. 6 [Chapter 1].
71. Patist A, Oh SG, Leung R, Shah DO. Kinetics of micellization: its significance to technological processes. *Colloids Surfaces A Physicochem Eng Aspects* 2001;**176**:3–16.
72. Fainerman VB, Lucassen-Reynders EH, Miller R. Adsorption of surfactants and proteins at fluid interfaces. *Colloids Surfaces A Physicochem Eng Aspects* 1998;**143**(2–3):141–65.
73. Karakashev S, Manev E, Nguyen A. Interpretation of negative values of the interaction parameter in the adsorption equation through the effects of surface layer heterogeneity. *Adv Colloid Interface Sci* 2004;**112**:31–6.

74. Koelsch P, Motschmann H. Relating foam lamella stability and surface dilational rheology. *Langmuir* 2005;**21**:6265–9.
75. Ma B, Zhang L, BaoyuGao, Zhang L, Zhao S, Yu JY. Interfacial dilational rheological property and lamella stability of branched alkyl benzene sulfonates solutions. *Colloid Polym Sci* 2011;**289**:911–8.
76. Regismond STA, Winnik FM, Goddard ED. Surface viscoelasticity in mixed polycation anionic surfactant systems studied by a simple test. *Colloids Surfaces, A Physicochem Eng Aspects* 1996;**119**:221–8.
77. Davies JT, Rideal EK. *Interfacial phenomena*. New York and London: Academic Press; 1961. p. 9–10.
78. https://commons.wikimedia.org/wiki/File%3ALaplace_pressure_experimental_demonstration.ogv By Jubobroff (Own work) [CC BY 3.0 (http://creativecommons.org/licenses/by/3.0)], [via Wikimedia Commons from Wikimedia Commons].
79. Stone HA, Koehler SA, Hilgenfeldt S, Durand M. Perspectives on foam drainage and the influence of interfacial rheology. *J Phys Condens Matter* 2003;**15**:S283–90.
80. Miles GD, Shedlovsky L, Ross J. Foam drainage. *J Phys Chem* 1945;**49**(2):93–107.
81. Plateau J. *Statique Experimentale et Theorique des Liquides Soumis aux Seules Forces Moleculaires*. Paris: Gauthier-Villars; 1873.
82. Bhakta A, Ruckenstein E. Decay of standing foams: drainage, coalescence and collapse. *Adv Colloid Interface Sci* 1997;**70**:1–124.
83. Koehler SA, Hilgenfeldt S, Stone HA. *Phys Rev Lett* 1999;**82**:4232. R6307 -6308, 1999.
84. Durand M, Martinoty G, Langevin D. Liquid flow through aqueous foams: from the plateau border-dominated regime to the node-dominated regime. *Phys Rev E* 1999;**60**.
85. Regismond STA, Winnik FM, Desmond Goddard E. Stabilization of aqueous foams by polymer/surfactant systems: effect of surfactant chain length. *Colloids Surfaces A Physicochem Eng Aspects* 1998;**141**:165–71.
86. Rulison CJ, Lochhead RY. Kinetic study of the adsorption of nonionic and anionic surfactants and hydrophobically modified water-soluble polymers to oil-water interfaces. In: Sharma Ravi, editor. *Surfactant adsorption and surface solubilization*. *ACS symposium series*, vol. 615; 1995. p. 280–315.
87. Lochhead RY, Welch CF. Effect of hydrophobically-modified hydroxyethylcellulose on the phase morphology of a model surfactant mesophases system in the liquid crystal regime. *Polym Mater Sci Eng* 2001;**85**:67. American Chemical Society.
88. Lochhead RY, McConnell- Boykin CL, Haynes C. Interaction of hydrophilic polymers with smectite clays. *Polym Mater Sci Eng* 2001;**85**:419. American Chemical Society.
89. Friberg SE, Ahmad SI. Liquid crystals and the foaming capacity of an amine dissolved in water and p-xylene. *J Colloid Interface Sci* 1971;**35**:175.
90. Friberg SE, Blute I, Kunieda H. *Langmuir* 1986;**2**:659.
91. Shrestha LK, Saito E, Shrestha RG, Kato H, Takase Y, Aramaki K. Foam stabilized by dispersed surfactant solid and lamellar liquid crystal in aqueous systems of diglycerol fatty acid esters. *Colloids Surfaces A Physicochem Eng Aspects* 2007;**293**:262–71.
92. Friberg SE, Chang S, Greene WB, Gilder RV. *J Colloid Interface Sci* 1984;**101**:593.
93. Shrestha LK, Shrestha RG, Sharma SC, Aramaki K. Stabilization of nonaqueous foam with lamellar liquid crystal particles in diglycerol monolaurate/olive oil system. *J Colloid Interface Sci* 2008;**328**:172–9.
94. Jubobroff. https://upload.wikimedia.org/wikipedia/commons/thumb/3/38/Marangoni_effect_experimental_demonstration.ogv/854px–Marangoni_effect_experimental_demonstration.ogv.jpg.
95. Marangoni C. *Sull'espansione delle goccie d'un liquido galleggianti sulla superficie di altro liquid (On the expansion of a droplet of a liquid floating on the surface of another liquid)*. Pavia, Italy: fratelli Fusi (Fusi brothers); 1869.
96. Bikerman J. *Foams*. Springer Verlag; 1973.
97. Ross S. *Chem Eng Prog* 1967;**9**:63.
98. Garrett PR. *The science of defoaming*. CRC Press; 2014.
99. Ekwall P, Brown G. *Advances in liquid crystals*. New York: Academic Press; 1975.
100. Tiddy GJT. Surfactant-water liquid crystal phases. *Phys Rep* 1980;**57**(1):1–46.
101. Friberg S. *Lyotropic liquid crytals, advances in chemistry series*. Washington DC: American Chemical Society; 1997.
102. Alexandridis P, Olsson U, Lindman B. Phase behavior of amphiphilic block copolymers in water–Oil mixtures: the Pluronic 25R4–water–p-xylene system. *J Phys Chem* 1996;**100**(1):280–8.
103. Montalvo G, Valiente M, Rodenas E. Rheological properties of the L phase and the hexagonal, lamellar, and cubic liquid crystals of the CTAB/benzyl alcohol/water system. *Langmuir* 1996;**12**:5202–8.
104. Radimant S, Toprakcioglu C, McLeish T. Rheological study of ternary cubic phases. *Langmuir* 1994;**10**:61–7.
105. Al-Bawab A, Bozeya A, Friberg SE, Aiken PA. Geranyl acetate emulsions: surfactant association structures and stability. *J Dispersion Sci Technol* 2010;**31**:606–10.
106. Lance-Gomez ET, Gipp MM, Lochhead RY, Seaman Jr CE. *Single-phase soap compositions*. October 13, 1998. U.S. Patent 5,820,695; European Patent EP0785985A1, World Patent WO9607724A1.
107. Lance-Gomez ET, Gipp MM, Lochhead RY, Seaman Jr CE. *Single-phase soap compositions*. December 28, 1999. U.S. Patent 6,007,769.
108. Cao H-C, Pagnoul P. *Pourable detergent concentrates which maintain or increase viscosity after dilution with water*. July 13, 1999. U.S. Patent 5,922,664.
109. Hildebrand J, Scott R. *Regular solutions*. Englewood Cliffs, NJ: Prentice Hall; 1962.
110. Hildebrand J, Scott R. *Solubility of son-electrolytes*. third ed. New York: Reinhold; 1949.
111. Hansen CM. Universality of the solubility parameter, industrial and engineering chemistry. *Prod Res Dev* 1969;**8**:2–11.
112. Hansen CM. *Hansen solubility parameters; a user's handbook*. CRC Press; 2007.
113. Barton AF. *Handbook of solubility parameters and other cohesion parameters*. CRC Press LLC; 1991.
114. Bailey Jr FE, Koleske JV. *Poly(ethylene oxide)*. Academic Press; 1976 [Chapter 4].
115. Hammouda B, Ho DL, Kline S. Insight into clustering in poly(ethylene oxide) solutions. *Macromolecules* 2004;**37**:6932–7.
116. Kjellander R, Florin E. Water structure and changes in thermal stability of the system poly(ethylene oxide)-water. *J Chem Soc Faraday Trans* 1981;**1**(77):2053–77.
117. Chen H-L, Morawetz H. Fluorometric study of the equilibrium and kinetics of poly(acrylic acid) association with polyoxyethylene or poly(vinyl pyrrolidone). *Eur Polvmer J* 1983;**19**:923–8.

118. Shannon P, Lochhead RY. Polyacid microstructural effects in complexation with poly(vinyl pyrrolidone). *ACS Polym Prepr* March 1996;**37**(1). New Orleans, LA.
119. De Gennes PG. *Scaling concepts in polymer physics*. Ithaca, NY: Cornell University Press; 1979.
120. Einstein A. Eine neue bestimmung der molekuldimensionen. *Ann Phys* 1906;**19**:289–306.
121. Huggins ML. Molecular weights of high polymers. *Industrial Eng Chem* September, 1943:980–6.
122. Flory PJ. *Principles of polymer chemistry*. Ithaca, NY: Cornell University Press; 1953. p. 266–316.
123. Costello PA, Martin JK, Slark AT, Sherrington DC, Titterton A. Branched methacrylate copolymers from multifunctional monomers: chemical composition and physical architecture distributions. *Polymer* 2002;**43**:245–54.
124. Tomalia DA, Baker H, Dewald J, Hall M, Kallos G, Martin S, Roeck J, Ryder J, Smith P. A new class of polymers: starburst-dendritic macromolecules. *Polym J* 1985;**17**:117–32.
125. Mourey TH, Turner SR, Rubinstein M, Frechet JMJ, Hawker CJ, Wooley KL. Unique behavior of dendritic macromolecules: intrinsic viscosity of polyether dendrimers. *Macromolecules* 1992;**25**:2401–6.
126. Weber D, Foster S, Lochhead R, Derks F, Maini A. *Shampoo preparations*. June 19, 2008. EP 2010013383 (A).
127. Weber D, Foster S, Lochhead R, Derks F, Maini A. *Shampoo preparations*. June 19, 2008. EP 201120832 (A).
128. Derks F, Foster S, Lochhead R, Maini A, Weber D. *Volume up shampoos II, preparation*. December 3, 2013. US Patent 8597625.
129. Derks F, Foster S, Lochhead R, Maini A, Weber D. *Shampoo preparations*. May 17, 2016. United States Patent 9,339,449.
130. De Gennes PG. *Macromolecules* 1976;**9**(4):594–8.
131. Hager BL, Berry GC. *J Polym Sci Polym Phys Ed* 1982;**20**(5):911–28.
132. Colby RH, Fetters LJ, Funk WG, Graessley WW. *Macromolecules* 1991;**24**(13):3873–82.
133. Cheng X, McCoy JH, Israelachvili JN, Cohen I. Imaging the microscopic structure of shear thinning and thickening colloidal suspensions. *Science* 2011;**333**:1276–9.
134. Becu L, Manneville S, Colin A. *Phys Rev Lett* 2006;**96**:138302.
135. Ragouilliaux A, Ovarlez G, Shahidzadeh-Bonn N, Herzhaft B, Palermo T, Coussot P. *Phys Rev E* 2007;**76**:051408.
136. Coussot P, Tocquer L, Lanos C, Ovarlez G. *J Non-Newtonian Fluid Mech* 2009;**158**:85–90.
137. Ovarlez G, Krishan K, Cohen-Addad S. *Europhys Lett* 2010;**91**:68005.
138. Cheng DC-H. Thixotropy. *Int J Cosmet Sci* August 1987;**9**(4):151–91.
139. Cousot P, Ansey C. Rheophysical classification of concentrated suspensions and granular pastes. *Phys Rev E* 1999;**59**(4).
140. Cheng D,C-H. *Chemistry & industry*. 1980.
141. Washburn EW. The dynamics of capillary flow. *Phys Rev* 1921;**17**(3):273.
142. Lucas R. Ueber das Zeitgesetz des Kapillaren Aufstiegs von Flussigkeiten. *Kolloid Z* 1918;**23**:15.
143. Bell JM, Cameron FK. The flow of liquids through capillary spaces. *J Phys Chem* 1906;**10**:658–74.
144. Donnan FG. Theorie der Membrangleichgewichte und Membranpotentiale bei Vorhandensein von nicht dialysierenden Elektrolyten. Ein Beitrag zur physikalisch-chemischen Physiologie [[The theory of membrane equilibrium and membrane potential in the presence of a non-dialyzable electrolyte. A contribution to physical-chemical physiology]]. *Z für Elektrochem Angew Phys Chem* 1911;**17**(10):572–81.
145. Derjaguin B. A theory of interaction of particles in presence of electric double-layers and the stability of lyophobe colloids and disperse systems. *Acta Phys Chim* 1939;**10**:333–46.
146. Derjaguin B, Landau LD. Theory of the stability of strongly charged lyophobic sols and of the adhesion of strongly charged particles in solutions of electrolytes. *Acta Phys Chim* 1941;**14**:633–62.
147. Verwey EJW, Overbeek JTG. *Theory of stability of lyophobic colloids*. Elsevier Amsterdam; 1948.
148. Napper DH. *Polymeric stabilization of colloidal dispersions*. Academic Press; 1983.
149. Vincent B, Whittington S. In: Matijevic E, editor. *Colloid and surface science*. Plenum; 1982.
150. Fritz G, Schadler V, Willenbacher N, Wagner NJ. Electrosteric stabilization of colloidal dispersions. *Langmuir* 2002;**18**:6381–90.
151. Walz JY, Sharma A. *J Colloid Interface Sci* 1994;**168**:485.
152. Asakura S, Oosawa F. *J Polym Sci* 1994;**22**:1255.
153. Bolhuis P, Frenkel DJ. *J Chem Phys* 1994;**101**:9869.
154. Mao Y, Cates ME, Lekkerkerker HNW. Depletion stabilization by semidilute rods. *Phys Rev Lett* 1995;**75**:4548–51.
155. Feigin RI, Napper DH. Depletion stabilization and depletion flocculation. *J Colloid Interface Sci* 1980;**75**:525–41.
156. Jenkins P, Snowden M. Depletion flocculation in colloidal dispersions. *Adv Colloid Interface Sci* November 15, 1996;**68**:57–96.
157. Salmon J-B, Ajdari A, Tabeling P, Servant L, Talaga D, Joanicot M. In situ Raman imaging of interdiffusion in a microchannel. *Appl Phys Lett* 2005;**86**:094106.
158. Dillon RE, Matheson LA, Bradford EB. Sintering of synthetic latex particles. *J Colloid Sci* 1951;**6**:108–17.
159. Routh AF, Russel WB. Horizontal drying fronts during solvent evaporation from latex films. *AICHE J* 1998;**44**:2088–98.
160. Steward PA, Hearn J, Wilkinson MC. An overview of polymer latex film formation and properties. *Adv Colloid Interface Sci* 2000;**86**:195–267.
161. Brown GL. formation of films from polymer dispersions. *J Poly Sci* 1956;**22**:423.
162. Kiil S. Drying of latex films and coatings: reconsidering the fundamental mechanisms. *Prog Org Coatings* 2006;**57**:236–50.
163. Joanicot M, Wong K, Cabane B. Interdiffusion in cellular latex films. *Macromolecules* 1996;**29**:4976–84.
164. Winnik MA. Latex film formation. *Curr Opin Colloid & Interface Sci* 1997;**2**:192–9.
165. Sharp DH. An overview of Rayleigh-Taylor instability. *Phys D* 1984;**12**:3–18.
166. Griffin WC. *J Soc Cosmet Chem* 1949;**1**:311.
167. Griffin WC. *J Soc Cosmet Chem* 1954;**5**:249.
168. Griffin WC. Off. Dig. Fed Paint Varn. *Prod Clubs* 1956;**28**:466.
169. Shinoda K, Arai H. The correlation between phase invemion temperature in emulsion and cloud point in solution of nonionic emulsifier. *J Phys Chem* 1964;**68**:3485–90.
170. Von Smoluchowski M. *Physik* 1916;**2**(17):557–85. 92, 129, (1917).
171. Davies JT. *Rec Progr Surf Sci* 1964;**2**:129.
172. Friberg S, Larrson K, Mandell L. *J Colloid Interface Sci* 1969;**29**:155.

173. Meyer J, Dahl V, Venzmer J, Jha B. *Society of cosmetic chemists annual scientific seminar*. June 2012. Charleston, SC.
174. Murray BS. Interfacial rheology of food emulsifiers and proteins. *Curr Opin Colloid & Interface Sci* 2002;**7**:426–31.
175. Tadros T. Principles of emulsion stabilization with special reference to polymeric surfactants. *J Cosmet Sci* 2006;**57**(2):153–69.
176. Stuart MAC, Huck WTS, Genzer J, Müller M, Ober C, Stamm M, Sukhorukov GB, Szleifer I, Tsukruk VV, Urban M, Winnik F, Zauscher S, Luzinov I, Minko S. Emerging applications of stimuli-responsive polymer materials. *Nat Mater* 2010;**9**:101–13.
177. Taylor P. Ostwald ripening in emulsions. *Adv Colloid Interface Sci* 1998;**75**:107–63.
178. Katchalsky. *J Polym Sci* 1951;**7**:571. 15, 69, (1955).
179. Flory PJ. *Principles of polymer chemistry*. Cornell Univ Press; 1953.
180. Lochhead RY, Eachus AC, Bremecker KD. The evaluation of alternative neutralizing bases for carbomers. In: *Siefen Ohlen Fettewasche, Kosmetikjahrbuch, Germany*; March 1992. p. 69.
181. Lochhead RY, Davidson JA, Thomas GM. Poly(acrylic acid) thickeners: the importance of gel microrheology and evaluation of hydrophobically modified derivatives as emulsifiers. In: Glass JE, editor. *Polymers in aqueous media: performance through association*. *Advances in chemistry series*, vol. 223. Washington, DC: American Chemical Society; 1989. p. 113.
182. Ketz Jr RJ, Prud'homme RK, Graessley WW. Rheology of concentrated microgel solutions. *Rheol Acta* 1988;**27**:531–9.
183. Lochhead RY, Rulison CJ. Investigation of the mechanism and associative thickening by hydrophobically-modified hydroxyethylcellulose and hydrophobically-modified poly(acrylic acid). *Polym Mater Sci Eng* 1993;**69**.
184. Lochhead RY, Rulison CJ, Bui HS, Pierce TD. Investigation of the mechanism of emulsification by hydrophobically-modified hydrogels. *Polym Prepr Am Chem Soc* 1993;**34**(1):863.
185. Lochhead RY. Electrosteric stabilization of oil-in-water emulsions by hydrophobically modified poly(acrylic acid) thickeners. In: Schulz DN, Glass JE, editors. *Polymers as rheology modifiers*. *ACS symposium series*, vol. 462. Washington, DC: American Chemical Society; 1991. p. 101 [Chapter 6].
186. Lochhead RY, Castaneda JY, Hemker WJ. *Stable and quick-breaking topical skin compositions from oil-in-water emulsions containing acrylic polymers*. May 25, 1988. European Patent 268164 A2; U.S. Patent 5,004,598, April 2, 1991; assigned to BF Goodrich.
187. Lochhead RY, Dodwell R, Hemker W. *Pemulen® polymeric emulsifiers: what they are, how they work*. Cosmetics and Toiletries Manufacture Worldwide; 1993. p. 77.
188. Lochhead RY, Rulison CJ. An investigation of the mechanism by which hydrophobically-modified hydrophilic polymers act as primary emulsifiers. *Colloids Surfaces* 1994;**A88**:27.

CHAPTER

# 4

# Scouting to Meet Unmet Needs

C.M. *Rocafort*

**BASF Corporation, Florham Park, NJ, United States**

## 4.1 INTRODUCTION

The inspiration for writing this chapter on scouting is based on my personal experience over most of my 35+ year career. As a formulator working for an international consumer goods company, I worked with the various marketing teams on their Consumer product "needs" briefs in which I identified ingredients and methodologies to meet the performance criteria and claims necessary for new product launches. I also participated in "State of the Art" exercises twice a year for new commercially launched products in which I investigated new product introductions, product forms, claims, and new ingredients used in the formulations, and conducted benchmarking studies. Part of this exercise also included patent literature searches in relevant marketed areas. These findings were used to support the market strategies for the brands and new product innovation plans in the marketed areas we participated in.

As a researcher working for various raw material suppliers in global formulation development and new polymer product development, scouting was a defined part of my job function. In this case, a "Needs" brief was developed and technical solutions were explored and eventually launched. For example, when Volatile Organic Compound (VOC) regulations were passed for hair sprays by the California Air Resource Board (CARB) in the early 1990s; the whole industry worked together (i.e., polymer raw material suppliers, aerosol can manufacturers, valve manufacturers, and propellant suppliers) for almost a decade to understand and define all of the problems associated with adding water to hair sprays. The whole industry systematically addressed the gaps and challenges until solutions were discovered and judged acceptable by the market, and new polymers were launched to address this market need. When I joined Baden Aniline and Soda Factory (BASF), I was hired as a full-time Technology Scout to help identify cross-segment technical opportunities and solutions for the unmet needs of the Home and Personal Care, Detergents and Cleaners, Industrial and Institutional (I&I), and Industrial Formulators markets. My team and I used a robust formal process to collect the unmet needs from the various business units and to assess technology opportunities to make recommendations. Today, a portfolio of scouting resources and tools is available in the marketplace. Based on the specific needs you are scouting for, and the budget allowed for such activities, you will need to assess and determine what is best suited for the job at hand. To most fully and efficiently access the large body of opportunities, a mix of scouting sources and models should be employed.

Much of the structure of this chapter is based on the key learnings from the various BASF Technology Scouting Network Workshops[2] and the interactive networking events held with universities, technology transfer companies, government agencies, industrial research institutes, etc., from 2011 to 2016. As well as work conducted by the Industrial Research Institute (IRI) is in the "Tech Scouting Starter Tool Kit- Key Elements and Tools."[3]

## 4.2 VALUE OF TECHNOLOGY SCOUTING

One of the strong points of technology scouting is its ability to detect advances in emerging technology at an early stage. Alternative methods such as publication or patent analysis have a natural time lag of 12–18 months due to the

*Cosmetic Science and Technology: Theoretical Principles and Applications*
http://dx.doi.org/10.1016/B978-0-12-802005-0.00004-5



Copyright © 2017 Elsevier Inc. All rights reserved.

publication and patent administrative processes. Secondly, the personal contacts established by the scouts for information gathering by building and using global networks of experts is a strong base for the sourcing of technology.[4]

Scouting contributes to Technology Management by:[5]

- Identifying emerging technologies via early identification and opportunity for adoption
- Finding a source of a missing technology and channeling this technology-related information into the organization
- Benchmarking your company's technologies
- Identifying disruptive technologies
- Identifying opportunities for technology codevelopment
- Bringing in solutions for existing problems/unmet needs
- Stimulating innovation
- Identifying technologies to fill portfolio gaps
- Supporting the expansion of your company's strategic portfolio
- Supporting the acquisition of technologies

It is actually a mechanism to practically implement and manage open innovation (OI).

Scouting is used at the fuzzy front end (starting point) of the OI funnel, which provides an interactive matching process between external technologies and internal requirements to meet unmet needs.

## 4.3 TECHNOLOGY SCOUT

The ideal Technology Scout has both technical depth and business breadth in their backgrounds. Broad competencies for Technical Scouts include keywords like facilitation, impact, collaborative, multitasker, and document. Further competencies include:[1,4–7]

- Creativity and deductive thinking
- Thinks laterally…not linearly
- Ability to "connect the dots" when looking at technologies residing in adjacent or unrelated industries.
- Networking skills… ability to form and maintain relationships/contacts for the long term.
- Ability to build and use global networks of experts
- Risk taker…willing to champion unpopular ideas
- Good experience of science and technology
- Organized
- Contract understanding
- Global mindset
- Entrepreneurial

Technology Scouting is a distinct job function, with a well-defined set of required competencies. Different organizational models can be considered based on tasks, function, and physical location of scouts and other stakeholders. For example, such models include full-time scouts, part-time scouts, and/or scouting requirements being written into job descriptions (or objectives) of senior technologists, new business development leaders, and strategic marketing leaders or consultants.

## 4.4 SCOUTING ORGANIZATION[2,3]

A scouting organization supports the broader innovation function within the company, and should be organized and accountable appropriately within the company structure, in relation to delivering on the mission. The organizational design may answer:

- Who is the Scouting function's customer (for example research and development (R&D), marketing, specific customer)?
- What does the Scouting function's customer actually want (deliverables)?
- Why is it important that Scouting deliver the goods?
- Where in the organization will Technology Scouting best get started, and grow over time?

## 4.5 ORGANIZATIONAL SCOUTING MODELS

Four common organizational Scouting models are:

- **Grassroots (Bottom up)**—This model is composed of individuals who conduct informal or occasional scouting, is loosely organized, with conditional sponsorship, and typically has limited resources.
- **Distributed/Isolated**—This model is made up of individuals or groups located within a business unit/division, focused on their own R&D or product needs, funded/sponsored within the operating group, and have localized resources.
- **Centralized (Top down)**—A corporate core group leads this model. It is a more formal organization for routine scouting across business needs on behalf of the entire organization/divisions, strategically aligned with enterprise and division needs, is centrally located and has maintained resources and scouting initiatives.
- **Hybrid**—This model is composed of corporate or functional groups (i.e., R&D, Marketing) which leads community of practice, staffs or assists scouts within divisions, and ensures alignment with the corporate innovation mission. In this case, scouting is often at the unit level and aligned with the New Product Development (NPD) group and centrally located where resources are maintained and are shared with and/or across units.

To take advantage of Technology Scouting, some form of organizational arrangement is essential for Technology Scouting to fulfill its mission to gather information and identify options for supporting the tactical or strategic development needs of an organization, operating unit, or project. A defined organization is recommended, consistent with the company's (or innovation function's) overall organizational model, and is essential to signal executive mandate, as well as to ensure that resources are assigned and accountable for carrying out the function. A defined organization further ensures a consistent understanding of roles and responsibilities.

Job descriptions are at the heart of the "People" element of a Scouting function.[3] It begins to articulate the roles and responsibilities within the organization. The job description is the source of truth for the role a person is to play within the organization by first aligning to the bigger picture (the mission) and spelling out duties, purpose, responsibilities, and job scope, and setting clear expectations on job activities.

## 4.6 SCOUTING FUNCTION

A Scouting function may include job descriptions for a Technology Scout, as well as for the function leader, administrators, and other adjunct functions within the Technical Scouting organizational model chosen. Central to the function is the Technology Scout, whose job description generally includes the ability to manage a variety of tasks stated in the "Wants, Finds, Gets, and Manages" (WFGM) paradigm of OI.[8,9] It is critical to consider the purpose, and organizational factors that will determine how much of the WFGM spectrum the scout will be involved with, and responsible for. High-level roles across WFGM include:

- **Wants**—Understands (if not also collecting or facilitating the creation of) the challenges, needs, gaps, or "wants" of the customer, business units, or innovation function, to be addressed by the Technology Scouting function.
- **Finds**—Engages internal or external networks, frames and organizes/leads searches with internal Scouts or external Scouting resources, and identifies opportunities that have the potential to address the "Wants."
- **Assesses** technology, performing or facilitating proof-of-concept studies or review of published data selecting the most promising technology opportunity candidates.
- **Gets**—Facilitates, with Legal or Procurement departments, the necessary agreements (i.e., Nondisclosure agreements (NDA); Material Transfer agreements (MTA); and Service, Development, or Purchase Agreements) to advance the evaluation, access, and partnering with the most promising technology opportunity candidates.
- **Manages**—Facilitates with R&D, New Product Development (NPD), or other internal organizations, the partnership development, licensing, and acquisition of the selected technology candidates.
- **Future**—Looks into the future state of technology (beyond the stated "Wants") to understand the potential impact on the business or in support of upstream technology strategy, road mapping, and education activities.
- **Balance**—A good job description for a technology scout offers a balance between structure and flexibility, to challenge existing paradigms of how and why things are done. It recognizes the serendipitous and iterative nature of innovation.

## 4.7 GENERAL SCOUTING PROCESS

The technology scouting process is actually a disciplined process workflow.[3] It is a formal process to collect and assess technology opportunities, and further select those for significant engagement and investment. To be successful, the process should be specifically and clearly aligned with the company's higher-level innovation process architecture and be visible and sanctioned. The workflow consists of successive stages with increasing resource dedication, to triage and grade opportunity versus business and other criteria, and to estimate resources for the next stage. The process is driven by clearly articulated "unmet needs" or "challenge" statements received from customers, the business units, product development teams, corporate R&D, marketing teams, strategy teams, acquisition teams, etc., but also allowing for the strategic or disruptive opportunities from scanning activities. There are milestone (gate) reviews (meetings or virtual) inclusive of "need" stakeholder and resource owners to "pass" the best opportunities and commit next-stage resources to further assess the opportunity. This process is tied in to the company's formal innovation, development, and commercialization processes, annual resource budgeting processes, and other key processes. Lastly, the technology scouting process needs to be aligned with the company's internal controls and Legal department. Clarity is needed in the process on when/how to transition from nonconfidential to confidential engagements, and other agreement structures or legal considerations that may be required. As an example, see Fig. 4.1 for a workflow diagram of a process for scouting to acquire or develop a technology.[10]

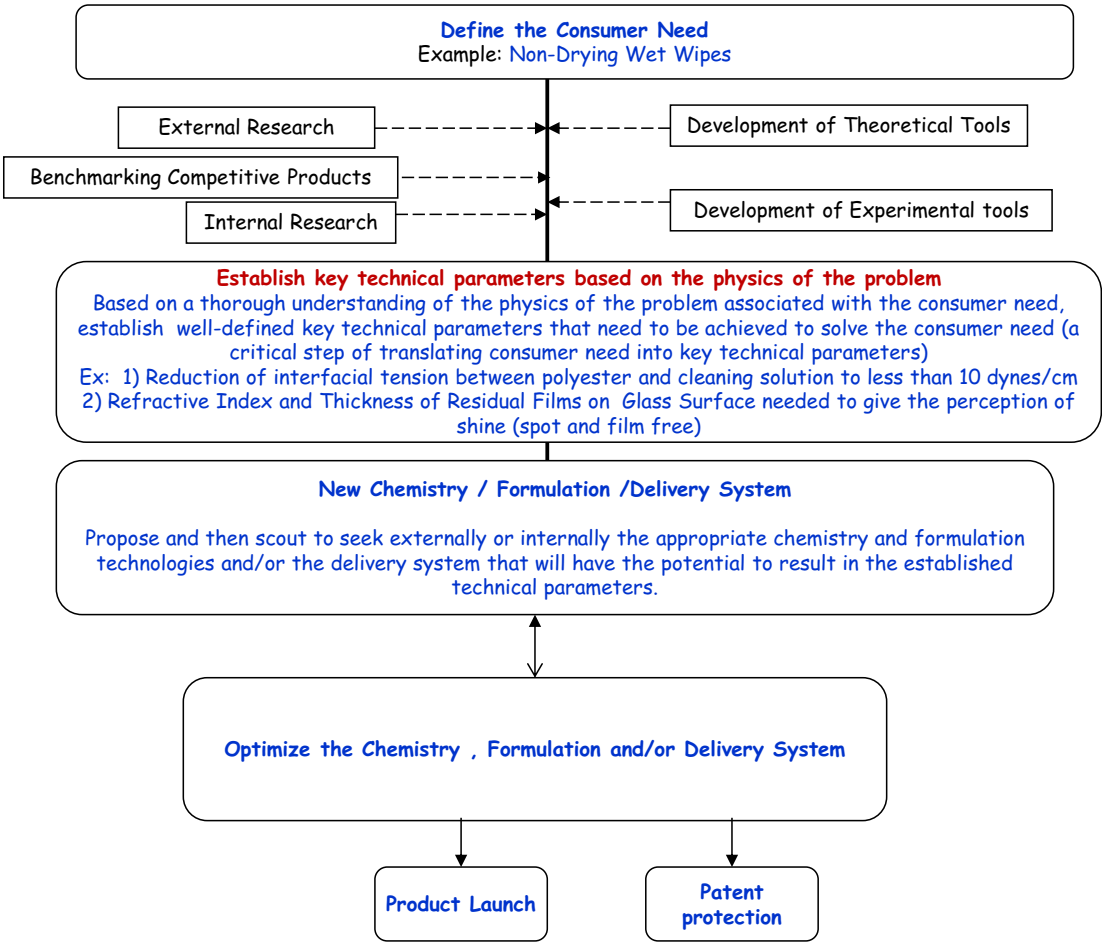



**FIGURE 4.1** Workflow diagram of a process for scouting to acquire or develop technology. *Y. Kim- BASF NA Technology scouting network, 09/27/2013.*

## 4.8 CHALLENGES

Technology Scouts will find a universe of technology opportunities, which appear to align with company needs. However, there is often internal resistance to this external technology, correctly recognizing that lack of domain knowledge, unrealistic business expectations, lack of familiarity/trust in solution providers, and/or other factors associated with many such opportunities have in the past not been recognized early, resulting in wasted resources. In some companies, "Not Invented Here" (NIH) is also a challenge as well. To overcome these challenges, it is recommended that a disciplined and phased scouting process be implemented for efficient application of resources to triage, assess and high-grade opportunities.[11] Communication is a great starting point.

The premise is that the company already has formal mainstream innovation and commercialization processes. The seamless tie-in of this structured scouting process to the existing innovation processes is clearly essential for efficiency and harmony with the mainstream innovation function. The "needs" will determine the kinds of scouting to be conducted. Because the technical scouting process will be tied to the larger innovation cycle used by the company—the "needs" and "wants" will be different at different stages of the innovation cycle. Front-end innovation needs will be high level and more exploratory to inform strategy and road-mapping. Downstream product innovation needs will be more tactical and require clear technical, business, and partnering criteria. The technology scouting process can enable this range of needs across the full spectrum. But when starting up a Technology Scouting function,[3] one must be clear about where and how the needs are being generated and for what purpose in the higher-level innovation cycle. The process must be formal to signal mandate from management. Inclusion of all stakeholders including resource owners is essential at gate reviews for agreement on continuing resource commitment for evaluation. Alignment with legal and company controls is essential, as external engagements invite exposures including loss of company's confidential information, expectation by opportunity providers for confidentiality, Intellectual Property (IP) contamination, etc.Although stages of activity are suggested, with gates to "pass"; the most promising opportunities to the next stage of assessment or tie-in to mainstream innovation process (and to allocate limited assessment resources), being overly prescriptive on gate requirements may prematurely kill the opportunities (i.e., out of the box) most important to the company's future.

## 4.9 FRONT-END HOMEWORK/CREATION OF THE "NEEDS" BRIEF

The "Needs" brief directly affects your search strategy and success of the scouting process. Front-end effort by the Technology Scout, continually refreshed, to identify and articulate the true unmet needs and challenges of the business units, on which the scouting and OI function is primarily to focus are:

- Access strategic plans, roadmaps, etc.
- Technology Scouts interview business managers, executives, customers, Technology Fellows, and other thought leaders, etc.
- Define one or more Needs or Challenge Types to be addressed by function (i.e., market gaps, technology enablers, new processes, etc.).
- Create Needs or Challenge statements, per the Needs Brief Template or Templates, if multiple types. See Fig. 4.2 for the Needs Brief Template.[12]
- Include parameters required for success
- Validate, prioritize, and periodically revisit with stakeholders

Most Needs and Challenges will be known, definable, and focused, but may also include prompt for "Scanning" of unknown strategic or disruptive opportunities.

A myriad of external opportunities exists that may appear relevant to any business. Recognizing limited resources, a manageable number of top needs can provide a first filter. Clear articulation of the need and the parameters for success enables better internal decision making on prioritizing, and much earlier (and less waste of resources) culling. The articulation of Needs is hard to do, and is itself a critical skill. Periodic engagement with stakeholders, including executives, is required for "buy -in". For some companies an avenue may be desired, which the Technology Scouting function may provide, for engaging technologies not responsive to focused needs—to ensure not being caught off guard by disruptive technologies, and to provide strategic opportunities. Technology forecasting can help watch for the weak signals that disruptions are coming or new technologies will be available which can help shape strategy and drive definition of new business needs.

**Problem Title**

**Submitter(s)**

| Name | Organization/Business Unit/Function |
|---|---|
| | |

**1. Problem Description/Statement**

**Unmet Needs**

What is the problem to be solved?

Have to at least address the following points:
- Market pull or Technology push
- Value to company/customer: market information (I.e. market size, growth rate, potential sales by specific date) - Business case highlights including financials and timelines

**Current Solutions**

Have to at least address the following points:
- What are the benchmarks?
- What are the issues/limitations with the current solutions?
- What is out of scope?

**Goal of the Project**

Have to at least address the following points:
- Define scope
- What are the key deliverables? (i.e. must haves versus nice to have)
- What might be the IP strategy?
- Describe potential risks/issues (I.e. market uncertainty, technical challenges, etc.)

**2. Solution Paths (include but are not limited to)**

Have to at least address the following points:
- What are the different options for solving this problem?
- Explore multiple solution paths.

**3. Technology Needs**

- Define technologies that might be needed for each option
- Define success criteria for ideal solution
- When necessary, provide industry / application test methods for which data has to be provided.

**4. Key Constraints for Desired Solution (for example, time-to-market, regulatory issues, level of technical maturity, etc.)**

**Must be:**

**Should be:**

FIGURE 4.2 Needs brief template. *Y. Kim, BASF NA Technology scouting network, 04/05/2013.*

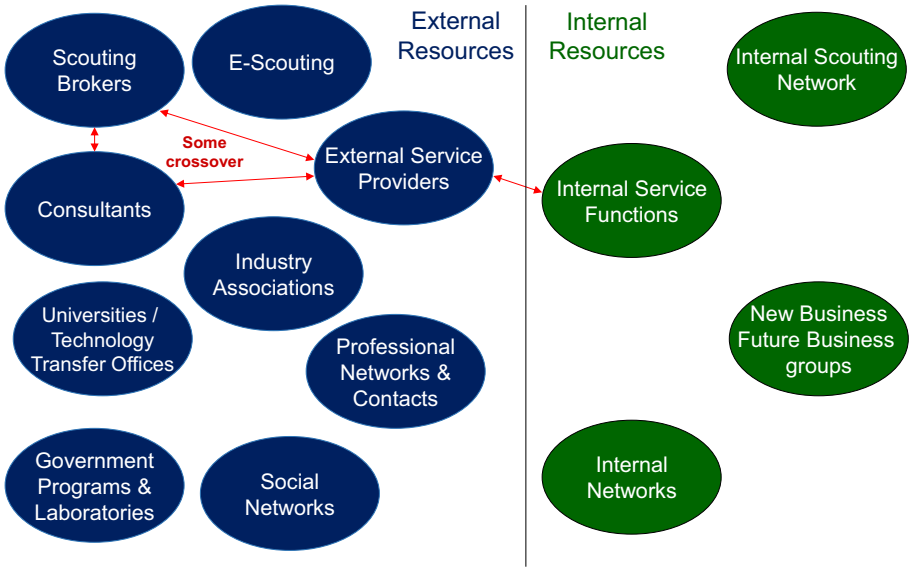



**FIGURE 4.3** Technology scouting tool box: external and internal scouting resources. *W. Kaufman, BASF NA Technology scouting network, 09/27/13.*

## 4.10 SCOUTING RESOURCES[2]

A portfolio of scouting resources is available to the company's Scouting community. These Scouting resources may be internal technical scouting leads (formally or informally trained) or search resources, or external technology scouting resources which can come in a variety of forms. The manner in which these resources are different and can evolve over time, but they constitute a range of scouting resource options which must be considered. See Fig. 4.3, the Technology Scouting Toolbox of Internal versus External Resources for the types of resources available.

Begin your search with your internal resources. Start with internal scouts, informal or formal, because they have insights about the company, strategy, and processes that are important for good scouting. Externally sourced scouts can come into play if internally you have limited bandwidth on the topic of your unmet need or challenge and/or have limited resources. There are instances in which leveraging outside scouting resources can be more efficient in certain instances. You will need to determine what is best suited for the job at hand. Some examples of scouting resources shown in Fig. 4.3 are:

- Each scout's individual professional networks and contacts
- Internal scouting network/community
- Inward looking (for large companies)
- Free content/contacts via industry associations and promotional associations etc.
- Free web-based content/social networks
- Paid subscriptions
- Paid intermediaries, e.g., for focused searches
- Portals
- Supplier networks
- Universities/technology transfer offices/contract research
- Government programs and laboratories
- Consultants
- Scouting Brokers

I have also provided some examples from the External Technology Scouting toolbox that might be helpful in your scouting efforts. See Figs. 4.4–4.7 for more specific details of the content in the tool boxes for universities, E-Scouting, external service providers, and scouting brokers.

To most fully and efficiently access the large body of opportunities, a mix of scouting sources and models should be employed. To maximize the value, the portfolio of sources (besides individuals' networks) should be periodically summarized and made accessible to your individual company scouting communities. Some examples of technology scouting resources are listed in Chart 4.1: Examples of Technology Scouting External Resources.[13]

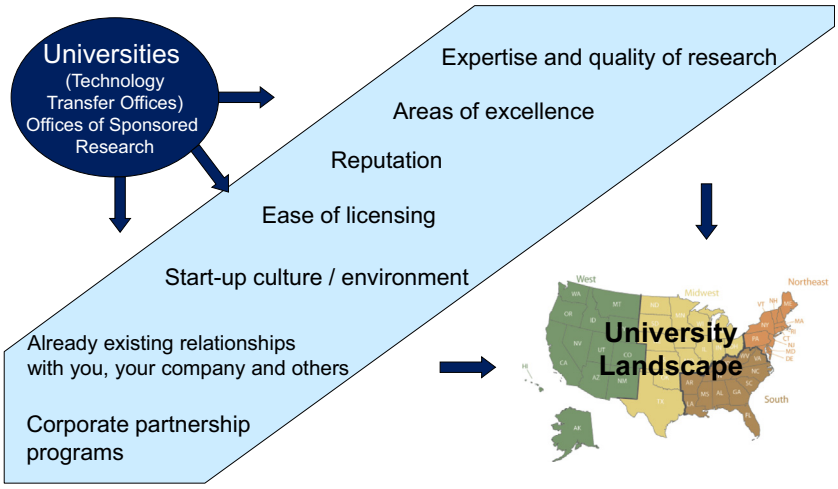



FIGURE 4.4 Technology scouting tool box: universities. *W. Kaufmann, BASF NA Technology scouting network, 09/27/13.*

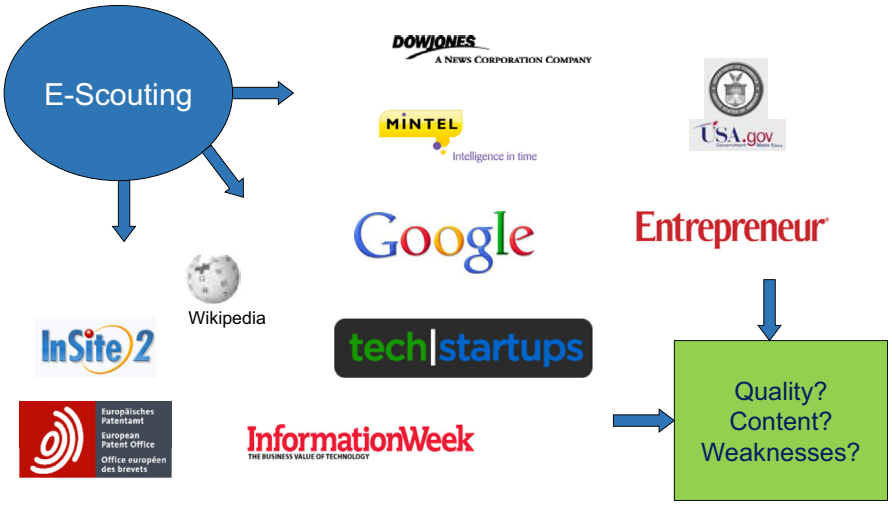



FIGURE 4.5 Technology scouting tool box: e-scouting resources. *W. Kaufman, BASF NA Technology scouting network, 09/27/13.*

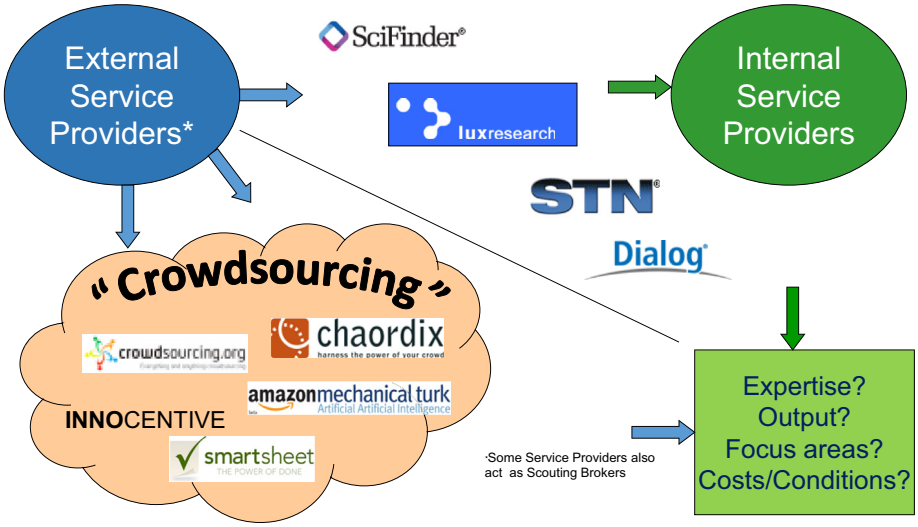



FIGURE 4.6 Technology scouting tool box: external service providers. *W. Kaufman, BASF NA Technology scouting network, 09/27/13.*




**FIGURE 4.7** Technology scouting tool box: scouting brokers. *W. Kaufman, BASF NA Technology scouting network, 09/27/13.*

**CHART 4.1** Examples of Technology Scouting External Resources

| Resource | Contact Info | Type of Resource |
|---|---|---|
| **Idea**CONNECTION | https://www.ideaconnection.com/ | Source of technology scouting companies |
| Harrison Hayes | http://www.slideshare.net/lsakoda/technology-scouting-overview | Technology scouting overview |
| Yet2. com | http://www.yet2.com/services/technology-scouting/?gclid=CIqwuZ7f6NECFYeFswod2EwNgA | Technology scouting broker |
| Lux Research | http://www.luxresearchinc.com/solutions/technology-scouting-and-open-innovation | Technology scouting and open innovation provider |
| TECHSCOUT | http://www.techscout.com/ | Innovator Circle- Connections |
| GEN3 PARTNERS | http://www.gen3.com/ | Technical innovation solution provider |
| NINE SIGMA | http://www.ninesigma.com/ | Open innovation provider |
| Industrial Research Institute (IRI) | https://www.iriweb.org/user/login | Tech scouting Starter tool Kit- key elements & tools |
| WellSpring Worldwide, Inc. | https://www.Wellspring.com/tech-scouting | Agile technology scouting: The disciplined process for finding, assessing, and sourcing the right technology |

*Internet.*

Each company must determine its preferred mix of sources and models, within financial and other constraints. An often overlooked resource is the existing knowledge within your own corporation. Some potential solutions to technology needs may have already been developed in house, possibly in the past or by another unit.

Standard forms (paper or digital) to prompt and collect inputs to the scouting process should be utilized for communicating among process participants. For example:[2]

- "Needs" or "Challenge" statements being gathered from the business units (i.e., for internal use)
- "Needs "or "Challenge" statements for external use (i.e., with scouting intermediaries
- "First Contact Template" with key questions for opportunity providers.

## 4.11 WHY DO YOU NEED IT?

An effective and efficient process requires inputs (needs) and outputs (scouting solutions) to be responsive, organized, and in consistent format.[2,3] Templates can drive that process, and their specific benefits include:

- Establish prompts for those inputs most critical to defining a challenge or scouting an opportunity.
- "Hint" tool for less experienced scouts.

- Consistent format and concise presenting of only relevant information (for both "needs" sought and "solutions" found) makes for more efficient stakeholder review.
- Supports required controls, e.g., limiting confidential information in either direction.
- Periodic (e.g., quarterly, or scouting project outcomes) report to stakeholders, and/or online dashboard, provides status of scouting challenges and opportunities.
- Enterprise and business unit reports
- May be filtered or sorted on challenge, stage, or other segmentation.
- Some reports as part of workflow, e.g., quad chart for particular opportunity to drive gate decisions
- Reports should be stored on a dedicated Scouting Information Technology (IT) database so there is a readily accessible place for tracking progress, and history of Scouting projects.

This process will provide visibility, to stakeholders, on the range of scouting activities across the enterprise (not just their own business unit) for leverage, synergy, and to avoid duplication. Executive sponsors will also have validation of organizational engagement and progression.

## 4.12 CONCLUSIONS

With the increased need for rapid innovation, technology scouting has become a key element of Open Innovation (OI), which becomes more and more an important part of corporate strategy. Professional technology scouting is a highly collaborative and sophisticated operation that requires a lot of communication. An industry survey on Technology Scouting programs[14] conducted by Lux Research and Industrial Research Institute in 2012 concluded that:

- New sources of technology and ideas have moved companies to look to OI and technology scouting as a faster means of accelerating growth.
- Technology scouting is effective at filling gaps, but most companies struggle to use it for new ideas.
- Growth scouting can help fill the front end of the funnel with qualified ideas by identifying high momentum and unmet needs.

Alignment between the Technology Scout and the OI, utilizing a robust scouting process, developing well-defined "Needs" briefs, and using both internal and external resources will help to bridge this gap and provide scouting success.

## Acknowledgments

I wish to acknowledge my former manager, mentor, and colleague Werner Kaufmann, Innovation Networks & Technology Scouting Network Manager—Market & Customer Development North America; Svetlana Dimovski, Senior Manager, Innovation Excellence; and Yoong Kim, Open Innovation Manager for information useful in the preparation of this chapter. Also to the members of the BASF Scouting Community who I have collaborated with, learned from, and networked with over the last 7 years. And lastly, to my former manager, Christian Wulff who created a full-time Technology Scouting role for me with BASF in 2009 for Care Chemicals.

## References

1. Rohrbeck R. Harnessing a network of experts for competitive advantage. *R&D Manage* 2010;**40**(2):169–80.
2. Kaufmann W. *BASF NA Technology scouting network, technology scouting workshops, technology scouting tools and NA scouting network team room*. 2011–2016. https://www.basf.com/us/en/company/research/open-innovation.html.
3. Industrial Research Institute. *Tech scouting starter tool kit- key elements and tools*. Industrial Research Institute (IRI) Spring 2016 External Technology Network meeting; 2016.
4. Haddad M. *Technology scouting: on the trail of hidden innovators*. 2014. www.paristechreview.com/2014/11/30/technology scouting/.
5. BASF NA Technology Scouting Network. *Outcomes from the technology scouting workshop*. April 5, 2013.
6. Holman M. *Technology scouting benchmarks and best practices*. Lux Research; June 2012. www.luxresearchinc.com/solutions/technology-scouting-and-open-innovation.
7. Leech R. *Open innovation and technology scouting*. October 21, 2010. Unilever Presentation.
8. Slowinski G. *An open innovation approach that works! want, find, get, manage*. Strategic Alliance Group; February 3, 2014.
9. Slowinski G, Sagel M. *Good practices in open innovation, research technology management (September/October 2010)*. 2004. p. 38–45. http://www.strategicalliance.com/articles/good_practice_article.pdf.
10. Kim Y. *Process for scouting to acquire or develop technology*. BASF NA Technology Scouting Network; 2013. 09/27/2013.
11. Sakoda, L. "Technology scouting overview", Harrison Hayes, http://www.slideshare.net/lsakoda/technology-scouting-overview.
12. Kaufmann W. *Needs brief template*. BASF NA Technology Scouting Network; April 5, 2013.
13. IdeaCONNECTION®. *List of technology scouting companies*. 2016. https://www.ideasconnection.com/scouting/.
14. *Industrial® Research Institute (IRI) and Lux research partnership: the technology scouting program & survey*. 2013–2016.

CHAPTER

# 5

# New Aspects of Cosmetics and Cosmetic Science

*J. Hosoi*[1], *J. Koyama*[1], *T. Ozawa*[2]

[1]**Shiseido Global Innovation Center, Yokohama, Japan;** [2]**Society of Cosmetic Chemists of Japan, Yokohama, Japan**

It is believed that makeup was invented not only for beauty but also to show power or divinity. Makeup and cosmetics have changed over time with change in materials, social structures, and living environments. Development of cosmetics has also advanced rapidly with the accelerated progress of measurement and analytical technology. In this chapter, we will look back at the original purposes of makeup and cosmetics, and study the functions of the human skin to view the future of the cosmetic science field comprehensively.

## 5.1 THE SCOPE OF COSMETIC SCIENCE

Cosmetics and makeup were invented as a medium to show power or beauty. Kings, sovereigns, and religious figures applied makeup to show their power in front of large crowds and so they could be seen from a distance. In Tutankhamun's cosmetic jar, ointment-like artifacts were found and it is believed that this was used for skin care or makeup foundation. Cleopatra bathed in hot water with milk and honey, and used coloring made from minerals and metals with duck oil for makeup. For thousands of years, such rough plant extracts and raw minerals were used until only a few hundred years ago. Use of these raw materials must have caused allergies and inflammatory symptoms, and more serious problems like intoxicating the whole body. Cosmetic science is a field where the subject is not only the cosmetics themselves but also involves the relationship and analysis of the skin it is used upon, and even the humans that use the cosmetics. Modern dermatology began from assuring the safety of cosmetics. As production and distribution methods evolved and cosmetics were distributed in extremely large volumes, damage caused by defective products also spread wider. In the early years, animal testing was used to study harmful model systems. However, as the animal rights movement spread, testing systems also needed to shift to cell-level and genetic-level testing. As technology advanced for processing large numbers of samples and analyzing large amounts of data, new testing methods have been established. For example, tests for sensitization capacity for allergic reactions were previously done on mice by examining the T cell growth with regional lymph, or on guinea pigs and examining their inflammatory reaction, but new testing methods have been developed, such as the DPRSA method[1] that examines the test substance's ability to directly bind to protein, or the hCLAT method[2] where THP-1, a dendritic cell line, is used to determine molecule expression required for antigen presentation (Fig. 5.1). These new testing methods are expected to evolve with basic dermatological immunology. Stimulation response against the permeability of chemical agents were previously tested on human and animal organs, but development and production of skin models have allowed us to test on materials that are more similar to skin. Many artificial films and tissues that are similar to organic tissue made from chitosan and fibrin have been developed as supplementary materials for medical treatment of burns and wounds and are evolving. These are used to develop skin models that are even more similar to human skin, and are expected to be used to determine the human skin's stimulant response against chemical agents and to be permeable easily and quickly. To understand the toxicity of genetic toxins, bacteria or cultured cells of mammals were previously used to research DNA mutation or expression of chromosomal abnormality as an index, but there have been efforts to replace even these difficult tests, and symposiums have been held to discuss this

*Cosmetic Science and Technology: Theoretical Principles and Applications*
http://dx.doi.org/10.1016/B978-0-12-802005-0.00005-7



Copyright © 2017 Elsevier Inc. All rights reserved.

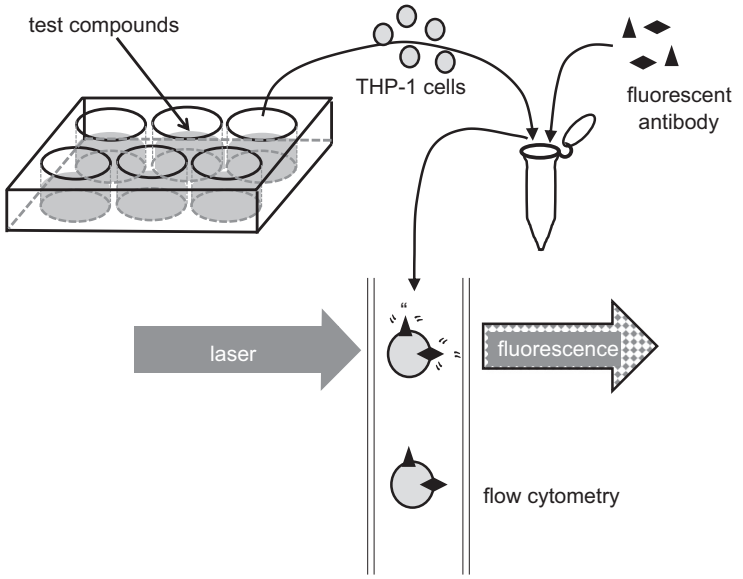



FIGURE 5.1 **Test for potency of sensitization (hCLAT).** Human monocyte cell line, THP-1, is treated with test compounds and stained with fluorescence-labeled antibodies for activation markers of Langerhans cells (CD40, CD86), then analyzed by flow cytometry for expression of activation markers.

topic at the Society of Alternatives to Animal Experiments (2015). While biochemical techniques evolve, progress has also been seen with the evolution of computers, using large-scale databases to determine the toxicity and sensitization capacity of chemicals with similar structures.[3] These methods are expected to be combined for more accurate toxicity determination methods.

Cosmetics moved past their original purpose as purely makeup and started to be used for skin care. Cosmetic science proved that they are effective to prevent or improve skin problems such as wrinkles, stains, and to inhibit aging. It has been important to understand the structure of the skin and its functions through basic anatomical and biochemical knowledge to show these effects of cosmetics. Skin care products such as antiaging products were developed based on this knowledge by studying the difference of the skin in older and younger generations, and determining the mechanism of skin aging. These cosmetic science methods have implemented progress in basic dermatology, and will continue to introduce new ideas. In basic research, experimental instruments have advanced, allowing, for example, to examine the hair growth cycle on the ears of mice,[4] and in skin immunity fields, Kabashima et al. of Kyoto University, Japan, and other teams have studied in vivo skin immunity by using a noninvasive method, with transgenic mice with fluorescent substances that label immune cells[5] (Fig. 5.2A). Amagai et al. of Keio University, Japan, used tight junction stereoscopic observation to analyze the mechanism of keratinocyte cornification with a mathematical model. This knowledge and these observation techniques on human skin will likely help the evolution of cosmetic science. There have also been methods that comprehensively and exhaustively analyze abundant data of various older and younger generations including images, and new factors that were not known are being found. Transcriptome techniques that are used to comprehensively analyze the change of genetic expression is shifting from cDNA arrays to more sensitive RNA array analysis. Furthermore, analysis of proteomes that comprehensively compares produced protein, epigenetics that analyzes methylation chromosomes or DNA, or single nucleotide polymorphism (SNP) analysis used to analyze mutation of genes have become more cost-efficient, and are being applied to cosmetic science, especially in skin diagnosis. By utilizing these methods, many reaction pathways that were not even predicted have been focused on and have the potential to be applied to more personal care.

So, what is the goal of cosmetic science? The goal of cosmetic science is to bring health to humans by creating and maintaining beauty. The World Health Organization defines health as "a dynamic state of complete physical, mental, spiritual and social well-being and not merely the absence of disease or infirmity." Cosmetic science is a science to help people live a wholesome life in their society through cosmetics. The effectiveness of cosmetics was evaluated by physical methods such as TWL and measuring the viscoelasticity of the skin, but has evolved to methods that combine biochemical and genetic engineering technologies. In 1993, it was proven that skin immune cells contact nerve fibers and are connected to the central nerve system[6] (Fig. 5.3). This discovery was praised as a hint to explain why the skin condition of dermatosis patients was aggravated when they were mentally stressed, and a Harvard group proposed the neuro-immuno-cutaneous-endocrionology (NICE) theory.[7] With this discovery, the concept

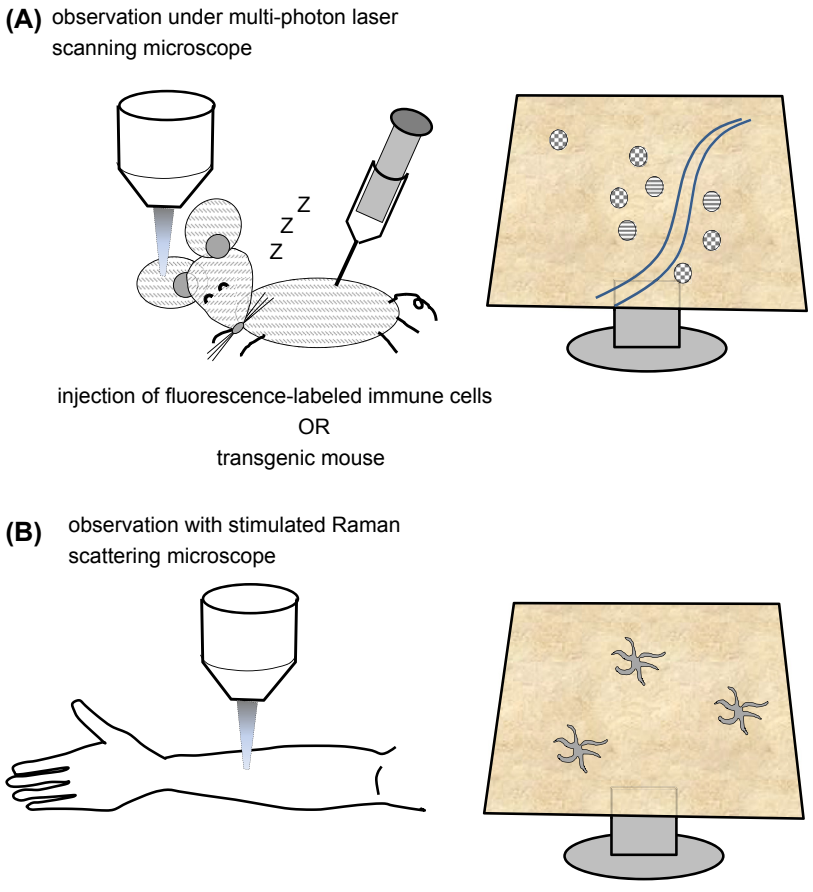



FIGURE 5.2 **In vivo visualization of epidermal structure and immune cells in the skin.** (A) In the academic studies, ears of mice with inoculated fluorescence-labeled immune cells or with transgene of fluorescence immune markers are now observed under multiphoton laser scanning microscope. (B) Recent advances of stimulated Raman scattering microscope may be applied to the observation of the structure of epidermis and immune cells in the human skin in vivo in the near future.

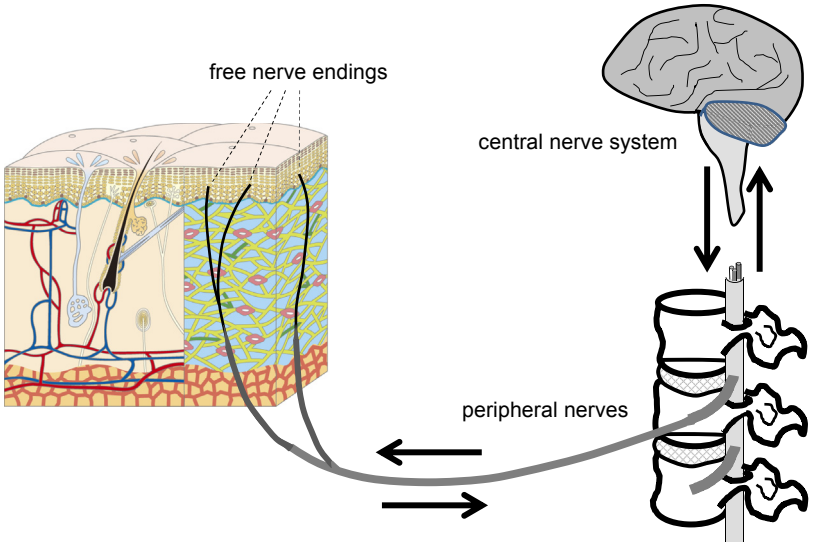



FIGURE 5.3 **Discovery of the association of nerve fibers with epidermal Langerhans cells.** Anatomical and functional association of free endings of nerve with epidermal Langerhans cells was discovered, suggesting the interaction of mind and skin.

that the skin condition is affected by the body condition including the neural system and the concept that the skin also influences the entire body has spread.

In developed countries the number of atopic dermatitis patients is increasing, and with adolescent patients, management of the condition is difficult and this can hinder growth. The number of adult patients is also increasing and a complete cure is yet to be found, and the only remedies are to inhibit recurrence or improve the symptoms.

In an academia-industry-government coproject, Tagami, one of the pioneers of the bioengineering of the skin, particularly in the assessment of skin surface hydration, and Ando intently promoted "the study on the prevention of atopic dermatitis development by employing skin care treatment." This task force of researchers from the academics, government, and industry worked together intensively on this project, resulting in the epoch-making findings that skin care with cosmetics can also contribute to the treatment of atopic dermatitis.[8] A recent report also shows that appropriate skin care from the neonatal period can reduce the occurrence of future atopic symptoms.[9] These studies implicate the importance of skin care from a young age. Atopy is not limited to dermatitis, but can also lead to asthma and rhinitis, and this transfer is called the allergic march. Skin care at young ages can be effective to prevent such systemic disease.

Another issue in Japan as well as many other developed countries is that as the population ages, dementia is becoming a larger social problem. There have been studies that show cosmetics can help vitalize older generations. Ikeyama has studied this topic as one of the projects in "Health and Life Extension Industry Creation Project of 2014," led by the Ministry of Economy, Trade, and Industry of Japan. In his August 25, 2015, speech on "The Role of Cosmetics to Bind the Elderly and Society − The Power of Cosmetics that Support the QOL of the Elderly," in which he explained that based on cosmetic remedy research, cosmetics and fashion have the potential to bind the elderly with society. In other words, cosmetics can support health throughout a lifetime, and cosmetic science is a field that maximizes its potential.

## 5.2 TECHNOLOGIES THAT SUPPORT COSMETIC SCIENCE

Many technologies have been developed or imported from other fields to investigate cosmetic science's main subject of research, the skin, and are used to reveal the skin's physiological functions or to study its change with aging. The evolution of science and the progress of technology is like a double helix.

The progress of technology to "see" the skin will eventually allow us to observe the internal structure of the human skin with a noninvasive method. Video microscopes have made it possible to enlarge the surface of the skin, but the internal structure could only be roughly observed with ultrasonic diagnosis. It was also challenging to improve the resolution with thin tissue like the skin. Under these situations, a competition of research has begun using intrinsic fluorescence methods such as multiphoton confocal microscopes to observe the internal structures. The development of optical coherent tomography (OCT) has led to observation of the deep internals of the skin such as collagen fiber, but furthermore, it has become possible to extract information on collagen only with microscopes using second harmonic generation.[10] The Raman method has been used primarily to determine the penetrability of substances to the skin, but this method has developed into stimulated Raman scattering and coherent anti-Stokes Raman methods, which can make visual images of components and differentiate the molecular structures quickly; this method is being developed to determine the type of cells or the differentiation state.[11] If these instruments become practical, it will become possible to observe human skin and chronological change in situ, and the stimulant response and chemical agent action mechanisms in the body will be revealed at a glance (Fig. 5.2B).

Cells, skin models, or tissue organ cultures are mainly used in current biological research, but these methods limit extrapolation to the body. If possible it would be better to directly see the cells in a living organism. Genetic vectors and congenic methods have developed, and there are alternate methods being developed such as Shimoyama et al.'s Nobel-winning study of green fluorescent protein and other fluorescent probes. These techniques are being applied and used in academic research, with various fluorescent pigments used to label the immune cells of mice ears so they can be observed alive to discover new immune reaction pathways[5] (Fig. 5.2A).

The technology of genetic modification has led to the spread of many methods, such as technology to inhibit the expression of specific genes (siRNA), or to express genes only when required (inducible transgene), and even technology that uses diphtheria toxin receptors to eliminate cells that express specific genes. However, the genes created with these methods have been difficult to use on a specific area of an intracellular gene. Very recently, a method to solve this problem was announced and has earned focus. This method is called genome editing,[12,13] and is a phenomenal method that uses artificial nuclease to create cells or animals with mutated genes in a short period (Fig. 5.4). Reagent manufacturers are competing to make this technology practical, and it will soon be a helpful tool in cosmetic science.

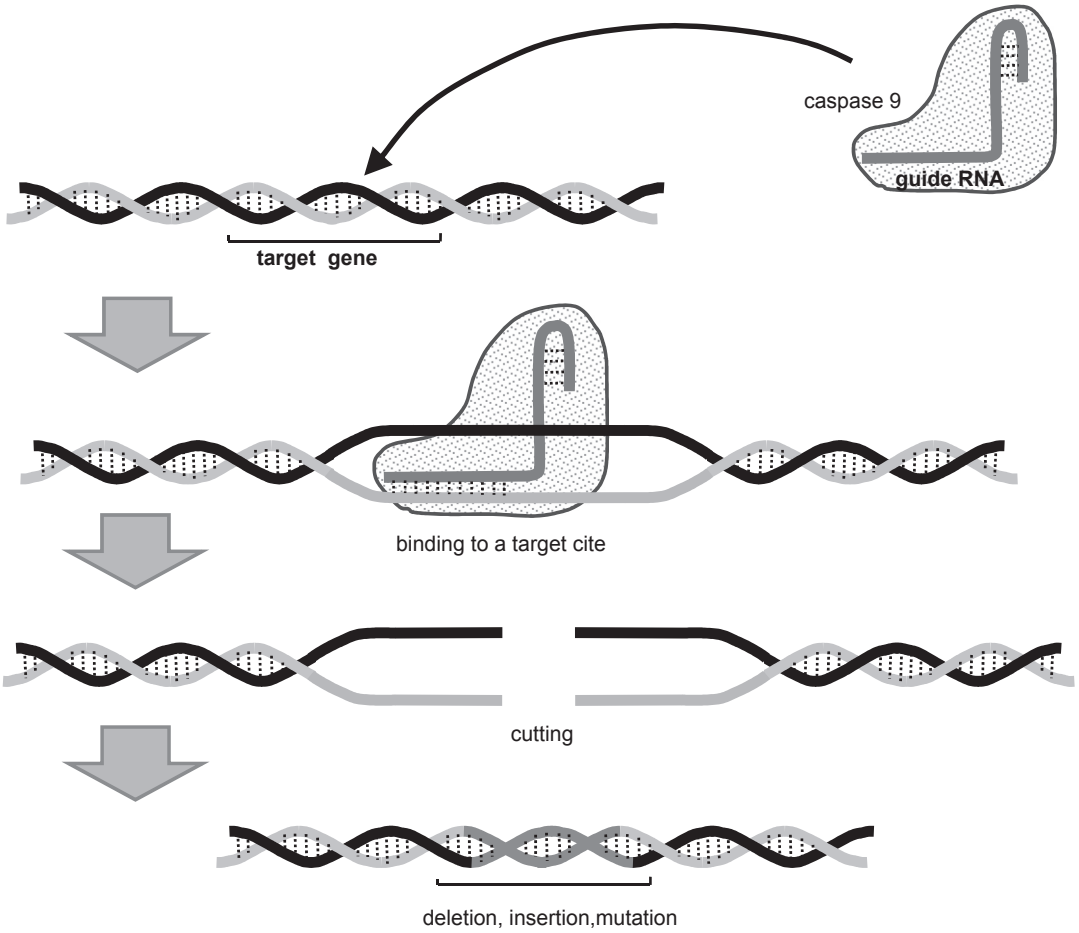



FIGURE 5.4 **Genome editing.** A vector encoding homologous RNA to the target DNA and digesting enzyme (Cas9) is introduced into eggs or mammalian cells. The complex binds and digests the target DNA and forms deletion, insertion, or mutation during the repair as designed.

Experiments using first-stage cultured human cells are becoming more prominent. Reagent manufacturers are manufacturing culture solutions that preserve primary cultured cells and stem cells, and there are synthetic culture medium products that do not contain blood serum. These culture solutions have made it easier to grow first-stage cultured skin cells. However, these culture solutions are developed to maximize the growth of the cells, and it is still questionable if they actually reflect the physiological environment. After the cells are grown, it is important to plan the experiments carefully such as performing the experiment in an environment close to the actual physiological condition.

## 5.3 FUNCTIONS OF THE SKIN

Cosmetic science is a field that analyzes its main focus subject, the human skin. The human skin is essential in order to maintain the health of the entire body, so if the skin functions decline, not only will the condition of the skin aggravate but this will also lead to damaging the health of the entire body. Skin care can be used to improve deterioration of the skin function, and will lead to helping the health of the body.

White firm skin, or healthy looking tanned skin, could maximize the individual's attractiveness, a factor that may contribute in preserving humans as a species. Beauty salons and makeup are used to help this function. The skin is not only an aesthetic tissue but it also has defensive functions that protect the body from various threats.

The skin, in other words, is a defensive tissue. The functions of the human skin are shown in Table 5.1.

Organisms that moved their habitat to the land from the sea had to adapt to the strict environment of dryness, and gained barrier functions to maintain the moisture in their cells and body liquids. To understand the details of these barrier functions, a great deal of research is conducted on the skin's stable cornification of the keratinocyte, the turnover or cornification process of the keratinocyte, or lipid secretion. When atopic dermatosis was found to be a barrier

**TABLE 5.1** The Functions of the Skin (Main Area)

| | |
|---|---|
| Dehydration Prevention | (Stratum corneum) |
| Blocking foreign material | (Stratum corneum) |
| UV blocking | (Melanin) |
| Removing foreign material | (Immune cells) |
| Sensory | (Neural terminal) |
| Flexibility/Durability | (Dermis) |
| Excretion of foreign material | (Hair, Stratum corneum, Sweat gland) |
| Body heat adjustment | (Circulation, Sweat gland) |
| Absorption of substances | (Pores, Stratum corneum) |
| Maximizing attractiveness | (Hair, Color, Smell) |

disorder, these studies became even more important. This process is also influenced by immune factors and neural factors, and research has spread starting with monoculture of keratinocytes.

### 5.3.1 Barrier Functions and Moisture Retaining

In the 1970s, Elias et al. proposed that the barrier functions were made of a mortar-block structure with the stratum corneum cells and the intercellular lipids,[14] and this concept has become commonly known. On the other hand, the importance of the moisture-retaining properties of free amino acids has also been recognized, which was first reported by Burke et al.[15] in 1966. In the 1980s, Horii et al. revealed the relation of dry skin and free amino acids[16] and Koyama et al. reported that the skin condition can be evaluated by the composition of free amino acids in the stratum corneum.[17] With this research, biochemical methods were established in addition to the previous physical methods to evaluate the effectiveness of cosmetics. Studies on free amino acids revealed the importance of skin moisturizing, and Ozawa et al. proposed a reasonable combination of water, oily substances, and humectant that were effective in treating the physicochemical condition of the stratum corneum to lead biological homeostasis of the epidermis[18] (Fig. 5.5). This is a milestone of the first generation of skin care and still remains as a basis of skin

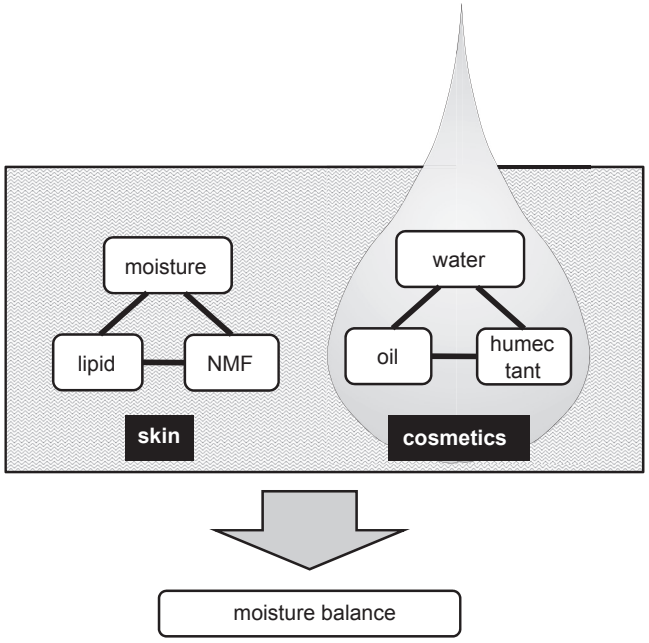



FIGURE 5.5 **The moisture balance of the skin.** As the barrier function of the skin is maintained by three components—moisture, lipid, and natural moisturizing factors—cosmetics containing proper combination of water, oil, and humectants, which maintain the moisture balance, are highly effective. This is the first generation of skin care.

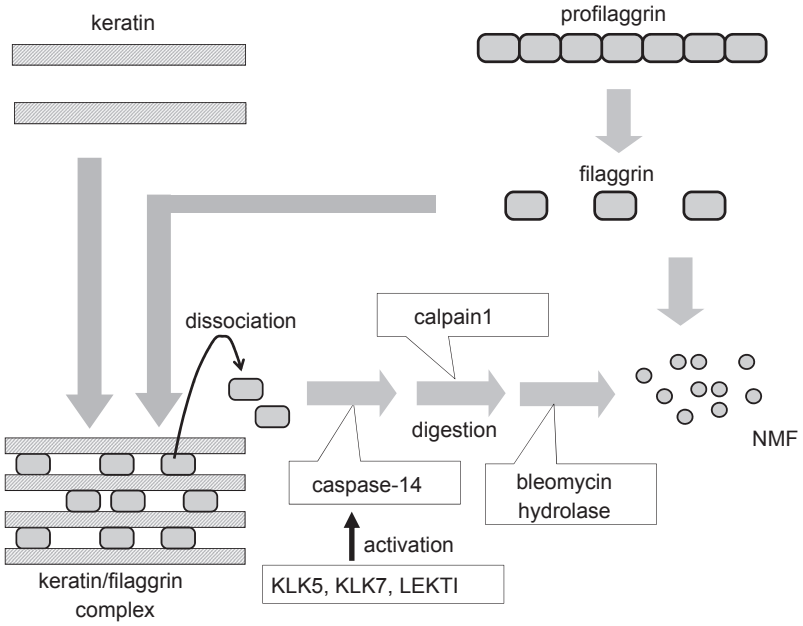



FIGURE 5.6 **Production of natural moisturizing factors (NMF).** Filaggrin forms a complex with keratin fibers, which contributes to the barrier function. NMF is produced by serial digestion of filaggrin with caspase-14, calpine-1, and bleomycin hydrolase, either a digested one from profilaggrin or a dissociated one from the keratin/filaggrin complex.

care treatment. Although this area was first focused on over 30 years ago, free amino acid research has progressed and has shown new developments. Since atopic dermatosis shows immunity disorders, atopy was believed to be an immunity allergic disorder, but after filaggrin gene mutation was found in some of the patients, it has been perceived as a barrier disorder. Filaggrin was found to supply free amino acids, and the specifics of the dissociation process were revealed by Hibino's group.[19,20] Profilaggrin is isolated from keratin fibers, and as it citrullinates, they are divided by various proteolytic enzymes. Bleomycin hydrolase is one substance that relates to this activity, which was originally used as a tolerance against carcinostatic agents, thus its name, but was shown that it can decompose partial filaggrin freed from keratin fibers into amino acids in the epidermis (Fig. 5.6). The effects are focused on the function with barrier and moisturizing functions of the skin, and should be a subject not only in atopic dermatosis but also in cosmetic science.

Amino acids have two isomers, L-isomers and D-isomers. The amino acids used in food products are L-glutamic acids. Most of the amino acids that compose the proteins in the body are L-amino acids, but there are also some D-amino acids, and enzymes (racemase) that transition L-amino acids to D-amino acids have also been found. Tojo et al. have developed an analysis method to identify L-amino acids and D-amino acids, and found that D-amino acids and racemase exist in the skin.[21] Furthermore, they found that the D-asparagine induces collagen fiber growth in the dermis. A large amount of D-amino acids is found in fermented foods. It has been proved that D-amino acid drinks help increase the D-amino acid content in the skin, and the progress of analytical technology in cosmetic science is being applied to foods.

### 5.3.2 Stratum Corneum Formation

The stratum corneum is known to thicken with age. As the skin itself becomes thinner, the peeling of the stratum corneum becomes slower. This may be a counter reaction to maintain the barrier function of the thinning skin. Cosmetic science has a role here as it may be used to induce the peeling of the stratum corneum and the turnover of the epidermis. Lundstrom et al.[22] and Koyama's group.[23] independently identified that chymotrypsin-like and trypsin-like enzymes (currently known as KLK-7 and KLK-5, respectively) are related to desquamation of stratum corneum, and revealed the influence of aging and the external environment, and they pioneered research that showed the measures as well (Fig. 5.7). Nakanishi et al.[24] identified that the enzyme that induces the trypsin-like enzyme is enteropeptidase. There are still many unknown mechanisms of peeling, such as the protein orientation

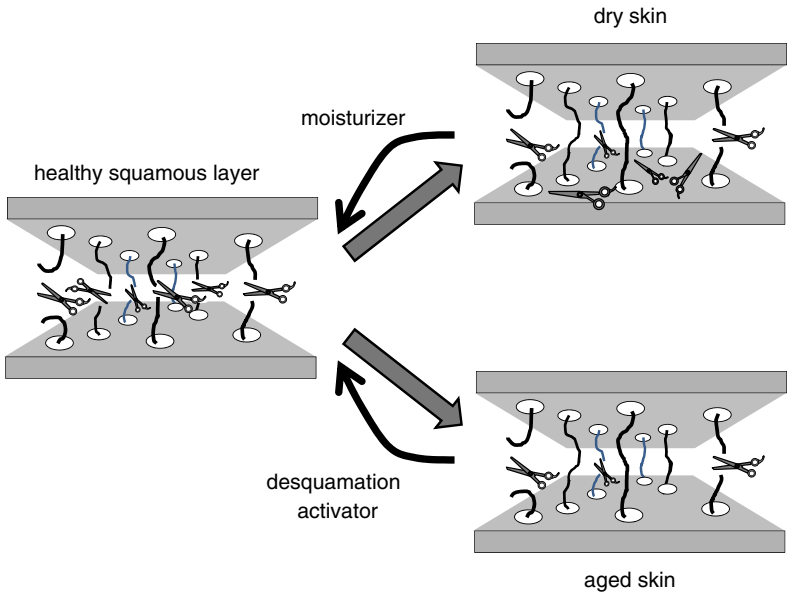



FIGURE 5.7 **Treatment of impaired desquamation.** The desquamation enzyme is inactivated in dry skin and decreased in aged skin, resulting in the thickening of the squamous layer. Moisturizers or desquamation activators in the skin care products reverse the impairment and form healthy skin.

in the stratum corneum or the change when holding and releasing water, and creating an environment that preserves the barrier functions while making the peeling enzymes active will be an important topic for further research.

If stratum corneum formation proceeds correctly, the cell nucleus disappears and protein is supplied, forming a strong barrier, but with distorted skin areas the cell nucleus remains at the skin surface. Hibino et al. have reported that there may be several pathways of the enucleation mechanism,[25] and revealing the entire mechanism is anticipated from future studies. There have been several models to explain the formation of the stratum corneum, such as biochemical analysis of intracellular signaling, and mathematical modeling based on stereoscopic observation using fluorescent labels in skin cells. For example, Amagai et al. are trying to reveal the order of stratum corneum formation by analyzing stereoscopic images of the skin using antibodies of tight junction composing protein as dyes. Such research can help reveal the mechanism of the barrier functions of the stratum corneum, and such biochemical information and mathematical analysis are expected to be used together to reveal the phenomena in the body.

### 5.3.3 Epidermal Cells

Maintenance of proper turnover of epidermal cells is required to keep the skin healthy. The finding by Kitamura et al. of the role of plasmin/plasminogen in the turnover[26] was one of the triggers of the treatment of dry skin.

Stem cell research is one of the hot spots now. Skin stem cells in the epidermis supply healthy keratinocyte. Preservation of these cells is vital to induce a healthy turnover. The epidermal stem cells were believed to exist in the bulge of hair follicles, but with the progress of analytic markers, it has been revealed that they also exist in basal layers other than the pores.[27] In cosmetic science, this indicates that the stem cells decrease with age and a solution is required to prevent the decrease. However, stems cells differ from other cells in how they rest most of the time and only divide when necessary. Thus, it is important to create an environment (a niche) where the stem cells can safely rest. Epidermal stem cells reside on the basement membrane (BM). The importance of the BM in cosmetic science has been proposed by Nishiyama and Amano et al.[28] It is believed that the adhesion with BM components is important in maintaining the stem cell characteristics (Fig. 5.8A and B). There are capillaries under the BM, and maintaining the health of the capillaries is vital to maintain the BM. Elucidation of this interaction pathway is anticipated, as well as development of a solution. Furthermore, myeloid stem cells have been studied with their interaction with the surrounding vessels and autonomic neurons, and there have been reports on their functions as switches that work in the blood when they wake up. Research on the stem cell niche requires considering the NICE system, explained later in this chapter.

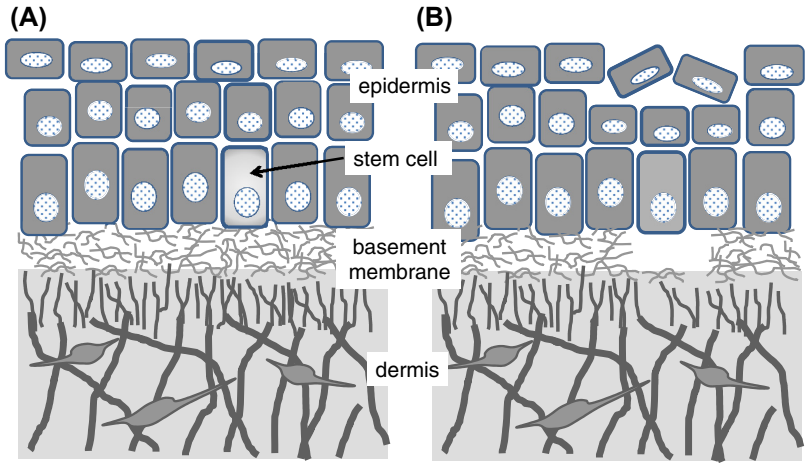



FIGURE 5.8 **Epidermal stem cell niche.** MCSP$^+$ cells in basal layer of epidermis are considered as interfollicular epidermal stem cells. Their stem cell phenotype is maintained by underneath basement membrane (A). Once the membrane is damaged, stem cells become senescent and the turnover of epidermis is impaired (B).

### 5.3.4 Epidermis Inflammation

The skin is directly stimulated by various stimulants from the outer world. To deal with these various stimulants, it has been revealed that the skin does not react to each stimulant separately but has a common reaction-controlling mechanism. There are factors called danger signals, or damage-associated molecular pattern (DAMP), that mediate the reaction. One of the first stimulants that were recognized as danger signals is extracellular ATP. Keratinocytes express various P2 receptors. When some keratinocytes are stimulated, ATP is released from the cells and bonds to the receptors of surrounding cells, spreading the reaction (Fig. 5.9). Inoue et al. have reported that induced expression of inflammatory factors caused by ultraviolet (UV) rays occurs with extracellular ATP-P2Y receptor pathways.[29] Additionally, the cells that are damaged with stimulation release DAMPs of high-mobility group box 1 proteins, which usually work in S100 proteins or cell nuclei. S100A8 and S100A9 have been reported to have a positive feedback on growth and inflammation.[30] Furthermore, SCCA1 has been known to be relevant to inflammation in the mouth or respiratory tract, and it was found that it is induced when the skin barrier is damaged,[31] and has an interesting relationship with the skin's inflammatory condition.

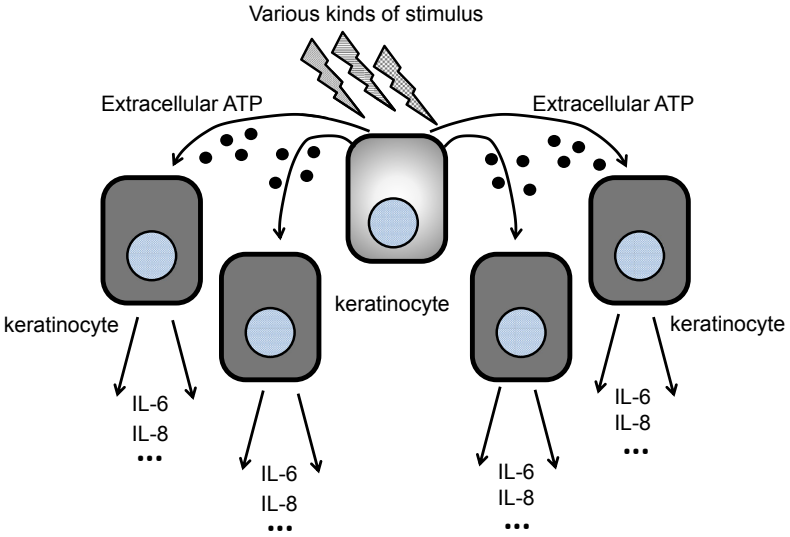



FIGURE 5.9 **Danger signal.** Various kinds of stimuli induce the release of extracellular ATP, which stimulates surrounding keratinocytes and produces inflammatory cytokines.

### 5.3.5 Melanocytes

Melanocytes are found in the epidermis, and the history of its research is long due to its unique character of producing pigment particles. Since they also have a strong visual impact, they have been widely studied as a field in basic biology with subjects such as fish and amphibians that change their skin color instantly according to the surrounding environment, or embryological studies on the stripes of zebras. Lerner et al.'s[32] research of injecting melanocyte stimulating hormones to observe the change of skin color is a prominent example of one of the many such research focused on humans. In our actual life, the social preference in beauty has been changing from tanned skin to whiter skin, and led to a transition in pigment studies in cosmetic science. In Asian countries, the preference for whiter skin has long been established, but in Western cultures, tanned skin is still considered healthy and sun bathing is a popular pastime. However, the knowledge that UV rays accelerate skin aging has spread in these Western countries, and sun-care products are becoming more commonly used. In these social situations, cosmetic science has developed, starting from controlling the genetic expression and activity of tyrosinase, which is the melanin synthesis rate-determining step. It is interesting that when observing skin sections of dark spots, melanocytes are not so dark. It can be observed that the melanin particles are injected into the surrounding keratinocytes, and the keratinocytes divide and do not move toward the surface and stay in the skin. This knowledge shows that the formation of dark spots is a result of complex factors such as direct stimulation to melanocytes, stimulation from surrounding keratinocytes, the change of keratinocytes with melanin, and even the body's hormone system, and the elucidation of the entire mechanism of dark spots formation is anticipated. Paralyzing the melanocytes is one of the easiest ways to inhibit stain formation, but with a notorious history in cosmetics of Rhododenol products that caused white spots, it is a challenge to maintain the safety of products and preserve the healthy functions when developing products.

### 5.3.6 Blood Vessels

There are usually no vessels in the epidermis, and they run under the epidermis. Previously, blood vessels were only thought as tissue to carry nutrients and oxygen to the skin cells, or to carry heat from the inner body to the surface. Research on circulation was mainly in physiological fields in relationship with functions such as body heat adjustment. However, it was found that fragile blood vessels and lymphatic vessels are formed when exposed to UV, and moisture and leukocytes leak from these fragile vessels and cause light inflammation. Since this discovery, vessels have become an important study topic in cosmetic science. Kajiya et al.'s research on apelin was innovative as they also considered solutions for this phenomenon.[33] Furthermore, recent studies show that the blood vessels under the epidermis are not merely substance carriers but also function to maintain the skin structure. As such, studies on blood vessels under the epidermis are becoming more important in cosmetic science.

### 5.3.7 Dermis

The extracellular matrix of the dermis has been widely studied to understand wrinkle formation and prevention, and many skin care products have been developed with indexes such as fibroblast growth or collagen synthesis induction/decomposing enzyme inhibition. Aside from these direct adjusting functions, the importance of stem cells in the dermis is becoming clear in recent studies. Yamanishi et al.[34] have shown that mesenchymal stem cells, which are precursors of collagen production cells, decrease with age, and they showed that PDGF-BB derived from platelets inhibits this phenomenon. Stem cells also exist in fat tissue. The effect of stem cells on the aging of skin is expected to be revealed with further research.

The subject of cosmetic science has mainly been the dermis, epidermis, or adnexa such as hair and nails. However, with the evolution of observation technology, research on deeper areas such as the condition of subcutaneous tissue is expected to become more focused upon. Since it is difficult to sample skin tissue on the face, studies on facial skin did not progress as much as other studies. Most of the studies on skin were with arms and other areas where observation and analysis was easier, and most of the diagrams and photographs of the skin are of the skin on the limbs. Facial skin has special functions, such as making expressions, and is different from other skin in many ways such as how it is directly connected to muscle terminals. Ezure et al.[35] observed the inner skin morphology in detail and revealed that the wedge structure weakens with age, and strongly influences facial sagging. In other words, the fat tissue under the skin grows larger with age and secretes a matrix decomposition enzyme called MMP9. The wedge structure of the dermis on the fat tissue starts to collapse with this phenomenon and the foundation can no longer support the skin, causing it to sag with gravity.

### 5.3.8 Total Body System

All of the subjects in cosmetic science introduced in this chapter so far were analysis of the reaction on partial skin. However, the skin is only a part of the whole body, and to analyze its change, it is vital to understand the relationship with the functions of the total body. A Harvard group was the first to announce this concept. O'Sullivan et al. announced a concept called neuro-immuno-cutaneous endocrinology in 1998,[7] explaining how the skin maintains its functions by interacting with the immune system, endocrine system, and neural system of the entire body. The basis of this theory was Hosoi et al.'s discovery on the skin's immunocytes, Langerhans cells, contact with the nerve fibers.[6] Dermatologists experienced in their clinical sites that stress has a negative effect on dermatosis and showed strong interest in this theory since it could help explain this phenomenon; it was named as one of the 50 discoveries of the year. Ever since the NICE concept was announced, many studies have been conducted on the effect of stress on the skin, and positive effects of stress relieving on the skin by researchers in dermatology as well as in cosmetic science. In 2002, a symposium on "Stress and Skin" was held in New York City. Such research has revealed that many neural factors have various effects on the skin, and the concept of NICE is becoming even more important. Peters et al.'s outline[36] summarizes the effects of neural factors on skin functions.

Neural factors also influence stress response systems. When stress is detected by the brain, the hypothalamus induces the secretion of corticotropin releasing hormone (CRH), and with this stimulation the pituitary secretes pro-opiomelanocortin (POMC). POMC is disconnected after peptides are synthesized, and becomes adrenocorticotropic hormone (ACTH), melanocyte stimulating hormones, or β-endorphin. ACTH circulates with the blood and acts on the adrenal cortex to secrete glucocorticoid. This is a type of steroid, cortisol, otherwise known as a stress hormone. The various functions of the skin are influenced by this stress hormone, so in cosmetic science solutions have been developed to prevent skin trouble by preventing negative effects of cortisol on the skin. On the other hand, Slominski et al.'s passionate research[37] proved that the reaction pathway from CRH to POMC and cortisol all exist in the skin (Fig. 5.10). When the skin is stimulated, a reaction similar to the entire body's stress reaction occurs in local areas of the skin. Fisher et al. recently reported that a POMC, β-endorphin is produced from keratinocytes with UV stimulation, and raises the pain threshold.[38] These results show that β-endorphin acts as an opioid and creates a lifting emotion, which suggests why we prefer sunlight. They have suggested that this reaction was rational during the evolution of humans because vitamin D is produced in the skin, but today it has become a cause of skin cancer. Many interesting studies have been announced as such, showing the importance of NICE-based studies.

If stimulation is diffused, the stress response systems in the skin also diffuse, and skin trouble solutions based on NICE research are anticipated. An example of a recent study is the utilization of the calming effect of Langerhans cells. As shown earlier, Inoue et al. have identified the keratinocyte receptors (P2Y) of the skin's stimulant response reaction against various stimulants.[29] When a stimulated keratinocyte releases ATP out of its cell, the surrounding cells with receptors all react simultaneously and spread the inflammatory reaction (Fig. 5.9). On the other hand, the surface of Langerhans cells is reported to have a unique extracellular ATP decomposing enzyme.[39] The significance

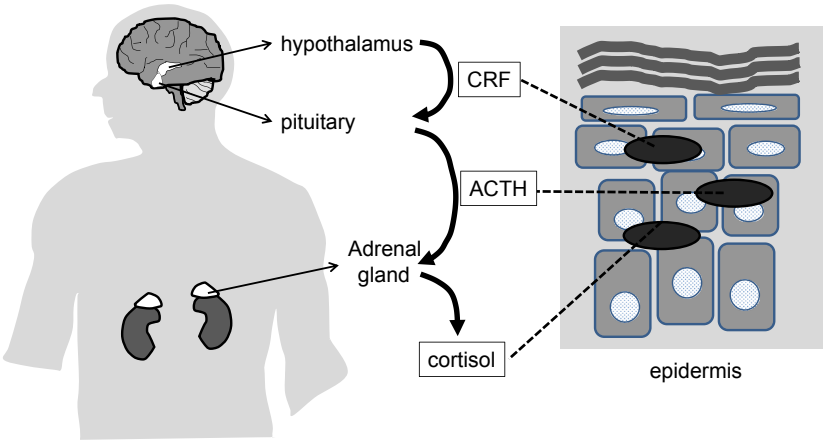



FIGURE 5.10 **HPA axis in the skin.** Psychological stress induces the release of corticotropin releasing hormone from hypothalamus (H), which induces secretion of adrenocorticotropic hormone (ACTH) in pituitary gland (P). ACTH activates the release of cortisol from adrenal gland (A). These three mediators of stress response are produced in epidermis.

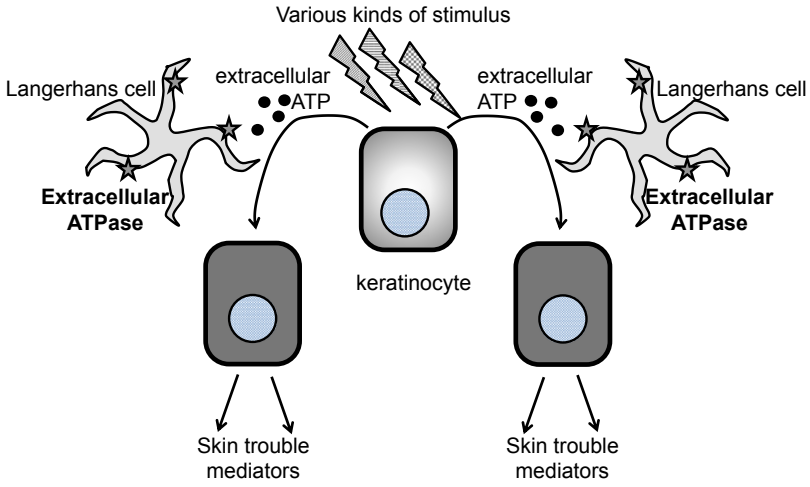



**FIGURE 5.11 Calming function of Langerhans cells.** Epidermal Langerhans cells express unique ATPase (CD39) on their surface and degrade extracellular ATP released from surrounding keratinocytes, which leads to the prevention of a hyper reaction or a prolonged reaction to stimuli, accelerating skin aging.

of the Langerhans cell's calming effect on the human skin has been discovered with the dermatitis symptoms of zinc-deficiency patients.[40] The skin maintains its homeostasis with its self-defense functions. Hosoi et al. have confirmed that the skin activates heparanase when it is stimulated, but the calming effect of Langerhans cells inhibits the activation and has been found to eliminate causes of various skin troubles (manuscript in preparation; Fig. 5.11). The Langerhans cell calming enzyme has also been found to decrease with aging, and skin care has been tested to improve such conditions. Accumulation of excess stimulant response can cause skin problems and accelerate aging. These approaches have shown significant roles in daily skin care in terms of prevention. Common products are designed to improve each problem of the skin, but skin care can also play a role of improving the homeostasis of each individual to prevent general skin aging. Solving problems of the skin is an important function and may attract academic attention, but this alternate method of skin care would hopefully be recognized.

## 5.4 CONCLUSIONS

The goal of dermatology is with the health of human beings, and the subject of analysis can be as small as molecular level and genetic level, to cell level, tissue level, individual level, and even social level. With the progress of analytical technology, structures that were previously unobservable can now be observed to study microscopic structures and phenomena. Comprehensive analysis has also allowed us to find changes that were not known.

Ever since the discovery of intercellular information transmission by small molecules such as reactive oxygen species and nitric monoxide, effects of UV and vasoconstriction are also being studied. Low molecules such as amino acids and ATP have also been studied after they have been recognized in neural systems, and in the skin they are studied not only as component molecules of protein or intracellular energy sources but also as intercellular information transmission substances. Genetic studies are also not only on the expression of mRNA, but large-scale research on mutation of single bases has revealed its correlation with dermatosis and skin condition, and high-level structure analysis of methylation or chromosomes is also being researched. Analysis of intracellular structures other than the nucleus is evolving, and research on autophagy and the intracellular protein digestion and reuse have started. The skin is divided into the dermis and epidermis, and most of the skin is composed of keratinocytes and fibroblasts. Previously, fundamental research was conducted on individually bred cells, but this was insufficient to show the actual phenomena in the skin, such as the interaction of keratinocytes and fibroblasts, and studying the interaction with the few but unique melanocytes, Langerhans cells, neural cells, vascular endothelial cells have also become required. The skin made from these cells is only a part of the human body and is influenced by neural, endocrine, and immune systems. The skin interacts with the centrum through these systems and is deeply related to the physiology of the brain and mental functions. As such, cosmetic science can range from molecular levels to social levels, but a comprehensive view of these subjects is required when considering the fundamental goal of improving human life. The studies we have seen in this chapter were mainly analysis of static reactions. However, the skin and body constantly changes with the change of the surrounding environment and preserves a dynamic equilibrium. Although not mentioned in this chapter, a day-and-night rhythm has been found with the expression of collagen

genes in the dermal fibroblasts. In the medical world, there is a field called chronopharmacology that studies chronological aspects such as cycles of symptoms or effective medicine intake timing. This aspect can be implemented into cosmetic science to help understand the dynamic change of the skin and can lead to maximizing the effects of the research results.

The progress of cosmetic science will not only help skin problems but will also help us to have a more wholesome life. We must always keep this ultimate goal in mind when studying cosmetic science from molecular levels to social levels.

## References


1. Lalko JF, Kimber I, Gerberick GF, Foertsch LM, Api AM, Dearman RJ. The direct peptide reactivity assay: selectivity of chemical respiratory allergens. *Toxicol Sci Off J Soc Toxicol* 2012;**129**(2):421−31.
2. Takenouchi O, Fukui S, Okamoto K, Kurotani S, Imai N, Fujishiro M, et al. Test battery with the human cell line activation test, direct peptide reactivity assay and DEREK based on a 139 chemical data set for predicting skin sensitizing potential and potency of chemicals. *J Appl Toxicol* 2015;**35**(11):1318−32.
3. Grafstrom RC, Nymark P, Hongisto V, Spjuth O, Ceder R, Willighagen E, et al. Toward the Replacement of Animal Experiments through the Bioinformatics-driven Analysis of 'Omics' Data from Human Cell Cultures. *Altern Lab Anim* 2015;**43**(5):325−32.
4. Hoffman RM. In vivo imaging with fluorescent proteins: the new cell biology. *Acta Histochem* 2004;**106**(2):77−87.
5. Egawa G, Honda T, Tanizaki H, Doi H, Miyachi Y, Kabashima K. In vivo imaging of T-cell motility in the elicitation phase of contact hypersensitivity using two-photon microscopy. *J Invest Dermatol* 2011;**131**(4):977−9.
6. Hosoi J, Murphy GF, Egan CL, Lerner EA, Grabbe S, Asahina A, et al. Regulation of Langerhans cell function by nerves containing calcitonin gene-related peptide. *Nature* 1993;**363**(6425):159−63.
7. O'Sullivan RL, Lipper G, Lerner EA. The neuro-immuno-cutaneous-endocrine network: relationship of mind and skin. *Arch Dermatol* 1998; **134**(11):1431−5.
8. Kikuchi K, Tagami H. Noninvasive biophysical assessments of the efficacy of a moisturizing cosmetic cream base for patients with atopic dermatitis during different seasons. *Br J Dermatol* 2008;**158**(5):969−78.
9. Horimukai K, Morita K, Narita M, Kondo M, Kitazawa H, Nozaki M, et al. Application of moisturizer to neonates prevents development of atopic dermatitis. *J Allergy Clin Immunol* 2014;**134**(4):824−30, e6.
10. Dumas D, Hupont S, Huselstein C, de Isla N, Rousseau M, Werkmeister E, et al. SHG as a new modality for large field of view imaging to monitor tissue collagen network. *Bio-Med Mater Eng* 2012;**22**(1−3):159−62.
11. Egawa M, Tokunaga K, Hosoi J, Iwanaga S, Ozeki Y. In situ visualization of intracellular morphology of epidermal cells using stimulated Raman scattering microscopy. *J. Biomed. Opt.* 2016;**21**(8): 86017 (online).
12. Cong L, Ran FA, Cox D, Lin S, Barretto R, Habib N, et al. Multiplex genome engineering using CRISPR/Cas systems. *Science (New York, NY)* 2013;**339**(6121):819−23.
13. Mali P, Yang L, Esvelt KM, Aach J, Guell M, DiCarlo JE, et al. RNA-guided human genome engineering via Cas9. *Science (New York, NY)* 2013; **339**(6121):823−6.
14. Elias PM, Friend DS. The permeability barrier in mammalian epidermis. *J Cell Biol* 1975;**65**(1):180−91.
15. Burke RC, Lee TH, Buettner-Janusch V. Free amino acids and water soluble peptides in stratum corneum and skin surface film in human beings. *Yale J Biol Med* 1966;**38**(4):355−73.
16. Horii I, Nakayama Y, Obata M, Tagami H. Stratum corneum hydration and amino acid content in xerotic skin. *Br J Dermatol* 1989;**121**(5): 587−92.
17. Koyama J, Horii I, Kawasaki K, Nakayama Y, Morikawa Y, Mitsui T. Free amino acids of stratum cormeum as a biochemical marker to evaluate dry skin. *J Soc Cosmet Chem* 1984;**35**:183−95.
18. Ozawa T, Nishiyama S, Horii I, Kawasaki K, Takahashi M, Kumano Y, et al. Function of Moisturizers and Their Roles in Cutaneous Aging. *Cutaneous Aging* 1988:607−18.
19. Kamata Y, Taniguchi A, Yamamoto M, Nomura J, Ishihara K, Takahara H, et al. Neutral cysteine protease bleomycin hydrolase is essential for the breakdown of deiminated filaggrin into amino acids. *J Biol Chem* 2009;**284**(19):12829−36.
20. Sakabe J, Yamamoto M, Hirakawa S, Motoyama A, Ohta I, Tatsuno K, et al. Kallikrein-related peptidase 5 functions in proteolytic processing of profilaggrin in cultured human keratinocytes. *J Biol Chem* 2013;**288**(24):17179−89.
21. Inoue R, Yoshihisa Y, Tojo Y, Okamura C, Yoshida Y, Kishimoto J, et al. Localization of serine racemase and its role in the skin. *J Invest Dermatol* 2014;**134**(6):1618−26.
22. Lundstrom A, Egelrud T. Cell shedding from human plantar skin in vitro: evidence that two different types of protein structures are degraded by a chymotrypsin-like enzyme. *Arch Dermatol Res* 1990;**282**(4):234−7.
23. Suzuki Y, Nomura J, Hori J, Koyama J, Takahashi M, Horii I. Detection and characterization of endogenous protease associated with desquamation of stratum corneum. *Arch Dermatol Res* 1993;**285**(6):372−7.
24. Nakanishi J, Yamamoto M, Koyama J, Sato J, Hibino T. Keratinocytes synthesize enteropeptidase and multiple forms of trypsinogen during terminal differentiation. *J Invest Dermatol* 2010;**130**(4):944−52.
25. Yamamoto-Tanaka M, Makino T, Motoyama A, Miyai M, Tsuboi R, Hibino T. Multiple pathways are involved in DNA degradation during keratinocyte terminal differentiation. *Cell Death Dis* 2014;**5**:e1181.
26. Kenji Kitamura KY, Ito A, Fukuda M. Research on the Mechanism by which Dry Skin Occurs and the Development of an Effective Compound for Its Treatment. *J Soc Cosmet Chem Japan* 1995;**29**(2):133−45.
27. Ghali L, Wong ST, Tidman N, Quinn A, Philpott MP, Leigh IM. Epidermal and hair follicle progenitor cells express melanoma-associated chondroitin sulfate proteoglycan core protein. *J Invest Dermatol* 2004;**122**(2):433−42.

28. Ogura Y, Matsunaga Y, Nishiyama T, Amano S. Plasmin induces degradation and dysfunction of laminin 332 (laminin 5) and impaired assembly of basement membrane at the dermal-epidermal junction. *Br J Dermatol* 2008;**159**(1):49–60.
29. Inoue K, Hosoi J, Denda M. Extracellular ATP has stimulatory effects on the expression and release of IL-6 via purinergic receptors in normal human epidermal keratinocytes. *J Invest Dermatol* 2007;**127**(2):362–71.
30. Nukui T, Ehama R, Sakaguchi M, Sonegawa H, Katagiri C, Hibino T, et al. S100A8/A9, a key mediator for positive feedback growth stimulation of normal human keratinocytes. *J Cell Biochem* 2008;**104**(2):453–64.
31. Katagiri C, Iida T, Nakanishi J, Ozawa M, Aiba S, Hibino T. Up-regulation of serpin SCCA1 is associated with epidermal barrier disruption. *J Dermatol Sci* 2010;**57**(2):95–101.
32. Lerner AB, Shizume K, Fitzpatrick TB, Mason HS. MSH: the melanocyte-stimulating hormone. *Archives of Dermatology and Syphilology* 1954; **70**(5):669–74.
33. Sawane M, Kajiya K, Kidoya H, Takagi M, Muramatsu F, Takakura N. Apelin inhibits diet-induced obesity by enhancing lymphatic and blood vessel integrity. *Diabetes* 2013;**62**(6):1970–80.
34. Yamanishi H, Fujiwara S, Soma T. Perivascular localization of dermal stem cells in human scalp. *Exp Dermatol* 2012;**21**(1):78–80.
35. Ezure T, Yagi E, Amano S, Matsuzaki K. Dermal anchoring structures: convex matrix structures at the bottom of the dermal layer that contribute to the maintenance of facial skin morphology. *Skin Res Technol* 2015.
36. Peters EM, Ericson ME, Hosoi J, Seiffert K, Hordinsky MK, Ansel JC, et al. Neuropeptide control mechanisms in cutaneous biology: physiological and clinical significance. *J Invest Dermatol* 2006;**126**(9):1937–47.
37. Slominski AT, Manna PR, Tuckey RC. Cutaneous glucocorticosteroidogenesis: securing local homeostasis and the skin integrity. *Expe Dermatol* 2014;**23**(6):369–74.
38. Fell GL, Robinson KC, Mao J, Woolf CJ, Fisher DE. Skin beta-endorphin mediates addiction to UV light. *Cell* 2014;**157**(7):1527–34.
39. Mizumoto N, Kumamoto T, Robson SC, Sevigny J, Matsue H, Enjyoji K, et al. CD39 is the dominant Langerhans cell-associated ecto-NTPDase: modulatory roles in inflammation and immune responsiveness. *Nature Med* 2002;**8**(4):358–65.
40. Kawamura T, Ogawa Y, Nakamura Y, Nakamizo S, Ohta Y, Nakano H, et al. Severe dermatitis with loss of epidermal Langerhans cells in human and mouse zinc deficiency. *J Clin Invest* 2012;**122**(2):722–32.

CHAPTER

# 6

# Psychology of Cosmetic Behavior

*T. Abe*

**Tohoku University, Sendai, Japan**

In 1985, the first book of psychological research on cosmetic behavior was published, The Psychology of Cosmetic Treatments by Graham and Kligman. The book revealed and spread the unknown psychological potential of cosmetic usage as an adjunct to medication, so-called cosmetic therapy. Not only cosmetic therapy but also various psychological studies have been undertaken since. The following authors also successfully published books on this topic after the 1990s in Japan: Shiseido Institute of Beauty Sciences,[50] Daibo and Kohyama,[15] Daibo,[16] and Shiseido Beauty Solution Development Center.[51]

The aim of this chapter is to introduce the psychological attainment of cosmetics and discuss the functional role that cosmetic behavior plays in everyday life, after reviewing the history of cosmetics.

## 6.1 PREHISTORY OF COSMETICS

Cosmetic behavior is a custom that is peculiar to humans. However, it is not difficult to find similar behavior among animals. Paramecia have taxes. They escape from harmful circumstances using their ciliary movement, which removes poisonous materials such as acid with the current. This behavior is intended to protect their own body surface. It might correspond to washing the human body. In other words, even paramecia perform skin care. The Japanese crested ibis spreads a secretion on its own feathers to display a mating color. This behavior corresponds closely to human makeup. Olfactory communication by urine is popular among many mammals such as dogs. This natural phenomenon is not so different from self-presentation by fragrance.

Nevertheless, these animal behaviors are performed by animals using their own organs or secretions. They are clearly distinguished from human cosmetic behavior, which uses artificial materials. Humans wash their faces with facial cleanser, color their lips applying lipsticks, and wear scented fragrances; human cosmetic behavior is a tool-potentiated behavior conducted using cosmetics. The activities are not different from increasing the power of striking an object with a hammer or acceleration of motion using a car.

The origin of cosmetics remains unclear, but many skulls colored with red ochre have been discovered at historic sites worldwide.[25,52] Even though the red ochre might be painted after death, humans colored themselves at least a few tens of thousands of years ago.[1]

Ancient Egyptians, citizens of one of the four great civilizations of the world, used various cosmetics that share the same sense as those of present-day cosmetics.[53] Unguent from fats and oils of various animals and vegetables was used widely. A supply of massage oil might form part of a workman's wages, as documented in a case from the nineteenth dynasty (1295–1186 BC). In addition to these skin care items, makeup items such as eye shadow, eyeliner, and mascara have advanced. Fragrant ointments produced by leaching the aromatic essences from myrrh, desert date, terebinth, or frankincense with a fatty oil have been used as modern fragrances. A face-paint palette excavated from Predynastic period ruins (about 3500 BC) was used to produce eye shadow pigments by crushing

[1] I appreciate valuable support from several specialists: Satoshi Ogihara (ancient Greek spelling), Yoshitaka Kanomata (archaeological advice on red ochre), and Keiko Nozawa (information about socio-estheticians).


Copyright © 2017 Elsevier Inc. All rights reserved.

and powdering green malachite, galena (lead sulfide), and other materials.[59] The usage of cosmetics, which started from the dawn of the civilization, has shown remarkable progress.[20]

## 6.2 HISTORY OF COSMETICS

Paquet[41] described the historical change of women's beauty and explained the history of cosmetics in detail. However, she wrote only about European history, especially about France, following ancient Egypt and Greece. Other countries were mentioned only at the end of the book in the appendix named "*beautés d'ailleurs*: beauty of others."

It is particularly interesting that Japanese cosmetic history presents a clear contrast with the Western cosmetic history described in the book. This section describes the cosmetic history of the Occident as described by Paquet in comparison to the cosmetic history of Japan by Abe.[4]

The first viewpoint of comparison is the terminological distinction between skin care and makeup. Paquet[41] reported that he distinguished *kosmêtikê technê* from *kommôtikê technê* related to cosmetic behavior in ancient Greece. *Kosmêtikê technê* refers to the technique of dressing (*l'art de la toilette*) to tidy up oneself by ornaments, clothes, hairstyle, and also hygiene and precaution against disease. *Kommôtikê technê* is the technique of vanity (*l'art du fard*), sham, and excess. Ancient Romans also distinguished *ars ornatrix* from *ars fucatrix*; the former entails body treatment and usage of harmless cosmetics, and the latter includes the usage of even harmful materials.[41]

In about 390 BC, the famous Greek philosopher Plato distinguished art and habitude (in other words, knack or flattering) in his work *Gorgias*. According to his definition, art pursues good, habitude pursues the pleasant. Furthermore, he referred to legislation and justice as arts of mind, and to medicine and gymnastics as arts of the body. He criticized self-adornment as well as sophistry, rhetoric, and cookery because they are not art for good but are only habitude, knack, or flattering for the pleasant.[42]

Table 6.1 presents a distinction of art/habitude by Plato.[1] The definition of Paquet[41] related to ancient Greece and Rome can be seen in the bottom of Table 6.1, as *kosmêtikê technê* and *ars ornatrix* at the art column, pursuing good; and *kommôtikê technê* and *ars fucatrix* at the habitude column, pursuing the pleasant. According to Paquet, *kommôtikê technê* brought the word *technê*, but Plato would not agree. He might assert that *kommôtikê* would not be art (*technê*) but only habitude, so "*kommôtikê empeiria* (self-adornment habitude)" appears to be suitable.

Modern cosmetic products are not harmful at all. Actually, they facilitate health with both skin care and makeup. Nevertheless, it seems that *kosmêtikê technê* and *ars ornatrix* correspond to skin care, and *kommôtikê technê* and *ars fucatrix* correspond to makeup. In the cosmetic history of the Occident, skin care and makeup might be distinguished in both word and concept since early times.

This distinction cannot be found in the Japanese history of cosmetics. Takahashi[56] described the history of the Japanese word *keshou*, which has meant makeup since the Kamakura period, in about the 13th century. Even in *Miyako fuzoku kewaiden*,[45] a total dressing guide of the Edo period, *keshou* meant makeup. Furthermore, skin care was called *keshou-shita*, that is, "under makeup." Skin care was a popular custom of Japanese women, but it did not have its own specific designation then.

**TABLE 6.1** Distinction of Art/Habitude in *Gorgias*, Written by Plato

| | | |
|---|---|---|
| Object | art → good<br>(τέχνη → ἀγαθόν) | Habitude (knack, flattering) → pleasant<br>(ἐμπειρία (Τριβή, κολακεία) → ἡδύ) |
| Mind | Legislation<br>(νομοθετική) | Sophistry<br>(σοφιστική) |
| | Justice<br>(δικαιοσύνη) | Rhetoric<br>(ῥητορική) |
| Body | Medicine<br>(ἰατρική) | Cookery<br>(ὀψοποιική) |
| | Gymnastic<br>(γυμναστική) | Self-adornment<br>(κομμωτική) |
| *By Paquet (1997)* | *kosmêtikê technê**<br>*(κοσμητική τέχνη)* | *kommôtikê technê**<br>*(κομμωτική (τέχνη))* |
| | *ars ornatrix*** | *ars fucatrix*** |

Arranged referring Kaku[27] and Lamb's translation.[42] The last row shows ancient Greek* and Roman** distinction of cosmetic behavior by Paquet.[41]

The name for skin care was *kiso-keshou* even in the middle of the 20th century[5]—preparation before makeup. In the 1990s, at length, many people came to use the words *skin care* and *makeup* in Japanese pronunciation: *sukinkea* and *meikyappu*. This verbal change might reflect the change of attitude or intention by which they apply skin care items for skin health and not as preparation for makeup.[4] Consequently, Japanese people today distinguish skin care from makeup using loan words.

A second viewpoint for comparison is the basic material used for skin care. Paquet[41] presented a photograph of relief on Tutankhamun's throne in which his wife Ankhesenamen applied skin care oil to him to protect him from developing dry skin because of the ultraviolet rays of the strong Egyptian sunlight. She also described skin care with oil in an ancient Roman public bathhouse. Since then, people in the Western world have used oils mainly as skin care materials, for example, as an emulsion or skin cream.

However, oil was seldom used for skin care in Japan because people did not eat meat or use oil for cooking during Japan's long history. In the middle age of the Edo period (about the 18th century), they used skin lotion made from flower essence, named *Hana-no-tsuyu* (dewdrop of flower), *Edo-no-mizu* (water of Edo), and *Kiku-no-tsuyu* (dewdrop of chrysanthemum), for the preparation of facial powder. *Nuka-bukuro* (a small bag of rice bran powder) was used for the same purpose and for washing the face and hair. Even when Japanese people came to use modern cosmetics from Europe during the 20th century, they hesitated to use oily emulsions. They accepted them only after they had been redesignated as "nutrient lotions."[5,49] The Japanese preference for water persists. When the ratios of women lotion users for night skin care were 35% in Paris and 32% in New York, the ratio was 98% in Japan (research by Shiseido in 2001).[7] National sales in Japan 2014 were reported as the following: emulsions, 68,773 million yen; skin cream, 81,647 million yen; and lotion, 157,697 million yen.[43]

A third point to consider is differences of attitudes related to hygiene or sanitation. People in ancient Egypt made remarkable progress in cosmetic culture to develop almost all prototypes of modern cosmetics. Ancient Roman people loved public bathhouses and spent long periods in them. However, after the spread of Christianity, cosmetic behavior was suppressed until the end of medieval times. It was thought that cosmetic behavior conflicted with Christian doctrine that everything natural is a work of God and that everything artificial is the work of the Devil.[41] According to Ref. 14, not only cosmetics but also bathing were suppressed in France in the 16th century because hazardous substances were believed to permeate into the body through pores. In the 18th century, this view spread in England, where one record by a doctor noted that men and women in London did not wash their bodies, except for the face and hands, for many years.

Japan had no religious suppression against physical hygiene or sanitation through history. According to ancient *Shinto*, the Japanese native traditional religion, it was performed as a ritual for spiritual purification (*Misogi*) by performing ablutions in rivers. Buddhism, introduced into Japan in the 6th century, also emphasized hygiene and sanitation. Wealthy people donated their large bath rooms to poor people to reward virtuous conduct. Many visitors from the Western world during the Meiji Restoration (c.1868), in their memoirs about Japan (e.g., Refs. 47,54,38), expressed their surprise that Japanese people were clean and sanitary.

Table 6.2 presents a contrastive history of cosmetic custom between the Western world and Japan.[8]

As described earlier, the cosmetic history of the West and Japan has contrasting features that persist even today. However, a common trend in both areas is that cosmetics became a custom of the privileged class in special situations in ancient times. Subsequently, they became popular gradually. Furthermore, it is also a common feature that women came to play a leading role in cosmetics. In addition, cosmetic customs are changing, becoming homogeneous worldwide, much like fashion in clothing. The psychological effects of cosmetics can be discussed on the premise that cosmetic behavior has substantial communality worldwide, with certain consideration of regional characteristics.

**TABLE 6.2** Historical Features of Cosmetic Customs in the Western World and Japan

| | **Western World** | **Japan** |
|---|---|---|
| Verbal distinction between skin care and makeup | Clear distinction from the ancient age of Greece and Rome | Skin care as preparation for makeup. Distinction after the 1990s. |
| Main material of skin care | Oil | Water |
| Longing for hygiene and sanitation (religious attitudes) | Weak (suppressed) | Strong (facilitated) |

*Modified from Abe T. Psychological studies of skincare in Japan: a review.* Tohoku Psychologica Folia *2004;**63**:53–60.*

## 6.3 PSYCHOLOGY OF SKIN CARE

The expectations for skin care in the morning and evening mutually differ. Fig. 6.1 presents results of questionnaire study of preferred skin care in the morning and evening using a method of paired comparisons.[3,8] Respondents preferred "refreshed," "cool," and "fast" in the morning. Regarding "wet/dry," dry appears to be slightly dominant. However, in the evening, "relaxed," "wet," "warm," and "slow" were preferred. This result suggests that in the morning, skin care facilitates awakening, with soothing in the evening.

Massage performed by professional beauticians, sometimes called spa or esthetic massage (beauty massage), is a special skin care technique. Massage itself exists from prehistoric times. Its true worth in health was realized at the end of the 20th century, and empirical research related to it increased.[19] For example, massage therapy decreases cortisol and increases serotonin and dopamine.[18]

Uvnäs-Moberg[62] emphasized the importance of massage to activate a "calm and connection system." This physiological system plays against the *fight–flight stress response*, which is controlled by the sympathoadrenal medullary axis and the hypothalamo–pituitary–adrenocortical (HPA) axis.[63] Whereas fight–flight stress response is a countermeasure against emergency with catecholamine and cortisol, the calm and connection system contributes to growth with oxytocin.

Uvnäs-Moberg[62] reported three effects of massage as follows: (1) Massage to adults decreases blood pressure, heart rate, and stress hormones to facilitate health; (2) Massage to children brings increased calm and interpersonal maturity, as well as decreased aggression and complaints of disorders; and (3) Affectionate massage to a premature baby facilitates its weight increase.

Beauty massage has a similar psychophysiological effect. It suppresses sympathoadrenal medullary and HPA activity. The effect is not simple suppression but a unique temporal change of successive soothing followed by slight activation. Fig. 6.2 presents a comparison of the heart rate change of two conditions: beauty massage to the body was performed by a beautician in experimental conditions; then using the same posture but no massage in control conditions.[3,4] The control condition educed increased heart rate when the posture changed from facedown to faceup through muscular activity, but the experimental condition showed a consistent decrease of heart rate and a slight rise at the end of the treatment.

With slight reactivation at the finishing procedure, a beautician patted the participant's face with cool astringent lotion, then bent and stretched the participant's arms. This treatment resembles "canceling," which is conducted at the end of autogenic training, a representative relaxation training. Canceling is a refreshing procedure to bring a person back to a usual state from a deep relaxation state. Mature beauticians adopt these canceling-like procedures aimed at their refreshing effects without knowledge of autogenic training. They perform the movements with tacit knowledge. Empirical research can enable the development of new methods of beauty massage by changing tacit knowledge into explicit knowledge.

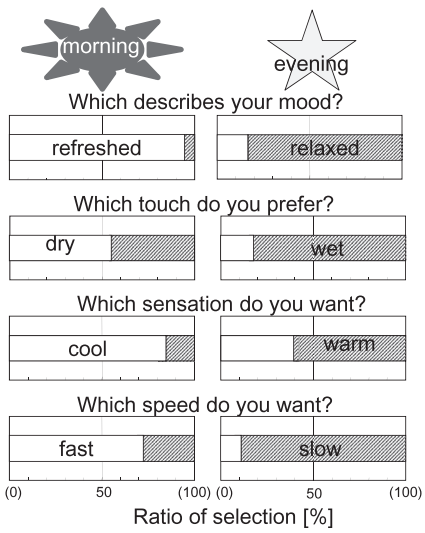



**FIGURE 6.1** Skin care product preferences in the morning and evening. Questionnaire administered in 1999 to 500 15–70-year-old women (371 replies). Forced choice was required. *Modified from Abe T. Psychological studies of skincare in Japan: a review.* Tohoku Psychologica Folia *2004;**63**: 53–60.*

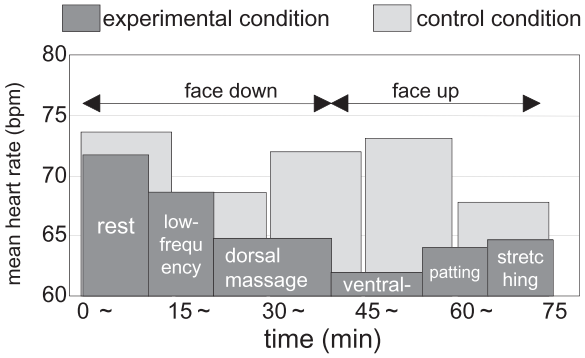



**FIGURE 6.2** Heart rate change by beauty massage to the body. *Modified from Abe T.* Sutoresu to keshou no shakaiseirishinrigaku (The social Psychophysiology of Stress and Cosmetic Behavior). *Tokyo: Fragrance Journal Inc 2002a [In Japanese].*

Continuous soothing following slight reactivation was observed not only for sympathoadrenal medullary activity (heart rate) but also for HPA activity (salivary cortisol concentration). Fig. 6.3 portrays the change of the heart rate and salivary cortisol concentration during a new treatment, which adopted massage for shaving at a barber shop.[2,4] This unique pattern of sympathoadrenal medullary activity and HPA activity form a "relaxation and refreshment curve"[8] that is a characteristic of beauty massage.

Beauty massage also brings unique subjective change. The feelings of relief and sleepiness significantly increased both in an experimental group with beauty massage and in a control group having the same posture but without massage. However, the feeling of tension decreased and the feeling of pleasantness increased significantly only in the experimental group.[1] The subjective change, in other words, emotional experience, might not cause unique psychophysiological response, but tactile stimulus of massage is apparently the cause of both emotional experiences and psychophysiological responses. Tsuchiya and Nakayama[61] examined the effects of mechanical and thermal stimulation of various facial skin areas on the adrenal sympathetic efferent nerve activity of anesthetized rats. Pinching of the forehead or cheek skin for 20 seconds elicited increased nerve activity, while brushing of the same skin decreased the nerve activity. This result indicates that soothing of sympathoadrenal medullary activity, which resembles beauty massage, was produced without consciousness of sensation. Vrontou, Wong, Rau, Koerber, and Anderson[65] reported that MRGPRB4 neurons in hairy skin of mice were activated only by massage-like stroking. In stark contrast, MRGPRD neurons were activated only by nocuous stimulus such as pinching. Considering these results obtained for rats and mice, the sensation by beauty massage might be conducted to the hypothalamus via a specific nerve. On one hand, it causes a physiological change of the relaxation and refreshment curve by the sympathoadrenal medullary axis and HPA axis. On the other hand, it brings the psychological change of favorable emotional experiences. A calm and connection system can be effected cooperatively.

The results described herein were obtained for a beauty massage by a beautician. Different effects were found for self-massage according to the initial conditions. When initial conditions were relaxed, self-massage caused tension.

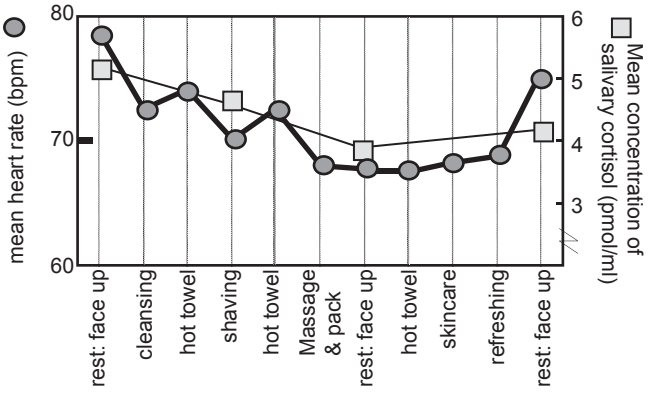



**FIGURE 6.3** Heart rate change by new treatment with massage in barber. *Modified from Abe T. Nichijouseikatsu no kaitekisei no sokutei (Measuring pleasantness in usual life). In: Yamazaki K, Fujisawa K, Kakigi S, editors.* Shin-seirishinrigaku (New Psychophysiology). *Kyoto: Kitaohji-Shobo; 1998; 129–132 [In Japanese].*

When initial conditions were tense, self-massage caused relaxation.[55] No clear effect of usual skin care without massage can be observed. However, the relaxation and refreshment curve can be obtained by special skin care with adoption of deep breathing with eau de cologne, using an emulsion by covering with both hands, and using a cool moisturizing eye mask.[3,4]

For both massage by a beautician and by oneself, massage cream is used to smooth the touch of fingers. Massage cream improves the massage sensations. The feel of skin care cosmetics is an important concern during product development. Factor analyses of the sensation of lotions have revealed seven factors. Factors related to applying lotion were sticky and slimy. Factors related to touching after application were stickiness, softness, and smoothness. The factors related to overall impressions were comfort and refreshment.[46] Psychophysiological research related to skin care contributes not only to clarification of the effects of skin care on humans but also to development of skin care products.

## 6.4 PSYCHOLOGY OF MAKEUP

A disease or external injury to the body that is visible by others might present psychosocial difficulty to a person. This visible disease or external injury used to be viewed as *disfigurement*. Recently, it was proposed that it be called *visible difference* to avoid negative nuance in the expression.[44] Visible differences cause severe difficulties when appearing on the head, especially the face. Many symptoms such as skin discolorations, bony deformities, and birthmarks derive from both congenital and acquired causes.[35] In spite of their symptom or cause, the difficulty arises from the color and shape of the location where makeup is applied. Cosmetic therapy is an effective means of minimizing visible differences using cosmetics (mainly makeup products). It mitigates psychosocial difficulties. For example, facial nerve paralysis produces facial asymmetry and results in visible differences. It compels a person to bear a psychological burden, which often gives rise to psychosocial difficulties related to social communication and social withdrawal. About two months after learning a makeup technique to attain facial symmetry, social attitudes of patients with facial nerve paralysis were improved, making them more pro-social.[28] Applying 0.9%, the incidence of visible differences in Great Britain,[34] to a nation with 100 million residents suggests that 900,000 people have visible differences. Cosmetic therapy can therefore play an important role in improving public welfare.

As described at the beginning of this chapter, the research of Graham and Kligman[21] triggered the development of cosmetic therapy. However, the first published example of the term might be a German article authored by Hey in Ref. 23: "*Dekorative Behandlung* beim Naevus flammeus (Cosmetic therapy on naevus flammeus)." In Japan, a cosmetic company started to make use of cosmetics for medical assistance from the 1970s.[64] Since 1996, about 10 years after the report by Graham and Kligman,[21] research into cosmetic therapy increased rapidly.[40] The numbers of articles retrieved on October 2, 2005, were the following: 30 articles about shape differences (e.g., facial nerve paralysis and cleft lip or palate) and 14 articles about color (e.g., leukoderma). Currently, cooperation between medical and cosmetic industries has strengthened. In the United States, many cancer patients suffering from appearance change during treatment can receive necessary support.[33,66] In France, *socio-esthéticiennes* (hereinafter, socio-estheticians), who are certified under the authority of the French Minister for Vocational Training, play important roles in the medical field (Refs. 13,39).[1] At present, cosmetic therapy is already popular worldwide. Nevertheless, more fundamental research is required to establish its theoretical background. Moreover, practical research must establish detailed programs for cases.

In fact, makeup techniques to decrease visible differences are commonly used with daily makeup. The techniques are undertaken on the premise that one can control facial impressions intentionally. The control of color, for example, by producing a healthy face color using foundation, or by covering a birthmark using concealer, might be readily accomplished. Nevertheless, it is extremely difficult to control facial shape and configuration (e.g., nose size, length between eyes) except when using special cinematic makeup. Makeup techniques for controlling facial shape and configuration often make use of a psychological technique—visual illusion. From this viewpoint, makeup techniques include knowledge related to the psychological difficulty of visual perception.

Visual illusion has been examined actively as an important subject of perceptual psychology. For example, the Ebbinghaus illusion, as well as the Baldwin illusion, is a size illusion that makes a target object appear larger when surrounded by smaller objects, but conversely, the target looks smaller when surrounded by larger ones. This phenomenon is explained by a contrast effect. A circle surrounded by a larger concentric circle appears to be smaller than when presented similarly by itself. It is particularly interesting that when the difference between concentric circles is small, an inner target circle appears to be larger than when presented alone. This phenomenon, called Delboeuf size illusion, might occur by assimilation of the inner target circle to the outer larger one.

Morikawa and Fujii[37] examined the effects of eye shadow and eyeliner on eye size perception using a method of adjustment to a face stimulus made by computer graphics. Results showed that application of eyeliner enlarged the perceived eye area by about 15%. Morikawa[36] pointed out that this effect reflected the Delboeuf size illusion by which artificial eyeliner acted as the outer (large) circle to assimilate the real eye contour as an inner (smaller) circle, like the enlarged effect of a double-edged eyelid.

Eye shadow did not affect eye size in the experiment using the method of adjustment.[37] However, Abe, Sato, and Endo[11] demonstrated that eye shadow exerted a clear effect on eye-size perception through the paired comparison method. A stimulus consisted of photographs of two eyes and their surrounding area in which the position, area, and eye shadow darkness were controlled using image editing software (Fig. 6.4). Participants separately chose which eyes were more hollowed out and larger. The choice results were analyzed and summarized into a scale value (by Thurston's case V) shown in Fig. 6.5. Regarding the upper (normal) position condition, both the levels of hollowing out and eye size were increased in proportion to the darkness. In addition, multiple regression revealed that the level of hollowing out significantly affects eye size (adjusted $R^2$ of wide area $= 0.24$, adjusted $R^2$ of narrow area $= 0.36$, $ps < 0.001$). These results indicate that distance illusion affects eye size perception through the *overhead illumination hypothesis* and *constancy scaling*: (1) Because the upper eye shadow is recognized literally as shadow, the eyes looked hollowed out (far from participants: observer) by the overhead illumination hypothesis; (2) Objects that were recognized far from the observer can be expected to appear larger if the retina size were the same by constancy scaling.

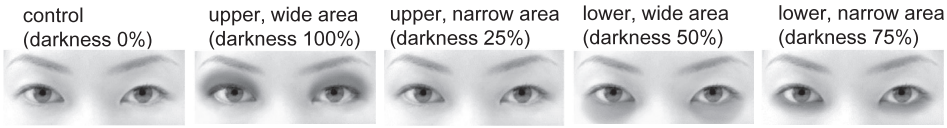



**FIGURE 6.4** Samples of stimuli used in eye depth and size experiment by position (upper/lower), area (wide/narrow), and darkness (25, 50, 75, 100%) of eye shadow. *Modified from Abe T, Sato C, Endo M. Effect of eye shadow on eye size perception: an experimental examination manipulating the position, area and darkness of eyeshadow.* Journal of Japanese Academy of Facial Studies *2009;**9**:111–118 [In Japanese with English abstract].*

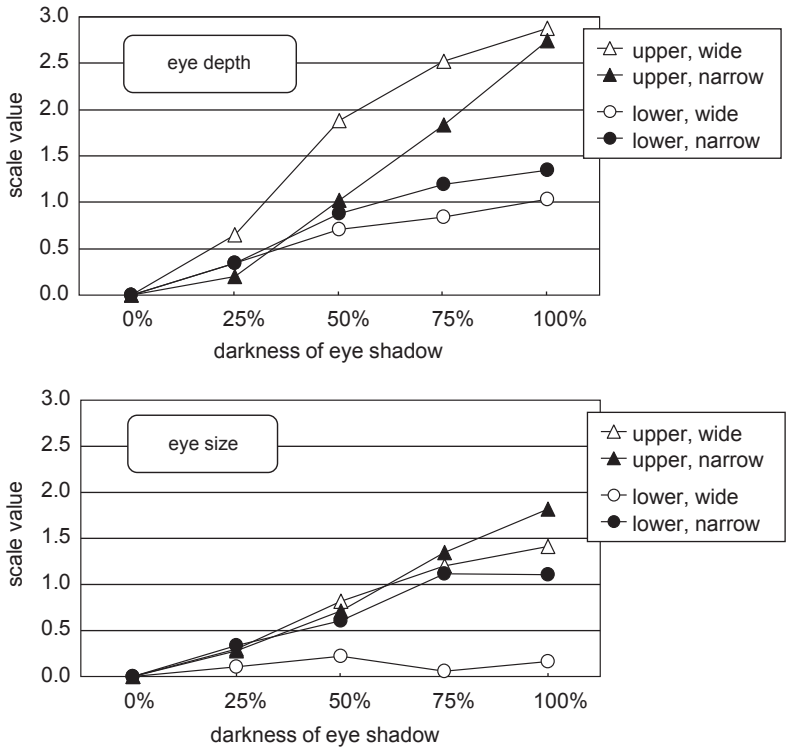



**FIGURE 6.5** Depth and size judgment of eye.[11] Twenty-four college students chose the deeper (hollowed out) and larger eye, respectively, by the method of paired comparison to calculate scale value (Thurstone's case V).

However, if this explanation were applied to a lower (odd) position condition, the eyes would look pop-eyed and small. In actuality, the scale value of hollowing out of the lower eye shadow condition increased in proportion to darkness, as in the upper eye shadow condition (but a little). Although the lower and wide area eye shadow condition exhibited no clear tendency in relation between the hollowing out and eye size, the level of hollowing out in the lower and narrow area eye shadow condition weakly but significantly affected eye size (adjusted $R^2 = 0.07$, $ps < 0.01$). Another explanation is required.

The illusion occurring with the human body has a limitation that it must look natural as human. Furthermore, its effect in terms of magnitude is smaller than that of a geometrical illusion. Nevertheless, small change brings a strong change in terms of impression. Morikawa[36] referred to such illusions in humans as "biological illusions." Makeup, particularly the eye shadow of the lower position condition, is an example of a biological illusion. The result presented in Fig. 6.5 might be affected by the limitations of biological illusion—real eyeballs must not pop out to cast a shadow on the cheek. Multiple related aspects remain to be resolved through psychological research.

As described before, makeup techniques seem to involve various visual illusion effects. However, the development of makeup techniques is attributable to beauticians and their tacit knowledge. Perceptual psychology can translate the tacit knowledge of skilled beauticians into explicit knowledge that can contribute to the spread of makeup techniques.

The Facial Features Map[2] is a typical fruit of that translation. When someone wants to portray a cool image, what shape of eyebrows is appropriate: straight or round, short or long? How about lipstick and cheek color? In such cases, concrete and effective information usually only exists in beautician's tacit knowledge, but it is necessary that it be available as explicit knowledge for everyone. The Facial Features Map is a navigation tool for personal image creation using explicit knowledge by clarifying the relation between morphological characteristics and the impression of a face (Fig. 6.6).

Two-dimensional solutions from similarity judgment of faces were extracted using multidimensional scaling.[57] Assigning these two dimensions to an $X$-$Y$ coordinate axis, one can posit that the $X$-coordinate correlates with the shape of each facial feature (feature shape axis); the $Y$-coordinate correlates with the proportion of facial features (feature proportion axis). The feature shape axis varied from a face with angular features to one with rounded

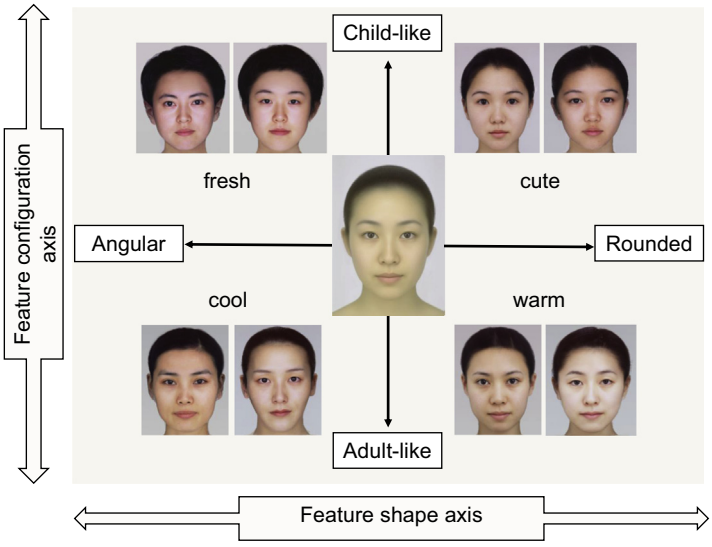



**FIGURE 6.6** Facial Features Map. Facial Features Map (patent of Shiseido) is makeup support tool for analyzing facial types on two axes of morphological characteristics. Four quadrants correspond to impressions: cute, fresh, cool, and warm. Photographs present examples of each quadrant, which are made by morphing. *Modified from Abe T, Ohkawa M, Takano R. Effect of overgeneralization on evaluation of facial impressions: an experimental approach to the theoretical background of the Facial Features Map.* Journal of Japanese Academy of Facial Studies *2008;8:87–96 [In Japanese with English abstract].*

[2] Facial Features Map is patented by Shiseido, Co., Ltd. (JPN: P3529954, USA: US6091836, EU: EP0828230, China: ZL97117584.5, Korea: KR342787, Taiwan: TW097793).

features; the feature proportion axis varied from adult-like look faces in which features were dispersed vertically with features concentrated horizontally in a long face to child-like look faces with features concentrated vertically but dispersed horizontally in a short face. Multiple regression analysis revealed that faces in the first quadrant (rounded × child-like) exhibit a strong tendency to be regarded as cute, and so forth, the second quadrant (angular × child-like) was fresh, the third quadrant (angular × adult-like) was cool, and the fourth quadrant (rounded × adult-like) was warm[58] (Expressions and the order of axes were modified here).

Consequently, the Facial Features Map was produced from relations between morphological characteristics and impressions of a face. The essential knowledge of skillful beauticians can be revealed to translate tacit knowledge into explicit knowledge by psychological experimentation. Anyone can locate a face according to its morphological characteristics on the map. It also shows the impression seen by others. If one wanted to create a facial image, one would add a touch of makeup to achieve morphological characteristics of the image one desires. For example, when a lady who has a fresh image (angular × child-like) wants to change her image to cute, we recommend drawing various features (eyebrow, eyes, lips, etc.) as rounded.

Two factors (friendliness and maturity) extracted by factor analysis of others' evaluations of faces were shown to correlate asymmetrically with the feature shape axis and feature proportion axis, respectively. They showed a significant positive correlation with the friendliness-shape, and the maturity-proportion,[10] which indicates an *overgeneralization effect*[68,69] in the relation between morphological characteristics and impressions of the Facial Features Map. Of course, angular features do not signal constant anger, but we feel some anger or refusal (emotion overgeneralization). Aged people have short faces as well as long faces, but we are prone to get a child-like impression from a short-face person (baby face overgeneralization). Nevertheless, we feel emotion (feature shape axis) and maturity (feature proportion axis) when we construct a cute, fresh, cool, and warm impression.

Psychology plays important roles in makeup skills. Makeup can also contribute to research on facial perception, a very hot issue in psychology, as an interesting subject.

## 6.5 PSYCHOLOGY OF FRAGRANCE

Fragrances are worn to produce pleasing impressions in others by aromas given off from one's own body. It is an olfactory self-presentation, just as makeup is a visual self-presentation. Therefore, guidance similar to that of the Facial Feature Map might be helpful when choosing a suitable fragrance. The first step is division into classes. The most popular means is Haarmann and Reimer's classification table, which is categorized by impressions of the main essence as Floral, Oriental, or Chypre (Haarmann & Reimer merged with Dragoco to form Symrise in 2003).

The next step is clarification of the fragrance impression structure.[24,67] It can be used to infer a distance between fragrances. Higuchi et al.[24] extracted sensory factors (intensity, clarity, softness) and emotional factors (enhancing, relaxing, stressful). Calculating their factor score as a scale, the distance between rose and jasmine was 0.23 (sensory factors), 0.35 (emotional factors); between rose and lemon was 1.42 (sensory factors), and 1.73 (emotional factors). Rose is more distant from lemon than jasmine. Although these scales might not be sufficient to describe qualitative differences among fragrances, it is interesting to note them as empirical and practical discriminations of fragrance.

The Facial Features Map is also available for examination of the effects of fragrance on the impression of those who wore it.[6,9] To evaluate the olfactory impressions of fragrances of two types using the Facial Features Map (cute, fresh, cool, and warm impression), they were put on the map. Similarly, four photographs of women were attached to the same map. Then, spraying the fragrance on the photographs, the photographs were put on the map again after the total impression of sniffing at them was evaluated. Results show that the positions of photographs with fragrance were positioned between the fragrance-less photographs and the sprayed fragrance (Fig. 6.7), which means that facial impressions can be made by wearing a fragrance.

When fragrance affects olfactory self-presentation, its target is others. At the same time, the first perceivers are the persons wearing it themselves. They enjoy it. From the viewpoint of psychology, aromatherapy or aromachology can be regarded as a psychophysiological effect of the fragrance wearer on themselves. Since the 1980s, studies of aromatherapy have been undertaken energetically, with over 100 articles in 1999.[26] Abe, Shoji, Kikuchi, and Higuchi[12] examined the recovery rate of transepidermal water loss (used as a skin barrier index) under a stress task comparing jasmine, lemon, rose, valerian, vanilla, and a control group, and found a significant effect only for valerian. Comparing the effects of rose and lemon on cardiac response patterns between a warning stimulus and imperative stimulus in a reaction time task, Kikuchi, Tanida, Uenoyama, Abe, and Yamaguchi[29] found a stimulative effect of lemon and a sedative effect of rose. Torii, Fukuda, Kanemoto, Miyanchi, Hamauzu, and Kawasaki[60] examined 19

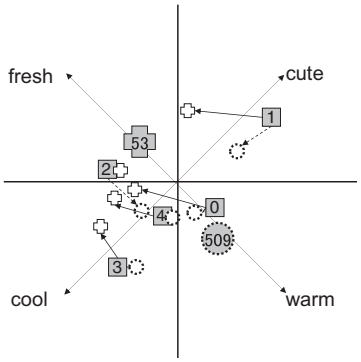



**FIGURE 6.7** Effects of fragrance on impressions of facial photographs. Mean ratings of fragrance No. 53 are shown as *gray crosses*. Those of fragrance No. 509 are shown as *gray broken circles*. The original impressions of facial photographs 0–4 are shown as *gray squares*. The ratings of impressions after exposure to scented photographs shifted to the corresponding white figure for each fragrance. The *diamond space* was constructed based on a rating continuum of −3.0 to 3.0. *Modified from Abe T. Odor, information and new cosmetics: the ripple effect on life by aromachology research.* Chem Senses *2005;30(Suppl. 1):i246–7.*

essential oils by contingent negative variation of electroencephalography. They found a stimulative effect of jasmine and a sedative effect of lavender.

In aromachology research, it is a characteristic to make use of various physiological indexes. Recently, cross-modal effects have become a major subject. Lemon-flavored lip balm is felt as smoother; vanilla-flavored lip balm was regarded as stickier than control.[30] Furthermore, research of olfaction, spreading to chemical senses including gustation, is making great advances today.[48] New perspectives on the psychology of fragrance are anticipated.

## 6.6 COSMETIC BEHAVIOR AS AN EMOTION CONTROL DEVICE

Reviewing psychological research related to skin care, makeup, and fragrance, cosmetic behavior reveals an emotion control device built into daily life.[4]

Fig. 6.8 presents a summary of this hypothesis. Skin care is designated as *caring* cosmetic behavior to fill the role of a facilitator for the health of the body surface. Furthermore, its remarkable effect is *healing* to bring comfortable relaxation. Makeup can be designated as *adorning* cosmetic behavior for self-presentation by adjusting appearance. Moreover, it plays the role of *encouragement*, contributing to facilitation of a pro-social attitude. Wearing a fragrance is also olfactory adornment. Fragrance can also affect one's psychophysiological state by playing the role of healing, as skin care does.

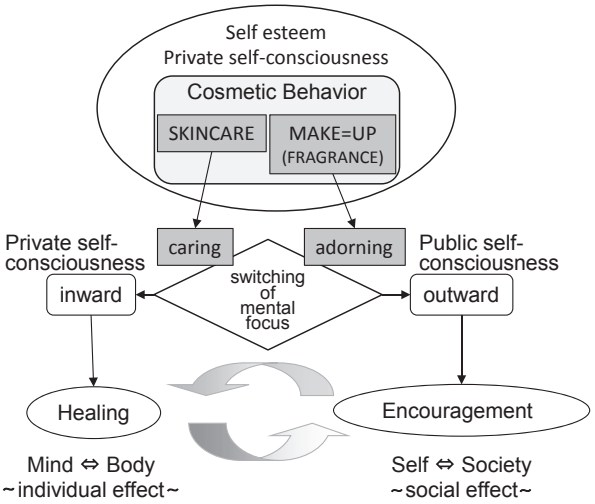



**FIGURE 6.8** Mechanisms of cosmetic behavior effects as an emotion control device.[4]

These effects of healing and encouragement might result from private self-consciousness and public self-consciousness with self-esteem. Our daily life includes various daily *hassles* and daily *uplifts*.[32] Cosmetic behavior is ambiguous. It is felt sometimes as daily hassles and sometimes as daily uplifts. It is affected by individual and situational differences as well. Specifically examining individual differences, persons who are willing to do skin care and also makeup as uplifts typically have high self-esteem.[4] In addition, people who use many skin care products have high private self-consciousness. Those who use a great deal of makeup are high in both private and public self-consciousness. The utility rates of moisturizing lotion do not correlate with the type of employment, although lipstick correlates with it; high rates of lipstick use are associated with better jobs.

Consequently, both skin care and makeup have a close relation to both self-esteem and private self-consciousness. Skin care seems more closely related to private self-consciousness. Skin care, the caring cosmetic behavior, actualizes private self-consciousness to bring attention to oneself. Furthermore, makeup has a relation to public self-consciousness and social viewpoints. Makeup, adorning cosmetic behavior, actualizes public self-consciousness to direct others and society. Cosmetic behavior acts as a switch of mental focus. Caring behavior directs it inward. Adorning behavior directs it outward. This is depicted in Fig. 6.8.

In fact, cosmetic therapies are sometimes effective for diseases without visible differences. The number of articles of senile dementia (30) and psychiatric disorder as depression (15) is rather larger than that describing visible difference cases (30).[40] Many of these studies unrelated to appearance are administered in Japan. Maybe, the presentation of Hama et al.[22] on cosmetic therapy related to depression, schizophrenia, and senile dementia at the International Congress of Applied Psychology encouraged Japanese psychologists. After that presentation, a trial at Naruto Yamagami Hospital achieved magnificent results from the use of cosmetic therapy for senile dementia; 30% of female patients became able to wear normal underwear instead of diapers.[17,31] It is not easy to interpret such cases, but based on Fig. 6.8, it has become possible to infer that behavior related to cosmetics, especially makeup, has encouraged mental direction to point increasingly outward and to society.

Cosmetic therapy consists not only of makeup but also of skin care techniques. Therefore, the idea is called cosmetic therapy instead of makeup therapy. For example, socio-estheticians in France care for patients by giving hand massages as well as makeup.[13] It might bring both a relaxation/healing effect and a stimulating/encouragement effect. It is difficult to distinguish the relation of skin care-caring-healing and makeup-adorning-encouragement. For that reason, Fig. 6.8 has a bidirectional arrow.

Fig. 6.9 presents a summary of the emotion-controlling effects of cosmetic behavior during a single day. In the morning, a woman looks at herself in the mirror in front of many cosmetics. Her private self-consciousness and self-esteem might be raised. Then, during application of cosmetics, the perspective changes to others' eyes. How am I viewed by others? This might be an opportunity to raise public self-consciousness and also to potentiate self-esteem. Her mental focus turns outward to gaining encouragement. One might say that after knotting the mind tightly, and after gaining momentum, she goes out to face the public only after putting on her "public face." After a long day of work, she comes home in the evening (sometimes at midnight). Sitting in front of the mirror again, and removing the makeup, she can confirm her own natural face in the mirror. At length, she can undo the mind knot and come back to herself during skin care, touching her cheek slowly and softly. Bit by bit, private self-consciousness arises and the mental focus turns inward to gain healing. Finally, she reverts to her "private face." This is a story of emotion control achieved through the use of cosmetics.




**FIGURE 6.9** Conceptual story of the emotion-controlling effect of cosmetic behavior along a day.

Psychological research might present some difficulties in acquiring rich fruits available to development of new products as chemistry and skin science. However, cosmetics have indeed persisted as a cultural custom throughout human history. In every category, skin care, makeup, and fragrance, there is a room to unravel a psychological enigma. Although the results might not produce a new product or idea of management, they can provide guidance and wisdom for cosmetics themselves and elucidate a new relation between cosmetics and humans.

## References


1. Abe T. Psychological Effect of esthetic, and relation to traditional Chinese medicine. *Fragrance J Special Issue* 1990;**10**:19–26 [In Japanese with English abstract].
2. Abe T. Nichijouseikatsu no kaitekisei no sokutei (Measuring pleasantness in usual life). In: Yamazaki K, Fujisawa K, Kakigi S, editors. *Shin-seirishinrigaku (New Psychophysiology)*. Kyoto: Kitaohji-Shobo; 1998. p. 129–32 [In Japanese].
3. Abe T. Sukinkea e-no kitai no hensen to shinrigakuteki kouka: Youbou no enshutsu, hada no kenkou, relaxation (Change of expectations about skincare and psychological effects of skincare: appearance direction, skin health, and relaxation). In: Daibo I, editor. *Keshou koudou no shakaishinrigaku (The Social Psychology of Cosmetic Behavior)*. Kyoto: Kitaohji-Shobo; 2001. p. 148–57 [In Japanese].
4. Abe T. *Sutoresu to keshou no shakaiseirishinrigaku (The social Psychophysiology of Stress and Cosmetic Behavior)*. Tokyo: Fragrance Journal Inc; 2002 [In Japanese].
5. Abe T. *Sukinkea no kindai: Heisei Nippon no sukinkea no genryu (Skincare in Modern Times: Origin of Present Skincare in Japan). Oiderumin tokushuugou: Nippon no keshoubunka: Meijiishin kara heisei made (Eudermin Special Issue: Cosmetic Culture in Japan: From the Meiji Restoration to Heisei era)*. 2002. p. 45–64 [In Japanese].
6. Abe T. Cosmetic behavior. In: Matsui Y, editor. *Interpersonal Psychology*. Tokyo: Brain Shuppan; 2002. p. 45–58 [In Japanese].
7. Abe T. Shiki no chonmage, Ryoma no boots: Keshou no naka no seiyou to Nippon (A topknot of Shiki and boots of Ryoma: Western and Japanese Characteristics in Cosmetic history). *Oiderumin (Eudermin)* 2004;**16**:164–77 [In Japanese].
8. Abe T. Psychological studies of skincare in Japan: a review. *Tohoku Psychol Fol* 2004;**63**:53–60.
9. Abe T. Odor, information and new cosmetics: the ripple effect on life by aromachology research. *Chem Senses* 2005;**30**(Suppl. 1):i246–7.
10. Abe T, Ohkawa M, Takano R. Effect of overgeneralization on evaluation of facial impressions: an experimental approach to the theoretical background of the Facial Features Map. *J Jpn Acad Facial Stud* 2008;**8**:87–96 [In Japanese with English abstract].
11. Abe T, Sato C, Endo M. Effect of eye shadow on eye size perception: an experimental examination manipulating the position, area and darkness of eyeshadow. *J Jpn Acad Facial Stud* 2009;**9**:111–8 [In Japanese with English abstract].
12. Abe T, Shoji H, Kikuchi F, Higuchi T. Stress reducing effect of natural essences: relationship between olfactory impression and stress response. *Jpn J Aromather* 2009;**9**:66–78 [In Japanese with English abstract].
13. CODES (cours d'esthétique à option humanitaire et sociale). *La socio-esthétique: Un métier aux compétences spécifiques*. 2013. Retrieved from: http://www.socio-esthetique.fr/socio_esthetique.php (April 22, 2016).
14. Collet P. *Foreign bodies: a guide to European mannerisms*. London: Simon & Schuster Ltd; 1993.
15. Daibo I, Kohyama S, editors. *Hifuku to keshou no shakaishinrigaku (The social psychology of clothing and cosmetics)*. Kyoto: Kitaohji-Shobo; 1996 [In Japanese].
16. Daibo I, editor. *Keshou koudou no shakaishinrigaku (Social psychology of cosmetic behavior)*. Kyoto: Kitaohji-Shobo; 2001 [In Japanese].
17. Doi Y, Nakauchi T, Yano Y. *Roujinbyouin ni okeru keshou no kouka (Effects of cosmetics in a geriatric hospital). Gekkan Fukushi (Monthly Welfare)*. 1994. p. 86–9. May (In Japanese).
18. Field T, Hernandez-Reif M, Diego M, Schanberg S, Kuhn C. Cortisol decreases and serotonin and dopamine increase following massage therapy. *Int J Neurosci* 2005;**115**:1397–413.
19. Field TM. Massage therapy effects. *Am. Psychol.* 1998;**53**:1270–81.
20. Forbes RJ. *Studies in ancient technology*, vol. 3. Leiden: E. J. Brill; 1955.
21. Graham JA, Kligman AM, editors. *The psychology of cosmetic treatments*. New York: Praeger; 1985.
22. Hama H, Matsuyama Y, Fukui K, Shimizu H, Nakajima T, Kon Y, Nakamura K. A clinical study of using cosmetics for therapy. In: Wilpert B, Motoaki H, Misumi J, editors. *General psychology and environmental psychology: Proceedings of the 22nd International Congress of Applied Psychology*, **3**. New Jersey: Lawrence Erlbaum Associates; 1990. p. 271–2.
23. Hey H. Dekorative Behandlung beim Naevus flammeus. *Cosmetologica* 1970;**19**(3):71–6 [In German].
24. Higuchi T, Shoji K, Hatayama T. A psychological study of sense-descriptive adjectives for characterizing fragrance. *Jpn J Stud Emotions* 2002;**8**: 45–59 [In Japanese with English abstract].
25. Ichige I. *Shinban shu no koukogaku (The Archeology of Vermilion, 2nd ed)*. Tokyo: Yuzankaku; 1998 [In Japanese].
26. Jellinek JS. Odours and mental states. *Int J Aromather* 1998/1999;**9**(3):115–20. http://dx.doi.org/10.1016/S0962-4562(98)80005-2.
27. Kaku A. *Yakusha chu (Comment by translator). Plato, Gorgias: With a Japanese Translation by Kaku, A*. Tokyo: Iwanami Shoten; 1967. p. 249–94 [In Japanese].
28. Kanzaki J, Ohshiro K, Abe T. Effect of corrective make-up training on patients with facial nerve paralysis. *ENT J (Ear, Nose Throat J)* 1998;**77**: 270–4 (passim).
29. Kikuchi A, Tanida M, Uenoyama S, Abe T, Yamaguchi H. Effect of odors on cardiac response patterns in a reaction time task. In: Queinnec Y, Daniellou F, editors. *Designing for everyone*, vol. 1. London: Taylor & Francis; 1991. p. 380–2.
30. Kikuchi F, Akita M, Abe T. Olfactory influences on the perceived effects of lip balm. *Jpn J Psychol* 2013;**84**(5):515–21 [In Japanese with English abstract].
31. Kobe Shimbun. *Chihoushou kanja mo okeshou de genki ni (Makeup invigorated senile dementia patients)*. 1994. January 11.
32. Lazarus RS, Folkman S. *Stress, appraisal, and coping*. New York: Springer Publishing Company; 1984.
33. Look good feel better. *About look good feel better*. 2015. Retrieved from: http://lookgoodfeelbetter.org/about-lgfb/our-mission (April 19, 2016).
34. Martin J, Meltzer H, Elliot D. *The prevalence of disability among adults*. London: Office of Population Censuses and Surveys; 1988.

35. Matsumoto M. Psychological problems related to visible differences in appearance: developmental perspectives. *Jpn J Psychol* 2008;**79**:66–76 [In Japanese with English abstract].
36. Morikawa K. New directions in research on visual illusions of shape and size related to the human face and body: illusions caused by makeup and clothing. *Jpn Psychol Rev* 2012;**55**:348–61 [In Japanese with English abstract].
37. Morikawa K, Fujii Y. Measuring the illusory effect of eye make-up. *J Jpn Acad Facial Stud* 2009;**9**:242. ISSN:1346–8081 [In Japanese with English title].
38. Morse ES. Japan day by day, 1877, 1878–79, 1882–83. In: Ishikawa K, editor. *Trans. in Japanese 1929*, vol. 1. Boston: Houghton Mifflin; 1917.
39. Nozawa K. *Chiryou no genba ni okeru biyou: socio-esthetic no shinriteki kouyou (Beauty treatment in medical site: psychological efficacy of socio-esthetic). Kokoro no kagaku: Youshi to bishu no shinri (Science of Mind: Special Issue on Appearance and Its Esthetic Evaluation)*, vol. 117; 2004. p. 63–7 [In Japanese].
40. Nozawa K, Sawazaki T. Review of the study on clinical psychological effects of cosmetic techniques. *Mejiro J Psychol* 2006;**2**:49–63 [In Japanese with English abstract].
41. Paquet D. *Une historie de la beaute: Miroir, mon beau miroir*. Paris: Gallimard; 1997 [In French].
42. Plato. *Lysis, Symposium, Gorgias: With an English Translation by W. R. M. Lamb*. Harvard University Press; 1975 [Original work published about 390 B.C.].
43. Research and Statistics Department, Minister's Secretariat, METI (Ministry of Economy, Trade and Industry). *2014 Yearbook of current production statistics: chemical industry*. 2015. Retrieved from: http://www.meti.go.jp/statistics/tyo/seidou/result/gaiyo/resourceData/02_kagaku/nenpo/h2dbb2014k.pdf. May 9, 2016.
44. Rumsey N, Harcourt D. *The psychology of appearance*. Berkshire: Open University Press; 2005.
45. Sayama H. *Miyako Fuzoku kewaiden (Cosmetic manners and customs of the Edo period)*. Tokyo: Heibonsha; 1982 [In Japanese. Original work published 1813].
46. Shimoda M, Abe T. Psychophysical factors structuring the feel of skin lotion. *J SCCJ (The Society of Cosmetic Chemists of Japan)* 1993;**27**:41–7 [In Japanese with English abstract].
47. Schriemann H. *La Chine et le Japon au Temps Presént (T. Fujikawa Trans. in Japanese 1982)*. Paris Librarie Centrale; 1867 [In French].
48. Shepherd GM. *Neurogastronomy: how the brain creates flavor and why it matters*. New York: Columbia University Press; 2012.
49. Shiseido. Special issue: for new graduates. *Hanatsubaki* 1964;**15**(3):7–11 [In Japanese].
50. Shiseido Institute of Beauty Sciences, editor. *Keshoushinrigaku (The psychology of cosmetic behavior)*. Tokyo: Fragrance Journal Inc; 1993 [In Japanese].
51. Shiseido Beauty Solution Development Center. *Keshou therapy: kokoro to karada wo genkinisuru atarashii chikara (Cosmetic therapy: the new type of power to rejuvenate the mind and body)*. Tokyo: Nikkei Business Publications; 2010 [In Japanese].
52. Shreeve J. *The Neandertal enigma: solving the mystery of modern human origins*. London: Penguin Books; 1997 (First published in New York by William Morrow & Company 1995).
53. Strouhal E. *Life in ancient Egyptians (D. Viney Trans.)*. London: Opus Publishing Ltd; 1992 [Original work published 1989].
54. Suenson E. *Skitser fra Japan. Fra Alle Lande (Y. Nagashima Trans. in Japanese 1989)*. Copenhagen: Fr. Wøldikes Forlag; 1869–1870 [In Danish].
55. Tagai K, Morozumi R, Yoshida T. The effect of self-administered facial massage on psychophysiological state. *J SCCJ (The Society of Cosmetic Chemists of Japan)* 1991;**26**:9–14 [In Japanese with English abstract].
56. Takahashi M. Kaisetsu (Comment on text). In: Sayama H, editor. *Miyako Fuzoku kewaiden (Cosmetic manners and customs of the Edo period)*. Tokyo: Heibonsha; 1982. p. 265–93 [In Japanese].
57. Takano R, Abe T. *The study of relationship between facial features and facial similarity. The proceedings of the Japanese Psychological Association 55th annual meeting*, **700**; 1996 [In Japanese].
58. Takano R, Abe T, Kobayashi N. Relationship between facial features and perceived facial image for application to image creation using cosmetics. In: *Copy of Abstracts of 70th Anniversary Conference on Colour Materials (Tokyo: Japan Society of Colour Material)*; 1997. p. 188–91.
59. Tokyo National Museum, NHK, & NHK Promotion. *Sekai yondaibunnmei Egypt bunmeiten (Egyptian Civilization: one of the four great civilizations of the world)*. Tokyo: NHK & NHK Promotion; 2000 [In Japanese].
60. Torii S, Fukuda H, Kanemoto H, Miyanchi R, Hamauzu Y, Kawasaki M. Contingent negative variation (CNV) and the psychological effects of odour. In: Van Toller S, Dodd GH, editors. *Perfumery: the psychology and biology of fragrance*. London: Chapman and Hall; 1988. p. 107–20.
61. Tsuchiya T, Nakayama Y. *Response of adrenal efferent nerve activity to mechanical and thermal stimulation of the facial skin in anesthetized rats*. *The Autonomic Nervous System*, **24**; 1987. p. 50–7 [In Japanese with English abstract].
62. Uvnäs-Moberg K. *The oxytocin factor: tapping the hormone of calm, love, and healing*. Boston: Da Capo Press; 2003.
63. Uvnäs-Moberg K, Arn I, Magnusson D. The psychobiology of emotion: the role of the oxytocinergic system. *Int J Behav Med* 2005;**12**:59–65.
64. Uyama M, Abe T. Cosmetic therapy: a review and expectations. *Fragrance J* 1998;**26**(1):97–106 [In Japanese with English abstract].
65. Vrontou S, Wong AM, Rau KK, Koerber HR, Anderson DJ. Genetic identification of C fibres that detect massage-like stroking of hairy skin in vivo. *Nature* 2013;**493**(7434):669–73.
66. Williams TR, O'Sullivan M, Snodgrass SE, Love N. Psychosocial issues in breast cancer. Helping patients get the support they need. *Postgrad Med* 1995;**98**(4):97–9. 103–104, 107–108 (passim).
67. Zarzo M. Relevant psychological dimensions in the perceptual space of perfumery odors. *Food Qual Preference* 2008;**19**(3):315–22.
68. Zebrowitz LA. *Reading faces: window to the soul?*. Boulder: Westview Press; 1997.
69. Zebrowitz LA. Commentary: overgeneralization effects in perceiving nonverbal behavior: evolutionary and ecological origins. *J Nonverbal Behav* 2003;**27**(2):133–8.

CHAPTER

# 7

# Dermatological Benefits of Cosmetics

*K. Kikuchi*[1], *H. Tagami*[2]

[1]Department of Dermatology, Tohoku University Graduate School of Medicine, Sendai, Japan; [2]Emeritus professor of Tohoku University, Sendai, Japan

## 7.1 INTRODUCTION

In our daily practice, we try to prescribe appropriate and effective drugs for the treatment of severe dermatoses. However, some potent drugs may also induce unexpected side effects if used for rather mild skin changes.[1,2] For such patients, it might be better to suggest a trial of various commercially available skin care products, including cosmetics, because our drug therapies are not always almighty. In fact, as compared to our traditionally employed ointments, many of the recently commercially available topical agents, which have been produced, thanks to dedicated studies of skin researchers and cosmetic scientists, have been proven to be not only much more effective but also to be associated with many fewer side effects. Most of all, we should know that there are many differences in various skin properties, even among normal individuals, and such differences occur even based on age, sex, and environment. The purpose of this chapter is to discuss important points that we should keep in mind concerning these issues.

## 7.2 SKIN CARE PRODUCTS

### 7.2.1 Moisturizers/Emollients

In wintertime our modernized house-heating system tends to reduce the indoor humidity, easily inducing dry skin in those older than 60 years. The skin of the trunk and limbs, especially that of the lower back and lower limbs, tends to become dry, rough, and scaly, known as senile xerosis.[3] This is also the case in many infants. They show superficial fissures in their skin, which induces the sensation of pruritus and is accompanied by involuntary scratching. Such involuntary scratching leads to the development of xerotic dermatitis, which subsequently can even lead to the development of nummular eczema.[4] Thus, to prevent such skin changes in the winter, we should teach older people to apply various moisturizing agents at least once daily before going to bed.

We dermatologists can also encounter the presence of similar xerotic skin changes consisting of a rough and dry, finely fissured skin surface in patients with infantile atopic dermatitis even in such skin areas that do not clearly show the presence of any inflammatory skin lesions, i.e., atopic xerosis.[5] Various topical corticosteroids and/or calcineurin inhibitors are utilized to treat atopic dermatitis depending on the severity of the lesional skin. However, the beneficial effects of moisturizers in treating atopic dermatitis are well known. It has been reported that concomitant application of moisturizer with topical corticosteroid ointment could reduce the amount of steroid ointment needed.[6] Furthermore, daily application of a moisturizer with intermittent treatment using anti-inflammatory medications may prevent relapse of dermatitis after resolving active eczematous lesions with a potent corticosteroid.[7] More recently, it has been suggested that percutaneous sensitization of allergens might cause development of food allergies.[8,9] There have been studies suggesting that the use of emollients from birth could prevent the development of atopic dermatitis.[10,11]

Dermatologists used to prescribe traditional topical ointments such as petrolatum or lipid ointments that have been also employed for the treatment of various other skin lesions. Nowadays, we know that commercially available creams or lotions are more pleasant to use than traditional ointments and effective enough to restore a smooth skin surface.[12]

*Cosmetic Science and Technology: Theoretical Principles and Applications*
http://dx.doi.org/10.1016/B978-0-12-802005-0.00007-0



Copyright © 2017 Elsevier Inc. All rights reserved.

These observations can also be easily and objectively confirmed by measuring the high frequency conductance or capacitance of the skin in areas where a certain amount of these agents have been applied.[13] The only negative point for these topical agents produced by cosmetic companies is that they are more expensive than those prescribed by dermatologists, because they are not covered by health insurance. As an exceptional case, prescribed moisturizers covered by health insurance are available in Japan.

### 7.2.2 Detergents, Shampoo

Lipophilic *Malassezia* fungi in pilosebaceous follicles and sebaceous lipids have been speculated to be etiological and aggregative factors in the development of seborrheic dermatitis, dandruff, and possibly scalp psoriasis. A reduction of *Malassezia* using antifungal agents is effective to control seborrheic dermatitis and dandruff. Although anti-inflammatory medications such as topical corticosteroid are indicated for highly inflamed cases, antifungal agents are utilized to prevent exacerbations. Shampoo containing ketoconazole, miconazole, or zinc pyrithione have been reported to be useful to control scalp seborrheic dermatitis and dandruff.[14–16] Dermatologists often recommend using such shampoos to patients with scalp psoriasis, seborrheic dermatitis, and dandruff.

### 7.2.3 Sunscreen

Now, given our increased lifespan, it is well known that exposure to sunlight for a long period of time can induce yellowish, wrinkled facial skin changes that develop even without any preceding special sunburn phenomena. Histologically, we can find such changes as actinic elastosis in the upper to mid dermis. Especially, in Caucasians who have grown up in Florida (USA) and tropical Australia, they may develop not only pigmented spots consisting of freckles and wrinkles but also precancers such as actinic keratosis, basal cell carcinoma, squamous cell carcinoma, and malignant melanoma, even in people still in their thirties.[17]

At present, in our society of longevity, severe photoaging can develop even among Asians such as Chinese, Koreans, and Japanese. To prevent its development people should wear hats, long-sleeved shirts, and long trousers in addition to the application of sunscreen in order to avoid prolonged skin exposure to the UV light of the glaring summer sunlight, which can lead eventually to the development of skin cancers.

Strict avoidance of sunlight is needed for patients with photodermatoses such as xeroderma pigmentosum, chronic actinic dermatitis, and polymorphous light eruption and patients with collagen diseases, systemic lupus erythematosus, and dermatomyositis, whose skin lesions may develop or be exacerbated from sunlight. Sunscreen with a high UV protection factor may be required for such patients. Newly formulated products, which become less obvious when applied or are easily removed by washing with soap, might also be suitable for male patients and children.

## 7.3 ANTIWRINKLE AND ANTIAGING AGENTS

For those who have developed deep skin wrinkles on their faces because of longtime exposure to sunlight, we now employ simple topical measures, i.e., daily applications of retinoic acid cream before going to bed, because they can reduce wrinkles by producing new collagen layers that cover the actinic elastosis noted in the dermis.[18]

In the past, it was thought that the development of pigmented spots and wrinkles were the result of simple skin aging. However, like those girls brought up with indoor tender care, the protection from sun exposure in a house or by wearing a hat and long sleeves has been found to be effective for keeping the skin young, as mentioned previously. Then, is it impossible for us to do anything for those who have developed skin wrinkles and spots on skin that has been exposed to the sun? Now, as already mentioned, we can treat them with repeated topical applications of retinoic acid or retinol cream, which are effective for improving even sun-damaged skin conditions.[18] With such topical treatment, fresh collagen formation develops to cover the dermal portion of actinic elastosis, restoring the smooth and soft skin like young people. Because the Japanese tend to develop irritation with such treatment, we can employ a less-irritating retinol cream instead of retinoic acid cream.[19]

Moreover, Kligman and Willis found that daily application of a formula consisting of 0.1% tretinoin, 5% hydroquinone, 0.1% dexamethasone, and hydrophilic ointment for several weeks was an effective treatment for melasma, ephelides, and postinflammatory hyperpigmentation.[20]

Recently Breathnach reported that topical treatment with 20% azelaic acid was also effective for hyperpigmentation and that its efficacy was enhanced by tretinoin.[21] Topical retinoid therapy in combination with hydroquinone or alpha hydroxy acids, such as glycolic acid and lactic acid, is also reported to be effective for melasma, hyperpigmentation, and small-type solar lentidines.[22] On the other hand, laser or phototherapy is more effective for large hyperkeratotic solar lentigines.

## 7.4 ACNE COSMETICS

Acne is common condition in adolescents that often affects the face, anterior chest, and upper back. The major pathogenic factors involved are obstruction of sebaceous follicles resulting from abnormal keratinization of the infundibular epithelium, excess sebum production by androgen, and inflammation promoted by *Propionibacterium acnes*.

Medical treatments including systemic and topical antimicrobials, topical benzoyl peroxide, topical retinoid, and systemic *13-cis* retinoic acid are utilized for patients with mild to severe inflammatory acne.[23] Adjuvant dermocosmetic therapy is available for treating acne after the initiation and during maintenance therapy. There are exfoliating agents such as glycolic acids and salicylic acid, anti-inflammatory agent glycyrrhizin, and antioxidant vitamin E.[24] Mild cleansers should be used by all acne patients to remove excessive sebaceous lipids. The use of a non-comedogenic moisturizer is recommended because it may reduce the irritation from topical and systemic retinoid therapy. Since inappropriate products and the procedures may cause irritation as well as exacerbate acne, appropriate instruction by dermatologists is important for patients who are under ongoing pharmacological therapy.

## 7.5 HAIR GROWTH AGENT

Androgenic alopecia (male-pattern baldness) develops to a varying extent in adult males. It has been not easy to treat with any topical agent. However, it was reported recently that, in its very early stage, at least a statistically significant increase in terminal hair growth in scalp hair could be observed with topical minoxidil application for four months in comparison with placebo therapy.[25] However, it is not yet satisfactory enough for every individual, and it requires further study.

## 7.6 ANTIPERSPIRANTS AND DEODORANTS

Sweating increases the proliferation of resident skin bacteria that may emit pungent body odor. Particularly, hyperactivity of the axillary apocrine sweat glands produces excessive body odor, i.e., osmidrosis, due to the production of low-molecular fatty acids liberated from nonodorous apocrine sweat by axillary resident bacteria. Thus, we should employ antibacterial agents as well as various absorbent chemicals for such body odor for the sake of etiquette.

## 7.7 MAKEUP PRODUCTS

Previously, the word "*cosmetic*" was used in Japan for such various makeup products as face powder, lipstick, and even perfume. But recently, because of increased longevity, the term *makeup* has come to be employed to describe various topical agents that conceal aged skin signs such as pigmented spots composed of freckles, solar lentigines, and fine wrinkles, namely the changes due to photoaging, which also include various benign and malignant skin tumors such as solar keratosis, basalioma, and squamous cell carcinoma. Concealers are also used to camouflage some kinds of birthmarks, vitiligo, postoperative or burn scars, while laser therapy is performed for lesional skin if it is effective. Dihydroxyacetone, used in self-tanning products, reacts with amino acids in the stratum corneum and provides a temporary suntan-like pigmentation camouflaging vitiligo.[26–28] Moreover, it has been reported that the usage of appropriate makeup products in female acne patients did not aggravate acne eruptions and improved quality of life.[29] In the past, dermatologists discouraged female acne patients from applying makeup cosmetics since they were considered to be one of the aggravating factors for acne. Appropriate non-comedogenic makeup products, which do not interfere with acne treatment, are no longer prohibited during treatment.

Thus, dermatologists encourage patients to camouflage lesional skin with makeup cosmetics if desired. Camouflage of lesional skin with makeup cosmetics is thought to be useful to improve quality of life (QOL) of patients with skin diseases.[30–32]

## 7.8 CONCLUSIONS

Dermatologists assess cutaneous symptoms and their severity, then prescribe pharmaceutical drugs for patients who require medical treatment. Even "normal" people may develop skin symptoms such as xerosis and irritation, which are not so bad to live with. Daily application of cosmetic products may relieve such mild symptoms without the need for medications. However, some cosmetics might cause troublesome skin problems such as contact dermatitis.

Even patients with skin disease who have ongoing medical treatment need daily skin care, i.e., cleaning, moisturizing, and UV protection. We dermatologists hope that skin care products for such patients will be safe and of high quality. Today, makeup products are not only used to decorate healthy skin but also to camouflage various skin lesions of patients to improve their QOL.

## References


1. Kolbe L, Kligman AM, Schreiner V, et al. Corticosteroid-induced atrophy and barrier impairment measured by non-invasive methods in human skin. *Skin Res Technol* 2001;**7**(2):73–7.
2. Ljubojeviae S, Basta-Juzbasiae A, Lipozeneiae J. Steroid dermatitis resembling rosacea: aetiopathogenesis and treatment. *J Eur Acad Dermatol Venereol* 2002;**16**(2):121–6.
3. Hara M, Kikuchi K, Watanabe M, et al. Senile xerosis; functional, morphological, and biochemical studies. *J Geriatr Dermatol* 1993;**1**(3):111–20.
4. Aoyama H, Tanaka M, Hara M, et al. Nummular eczema: an addition of senile xerosis and unique cutaneous reactivities to environmental aeroallergens. *Dermatology* 1999;**199**(2):135–9.
5. Watanabe M, Tagami H, Horii I, et al. Functional analyses of the superficial stratum corneum in atopic xerosis. *Arch Dermatol* 1991;**127**(11): 1689–92.
6. Grimalt R, Mengeaud V, Cambazard F. The steroid-sparing effect of an emollient therapy in infants with atopic dermatitis: a randomized controlled study. *Dermatology* 2007;**214**(1):61–7.
7. Hanifin J, Gupta AK, Rajagopalan R. Intermittent dosing of fluticasone propionate cream for reducing the risk of relapse in atopic dermatitis patients. *Br J Dermatol* 2002;**147**(3):528–37.
8. Du Toit G, Katz Y, Sasieni P, et al. Early consumption of peanuts in infancy is associated with a low prevalence of peanut allergy. *J Allergy Clin Immunol* 2008;**122**(5):984–91.
9. Lack G. Epidemiologic risks for food allergy. *J Allergy Clin Immunol* 2008;**121**(6):1331–6.
10. Simpson EL, Chalmers JR, Hanifin JM, et al. Emollient enhancement of the skin barrier from birth offers effective atopic dermatitis prevention. *J Allergy Clin Immunol* 2014;**134**(4):818–23.
11. Horimukai K, Morita K, Narita M, et al. Application of moisturizer to neonates prevents development of atopic dermatitis. *J Allergy Clin Immunol* 2014;**134**(4):824–30. e6.
12. Tabata N, O'Goshi K, Zhen YX, et al. Biophysical assessment of persistent effects of moisturizers after their daily applications: evaluation of corneotherapy. *Dermatology* 2000;**200**(4):308–13.
13. Kikuchi K, Tagami H. Noninvasive biophysical assessments of the efficacy of a moisturizing cosmetic cream base for patients with atopic dermatitis during different seasons. *Br J Dermatol* 2008;**158**(5):969–78.
14. Gupta AK, Nicol KA. Ciclopirox 1% shampoo for the treatment of seborrheic dermatitis. *Int J Dermatol* 2006;**45**(1):66–9.
15. Buechner SA. Multicenter, double-blind, parallel group study investigating the non-inferiority of efficacy and safety of a 2% miconazole nitrate shampoo in comparison with a 2% ketoconazole shampoo in the treatment of seborrhoeic dermatitis of the scalp. *J Dermatolog Treat* 2014;**25**(3): 226–31.
16. Pierard-Franchimont C, Goffin V, Decroix J, et al. A multicenter randomized trial of ketoconazole 2% and zinc pyrithione 1% shampoos in severe dandruff and seborrheic dermatitis. *Skin Pharmacol Appl Skin Physiol* 2002;**15**(6):434–41.
17. Gilchrest BA. Skin aging and photoaging: an overview. *J Am Acad Dermatol* 1989;**21**(3 Pt 2):610–3.
18. Kligman AM, Grove GL, Hirose R, et al. Topical tretinoin for photoaged skin. *J Am Acad Dermatol* 1986;**15**(4 Pt 2):836–59.
19. Kikuchi K, Suetake T, Kumasaka N, et al. Improvement of photoaged facial skin in middle-aged Japanese females by topical retinol (vitamin A alcohol): a vehicle-controlled, double-blind study. *J Dermatolog Treat* 2009;**20**(5):276–81.
20. Kligman AM, Willis I. A new formula for depigmenting human skin. *Arch Dermatol* 1975;**111**(1):40–8.
21. Breathnach AS. Melanin hyperpigmentation of skin: melasma, topical treatment with azelaic acid, and other therapies. *Cutis* 1996;**57**(1 Suppl): 36–45.
22. Ortonne JP. Retinoid therapy of pigmentary disorders. *Dermatol Ther* 2006;**19**(5):280–8.
23. Leyden J. Recent advances in the use of adapalene 0.1%/benzoyl peroxide 2.5% to treat patients with moderate to severe acne. *J Dermatolog Treat* 2016;**27**(Suppl. 1):S4–13.
24. Mills OH, Criscito MC, Schlesinger TE, et al. Addressing free radical oxidation in Acne Vulgaris. *J Clin Aesthet Dermatol* 2016;**9**(1):25–30.
25. Olsen EA, Weiner MS, Delong ER, et al. Topical minoxidil in early male pattern baldness. *J Am Acad Dermatol* 1985;**13**(2 Pt 1):185–92.

26. Fesq H, Brockow K, Strom K, et al. Dihydroxyacetone in a new formulation—a powerful therapeutic option in vitiligo. *Dermatology* 2001;**203**(3): 241–3.
27. Suga Y, Ikejima A, Matsuba S, et al. Medical pearl: DHA application for camouflaging segmental vitiligo and piebald lesions. *J Am Acad Dermatol* 2002;**47**(3):436–8.
28. Rajatanavin N, Suwanachote S, Kulkollakarn S. Dihydroxyacetone: a safe camouflaging option in vitiligo. *Int J Dermatol* 2008;**47**(4):402–6.
29. Hayashi N, Imori M, Yanagisawa M, et al. Make-up improves the quality of life of Acne patients without aggravating acne eruptions during treatments. *Eur J Dermatol* 2005;**15**(4):284–7.
30. Holme SA, Beattie PE, Fleming CJ. Cosmetic camouflage advice improves quality of life. *Br J Dermatol* 2002;**147**(5):946–9.
31. Tanioka M, Miyachi Y. Camouflage for vitiligo. *Dermatol Ther* 2009;**22**(1):90–3.
32. Seite S, Deshayes P, Dreno B, et al. Interest of corrective makeup in the management of patients in dermatology. *Clin Cosmet Investig Dermatol* 2012;**5**:123–8.

CHAPTER

# 8

# Development of Cosmetics and Intellectual Property Rights

*T. Kitano*
**OHNO & PARTNERS, Tokyo, Japan**

## 8.1 INTRODUCTION

In research and development, manufacture, and sales of cosmetics, intellectual property rights play a role of great importance.

For example, it can be seen in airport duty-free shops or department stores that highly reputed cosmetics manufacturers set up booths for their own exclusive use to sell their products. In such a situation, each manufacturer markets its products by prominently displaying large signs of a corporate name or brand name(s) (trademark rights) in the shop to bring appeal of its own products to the attention of customers.

Then, turning our eyes to customers who purchase any cosmetics, they rely on the displayed corporate name or the brand name(s), leading to a drop-by at each of the booths of cosmetics manufacturers.

This consumers' favorable attitude can be expected because of an endorsement of the "GOODWILL" created as a consequence of continuing sales of such products, which are useful and novel (patent rights and design patent rights), safe and secure as cosmetics, and have stable qualities, by respective cosmetics manufacturers over many years. By virtue of the presence of such goodwill, customers feel secure to purchase such products (trademark rights or the right to prevent any other company's free ride under the Unfair Competition Prevention Law).

In addition, conveyance of certain images embodied by and contained in respective brands through commercials and fashion magazines (copyrights) by respective cosmetics manufacturers to their customers may serve to form the brand image on the customers' side, which in turn serves as one of the criteria to determine purchase of the product.

For example, purchase and use of a product of such a highly reputed cosmetics manufacturer as mentioned earlier may give rise of such a sense of "having put on (been identified with) the brand image" in the mind of the customer. In addition, cosmetics, for example, have some kind of such a magical power that change of facial appearance by makeup may in turn serve to change the mental status of the customer for the better.

Further, for men who do not use cosmetics on a regular basis, the corporate names of cosmetics manufacturers and their brand names are of great benefit in their purchases of cosmetics as a gift for women. If he purchases cosmetics of a certain famous brand, the goodwill embodied by such a brand will help him avert the perception of a "failed" purchase in most cases, and at the same time, will give the woman who received the cosmetics as a gift a feeling of happiness.

In this chapter, explanation will be provided as follows on what is the essential element of intellectual property right, and how it is involved with, and which sort of role it plays for, research and development, manufacture, and sales of cosmetics.

## 8.2 THE NEED FOR INTELLECTUAL PROPERTY RIGHTS

We are living everyday life surrounded by objects that we can actually touch with our hands, and intangible objects that we cannot touch. Then, so far as a tangible object is concerned, who possesses the object (who has its

*Cosmetic Science and Technology: Theoretical Principles and Applications*
http://dx.doi.org/10.1016/B978-0-12-802005-0.00008-2

Copyright © 2017 Elsevier Inc. All rights reserved.

property right) can be distinguished relatively easily. Those who violate any property right of other persons will inevitably have criminal liability (such as burglary charge) and civil liability (such as that for damage).

On the other hand, when it comes to an intangible object (such as an invention, a design, or a piece of music), it is not easy to identify who would have conceived and who would possess the relevant property right. Nevertheless, in the event that anyone other than the person who has conceived the intangible object would imitate the intangible object and reap the benefit therefrom, the effort devoted by the person who has conceived the object would be diminished to his/her significant detriment. To prevent such a situation, the necessity will arise for some kind of legal protection for those persons.

## 8.3 WHAT IS AN INTELLECTUAL PROPERTY RIGHT?

Now, it is worth defining here what an intellectual property right is. It means the right that the person who has conceived a specific intangible object, as mentioned previously, possesses said intangible object, and is protected roughly by means of various laws as follows:

- Patent Law (for inventions)
- Design Patent Law (for designs)
- Trademark Law (for manufacturer's name, brands, or individual names of goods)
- Copyright Law (for expressions of thoughts or emotions)
- Unfair Competition Prevention Law (for suppression of free rides by any other persons)

## 8.4 CHAPTER I PATENT LAW

### 8.4.1 Intellectual Property Right Subject to Protection Under the Patent Law

The objects covered by the protection under the Patent Law are inventions. Although specific definitions on what sort of inventions would be subject to the protection under the Patent Law vary depending on countries, it is stipulated roughly in most cases that novelty, inventive step, and industrial applicability are the requirements for patent protection.

Further, inventions subject to the protection under Patent Law play roles of significance in each process of research and development, manufacture, and sales of cosmetics. Patents as roughly categorized in the following forms can be obtained on the basis of the types of inventions.

#### *8.4.1.1 Substance Patent*

First, in the development of cosmetics, if you have obtained a novel substance used in cosmetics, it is possible to obtain a patent for the "substance" itself. Such a substance is usually represented by the name of the substance or in a structural formula.

Given this, any manufacture or sales of cosmetics using the specific patented substance without permission of the patent owner (Patentee) constitutes an infringement of the patent right. In addition, in case when any other company is engaged in manufacture and sales of cosmetics using the specific substance in question, the person who has obtained the relevant patent is entitled to seek for an injunction and to claim for damages against the other company.

### COLUMN: 01

In patent applications with regard to chemical substances, a "Markush-type claim," as exemplified as follows, is often used, rather than the name of the substance itself. This enables acquisition of a patent right not only for the substance that becomes a central aspect of the invention, but also for any analog thereof. However, even a disclosure of only one substance among them in any prior art documents leads to such a judgment that the substance in question lacks novelty. In such circumstances, it is expected to cope with such an objection by effecting suitable amendment and deleting such chemical compound.

A specific example of a substance according to the Markush type.

A substance represented by the following formula (8.1):

$$R^1{-}CH_2{-}COOR^2 \qquad (8.1)$$

wherein $R^1$ is a linear or branched alkyl or alkenyl group having 1−12 carbon atoms, and $R^2$ represents a methyl group, an ethyl group, or a butyl group.

#### *8.4.1.2 Composition of Matter Patent*

If it is discovered that combination of a specific substance X and another specific substance Y is capable of producing a remarkable effect or a heterogeneous effect, such a discovery is also a subject of the patent.

Then, even though it would have already been known that the substance X and the substance Y are each independently used in cosmetics, if such a combination has yet to be known, it may be patentable in itself.

In this instance, terms of scope of claim for patent will be described as "a cosmetic composition comprising substances X and Y."

#### *8.4.1.3 Patent for a Method of Manufacturing*

For novel substances, when any new method for manufacturing a certain specific substance is conceived, such a method of manufacturing may also be a subject of the patent. However, it should be noted that filing of a patent application leads to a disclosure of the relevant method of manufacturing, and even if any other person would have used the method of manufacturing, it is very difficult to verify the method of manufacturing adopted by the other person. In view of this, so far as a method of manufacturing is concerned, one of the patent strategies is to deliberately refrain from filing of a patent application and to treat the method as a matter of know-how in a company.

#### *8.4.1.4 Patent for a Method for Use*

In addition to novel substances and novel combinations, if any novel method for use is discovered, such a discovery may also be a subject of the patent. For example, even for any substance or combination that has already been known as cosmetics, if it is discovered that application of a certain cosmetic cream in a certain specific amount twice a day, in the morning and at night, is capable of producing any remarkable effect or any heterogeneous effect, such a discovery is patentable.

### 8.4.2 Requirements for Obtaining a Patent

For obtaining a patent, requirements such as "novelty," "inventive step," and "qualification as a prior applicant" for an invention need to be satisfied, and a document for a patent application is required to satisfy the "description requirement." The necessary requirements of particular importance among others will be listed below for further clarification.

#### *8.4.2.1 Novelty*

In the nature of things, it is required that an invention that is applied for a patent be new. The reason for this is: suppose that a certain invention has already been published and put into practice by any persons and that only a specific applicant could be qualified to obtain the relevant patent despite said situation; this could cause the cosmetics industry considerable degree of confusion.

Then, the examination as to whether an invention has novelty will be carried out from the standpoints (1) the invention has not yet been known, (2) the invention has not yet been put into practice, and (3) the invention has not yet been described in any prior printed publications as of the time when the relevant patent application was filed.

#### *8.4.2.2 Inventive Step*

Even if an invention that was filed would satisfy the novelty requirement mentioned in Section 8.4.2.1, when such an invention could have easily been conceived by a person who has ordinary knowledge in the technical field to which the invention belongs (a person skilled in the art) on the basis of an invention that has already been known in Section 8.4.2.1 previously, a patent cannot be granted to the invention.

The reason for this requirement is: if only a specific person could obtain a patent even with regard to any inventions that could be conceived by anyone who is a person skilled in the art, it is likely to lead to significant detriment for any other persons skilled in the art.

#### *8.4.2.3 Prior Applicant*

In the event that more than one patent application would separately exist with regard to the same invention, the applicant who filed the application that is earliest in terms of day is qualified to obtain a patent. The reason underlying this principle is the nature of the patent right as one of the intellectual property rights. As already discussed in

Section 8.1, possession of a property right by more than one person at the same time for the same object, whether a tangible or an intangible object, leads to any dispute between them with regard to the right. It is easy to understand this by considering such an example that it cannot be allowed to permit the property right of one parcel of land for more than one person.

#### *8.4.2.4 Description Requirement*

For obtaining a patent, it is required to submit to the Patent Office scope of claim for patent, specification, and so on, in compliance with specific formalities.

##### 8.4.2.4.1 Scope of Claim for Patent

What is of particular importance is a part called "scope of claim for patent" (claim), and only an invention described in that part will be subject to examination by patent examiners, and the part will be the scope to which the effect of the patent right extends after grant of a patent.

In view of this, it is not allowed to make such assertions as "this requirement is necessary" and/or "this requirement is not necessary" once a patent is granted to any invention.

##### 8.4.2.4.2 Specification

It is required that the specification contains descriptions of "technical field," "background art," and "mode for carrying out the invention," concrete descriptions of an invention identified in "the scope of claim for patent," and description of the specification is required to be clear and sufficient to such an extent that a person skilled in the art can carry out the invention.

In this respect, to demonstrate an effect of an invention in a concrete manner, the necessity arises for actual results of experiments called Working Example and Comparative Example. In certain specific technical fields, an Example is sometimes not required; however, so far as cosmetics are concerned, it is obligatory to concretely demonstrate an effect anticipated in the use of the relevant cosmetics, and thus it may be understood that Working Example(s) and Comparative Example(s) are necessary for almost all patent applications.

### 8.4.3 Flow From Filing of a Patent Application to Registration

#### *8.4.3.1 Filing of a Patent Application*

In filing a patent application, it is required to describe the "application," "scope of claim for patent," "specification," "necessary drawing(s)," and so on in accordance with the formalities, and to submit these documents to the Patent Office.

#### *8.4.3.2 Laid-Open Publication*

Generally, after 18 months from the filing date; i.e., after an application for a patent is filed, the content of the application is published and it becomes available for inspection by any person. The purpose of this procedure is to prevent any useless research with regard to the invention filed by any other researcher who is also engaged in the research with the same content, and to contribute to further creation of any new invention on the basis of the published invention.

#### *8.4.3.3 Examination*

In the United States, upon submission of filing documents in appropriate formalities to the United States Patent and Trademark Office (USPTO), examination will be started by an examiner as to whether an invention filed for patent satisfies the respective requirements set forth in Section 8.4.3.2 previously.

In contrast, in Europe and Japan, upon filing of a "request for examination of application" (Request for Examination) within a predetermined period of time counting from the filing date, examination by an examiner will be started. The reason for this procedure is to prevent unnecessary examination of such an invention that was deemed technology of great account for the applicant at the time of filing the application, but is determined to be of less value years later at the time of filing the Request for Examination.

#### *8.4.3.4 Notice of Reasons for Rejection*

When it is judged by an examiner that the relevant patent application does not satisfy the requirement(s) for novelty, inventive step, and/or any other requirement as a result of an examination carried out as mentioned in

Section 8.4.3.3 previously, then the examiner in charge will inform the reasons to the applicant and require the applicant to file a reply within a predetermined period of time. In this respect, when the rejection is issued on the basis of the judgment on the novelty and/or the inventive step, the prior art document(s) (such as published patent specification, scientific literature, and so on) that support the judgment will be shown.

#### *8.4.3.5 Response to Notice of Reasons for Rejection*

On and after making a comparative analysis of scope of claims for the patent filed by itself and any prior art document as mentioned earlier, the applicant will submit to the patent office an argument describing such counterstatements as being different from an invention described in the prior art document(s) (satisfaction of the novelty), and/or as being incapable of being easily conceived on the basis of the prior art document(s) (satisfaction of the inventive step). In addition, when the scope of claims for patent is partially identical with the invention described in a prior art document, the applicant also may file an amendment to restrict the scope of claims for patent and to make assertion that it is not the invention described in the prior art document.

It is often the case that these series of actions to cope with such rejections require expert knowledge. Accordingly, it is a common practice that an inventor(s) of the rejected invention will cope with the Notice of Reasons for Rejection in corporation with a patent attorney, who is an expert in intellectual property rights, as well as with the person(s) belonging to the intellectual property department, if any.

In addition, in companies that do not have any intellectual property department, it is a common practice that an inventor and a patent attorney have a consultation session to decide how to cope with the Notification of Reasons for Rejection.

#### *8.4.3.6 Notice of Allowance*

When it is revealed because of an examination that a patent application satisfies each and every patent requirement, or, after coping with the Notice of Reasons for Rejection as set forth in Section 8.4.3.5 earlier, it is judged from the content developed in an argument and/or an amendment that a patent application satisfies each and every patent requirement, then the examiner in charge will issue a Notice of Allowance for a patent (decision for grant a patent). At such time, the patent application will mature into registration and will become a patent right by means of subsequent payment of the registration fee by the applicant to the patent office.

#### *8.4.3.7 Patent Gazette*

An invention that eventually matured into a patent will be described and published in the Patent Gazette to become available for inspection by any person as to who is the inventor of the patent, or as to who holds the relevant intellectual property right (the patent right).

**COLUMN: 02**

When it is eventually determined by an examiner that an invention does not satisfy the patent requirements, the examiner in charge will render a Decision of Rejection for the relevant application and show the applicant the reason(s) for the decision. When the applicant is in a disagreement with the decision, the applicant is entitled to file an Appeal against the examiner's Decision of the Rejection with the Patent Office, and consequently, the rejected patent application in turn will proceed to review and judgment by trial examiners; that is to say, an appeal board, as to whether or not the invention of the rejected application would be patentable.

### 8.4.4 Effect of Patent Right

In the event that any other person infringes (infringer) a patented invention described in "the scope of claims for patent," Patentee is entitled to demand prohibition of manufacture and sales of the relevant product against the infringer (Injunction).

In addition to the aforementioned, a Patentee is entitled to claim as Damages against the infringer any profit that the Patentee has lost due to the infringement, or profit obtained by the infringer by means of the infringement of the invention.

COLUMN: 03

Injunction demand serves for preventing an infringement of the patent right for the future as from the time when the demand is sought. More concretely, it works for prohibiting manufacture and sales of the product covered by the patent.

On the other hand, demand for Damage serves for claiming compensation for damages suffered in connection with any infringement of a patent right that occurred in the past.

## 8.4.5 Duration of Patent Right

Generally, the duration of the patent right runs 20 years counting from the filing date of a patent application, and then, after an expiry of the 20 year period, the patented invention will be made available for use by any person.

COLUMN: 04

Opinions on why an invention needs to be protected are widely divided; one among others is such an interpretation that a patent right (i.e., an exclusive right) is admitted as "a compensation for" a positive "publication of an invention" by an inventor. It is further stated that by virtue of a patent right, it becomes possible for the Patentee to reap profits arising from exclusive sales of the product using the patented invention, and the reaped profits in turn may serve for advancing further research and development, eventually leading to possible creation of a useful invention.

The cited opinion further follows to the effect that an invention has to be protected, because by promoting such a positive publication of new inventions in this fashion, inventions can be prevented from falling into dead storage, and because it can be expected for any person to make a new invention on the basis of the published invention.

## 8.4.6 Materiality of the Prior Patent Search

### *8.4.6.1 Research and Development Stage*

As set forth in Section 8.4.3.2 previously, the content of a patent that any person has applied for will be published after 18 months from the filing date of an application for patent. On this premise, it is required for a researcher who is engaged in research and development to make an advance search as to whether or not the research content that he/she is going to undertake for future tasks would have been filed for patent applications by any other persons. This is because failure to carry out such an advance search may result in engagement in research for technology that has already entered into the public domain, ending up in vain without making any contribution whatsoever to the company.

### *8.4.6.2 Commercialization Stage*

Although the prior art search as clarified in Section 8.4.6.1 in the preceding paragraph serves for searching any invention (technology) that has already entered into the public domain, prior patent search for which the necessity arises at the early stage of commercialization serves for ascertaining whether or not a new product that a certain company is ready to launch would fall under the technical scope of any patented inventions which have already been registered under the ownership of any other parties.

There is fear that by failure to carry out the prior patent search, manufacture and sales of the relevant product may lead to an infringement of any patent right of any other person, and may result in an injunction demand which may inevitably force the company to cease manufacture and sell the product. In addition, it is likely that profit obtained by actual sales of the product will be paid to a Patentee as compensation for damages.

Actual sales of cosmetics generally involve an enormous cost in connection with their planning, research and development, manufacture, decision of brand name and/or product name, development of the design of a container,

creation of commercial for advertisement and promotion and its broadcasting, shooting and distribution of advertisement posters, and so on, and thus in view of this, if forced into a situation to have no choice but to inevitably cease manufacture and sales of the product once launched, the company would suffer immeasurable damage therefrom.

#### *8.4.6.3 Measures to Cope With Patent Rights of Other Persons*

In the event that it has turned out, by conducting the prior patent search as clarified in Section 8.4.6.2 earlier, that any patent right by any other person exists, the following ways are available for coping with the matter:

**(a)** to enter into negotiation with the Patentee seeking for assignment or grant of a license with regard to the patent right;
**(b)** to make a full collection of evidence satisfactory for invalidating the patent right (any prior art document not cited in the examination procedures due to oversight) to be ready for possible infringement suit brought by the Patentee and to make assertion of the invalidation of the patent right;
**(c)** to make a full collection of evidence satisfactory for invalidating the patent right (any prior art document not cited in the examination procedures due to oversight) to file a request for invalidation of the patent to the Patent Office to invalidate the patent right; and
**(d)** to replace the product with any other product that does not fall under the scope of claims for patent.

### 8.4.7 Patent Rights in Foreign Countries

Patent rights will be granted registrations in respective countries after the relevant patent applications are examined in accordance with the Patent Laws established in the respective countries. That is to say, a so-called "world patent"; i.e., one that is examined by a certain international organization and extends the effect throughout the world, does not exist for the time being.

For this reason, for example, such a case often happens that a patent application for a certain invention was patented in country A; nevertheless, a patent application for the same invention was not granted as a patent in country B. It is also often the case that patent applications filed in countries C and D for the same content would have resulted in restriction of some parts of scope of claims for patent after being examined in respective countries, leading to inconsistency in the relevant "scope of claims for patent."

Such situations occur because each patent application will be examined independently in respective countries, as just clarified earlier. In recent years, such an operation has already been started that a plurality of countries share information on examinations carried out by the patent offices in respective countries to improve the efficiency of examinations.

### 8.4.8 Flow From Filing of a Patent Application to Acquisition of Right in Foreign Countries

In what way should patent rights be obtained in foreign countries? Most popular courses of actions required for this purpose will be clarified as follows:

#### *8.4.8.1 Filing of Patent Applications in Respective Countries in Accordance With the Paris Convention*

It is a common practice that, in the first place, a patent application is filed in a country where a researcher who made an invention resides or stays (the first country).

Then, if filed in another country within 1 year starting from the filing date of a patent application in the first country (the priority date), the patent application in the second country will be treated as filed also on the "priority date" and will be examined as to whether it would satisfy the patent requirements such as novelty and the inventive step as of the time of and on the basis of said priority date [the priority right in accordance with the Paris Convention for the Protection of Industrial Property (the Paris Convention)].

That is to say, it may as well be interpreted in such fashion that one year after filing of the patent application in the first country can be afforded as a grace period for making determination as to whether such an invention is so useful and of value that filing applications in foreign countries is also required. In addition, your attention is drawn to the fact that when a patent application is filed in another country, as a general rule, there is a requirement to prepare a translation of the patent document into the language of that country.

COLUMN: 05

The Paris Convention for the Protection of Industrial Property is a convention that was entered into in 1883, and later on, after several amendments, it has been developed to set the basic idea on the international protection of intellectual property rights.

As the remarkable provision set forth in the Convention, an idea; i.e., "the priority right," is set. The description "the patent application in the second country will be treated as filed also on the 'priority date'" included in the previous explanation reads in more precise wording that: "any subsequent filing in any of the other countries of the Union before the expiration of the period referred to earlier (1 year from filing the first application: writer's note) shall not be invalidated by reason of any acts accomplished in the interval, in particular, another filing, the publication or exploitation of the invention, the putting on sale of copies of the design, or the use of the mark, and such acts cannot give rise to any third-party right or any right of personal possession."[1]

Also, in "Annex 1C of the Marrakech Agreement Establishing the World Trade Organization; Agreement on Trade-Related Aspects of Intellectual Property Rights" (commonly known as "TRIPS Agreement"), which has incorporated the basic system of the Paris Convention and entered into force in 1995, it is stipulated that the priority right as mentioned previously is admitted in the member countries of the World Trade Organization (WTO).

### *8.4.8.2 Filing of Patent Applications in Other Countries Using the Patent Cooperation Treaty*

#### 8.4.8.2.1 The First Country Application

The flow of a patent application using the Patent Cooperation Treaty (PCT) is the same as that of a patent application in other countries based on the Paris Convention in that, in the first place, a patent application is filed in a country where a researcher who made an invention resides or stays (the first country) (see Fig. 8.1).

Further, a patent application using the PCT shares the common feature with a patent application in accordance with the Paris Convention in that one year after filing of the patent application in the first country can be afforded as a grace period for making determination as to whether or not to carry out the PCT application.

#### 8.4.8.2.2 PCT Applications

Subsequent to the first country application, then in turn, at the time of filing a patent application in any other country, filing of an international application in compliance with the PCT will be carried out, instead of filing applications in respective countries in accordance with the Paris Convention as mentioned in the preceding paragraph.

What should be noted with regard to this type of application is that only by means of filing a patent specification described in specific languages such as English, Japanese, German, and French to any specific Receiving Offices [the USPTO in the United States, the European Patent Office (EPO) in Europe, and Japan Patent Office (JPO) in Japan], such an effect that is equivalent to that expectable for applications actually filed in each and every PCT member country (148 countries as of February 15, 2016) can be obtained.

#### 8.4.8.2.3 International Search Report, International Preliminary Examination Report

When a PCT application is filed, the International Searching Authority in turn automatically carries out a search as to whether the application would satisfy the requirements such as novelty and inventive step and provides the Written Opinion to the applicant.

In addition, if desired and requested by the applicant, it is possible for the applicant to further seek the International Preliminary Examining Authority to issue a Written Opinion as to whether the invention filed for the International Application would be patentable, which enables the applicant to make estimation to some extent as to whether or not the invention filed for the International Application would satisfy the requirements such as novelty and inventive step, and also to determine as to whether it would be appropriate to proceed further to enter into the national phase.

#### 8.4.8.2.4 Amendment in the International Phase

Within a certain period of time as from issuance of the International Search Report or within certain period of time as from filing of a request for International Preliminary Examination, it is possible to amend the scope of claims for patent. That is to say, it can be said that this is a useful measure if it is determined from the perusal of the

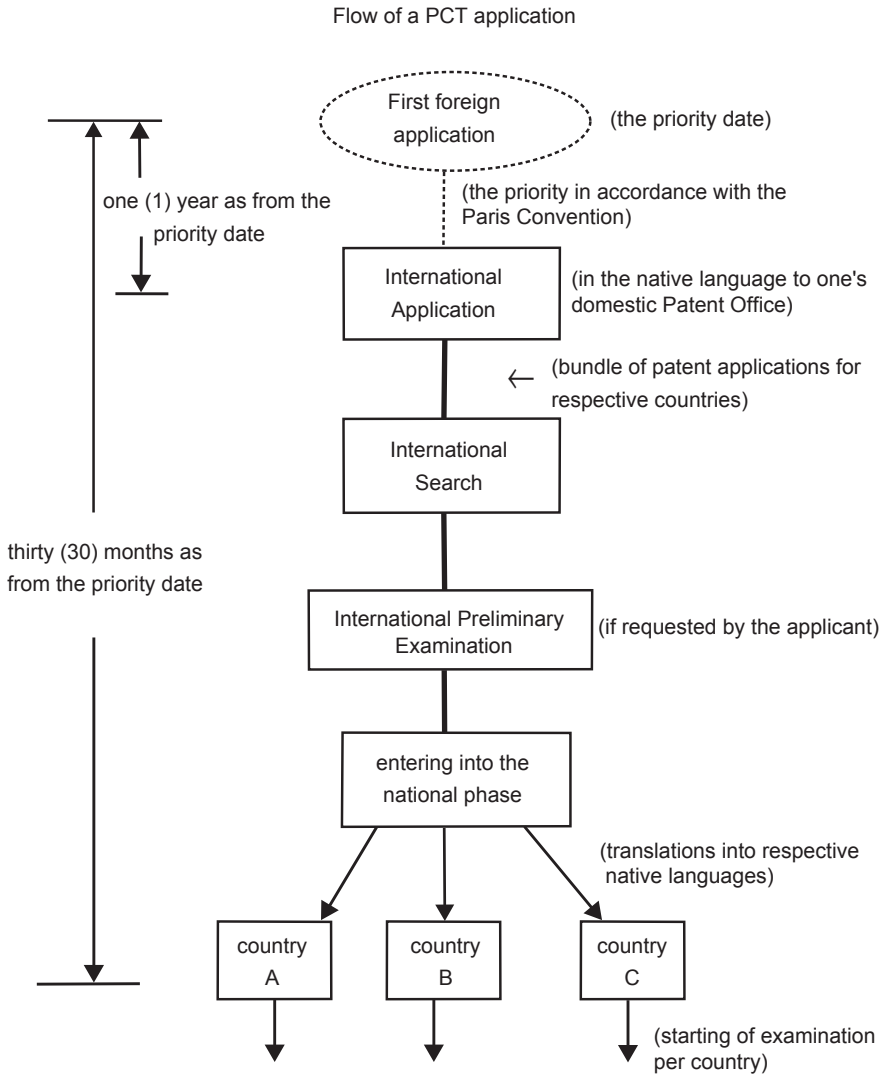



FIGURE 8.1 Flow of a patent cooperation treaty application from first foreign application through start of application for each country.

International Search Report that any restriction of scope of claims for patent enables the application to mature into a patent,[2] or if it is determined that by carrying out an Amendment, issuance of such a Written Opinion that is affirmative with regard to the patentability of the application is expectable.[3]

That is to say, by carrying out the Amendment in the International Phase, the applicant may save the effort to implement the procedures for the Amendment in respective countries, and moreover, this leads to the benefit for the applicant that is equivalent to the benefit obtained by Amendment carried out in respective countries, by means of only a single procedure.

#### 8.4.8.2.5 Entering Into the National Phase

An International Application that the applicant determined useful and thus required to obtain a patent also in other countries will be transferred to the respective countries (the national phase) desired by the applicant (the designated states), and subsequent to that phase, the International Application will be subject to examination such as novelty and inventive step by each designated state.

The due date for entering into this national phase is 30 months (2 years and 6 months) counting from "the Priority Date" as clarified in the preceding paragraph with regard to the Paris Convention. (Some among the PCT member states actually allow a grace period of more than 30 months under the respective national laws.)

Incidentally, it should be noted that at the time of national phase as just mentioned, respective designated states may require translation of the relevant specification into the native language.

#### 8.4.8.2.6 Characteristics of PCT Applications

As clarified previously, a PCT application enables one to bring about an effect that is equivalent to that expectable for applications actually filed in all the PCT member countries by taking only a single procedure.

Further, only by filing an International Application in its native language to one's domestic Patent Office, a result of preliminary search for patentability of the relevant invention can automatically be obtained, which the applicant can use as a criterion to determine whether subsequent national phase would be required.

Moreover, a grace period of 30 months as from the priority date is provided for entering into the national phase, by which the applicant can afford a relatively long period of time to determine whether or not a subsequent national phase would be required, in comparison with the fact that the due date for filing patent applications in respective countries in accordance with the Paris Convention is within 1 year as from the priority date.

However, a patent application filed under the PCT will eventually be judged for patent requirements by respective designated states, and thus it is sometimes expressed as a "bundle of patent applications" for each designated state.

### COLUMN: 06

In Europe, if a patent will be sought for in a country that is the member of the European Patent Convention (EPC), it is a common practice to file an application in the EPO, skipping filing of applications to respective countries. Subsequent to filing of an application in the EPO, the application will be examined with regard to the patent requirements such as novelty and inventive step by the EPO, and if it is revealed that the application involves no reasons for rejection, then a patent is registered with regard to the relevant invention and the patented invention will take effect as a patent in respective countries.

What is different from the PCT applications lies in the aspect that the EPO carries out the substantial examination of an application, and if the application is judged as patentable by the EPO, no additional examinations by respective countries are required for granting a patent.

## 8.5 CHAPTER II DESIGN PATENT LAW

### 8.5.1 Intellectual Property Rights Protected Under the Design Patent Law

When it comes to the cosmetics industry, it can be said that the object that will be subject to protection under the Design Patent Law will predominantly be designs of containers. That is to say, any container with any unprecedented shape, pattern, or color and thus having any aesthetic appeal may sometimes capture the attention of customers, and may serve as a motivator for purchase of the cosmetics.

### 8.5.2 Requirements for Design Patent Registrations

In the United States and Japan, the Design Patent Laws set forth the requirements for novelty and inventive step,[4] as is the case in the patent rights.

On the other hand, in Europe, examination will be carried out only with regard to the points; i.e., as to whether a design patent applied would be categorized as a subject of protection, and as to whether it would be offensive to public order and morals, and design patent applications will mature into registrations without any course of substantial examination (nonexamination registration principle). Later, if requested by any other person for invalidation of a design patent, substantial examination will be carried out with regard to the relevant registered design patent for its novelty, inventive step, and so on.[5]

### 8.5.3 Scope of Rights of Registered Design Patent

On the other hand, with regard to registered design patents, in both the United States and Japan, the validity of a design patent right extends to the registered design itself as well as similar designs of the same, although the wordings of the corresponding articles of the Laws are somewhat different between the countries.[5]

This principle is intended in view that allowance to any other person to sell any similar product that is actually only a minor modification of a registered design is not appropriate. Further, because design is an abstract idea and is created as a concept having a certain range, adjustment of protection is intended by means of extension of the right to similar designs.

### 8.5.4 Duration of Design Patent Rights

Duration of a design right varies depending on countries, and in case of the United States, it runs 14 years as from the registration. In case of some major countries in Europe, it runs 5 years from filing of the application, which will be 25 years at the maximum upon renewal of the same. In case of Japan, it runs 20 years as from the registration, and after expiration of the duration of the design registration, the design will be made available for use by any person.

It should be noted, however, that when consumers eventually have come to recognize the relevant product as a container of a specific cosmetics manufacturer as a result of continued use of the design, then registration of the three-dimensional shape of the container as a trademark will become possible, leading to the exclusive and permanent availability of the container for the manufacturer.

### 8.5.5 Search for Registered Designs in Commercialization Stage

In the development of cosmetics, for example, if a new design of container is created and is proposed to be used for a certain product, it is advisable to carry out a search for prior registered design patents, as is the case of the patent rights. The reason for this recommendation is that manufacture and sales of cosmetics using a container that is identical or similar to any existing registered design patent constitute an infringement of the design patent right owned by another company.

## 8.6 CHAPTER III TRADEMARK LAW

### 8.6.1 Intellectual Property Rights Protected Under the Trademark Law

The object that is subject to protection under the Trademark Law is the goodwill of business embodied by a trademark, which corresponds to use of any specific character, graphic, sign, three-dimensional shape, color, and/or sound with regard to any product or service.

To be more concrete, the trademark right is a right that enables the description of the name of the manufacturer, the brand name, the product name, and so on of cosmetics on respective goods in order to exclusively sell the product bearing said names. When it comes to services, for example, the trademark right enables the holder to display the name of manufacturer, brand name, as a signboard at a cosmetics sales counter of a department store and to provide product explanation by a cosmetics sales clerk, for the same purpose.

### 8.6.2 Requirement for Effectuation of Trademark Rights

The requirement for effectuating a trademark right varies depending on respective countries, and in the United States, "the first-to-use principle" is adopted. That is to say, if you could successfully demonstrate that you have used a certain trademark earlier than another company, you can bring a suit for trademark infringement against the company that uses the trademark that is identical or similar to your own trademark.

However, because it is sometimes not easy for any company to establish from what time any specific trademark of its own has been used, by virtue of obtaining "federal registration" of its own trademark, a trademark owner will reap such benefits as presumption of being an exclusive right, constructive use all over the United States, and constructive notice of being a proprietor.[6]

Furthermore, for the purpose of obtaining trademark registrations in Europe, there are two alternatives available; i.e., filing of applications for trademark registrations separately in each European country, and filing of applications for Community Trade Mark (CTM) to the Office for Harmonization in the Internal Market (OHIM). If the CTM route is used, a single procedure provides benefit that is equal to that obtained by filing trademark applications in all the European Union (EU) member states, and, if registered after undergoing examination, trademark registration that extends its validity to all the EU member states can be secured.

In the case of Japan, an application for trademark registration will be filed with the JPO, and it will be registered after undergoing examination by the JPO.

COLUMN: 07

For the purpose of obtaining a trademark registration, the requirements of novelty and inventive step will not be made an issue, unlike patent or design patent. This is because invention and/or design is believed to be "creation" that a human being has created; in contrast, trademark is considered to be "selection"; i.e., the result of mere selection among names which have already existed. (As a matter of course, there may be any new name that someone has come up with for the first time; however, the Trademark Law protects even such names consistently as "selection," instead of "creation.")

### 8.6.3 Scope of Rights of Registered Trademarks

Trademark right extends its validity to a registered trademark itself as well as any trademark that is similar to the registered trademark. This principle serves for preventing occurrence of such a circumstance that if any other person is allowed to use any similar trademark, consumers would be misled to believe it as one of specific brands and to be confused as to which company is selling a product bearing a similar trademark.

### 8.6.4 Functions of Trademarks

Regardless of being a registered trademark or not, a trademark has functions as follows:

**1.** Function to distinguish one's own goods from others
   This is a function to identify as to whether a certain good is one's own product or product of any other company, and as a result of successive use of the trademark, the goodwill of business will be constituted to the cosmetics manufacturer.
**2.** Function to indicate the origin
   This is a function to indicate from which cosmetics manufacturer the product bearing the trademark is sold.
**3.** Function to assure the quality.
   This is a function to guarantee that the goods bearing the trademark have equal quality.
**4.** Function as advertisement and promotion
   This is a function to serve as advertisement and promotion for the cosmetics manufacturer exactly by means of the sales itself of the product bearing the trademark that accompanies and embodies credit from customers acquired during the course of sales of the product bearing the trademark.

### 8.6.5 Duration of Trademark Rights

Duration of a trademark right varies depending on respective countries, and in the United States and Europe, it runs 10 years as from filing of an application, whereas in Japan it runs 10 years as from registration. Further, it is possible to exclusively use the trademark in any countries on a permanent basis by applying for renewal of the duration. The reason for this principle is that it is considered appropriate to sustain any trademark that has acquired goodwill of business from customers in virtue of use over years.

COLUMN: 08

When the filing of an application for trademark registration is carried out, not only is "the trademark" intended for use required, but also "goods, service" intended for use are required to be designated and submitted to the Patent Office. For example, designated goods for a trademark will be set as "cosmetics." Further, because it is unlikely that any confusion would arise among consumers with regard to any goods (for example, an electrical power tool) that are not similar to said designated goods, as a general rule, use by any other company of the identical "trademark" in connection with electrical power tools will not intrinsically constitute infringement of a trademark right. It is even possible for any other persons to obtain a registration of the identical "trademark" in connection with electrical power tools.

### 8.6.6 Selection of Trademark

It is a matter of public knowledge that in case of development and sales of cosmetics, brand names and/or individual product names = trademarks play important roles. Then, in the planning stage, development stage, and/or the commercialization stage, it is required to select a trademark.

For example, suppose that in the planning stage, a proposal for trademarks is sought and collected by a planning team or companywide, and subsequently one among these candidate trademarks that is consistent with the product concept is selected.

Then in turn, it becomes necessary to conduct a search as to whether or not the selected trademark is identical or similar to any registered trademark owned by any other company, and if it is judged by means of this search that the candidate trademark is identical or similar to a certain registered trademark owned by certain other company, consequently, selection of a trademark will be back to where it was started.

In particular, when it comes to the goods intended for marketing not only in one's own country but also overseas, it is required to ascertain in respective countries that no identical or similar trademark exists.

For this reason, there is a risk that only by following the flow; i.e., starting from collection of candidate trademarks, then through selection of the trademark, and finalizing in search of identical and/or similar trademarks, it would take forever to decide the trademark.

Then, to cope with such risk, it is most practical to obtain registrations of a lot of trademarks assumed for use in cosmetics in advance in one's own country and overseas, and to select a trademark that conforms to a concept from among registered trademarks already in possession. Moreover, with regard to collected candidates of trademarks, so far as trademarks assumed acceptable to use for cosmetics among them are concerned, it is also a strategy to file applications for trademark registrations of such trademarks in respective countries and store them as candidate trademarks for future cosmetics. It should be noted, however, that for any trademarks which have been stored as registered, those candidates would be canceled if they are not in actual use.

## 8.7 CHAPTER IV COPYRIGHTS

### 8.7.1 Copyrights and Development of Cosmetics

On the surface, it is hard to comprehend the relationship of copyrights and cosmetics; i.e., in what manner the former is involved with development and sales of the latter. However, it is often the case that the copyright has involvement with the manufacturing and marketing stages of cosmetics, as clarified below:

### 8.7.2 What is the Copyright?

A copyright work is defined as being creative expression of idea and/or emotion. Further, the copyright is regarded as being the right that enables one to exclusively carry out reproduction of the copyright work.

As exemplification of those that involve copyright specifically in manufacture and sales of cosmetics, posters displayed, e.g., at a beauty counter for the purpose of product advertisement, and catalogs, as well as commercials to be broadcast on television will be subject to protection under the copyright.

### 8.7.3 Time of Accrual and Duration of the Copyright

The copyright accrues as from the time of creation of the copyright work and expires with the lapse of 50 years after the death of the creator. That is to say, it is not necessary to register an accrued copyright at any public sector agency (such as the US Copyright Office or the Agency for Cultural Affairs of Japan), provided, however, that by virtue of seeking for registration of copyright, the effects to prevent the piracy by, for example, demonstration of the time of creation can be expected.

COLUMN: 09

Whereas a patent right accrues by means of registration of the patent in the Patent Office, in contrast, the copyright accrues immediately as from the time of creation of a copyright work without any need for such a registration. In the case of patent right, more than one proprietor will not exist for one identical invention (absolute exclusive right) except when the relevant patent right is sought in a joint application. However, in the case of copyright, if respective creators created one identical copyright work independently [i.e., without relying upon the creation of other person(s)], then copyrights will be endowed to respective creators (relative exclusive right).

This is because the Copyright Law is intended to make contribution to the development of culture, and also due to the spirit thereof to consider it reasonable and appropriate to provide protection to respective unique creations by individual persons.

## 8.8 CHAPTER V UNFAIR COMPETITION PREVENTION LAW

### 8.8.1 Subject of Protection Under the Unfair Competition Prevention Law

The Unfair Competition Prevention Law is a law that is aimed at prevention of unfair competition, for the purpose of ensuring, e.g., fair competition among business operators. It should be noted, however, that the subject of protection under Laws against Unfair Competition varies depending on respective countries. Given this, what should be noted in sales of cosmetics as modes of "unfair competition" will now be listed as follows.[7]

#### *8.8.1.1 Act to Create Confusion With an Object of Well-Known Indication of Goods*

By this categorization of mode, prohibition of an act to create confusion with goods of another person by carrying out sales using an indication of goods that is identical or similar to that widely recognized as an indication of goods of another person is intended.

If such an indication of goods would have simply been registered as a trademark, as a matter of course, this act constitutes a cause to bring a suit against the other party for violation of the Trademark Law. However, this Unfair Competition Prevention Law serves to protect even such an indication of goods that has not been registered even as a trademark but has become widely recognized by consumers as an indication of a certain specific company through TV commercial and/or over-the-counter sales.

Conversely, from the standpoint of the owner of the well-known indication, if any other person would sell their goods using the owner's well-known indication of goods, such an act falls under unfair competition. This act can be subject to injunction demand and/or damages, which is intended to prohibit free rides by other persons on the goodwill of business achieved and fostered by continuous marketing efforts devoted by the owner up to the present.

#### *8.8.1.2 Act to Make an Unauthorized Use of Famous Indication of Goods*

By this categorization of mode, prohibition of an act to make unauthorized use of any indication that is identical or similar to a famous indication of goods of another person is intended.

In contrast with the mode in Section 8.8.1.1 previously that requires the indication of goods being "well-known" and prohibits such an indication of goods that may create "confusion," any indication of goods falls under this mode only if it is "famous," and the issue as to whether or not any "confusion" would be caused is not questioned.

For example, in the case of any brand that is famous as cosmetics, it is intended to prohibit other persons from selling goods by taking unfair advantage of (free ride on) customer attraction to the brand that has already accrued. Further, it is also intended to prevent weakening (dilution) of the relationship based on trust with customers that has ever been established to the present.

#### *8.8.1.3 Act to Imitate Configuration of Goods*

By this categorization of mode, prohibition of sales of goods that imitate configuration of goods of another person is intended.

Now, it is worth noting that configuration of goods means shape, patterns, color, gloss, and texture of goods which may be perceived by consumers, and has a character that is similar to that of the design patent rights as mentioned earlier.

However, the range of configuration of goods that is subject to protection under the relevant provision with regard to this mode is not so wide as "scope of similarity" admitted in the design patent rights.

But the relevant provision of the Unfair Competition Prevention Law relating to this mode in turn enables prevention of the free ride in case of launching new goods using new configuration.

## 8.9 CHAPTER VI COOPERATIVE RESEARCH AND DEVELOPMENT AGREEMENT IN RESEARCH AND DEVELOPMENT OF COSMETICS

In the development of cosmetics, it sometimes occurs that different companies carry out joint research and development. For illustrative purpose, joint research carried out between a company that supplies raw materials of cosmetics and a cosmetics manufacturer that develops cosmetics using the raw materials to develop useful product is one such example.

In such circumstances, it is common practice for the two parties to mutually enter into agreements as clarified below in a stepwise fashion:

### 8.9.1 Confidentiality Agreement

Confidentiality agreement is a sort of agreement that serves for judgment by companies concerned with regard to confidential information of mutual companies as to whether or not it would be beneficial to disclose to the other company concerned the content of the confidential information and to conduct joint research and development. In addition, there may be a unilateral agreement that only one of two companies concerned discloses its technical content to the other company.

In this agreement, the purpose of confidentiality agreement, identification of the confidential information subject to disclosure, confidentiality period, and so on will be stipulated.

Given this, what should be noted now is that in case of a meeting held between the parties while disclosing mutual technology, such proposal between mutual researchers as "I wonder if this technique could be better if improved in this manner" results in deviation of the range to be stipulated in the confidentiality agreement. It is for the reason that not only does this involve the disclosure of secret, but also this constitutes "an act of mutually exchanging opinions with regard to content of future research and development," and consequently leading to the significance that "the joint research and development" has already been started.

In view of this, if directionality of joint research and development could have been shared to some extent, it is sometimes likely that not a confidentiality agreement but a joint research agreement as clarified in what follows will be entered into in the first place.

### 8.9.2 Joint Research and Development Agreement

A joint research and development agreement is entered into at the time when it is decided by companies concerned to conduct joint research and development, taking into account the technology of the other company disclosed in accordance with the confidentiality agreement as well as one's own technology.

In this agreement, the purpose of joint research and development, the object of the joint research and development, the period of the joint research and development, confidentiality, and so on will be stipulated, whereas what is of the most crucial importance lies in an article on "vesting of results" brought by the joint research and development.

That is to say, it is a stipulation with regard to the result that could have been achieved by the joint research and development (=the intellectual property rights), that is, what kinds of rights parties concerned are to obtain eventually.

For example, in joint research and development between a manufacturer of cosmetics raw materials and a cosmetics manufacturer, as far as the cosmetics manufacturer is concerned, it is a matter of course that it would be very reluctant to allow any other rival cosmetics manufacturer to use the relevant technique resulted from the joint undertaking. Conversely, from the side of the manufacturer of cosmetics raw materials, it is also a matter of course that it would be very willing to supply the raw material not only to one company but also to many others.

That is to say, it is often the case that any negotiation that is started between companies concerned with regard to vesting of results even after the development of certain beneficial technique by virtue of joint research and development may fail to reach an agreement.

In view of this, one is required to, prior to entering into the joint research and development, have a clear-cut definition in joint research and development agreement on how to handle the intellectual property rights obtained by the joint research and development.

Moreover, it is also important to identify an object of joint research and development, in view of the necessities to make a sharp distinction between the results obtained only from the research and development of one's own and the results obtained from the joint research and development. Unless such a stipulation is clear, consequently, it is likely that any dispute would occur between the parties concerned.

## 8.10 IN CONCLUSION

As set forth heretofore, Intellectual Property Rights play roles of importance in each of research and development, manufacture, and sales of cosmetics, and accordingly, it is important also for each researcher to have basic knowledge on these rights.

Then, it is required for researchers to conduct prior art searches before starting research to ascertain that an object of his/her intended research does not fall under any technique already developed by any other company.

Further, it should be noted that it would take considerable time and costs (personnel costs and costs for sample and/or equipment) for each researcher to accomplish one certain invention. Also note that the sole means for collecting such costs will be filing of a patent application and subsequent acquisition of a patent right (except for the case of hiding them as know-how) for exclusive sales of the product that uses the patent right or for grant of license thereof to other companies.

It is often the case that inventions accomplished by each researcher may be taken into account without turning into a commercial reality. Nevertheless, it is my belief that it is nothing less than the challenges faced by each researcher for subjects of research of great individuality and even having "novelty" and "inventive step," instead of imitating any technique accomplished by other persons, that drive further forward the growth and development of the cosmetics industry.

## References

1. Paris Convention Article 4-B.
2. PCT Article 19.
3. PCT Article 34.
4. Haruhiko Kakigi, et al. Patent Magazine (the monthly bulletin issued by the Japan Patent Attorneys Association), vol. 68. No. 9, 31–56.
5. Hiromichi Aoki. "Tokugikon" (the bulletin issued by "Tokugikon", the JPO Social Gathering on Technology), No. 232, issued on March 30, 2004.
6. Kanako Aya. "Tokkyo Kenkyu" ("Patent Studies" the bulletin issued by National Center for Industrial Property Information and Training), No. 49, 2010/3, 55–63.
7. Shigeki Chaen. *Unfair Competition Prevention Law.* Yuhikaku Publishing Co., Ltd.; 2015.

CHAPTER

# 9

# Regulations on Cosmetics

M. Takahashi[1], K. Sakamoto[2]

[1]Takahashi Cosmetic Consulting, Tokyo, Japan; [2]Tokyo University of Science, Chiba, Japan

## 9.1 INTRODUCTION

Cosmetics are consumer products used in our daily life to maintain and enhance beauty and health. As consumers, we use these products over a long period of time based on the assumption that its safety is on par with food products; due to this assumption, government restrictions are set for both food and cosmetics to prevent health damage. Consumers can perceive potentially harmful changes in food products such as putrefaction or acidification, so they will be able to manage damage control with the exception of accidental ingestion. However, changes in cosmetics such as separation of emulsion products or change in viscosity do not always mean quality decline that leads to health damage, so consumers may notice such changes but it will be difficult to perceive changes that direct to health damage such as microbe contamination or putrefaction. For such reasons, cosmetics are restricted under medical-related regulations in most governments.

In the modern world where products are traded globally, many trade treaties are constantly negotiated and signed, and this also applies for cosmetics. From the late 1980s, the leading markets of Europe, Japan, and North America have worked together to find the barriers between their restrictions and unify them through the "Mutual Understanding of Cosmetic Regulation."

In this chapter, we will comprehensively cover restrictions on cosmetics in comparison with Japan, a country that has supported the international cosmetics market from a unique standpoint to connect different cultures and technologies. In Japan, the first regulations on cosmetics required approval for each individual product, then shifted to category approval. In 2001, the regulations changed to similar to those of the European Union (EU) and other regions, where ingredients can be used as long as they are not prohibited or restricted and all used ingredients are listed. With this change, the regions covered in this chapter share a similar rule where restricted materials are categorized into positive and negative materials. However, the restrictions on cosmetics ingredients still vary greatly depending on the country and region. Japan has changed its established safety standards gradually to comply with the international standards, and here we will look at specific material restrictions in each region in comparison to Japan from this aspect.

## 9.2 REGULATIONS ON COSMETICS PER REGION

We cover Japan, EU, the Association of Southeast Asian Nations (ASEAN), the United States, China, South Korea, and Taiwan. In most countries and regions, various regulations from the selection of materials to labeling/marketing of final products are often based on the standards of the EU. In particular, ASEAN is an association like EU and the restrictions are almost identical. When limited to ingredients, China and South Korea are also very similar to the EU.

There is an intermediary category called quasi-drugs (medical cosmetics) in Japan, and similarly there are special-use cosmetics in China, over-the-counter (OTC) cosmetic drugs in the United States, and cosmetics containing medical, poisonous, or potent drug(s) in Taiwan. In addition to quasi-drugs like Japan, South Korea also has categories of common cosmetics, functional cosmetics, and organic cosmetics. Unlike common cosmetics products that can be produced by registration, these products must be approved and the approval process must follow each country's approval procedures following the laws and regulations of said country. Table 9.1 shows the intermediary categories for each country. There are no intermediary categories in the EU and ASEAN unlike the other countries just listed,

Cosmetic Science and Technology: Theoretical Principles and Applications
http://dx.doi.org/10.1016/B978-0-12-802005-0.00009-4



Copyright © 2017 Elsevier Inc. All rights reserved.

**TABLE 9.1** Intermediary Categories for Each Country

| Country | Type | Item |
|---|---|---|
| Japan | Medical cosmetics | Skin toners, emulsions/creams, sun blocks, shampoos, hair conditioners, etc. |
| | Quasi-drugs excluding medical cosmetics | Deodorants, hair dyes, hair growth formula, bathing salts, toothpastes, perming agents, etc. |
| South Korea | Functional cosmetics | Sun-blocking cosmetics, whitening cosmetics, etc. |
| | Organic cosmetics | Permitted materials stipulated |
| | Quasi-drugs | Deodorant, hair growth stimulants, hair dyes, etc. |
| Taiwan | Cosmetics containing medical, poisonous, or potent drug(s) | Sun blocks, hair dyes, perming agents, whitening cosmetics, deodorants, etc. |
| China | Special-use cosmetics | Hair growth agents, hair dyes, perming agents, hair removers, breast beautification, slimming, deodorants, antistain products, sun blocks |
| USA | Cosmetic drugs | Deodorants, antidandruff products, sun blocks, etc. |

and in these districts all products are categorized as cosmetics. Thus, caution is required when selling products in countries with intermediary categories, as there are ingredients that are not approved for cosmetics but are approved for intermediary categories such as hair dyes or perming agents. In the EU and ASEAN, ingredients that are prohibited for cosmetics but are approved for intermediary categories are categorized as restricted ingredients (Annex III) and the use is limited to specific cosmetics.

Manufacturers and sellers must be aware of such regional differences regarding cosmetic ingredients and comply with each country/region's regulations and laws. When looking at Japan, the manufacturer/seller is fully responsible for the safety and stability of the cosmetic products they approved to sell. In the EU, the responsible member(s) of the import company must register to the EU committee, and in China only corporate entities approved in China can sell and produce cosmetics. These are listed in Table 9.2. Due to such regional restrictions, it is vital to appoint the best personnel who understands the regulations of the region.

**TABLE 9.2** Regional Regulations to Register the Production, Import and Sale of Cosmetics

| Country/ Region | Type | Documentation Personnel | Submission Agency | Submission Deadline | Notes |
|---|---|---|---|---|---|
| EU | Cosmetics | Head of import company | EU committee | Before sales | Submission |
| ASEAN | Cosmetics | Head of import company | Ministry/department of restriction per country | Before sales | Submission |
| China | Cosmetics | Certified corporate entities in China | CFDA | Before sales | Submission |
| | Special-use cosmetics | | | | Approval |
| USA | Cosmetics | Labeling company of one of the following: manufacturer, packaging company, or seller | FDA | Within 60 days of selling | Voluntary registration (submission) |
| | Cosmetic drugs | | | Within 5 days of selling | Submission |
| South Korea | Cosmetics | Marketing authorization holder | *Report imported items and total volume, used materials, types, and total volume to the KFDA annually* | | |
| | Functional cosmetics | | KFDA | Before sales | Approval |
| Taiwan | Cosmetics | Licensed importer (corporate) | (*Exempted but required when importing*) | | |
| | Cosmetics containing medical, poisonous, or potent drug(s) | | TFDA | Before sales | Approval |
| Japan | Cosmetics | Marketing authorization holder | Prefecture | Before sales | Submission |
| | Quasi-drugs | | Ministry of Health, Labor and Welfare | Before sales | Approval |

*CFDA*, China Food and Drug Administration; *KFDA*, Korean Food and Drug Administration; *TFDA*, Taiwan Food and Drug Administration.

## 9.3 LABELING

Generally, the regulations regarding market cosmetic labeling are common between different regions. Most countries/regions require that the product name, manufacturer (importer) address, country of production, content volume, full list of ingredients, manufacturing number (lot number), sell-by date (use-by date), warning/cautions, amount/use, etc. are labeled on the product. In addition to these items, the product type defined by the Fair Competition Code is required in Japan, and in China the registration number and approval number is required, and in South Korea, the MSRP (Maker Suggested Retail Price) is required.

### 9.3.1 Usable Product Lifespan

The guaranteed product lifespan of cosmetics is set for at least 30 months in the EU and ASEAN, and in other regions it is set for at least 36 months. China is presumably the only country that requires labeling for this period, and in other areas the period must be labeled if the product lifespan is shorter than the general lifespan. However, the period is commonly labeled for all products in regions other than Japan. In Japan, the Ministry of Health and Welfare issued a notification in September 1980 that the following rules apply for labeling the product lifespan.

"Cosmetics that apply to the following must label the product lifespan."

1. Cosmetic products containing ascorbic acid, ester, their salts, or their enzymes.
2. Cosmetic products that do not apply to the above but have the risk of quality decline under proper storage within 3 years from manufacturing or import.

Later in October the same year, the ministry issued the following notification.

"If the product applies to the category above and contains ascorbic acid but the stability of the product's form and quality is maintained under proper storage for 3 years from manufacturing or import, the product is not subject to labeling." With this notification, most cosmetics including imported products do not have the product lifetime labeling in Japan. The following is a list of some symptoms degradation of low stability cosmetics.

1. Products with mold, etc.
2. Notably separated emulsion products
3. Products with odor
4. Products with notable color change
5. Water- or alcohol-solubilized products with notable amount of sedimentation
6. Products with hazardous materials due to decomposition of components
7. Products that use ascorbic acid, enzymes, etc. where the amount has reduced or weakened due to evaporation or decomposition, excluding products using these materials for stabilizers

### 9.3.2 Full Ingredient Labeling

Currently, most regions adopt full ingredient labeling. The list of the ingredients is based on the International Nomenclature of Cosmetic Ingredients (INCI) created by the Personal Care Products Council (PCPC) of the United States, and currently most regions use this list. Many countries use translated names for the materials on the list, but in Taiwan, English labeling is allowed instead of Chinese.

This INCI was originally called Cosmetic Adopted Name. Due to the nature of being a union of multilingual nations, the EU initially did not label the parts, liquids, or seeds for plants and was called the EU Inventory. Furthermore, the terms "aqua" and "cera" are often used for the corresponding ingredients "water" and "wax" on the INCI, and although the labeling is now based on the INCI, these names are still often seen on cosmetics in the EU. When Japan adopted the list, they initially intended to create a list with the names translated, but due to an unexpected number of applications, they discussed the rules to maintain consistency and currently the names are either transliterations or translations of the items on INCI.

Other rules that are common among most regions are that ingredients that account for over 1% are to be listed by volume in decreasing order; materials such as pigments in the same series of a product may be listed as "may contain" or +/−; and carry-over materials, which are contaminants and/or materials derived from the ingredients and do not affect the product quality, do not need to be listed. However, there are some countries that do not explicitly specify the order of ingredients.

**TABLE 9.3** Examples of Changes Made to the International Nomenclature of Cosmetic Ingredients (INCI)

| | INCI (Original) | INCI (After Change) |
|---|---|---|
| 1 | *Salvia officinalis* (EU) | *S. officinalis* (sage) extract, *S. officinalis* (sage) flower/leaf/stem extract, *S. officinalis* (sage) flower/leaf/stem juice, *S. officinalis* (sage) flower/leaf/stem water, *S. officinalis* (sage) leaf extract, *S. officinalis* (sage) leaf, *S. officinalis* (sage) oil, *S. officinalis* (sage) root extract, *S. officinalis* (sage) water |
| 2 | *Acacia farnesiana* extract | *A. farnesiana* flower/stem extract |
| 3 | Acetyl glutamyl hepta-peptide-1 | Acetyl octapeptide-3 |
| 4 | *Angelica keiskei* extract | *A. keiskei leaf/stem extract* |
| 5 | Human oligopeptide-8 | Rh-polypeptide-6 |

The INCI is posted on the *International Cosmetic Ingredient Dictionary and Handbook* (ICID), and this handbook is renewed every 2 years. Because the listed materials are deleted or changed, it is vital to know the changes to the list. Table 9.3 shows some examples of changes made to the INCI. Column 1 shows items that were moved from "Inventory" to INCI in the EU. Column 2 shows the most common example of additions, where parts were added to the list.

## 9.4 COSMETICS INGREDIENT RESTRICTIONS

Countries and regions around the world categorize cosmetic materials under their regulations in negative materials (prohibited/restricted materials) and positive materials (coloring, preservatives, UV-absorbing/scattering agents). Most countries and regions adopt the same EU standards on materials, and not only ASEAN but also China and South Korea have restrictions that are similar to those of the EU. The restrictions of Taiwan is still similar to those of Japan, but they also react quickly to the new changes of EU and the restrictions are now becoming similar to those of the EU.

### 9.4.1 Prohibited Materials

Table 9.4 shows the 30 materials that are prohibited under Japanese regulations, along with the corresponding items on the EU list of prohibited materials (Annex II) and the US list of prohibited materials (21CFR).

As shown on this table, the number of restricted materials is 30 in Japan, but there are 1378 materials that are listed as restricted items in the EU (30 are either moved or deleted). The number of prohibited materials in the United States is 14, and although this may seem small compared with the EU, materials that do not apply to Medical Drug Ingredients or Standards for Biological Materials are also prohibited accordingly, so the number is greater than the listed items of Japan. In the EU, Annex 2-419 applies to such biological materials, and, likewise, 21CFR700.27 applies in the United States; the US Food and Drug Administration (FDA) promotes that materials approved as safe materials by the Cosmetic Ingredient Reviews (CIR) should be used for cosmetics.

There are some materials that are not listed in the EU Annex II in Table 9.4, but most of these are listed on Annex III (restricted materials) or are prohibited in either South Korea or Taiwan (shown with asterisks in the table).

As you can see, most countries and regions comply with the standards of the EU. Furthermore, as seen on the table, materials prohibited in Japan are also prohibited or restricted in other countries. In the case of Japan, it is vital to know that there are materials that are not listed in the cosmetics standards of Japan (i.e., permitted for use) but are prohibited in the EU and other areas. Table 9.5 shows an excerpt of materials that are prohibited in the EU but permitted in Japan, based on the ICID 14th Vol. 3, EU Annex Index. Caution is especially required when exporting such products abroad.

Furthermore, when importing from other countries to Japan, caution must be held with materials that are restricted in the EU, namely formalin or methanol. Methanol is used as a denaturating agent for ethanol in some countries. Since formalin is found in formalin donor type preservatives, it could possibly elute from this preservative, and sometimes formalin can also be found as a decomposed material derived from organic compounds.

Although South Korea follows the standards of EU, modified human gene materials (e.g., human oligopeptides) are exceptions, being prohibited in the EU but permitted since they are studied and produced in South Korea.

**TABLE 9.4** Differences of Prohibited Material as Cosmetic Ingredients

| Prohibited Substance in Japan | EU Annex II No. | USA 21 CFR No. |
|---|---|---|
| 6-Acetoxy-2,4-dimethyl-*m*-dioxane | 368 | |
| Antihistamines except those of aminoether type (such as diphenylhydramine) | 339 | |
| Hormones and derivatives except estradiol, estrone, and ethinylestradiol | 260[a] | |
| Vinyl chloride monomer | 334 | 700.14 |
| Methylene chloride | [b] | 700.19 |
| Bismuth compounds other than bismuth oxychloride | [c] | |
| Hydrogen peroxide | [c] | |
| Cadminium compounds | 68 | |
| Sodium perborate | [c] | |
| Chloroform | 366 | 700.18 |
| Progenolone acetate | [b] | |
| Dichlorophene | [c] | |
| Mercury and its compounds | 221 | 700.13 |
| Strontium compounds | 402, 403 | |
| Sulfamide and its derivatives | | |
| Selenium compounds | 297 | |
| Nitrofuran-type compounds | 251 | |
| Hydroquinone monobenzylether | [b] | |
| Halogenated salicylanilide | 348–351, 373 | 700.15 |
| Vitamin L1 and vitamin L2 | [b] | |
| Bithionol | 352 | 700.11 |
| Pilocalpine | 283 | |
| Pylogallol | 409 | |
| Inorganic fluorine compounds | [c] | |
| Pregnanediol | [b] | |
| Local anesthetics such as procaine | 25 | |
| Hexachlorophen | 371 | |
| Boric acid | [c] | |
| Formalin | [c] | |
| Methyl alcohol | [c] | |

[a] *All estrogens including estradiol, etc. are restricted materials in Japan but prohibited in the EU.*
[b] *Prohibited in South Korea and/or Taiwan.*
[c] *Restricted materials listed on Annex III in EU.*

Additionally, in the EU, materials in the same group with different CAS numbers are all listed, for example—No. 493: gases (petroleum), C3-4, isobutene-rich, if they contain >0.1% w/w butadiene; CAS No. 68, 477-33-8; No. 509: gases (petroleum), C6-8, catalytic reformer recycle, if they contain >0.1% w/w butadiene; CAS No. 68, 477-80-5; No. 514: gases (petroleum), C4-rich, if they contain >0.1% w/w butadiene; CAS No. 68, 477-85-0. In South Korea, these are all listed as "petroleum refined materials (gas, hydrocarbons, alkanes, distillates, and refined oils) with more than 0.1% butadiene," and in China, they are listed independently, like the EU.

Whenever there is new knowledge or information on the safety of cosmetics, especially on CMR (carcinogenic, mutagenic, reproductive toxicity), this is listed on the Annex II or Annex III without exception. Whenever such a

**TABLE 9.5** Excerpt of Materials That Are Prohibited in the European Union (EU) but Permitted in Japan

| Annex II No. | INCI |
|---|---|
| 7 | 6-Aminocaproic acid |
| 46 | Barium chloride |
| 54 | Beryllium and its compounds |
| 74 | Catalase |
| 99 | *Conium maculatum* root extract |
| 201 | Hydrazine, its derivatives, and their salts |
| 260 | Estrogens |
| 335 | Ergocalciferol and cholecalciferol |
| 358 | Furocoumarins except for normal content in natural essences used. In sun protection and in bronzing, shall be below 1 mg/kg |
| 375 | Retinoic acid |
| 411 | Secondary alkyl- and alkanolamines and their salts |
| 416 | Cells, tissues, or products of human origin |
| 419 | Cerebrosides |
| 436 | *Ficus carica* (fig) extract |
| 453 | Cobalt chloride |
| 1168 | Nonylphenol [1]; 4-Nonylphenol, branched [2] |

*Based on the ICID 14th Vol. 3, EU Annex Index.*

change is applied in the EU, it is followed by similar material restrictions in other regions such as China or ASEAN, but delay cannot be avoided and the restriction is later than the notification from EU.

### 9.4.2 Restricted Materials

Restricted materials are materials that should basically be avoided in cosmetics, and use is limited to specific types of cosmetics. Additionally, the use of these cosmetics are limited to specific body parts and the maximum content is also limited, but due to historical differences they differ greatly between regions and countries. For example, 307 materials are listed in the EU Annex III, 66 in South Korea, 47 in China, 14 in the United States including prohibited materials, and 21 in Japan. In Taiwan, there is no similar list of these materials in the same context as other countries, but they are listed in the prohibited materials list and are allowed under the condition that they are used for specific purposes. Although there is a delay, the restriction is generally the same as that of EU.

Although the prohibited materials and positive materials of China and South Korea are based on EU's list, the number of restricted materials differs greatly due to the intermediary categories of special-use cosmetics in China and functional cosmetics and quasi-drugs in South Korea, so hair dyes, etc. are not restricted as cosmetics materials but are restricted under the regulations of these categories. On the other hand, there are no intermediary categories in the EU and all products are classified as cosmetics, so, as an example, materials that are compounds of hair dyes only are classified as restricted materials and the compound rules are stipulated. Table 9.6 shows the restricted materials of EU (Annex III).

Table 9.6 shows part of the Annex III and compares them with the materials of Japan: (8a) paraphenylenediamine is an active component for hair dyes in the quasi-drug category and is not used for cosmetics. Furthermore, quasi-drugs in South Korea, special-use cosmetics in China, and cosmetics containing medical, poisonous, or potent drug(s) in Taiwan also all require approval and are not subject to cosmetic material restrictions. Although (13) formaldehyde is a prohibited material in Japan, up to 5% is allowed for the use of solidifying nail polish, and in China and ASEAN, it is permitted for use up to 0.2% in common cosmetics as preservatives. Due to such differences, cosmetics must be imported carefully. Handling of (13) hydroquinone is limited to specialists and can be used up to 0.02% in

**TABLE 9.6** Excerpt of Restricted Materials of European Union (Annex III)

| Ref. | Name of Common Ingredients Glossary | Product Type Body Parts | Maximum Concentration in Ready-for-Use Preparation | Other |
|---|---|---|---|---|
| 8a | *p*-Phenylenediamine and its salts | Hair dye substance in oxidative hair dye products | | After mixing under oxidative conditions, the maximum concentration applied to hair must not exceed 2% calculated as free base |
| 13 | Formaldehyde | Nail-hardening products | 5% (as formaldehyde) | |
| 14 | Hydroquinone | Artificial nail systems | 0.02% (after mixing for use) | Professional use |
| 15a | Potassium hydroxide Sodium hydroxide | **1.** Nail cuticle solvent<br>**2.** Hair straightener<br>**3.** pH adjuster for depilatories<br>**4.** Other uses as pH adjuster | **1.** 5%<br>**2.** 2% general, 4.5% professional | **3.** up to pH 12.7<br>**4.** up to pH 11 |
| 53 | Etidronic acid | **1.** Hair product<br>**2.** Soap | **1.** 1.5%<br>**2.** 0.2% | |
| 278 | Basic violet 2 | **1.** Hair dye substance in oxidative hair dye products<br>**2.** Hair dye substance in non oxidative hair dye products | 0.5% | After mixing under oxidative conditions, the maximum concentration applied to hair must not exceed 1.0% |

artificial nails in the EU, but in Japan it is used in products sold as whitening cosmetics and is not restricted under cosmetics standards, so it can be freely used under corporate responsibility. And (15a) sodium/potassium hydroxide is restricted in many countries but is a common cosmetics component in Japan and is vital for producing soap emulsion products. However, the pH of the final product should be carefully controlled. Further, (53) etidronic acid is used as antioxidatives under the name 1-hydroxyethane-1,1-diphosphonic acid and can be used for all cosmetics with any amount under the current regulations of Japan, but previously it was restricted under cosmetic categorization regulations and the volume was restricted to 2% for cleansing cosmetics and 0.1% for common cosmetics. In Japan, (278) basic violet 2 is a listed material and can be used for common cosmetics, but the use should be limited to hair dyes and the amount should match the EU standards of 0.5% if each company cannot ensure the safety of their products.

There are also other materials that are restricted in the EU but permitted in Japan, but these materials must be chosen and used carefully with safety assurance.

### 9.4.3 Coloring, Preservatives, and UV-Absorbing Materials

These permitted materials are categorized as positive materials in each country/region, and in addition to restricting the materials and their content, it is common that the products' use is designated—for example, if it is a rinse-off or leave-on cosmetic product or if it can be used for mucosa areas such as the lips.

**Coloring**: Among positive materials, coloring has the largest differences between countries and regions. However, ASEAN, China, and EU basically share the same rules. Additionally, in Japan, inorganic pigments and natural colorings can be used as common cosmetic ingredients and only tar-based pigments are classified as positive materials, but in other countries, both inorganic pigments and natural colorings are classified as positive materials.

The United States allows the least number of colorings for cosmetics. Not only are the numbers limited in the United States, but when selling products with tar-based pigments, all products must be examined per lot if they comply with the 21CFR74 by the FDA and receive a certification number before selling. On the contrary, EU, ASEAN, and China have more coloring materials that are permitted compared with Japan. Table 9.7 shows coloring materials permitted in the EU but are prohibited in Japan and tar-based pigments that are permitted in Japan but are prohibited in the EU, and as shown in Table 9.7, there are many more colorings that are prohibited in Japan. Knowing such facts helps us understand why the color lineup of lipsticks in EU has more shades compared with those in Japan. It is highly possible that makeup products imported to Japan could have colorings that are not permitted, so that precaution must be paid to import color cosmetics in to Japan.

**TABLE 9.7** Discrepancies of Regulatory Status Between European Union (EU) and Japan for Coloring Materials and Tar-Based Pigments

| Prohibited in EU but Permitted in Japan Color Index No. | Permitted in EU but Prohibited in Japan Color Index No. |
|---|---|
| 11380, 11390, 12073, 12100, 12140, 12315, 13065, 14600, 15585, 15585:1, 16150, 16155, 18950, 20170, 21090, 21110, 26105, 42052, 42085, 42095, 45170, 45425, 45425:1, 45440, 61520, | 10006, 11710, 11920, 12010, 12370, 12420, 12480, 12490, 12700, 13015, 14270, 14720, 14815, 15525, 15580, 16035, 16230, 16290, 18050, 18130, 18690, 18736, 18965, 20040, 21100, 21108, 21230, 24780, 27755, 28440, 40215, 40800, 40820, 40825, 40850, 42045, 42051, 42100, 42170, 42510, 42520, 42735, 44045, 44090, 45220, 45396, 45405, 50325, 50420, 51319, 58000, 60724, 61585, 62045, 69800, 71105, 73385, 72900, 73915, 74100, 741800, 74260 |

**Preservatives**: Preservatives are also positive materials that have different regulations on both the materials and the standards between regions and countries. For example, photosensitive substances (e.g., products known as Pionine) or resorcinol are Japanese preservatives but are restricted materials in South Korea. Furthermore, the EU categorizes preservatives in materials that are used to inhibit microbes as preservative materials (Annex V) and materials that are used for other purposes as restricted materials (Annex III). In this case, the purpose must be explicit if the material is used for purposes other than as a preservative. For example, C16-18 alkyltrimethylammonium chloride is one of these materials. If they are used as a preservative, the maximum amount is limited to 0.1%, but if it is used as a restricted list material, the limit is (1) 2.5% for rinse-off hair products, (2) 1.0% for leave-on hair products, and (3) 0.5% for leave-on facial products.

There are differences in the permitted use or content for the same material between Japan and the EU, but there are also materials that have different rules for the target body parts. For example, DMDM hydantoin and imidazolidinyl urea are permitted only for rinse-off products in Japan but are permitted for leave-on cosmetics in EU. On the other hand, only the maximum amount of chlorobutanol is stipulated for any product in Japan, but in the EU, use in aerosol products is prohibited; similarly, the rules for salicylic acid are restricted to certain ages, under the rule "do not use in preparations for children under 3 years old, excepting shampoos."

EU also renewed its regulations for parabens, the most globally used preservative, in September 2014. Table 9.8 shows the kinds and amounts of parabens in the old and new regulations in the EU in comparison with those of Japan.

**TABLE 9.8** Kinds and Amounts of Parabens in the Old and New Regulations in the European Union (EU) in Comparison With Those of Japan

| Japan | | EU (Old) | | EU (New) | |
|---|---|---|---|---|---|
| **Kinds of Paraben** | **Max (%)** | **Kinds of Paraben** | **Max (%)** | **Kinds of Paraben** | **Max (%)** |
| Benzylparaben<br>Isobutylparaben<br>Isopropylparaben<br>Ethylparaben<br>Propylparaben<br>Methylparaben<br>Sodium methylparaben | Total 1.0% | 4-Hydroxybenzoic acid<br>Calcium paraben<br>Isobutylparaben<br>Isopropylparaben<br>Ethylparaben<br>Phenylparaben<br>Potassium butylparaben<br>Potassium ethylparaben<br>Potassium methylparaben<br>Potassium paraben<br>Potassium propylparaben<br>Propylparaben<br>Methylparaben<br>Sodium butylparaben<br>Sodium ethylparaben<br>Sodium isobutylparaben<br>Sodium paraben<br>Sodium propylparaben<br>Sodium methylparaben | Single 0.4%<br>Total 0.8% | 4-Hydroxybenzoic acid<br>Calcium paraben<br>Ethylparaben<br>Potassium ethylparaben<br>Potassium methylparaben<br>Potassium paraben<br>Methylparaben<br>Sodium ethylparaben<br>Sodium paraben<br>Sodium methylparaben | Single 0.4%<br>Total 0.8% |
| | | | | Butylparaben<br>Propylparaben<br>Sodium butylparaben<br>Sodium propylparaben<br>Potassium butylparaben<br>Potassium propylparaben | 0.14% (as acid) for the sum of individual concentration) |

**TABLE 9.9** Differences of the Approved UV Absorbers in Japan and European Union (EU)

| Approved for Japan and EU | Approved in Japan but Not in EU | Approved in EU but Not in Japan |
|---|---|---|
| 1. Homosalate | 1. Isopentyltrimethoxy cinnamate trisiloxane | 1. Benzylidenecamphor sulfonic acid |
| 2. Octocrylene | 2. Pentyldimetyl PABA | 2. PEC-25 PABA |
| 3. Butylmethoxydibenzoylmethane | 3. Isopropylmethoxycinnamate and diisopropylmethylcinnamate | 3. Isoamyl-*p*-methoxy- cinnamate |
| 4. Ethylhexylsalicylate | 4. Ferulic acid | 4. Diethylhexylbutamido triazone |
| 5. Diethylaminohydroxybenzoyl hexylbenzoate | | 5. 4-Methylbenzylidene camphor |
| 6. Polysilicone-15 | | 6. 3-Benzylidene camphor |
| 7. Terephthalidenedicamphor sulfonic acid | | 7. Camphor benzalkonium methosulfate |
| 8. Ethylhexyltriazone | | 8. Disodiumphenyl dibenzimidazole tetrasulfonate |
| 9. Drometrizoletrisiloxane | | 9. Polyacrylamidomethyl benzylidene camphor |
| 10. Ethylhexyldimethyl PABA | | 10. Potassium or sodium or TEA-phenyl-benzimidazole sulfonate |
| 11. Ethylhexylmethoxycinnamate | | 11. *Tris*-biphenyl triazine |
| 12. *Bis*-ethylhexyl-oxyphenol-methoxyphenyl triazine | | |
| 13. Benzophenone-3 | | |
| 14. Benzophenone-4 | | |
| 15. Benzophenone-5 | | |
| 16. Phenylbenzimidazole sulfonic acid | | |
| 17. Methylene *bis*-benzotriazolyl-tetramethyl-butyl-phenol | | |

**UV-Absorbing Agents**: In countries/regions other than Japan, the EU, and ASEAN, cosmetics with UV-absorbing agents are usually classified in the intermediary categories and require approval. Due to their functions, these materials are naturally used for the effects other than blocking sun rays, namely as stabilizers. Although it relates to the actual amount used, there have been reports that products using UV absorbers are not approved for general cosmetics depending on the country or investigator even if its function is for stability.

In Japan, the active component of sun blocks in medical cosmetics is usually not UV-absorbing agents, and the active component is, for example, dipotassium glycyrrhizinate for "preventing rashes from sun/snow," or ascorbic acid derivatives such as arbutin, etc. to "inhibit melanin and prevent stains and freckles." However, UV absorbers listed on the Quasi-Drug Material Standards can be used for sun blocks without approval. In this case, the total amount of UV absorbers is limited up to 10% in total.

Other than UV absorbers, zinc oxide and/or titanium oxide is also used as UV-scattering agents for sun blocks. In Japan, both titanium oxide and zinc oxide can be used for common cosmetics, but in most countries, they are categorized as positive materials and the amount is limited. Since these materials show higher efficacy in small-particle technology to make nano-size particles has evolved, but nanomaterials have become an issue in countries out of Japan, and when using these materials in countries and regions such as the EU, the material must be listed with "nano" as a prefix. In this case, nanomaterials are substances that are 1−100 nm, are not soluble in water or oil, and are artificially created without biodegradability.

Table 9.9 shows the UV absorbers that are common between Japan and the EU and UV absorbers that are not common between these two regions. Compared with colorings or preservatives, there are fewer materials that are not in common, but nevertheless caution must be taken when importing/exporting these products.

## 9.5 CLOSING REMARKS

Regardless of the size of the business, overseas operations are unavoidable in today's global economy. In this chapter, we studied the regulations on cosmetics, especially the regulations of materials in various parts of the world. Most nations other than Japan and the United States comply with the EU standards, and this trend is expected to spread. Table 9.10 shows some products (presumably imported products) that have been recalled due to violation of cosmetics regulations in Japan along with the reasons and materials subject to violation. Cosmetics production requires submission and approval, but this is merely a minimum requirement, and the manufacturers must carefully check if the materials comply with the regulations of each country/region when manufacturing and importing/exporting their products.

**TABLE 9.10** Some Products (Presumably Imported Products) Recalled Due to Violation of Cosmetics Regulations in Japan

| Materials (INCI) Subject to Violation | Reasons Subject to Violation |
|---|---|
| Sodium Hydroxymethylglycinate | Permitted as a preservative in the EU but not permitted in Japan |
| Phenoxyethanol | Exceeds limit volume (1.0%) |
| CI 16035 | Coloring approved in the EU but not approved in Japan |
| Chlorphenesin | Mucous membrane product using materials prohibited for mucous membrane use in Japan but approved in EU |
| Salicylic acid | Exceeds limit volume (0.2%) of Japan, but within the 0.5% limit of EU |
| CI 14720 | Coloring not approved in Japan |
| Imidazozolidinylurea | Used for leave-on product but approved only for wash-off products in Japan permitted for leave-on products in EU |
| Ubiquinone | Mucous membrane product using materials prohibited for mucous membrane use |
| Methanol | Prohibited material in Japan, restricted material in EU. |
| Formaldehyde | Prohibited material in Japan, restricted preservative material in EU |

## References

1. International Cosmetic Ingredient Dictionary and Handbook 14th PCPC.
2. http://ec.europa.eu/growth/tools-databases/cosing/.
3. http://www.fda.gov.tw/TC/index.aspx.
4. http://www.mhlw.go.jp/file/06-Seisakujouhou-11120000-Iyakushokuhinkyoku/0000032704.pdf.
5. http://www.sda.gov.cn/WS01/CL0001/.
6. http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=74.

CHAPTER

# 10

# Introduction to Cosmetic Materials

*M. Hayase*

**Kao Corporation, Odawara, Japan**

## 10.1 INTRODUCTION

No product can be designed without utilizing information about the properties of its materials. In this chapter, I will introduce various materials used in cosmetics. However, understanding the entirety of the perspective of cosmetic materials is not an easy task and cannot be done by only accumulating knowledge on independent materials. Therefore, I aim to provide a comprehensive overview on cosmetic materials by focusing on three aspects: the purpose of materials, precautions on choosing and using materials, and future challenges.

## 10.2 PURPOSES OF COSMETIC MATERIALS

I will start by organizing the purposes of materials that are formulated in cosmetics. It is common for a single ingredient to have multiple functions and thus cannot be strictly classified for one function, but for easier understanding, each material is intentionally categorized in this chapter. It is also important to remember that cosmetics are complex systems composed of various materials. We will refer to biological structures of materials, which are also complex systems, to understand the entirety of cosmetic materials.

### 10.2.1 Formulation Structuring Materials

In contrast to pharmaceutics development where the active component and its concentration is the main focus, cosmetic development must concentrate on the functions and user experience of the formulation itself in addition to the properties of the functional materials. Therefore, designing the structure of the formulation is considered an extremely important process in cosmetic development, and is as vital as, if not more than, considering new functional materials. I will categorize cosmetic materials that play important roles in forming the structure of formulations into the following three types. A wide variety of formulations is created by combining these three types, and also from their state in the product.

#### *10.2.1.1 Water/Hydrophilic Base Materials*

As of 2016, life is yet to be found on planets other than Earth. One of the reasons is because Earth is the only planet known to have abundant water (hydrogen oxide) in liquid form. Proteins and lipids, which will be described later in this chapter, are also key materials in creating life. However, most of these materials need water in order to show their functionality. Likewise, oleaginous bases and amphiphiles are formulated in cosmetics in various forms, but water is required for these materials to show their unique functions.

Water is the most universal ingredient used in cosmetics. Since water is so common we tend to take it for granted, but water is actually a unique substance. It provides a system for chemical reactions, and it also has significant characteristics, such as its property as a solvent, its low refractive index, and volatility.

Hydrophilic base materials such as ethanol and polyols have the potential to partially replace water as formulation structuring materials. This replacement can change the characteristics of formulations such as the moisture-retaining property or the property as a solvent.

*Cosmetic Science and Technology: Theoretical Principles and Applications*
http://dx.doi.org/10.1016/B978-0-12-802005-0.00010-0



Copyright © 2017 Elsevier Inc. All rights reserved.

#### *10.2.1.2 Oleaginous/Hydrophobic Base Materials*

Organelles have been found to have structuring units of membranes composed of lipids. This shows how lipids and oleaginous substances are vital biological tissue-structuring substances. In many cosmetics, so-called "oils" and many oleaginous base materials (hydrophobic base materials) are used as structuring substances. Hair waxes and lipsticks are formulated with evenly distributed solid waxes or fats. Fragrances in translucent skin moisturizer are solubilized in the water phase. Oil-in-water creams have lipid particles dispersed in the water phase. These are some examples of how oleaginous bases are used in cosmetic formulation in various shapes.

Among the various oleaginous bases used in cosmetics are materials such as hydrocarbons, esters, and ethers. Silicones and fluoride compounds and other hydrophobic-lipophobic substances are also often considered as oleaginous bases (oil-based materials in broad terms). Since these substances have a wide variety of structures, oleaginous base materials show various properties such as in their polarity, melting point, or compatibility. This large variety leads to various unique application experiences or specific functions (i.e., ultraviolet light absorption, promotion of percutaneous absorption) of cosmetic products.

#### *10.2.1.3 Amphiphilic Substances*

Engels once said, "Life is the mode of action of proteins." Borrowing his rhetoric, most cosmetics can be explained as "the mode of action of amphiphiles." In most cases, various amphiphiles are used in cosmetics as surfactants or dispersion promoters.

Amphiphiles are used as surfactants to emulsify, solubilize, or disperse oleaginous bases or hydrophilic bases to the other. These formulation methods are applied to formulate various formulations. There are also some amphiphiles such as higher fatty acids that change their function as surfactants or as oleaginous bases depending on the pH. On a side note, there are amphiphiles that are originally formulated in products as structuring materials, but are kept in the formulas for their functions such as moisturizing or to adjust the application touch. For example, solubilizers are not required for unscented products, but there are unscented skin toners that have surfactants dissolved at a concentration where it can solubilize oils.

### 10.2.2 Adding Functions and Effects

Proteins, lipids, and water are not the only necessary substances that are required to maintain life. In cosmetics, ingredients other than oleaginous bases, water (and water-soluble bases), and amphiphiles are required in the formulation, and many of these ingredients are added in order to add functions and effects. We will categorize these materials into three types to understand their details.

#### *10.2.2.1 Materials That Add or Improve Functional Value*

Cosmetics are usually sold with various values added to appeal to the consumers. The most important value of these multiple values depends on each product. In cosmetics, there are both functional value and emotional value, and most products require both of these values. Functional value often connects directly to the main feature of the product, and cosmetic development focuses on how to improve these functional values. The functions and effects that create the functional values can be categorized into physiological and physical functions and effects.

Physiological effects and functions are not limited to skin care and hair growth products, but are also expected in certain makeup cosmetics. Since the 1980s, dermatology has shown a large advancement and much information on healthy skin has been accumulated. New evaluation methods, such as experiments using cultured cells, have also been developed. Many new dermatological methods have been proposed in the fields of whitening and antiaging based on the information and development of studies in dermatology. Utilizing these new methods, a variety of materials such as vitamins, amino acids, peptides, and botanical extracts have been formulated to cosmetics as physiological active ingredients that aim to improve the physiological effects and function.

On the other hand, physical functions such as cleansing, moisturizing, and occlusion also add value for cosmetics. Moisturizing and emollient properties are especially vital physical functions, and are the basic functions for cosmetics. In many regions and countries other than the United States sunscreens are also categorized as cosmetic products. Therefore, ultraviolet (UV) screening and absorption are also important physical functions for cosmetics. These physical functions are evaluated through physical property evaluation of formulations as well as through human use testing. The evaluation systems of these physical functions and effects have also progressed rapidly in recent years, and now we can gather more detailed information.

The physical functions and effects are often found in the formulation itself. However, there have been attempts to add specific ingredients to change or improve the physical properties. For example, there are oleaginous materials that show unique functions such as water holding, occlusion, UV absorption, or promotion of percutaneous absorption. These functional oleaginous materials are used to partially replace the structuring oleaginous material to add their function to the formulation.

It is important to understand that maximizing the effects or functions is not always the best choice for cosmetics, and mild effects are preferred in most cases. For example, cleansers are designed to have the optimal cleansing property, and strong cleansers that remove too much oil are not considered to be the best practice.

#### *10.2.2.2 Materials That Add or Improve Emotional Value*

Many cosmetic products like perfumes value preference over functionality. Even antiaging creams, which have materials that show specific physiological effects, are not considered as just a percutaneous absorbent but are considered products to enjoy the feeling and scent. The emotional value of these preferences cannot be neglected in cosmetics, and cosmetics are designed to provide more emotional value.

Among our five senses, sight, smell, and touch are the main focus in the preference of cosmetics. Color and smell are very distinct and consumers can tell slight differences, and they strongly influence the preference of products. There is an abundant variety of materials that directly change the sight and smell to meet consumers preferences, such as various pigments, coloring, and aromatic substances. Touch is the most important sense, and many materials are combined to adjust the touch of products. In most cases the structure of the formulation defines most of the touch and feeling. However, the application feeling and use experience can be improved or changed. Details of materials such as powders, polyols, polymers, and/or tonics are considered and chosen to improve the touch in formulation prescription design. There are even cases where the feeling of unstable formulations is preferred. Needless to say, balance of the touch and maintaining/improving the stability is vital in cosmetic formulation improvement.

#### *10.2.2.3 Materials for Quality Control*

Most cosmetics are designed to have a long shelf life of at least three years (sometimes the storage period is not explicitly stated). Furthermore, the products are not always stored in the best condition during this long storage period. As such, the standards for the stability of a cosmetic formulation's condition, color, and/or smell are strict, and many materials are formulated to stabilize the products. Although these materials do not directly appeal to the consumers, they are materials vital for providing safe and sound products to the consumers.

Many cosmetic formulations use emulsification methods, but emulsions are thermodynamically unstable and in most cases they must be stabilized. Emulsion stabilizers such as polymers (e.g., carbomers and xanthan gum) or higher fatty alcohols are added to cosmetics to stabilize the emulsion. Putrefaction can change the composition of products and can lead to health issues or lower the appeal of the products. Preservatives and other antimicrobe methods are vital to cosmetics in order to prevent such degrading. On a side note, many preservatives function by working on the cell membranes of microbes, but their mechanism can affect the stability of the emulsion so the condition of the formulation must be observed carefully when adding or increasing preservatives. There are other materials such as chelating reagents, discoloration-preventing reagents, antioxidative reagents, and pH buffering agents that are formulated to cosmetics for stabilization.

## 10.3 PRECAUTIONS ON CHOOSING AND USING COSMETIC INGREDIENTS

Many consumer goods such as foods, pharmaceutical products, and detergents use materials similar to cosmetic materials. However, the purposes, regulations, and quality targets of cosmetics differ in many ways compared to these other products. Such differences relate to the precautions of using these materials as ingredients for cosmetics.

As mentioned previously, the shelf life of cosmetics is long, so in addition to stabilizing the cosmetics, the materials themselves must have high stability. Furthermore, based on the fact that the frequency or amount a cosmetic product is used cannot be strictly controlled, safety is a priority that must be considered as much as possible. Due to these conditions that are different from other products, there are many quality standards that apply only to cosmetic materials.

Many countries control cosmetics under the same regulations of pharmaceutical products for production, sales, and usage. However, the prerequisite regulations of cosmetics are very different from pharmaceutical products and also change depending on the era or region. For example, the recent regulations against animal testing strongly influence cosmetics development. Evaluations of percutaneous absorption and safety of cosmetics and their

ingredients are designed based on evaluation methods of pharmaceutical products. Most of the testing shared the same methods, namely *in vivo* methods on small animals and *in vitro* methods on excised skin. However, animal testing has been restricted for cosmetics in Europe, followed by self-regulations by manufacturers under the animal rights movement, making these evaluation methods no longer available for cosmetics development.

Although the quality standards and restrictions mentioned in this chapter must be considered, they are not the only points to keep in mind. There are other factors that must be considered due to the nature of cosmetics as products chosen by preference.

Unlike other consumer products, cosmetics are strongly affected by personal principles based on opinion, taste, and beliefs. It is not rare that some materials are avoided in cosmetic prescription since they are against their principles, even if there is no scientific basis to back up these claims. For example, perfumes, ethanol, and methyl parahydroxybenzoate are generic materials that have long been used in cosmetics, but there are many customers who do not think well of these ingredients. In order to meet the personal principles of such consumers, there are products in the cosmetics market where manufacturers willingly choose not use these materials in their formulation. Such principles against materials based on cultural differences exist not only in the consumers' minds but also in the formulators in the development stage. Formulators often pass on their preferences when they teach their methodology. For example, alkyl benzoate is a product that is widely used in Europe but is rarely used in Japan. The choice of polyols also differs between the preferences of formulators in Europe and Japan. In this way, materials are sometimes chosen depending on the preference of the formulator.

Another important aspect to consider is that the development standards also vary depending on the region. Today cosmetics are not developed, produced, and sold in specific regions, so it is important to know the material regulations of each country. However, the local legal regulations are not the only factor that is important under such situations. The development style of cosmetics varies from region to region, and the requirements for materials also have regional differences. There are also cases where the stability standards of cosmetic formulation differ depending on the region. In Europe, prototypes are scented even for evaluation, but in Japan, the testing prototypes are usually unscented. Since the experimental styles differ, the acceptable chronological smell change of materials also differs. Furthermore, quality targets differ depending on the region, and as a result the acceptable stability can also differ. In Japan transparent soluble formulations are usually sold as skin toners, whereas in Europe emulsions are sold as skin toners. Due to this difference, the accepted sedimentation of materials differs for skin toners. These differences in acceptance influence to the option of materials in different regions.

## 10.4 FUTURE CHALLENGES IN COSMETICS MATERIAL DEVELOPMENT

The largest possible challenge in cosmetic materials is the sustainability of obtaining materials. In future cosmetic material development and use, two contradicting challenges must be cleared: the increased material demand and the limited supply of resources.

As cosmetic engineers, our wish is to deliver the value of cosmetics to more people around the world. This wish leads to expanding business, and as a result more resources will be needed in the future. There are many parts of the world where cosmetics are not used in daily life. When globalism expands and cosmetic use spreads to these people, consequently the demand for materials in the future will be much larger than current use.

However, every resource on Earth is believed to be limited. The resources that can be used in cosmetics are even more limited. A reason for the limited choice of resources is that some materials are used exclusively for cosmetics. In the past, cheap materials with easy acquisition were mainly used, just like any other industrial product. However, to meet the high requirements of safety and stability as mentioned in this chapter, cosmetics materials must meet specific regulations, and now some materials are used exclusively for cosmetics. Furthermore, there are many materials where cosmetic manufacturers voluntarily stopped using them although their use is common in other industries, such as petroleum-derived materials and animal-derived materials. This voluntary limitation also narrows the resources available for cosmetics. Additionally, there can be movements to restrict the distribution of specific resources to cosmetics in the future, like campaigns to restrict the use of edible biomass in cosmetics. Biomass has gained attention as an industrial material that can replace petroleum resources as biologically derived resources. Since cosmetics can potentially be orally consumed, edible raw materials are preferable whenever possible, and biomass is an anticipated raw material for cosmetics. However, some believe that edible biomass should be prioritized for food products considering the global population growth.

As mentioned before, the restrictions regarding resource access in the cosmetics industry are strict compared to other industries. On the other hand, cosmetics are undoubtedly a necessity for a moderate lifestyle in today's society,

just as electronics, automobiles, movies, and books are. As this lifestyle spreads with globalism, the necessity of cosmetics is also likely to spread. Of course, cosmetics are not vital for maintaining life like food, but this definitely does not mean that they should disappear from the world. As cosmetic engineers we have the duty to continue supplying cosmetics, and to do so we also have the duty to propose methods for obtaining resources. Here I will show two possible options on maintaining access to such resources.

### 10.4.1 Exploring New Raw Materials

The first option to consider is to explore new raw materials. There are many materials that have not yet been thoroughly examined. We must look toward materials that have not been focused on, including unused industrial coproducts or other materials that can be obtained from other industries in large quantities.

One direction that has large potential for future development is marine resources. Currently algae-derived substances are used as thickeners in cosmetics. Fish-derived cholesterols, esters (orange roughy oils), and collagen hydrolysates are now replacing other cosmetic materials. Not limited to these examples, there are currently many materials that are already utilized in cosmetics, but many more are unexamined materials that can also potentially be applied to cosmetics. Unicellular algae-derived materials have especially gained attention. These unicellular algae contain commonly used materials such as polysaccharides and pigments and are also being investigated for application to produce oils.

When considering appropriate distribution of resources, another direction that should be explored is to actively utilize resources that are difficult to use in other industries. Materials for any industrial product should have a low cost and have easy acquisition, but not all materials meet such requirements. Cosmetics are somewhat unique where there are some products that are more expensive than food products even though they have less content, and there are even products that limit their availability for exclusiveness. These characteristics of cosmetics can be harnessed by actively using materials that do not meet the cost/supply requirements in other industries in order to keep resources.

An example of utilizing such materials is using high-cost materials. Due to the characteristics of cosmetics mentioned before, cosmetics with "meaningfully expensive" materials are accepted with certain products. No matter what the product is, the costs of materials cannot and should not be ignored in development. However, even if the cost is expensive in development, there is a high possibility that they can be developed if they are for cosmetics materials. Of course, the cost for materials should be low even for cosmetics, and efforts should be taken to lower the cost.

It may also be possible to utilize materials with low production yield if they are for cosmetics. Jojoba is a plant that takes time to grow, and edelweiss can only be grown in special highlands. Jojoba seed oil and edelweiss extract are materials that have lower production yield compared to other industrial botanical materials and do not appear to be suitable for industrial materials. However, this is not a much of a problem in cosmetics that have limited production volume. These materials can be marketed as materials that do not require much water for cultivation, or for their rarity, and are optimal for cosmetics since they can add value. Utilizing such rare materials is another possibility for securing resources in cosmetics.

### 10.4.2 Redesigning Production Methods

New materials should not be made only from resources but also from production methods. Enzyme transformation and fermentation are material production methods that have gained attention for future resource access. There is an abundant variety of microbe resources on Earth, and since ancient times humans have used them to produce or change substances. As consumers become more conscious about sustainability or environmental load, there is high expectation in fermentation-produced materials since they do not have petroleum-derived substances in their structures and also from their biodegradability. As shown in Fig. 10.1, many materials that are produced with fermentation are now used in cosmetics. There are materials such as hyaluronic acids, which were traditionally obtained from animal derivatives but are now being replaced with fermented materials in cosmetics. Squalane and propanediol were previously unable to be produced with fermentation methods, but in recent years these materials have been produced with fermentation. Surfactants are vital to many cosmetic formulations, and materials such as mannosylerythritol lipid B, sodium surfactin, sophorolipid derivatives, and cerebrosides produced by *Sphingomonas* are already used in cosmetics today, and new materials such as lactic-fermented rice are proposed as well. Physiological activators such as some vitamins and coenzymes are also produced with fermentation. If enough effort is put into research, it is now becoming possible to produce most of the components of cosmetics with only fermented

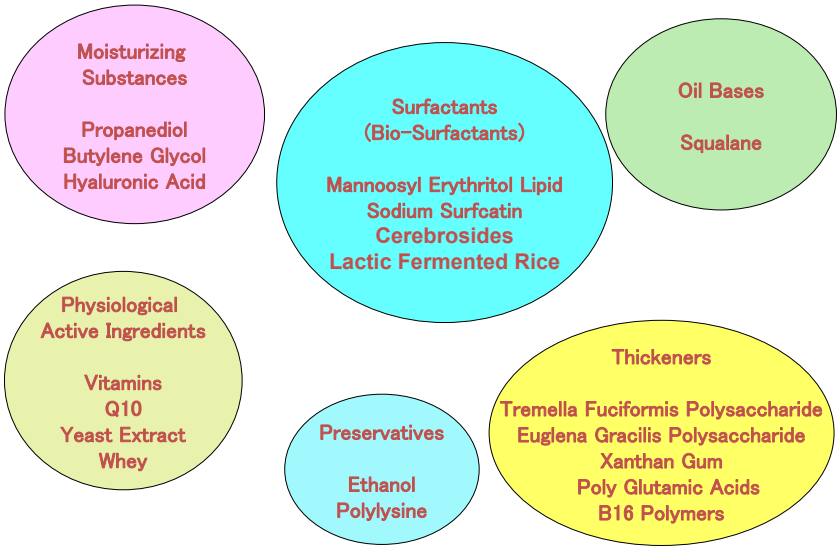



FIGURE 10.1 Fermented Products Used in Cosmetics.

materials. Recently attention has also been focused on algae, along with fungi, and the polysaccharide derived from euglena is already used in cosmetics. It is not hard to imagine that a wider variety of fermented materials will be more commonly used in cosmetics, and promoting this method will lead to a more stable supply of cosmetic materials.

## 10.5 CLOSING REMARKS

It is vital to understand the materials that are currently used for cosmetics and to utilize this knowledge in order to develop and expand new materials for the evolution of cosmetic technology. Gathering information on cosmetic materials from multiple aspects is effective to understand the nature of the materials. In addition to the aspects we have studied in this chapter, there are other materials (animal-derived materials, botanical materials, synthesized materials) and other products (skin care products, makeup products) that can help understand and organize cosmetic materials. I hope this chapter has provided the first step to understand cosmetic materials from multiple perspectives.

CHAPTER

# 11

# Nomenclature of Ingredients

*J. Nikitakis*[1], *J. Sanzone*[2]

[1]Personal Care Products Council, Washington, DC, United States; [2]Estee Lauder Companies, Inc., New York, NY, United States

## 11.1 INTRODUCTION

The purpose of this chapter is to explain the system of standardized names for cosmetic ingredients, called INCI, and provide a better understanding for its importance and practical application for the industry. INCI stands for International Nomenclature Cosmetic Ingredients and is a globally recognized nomenclature system for ingredients used in cosmetic products around the world. In many regions, INCI names are required for the ingredient labeling of cosmetics and personal care products. They are nonproprietary terms developed by the International Nomenclature Committee (INC), publicly available, and published in the *International Cosmetic Ingredient Dictionary and Handbook*. Oversight for the INCI program is provided by the Personal Care Products Council (PCPC), which is the United States trade association representing the cosmetics and personal care products industry.

## 11.2 HISTORY

The program for a standardized system of cosmetic ingredient names emerged from the consumer movement in the United States during the latter part of the 20th century when the Fair Packaging and Labeling Act was enacted,[1] and the US Food and Drug Administration (FDA) published regulations requiring the declaration of ingredients for cosmetic products.[2] The overall intent of the law was to prevent deception and help consumers make fair value comparisons between products. At the time, uniform names for cosmetic ingredients did not exist, which created a potential quagmire for businesses faced with the new product labeling regulations. PCPC, at the time called the Cosmetic, Toiletry and Fragrance Association (CTFA), stepped forth to codify labeling terminology for cosmetic raw materials. The task was carried out by a committee made up of scientists from the industry, academia, the FDA, the US Adopted Names Council, and the Food Chemicals Codex. The names established by the committee were called CTFA Adopted Names, and were compiled with related technical, regulatory, and commercial information and published by the trade association as a reference book originally known as the *CTFA Cosmetic Ingredient Dictionary* and today called the *International Cosmetic Ingredient Dictionary and Handbook.*

A similar regulatory initiative occurred in Europe beginning with the 1976 Cosmetics Directive, and eventual Cosmetics Regulation in 2009, and in Japan with amendments to the Pharmaceutical Affairs Law beginning in 2000. To facilitate a harmonized approach for standardized cosmetic ingredient names, members from these jurisdictions participated on the Nomenclature Committee. The collaborative effort created a uniform system of names, which gained recognition around the world, particularly as ingredient labeling emerged in other regions. Reference to the codified terms as "CTFA Adopted Name" was changed to "INCI" during the 1990s, in acknowledgment of the heightened international acceptance.

[1] Fair Packaging and Labeling Act, 15 U.S.C. 1451.

[2] CFR Title 21 Part 701.3.

*Cosmetic Science and Technology: Theoretical Principles and Applications*
http://dx.doi.org/10.1016/B978-0-12-802005-0.00011-2



Copyright © 2017 Elsevier Inc. All rights reserved.

## 11.3 INCI BASICS

The INCI nomenclature system is fundamentally based on these core principles: the names should be science-based, systematic, informative, and unambiguous; reflect chemical composition; be of minimum length where possible; utilize existing food and drug terminology where appropriate; and be consistent with minimal change to avoid confusion and preserve understanding. Although a robust set of conventions has evolved that codify the systematic approach for designating INCI names, INCI nomenclature is dynamic and adaptive to the increasing complexities associated with substance identification. The INCI conventions are continuously reviewed by the Nomenclature Committee, and published in the Dictionary and in the INCI Application website. Some of the essential core principles for assigning INCI names are summarized for the purposes of this chapter and described following:

- INCI names are based on the intended product. Components, such as by-products, impurities, or additives, are not normally identified as part of the INCI name. This principle is consistent with the criteria outlined in the *Guidance for the Identification and Naming of Substances Under REACh and CLP*, Version 1.3, Feb. 2014 (ECHA-11-G-10.2-EN). As defined in REACh, the main component of a substance of well-defined composition is typically present at a minimum level of 80%; and impurities and additives may contribute to the identifiable composition but not to the naming of the substance.
- Compounded mixtures consist of one or more components, and are created by physically blending materials together. These mixtures are named by listing each component in descending order of predominance, separated by the term "and." The conjoining term "and" is only intended to describe the mixture, and is not intended to be included on the ingredient declaration of a finished product. This principle is consistent with the REACH description for mixtures; however, it is not to be confused with the REACH description for multiconstituent substances. A multiconstituent substance has several main constituents that are derived through a reaction process. Occasionally, there may be instances with INCI names where an ingredient is produced through a reaction but named as a mixture. These cases generally correspond to a substance that contains an appreciable amount of by-product and falls outside of the scope of a substance named as a single entity.
- There are cases where an INCI name is based on starting materials, and/or manufacturing process, rather than the intended product. Some examples of this approach include the INCI names for organic and silicone polymers where the name is assigned according to the starting monomers, e.g., Styrene/Methylstyrene/Indene Copolymer; botanical extracts where the name is based on the binomial name along with the plant part, e.g., Viola Odorata Flower/Leaf Extract; and materials derived through fermentation, where the name is described by the microorganism used for fermentation followed by the material(s) being fermented and terms to describe downstream processing, e.g., Lactobacillus/Panax Ginseng Root Ferment Filtrate.
- Slash marks ("/") are used in INCI names to designate substances that are manufactured through a process to yield a material composed of more than one entity. In these cases, the ingredient is not a physical mixture. As noted in the previous examples, slash marks are used to separate the monomer components of a polymer, the constituents of a ferment, or multiple plant parts in an extract. Other examples include esters synthesized with multiple fatty acids, e.g., Ethylhexyl Caprylate/Caprate, Pentaerythrityl Adipate/Caprate/Caprylate; or calcined minerals, e.g., Lithium/Potassium/Titanium Oxides. Generally speaking, the components are presented in alphabetical order for INCI names where slash marks are used.
- The common English name is used in many cases for plant materials. The reason for this is because the original names for ingredient labeling were assigned using the English common term, e.g., Peppermint Extract or Coconut Oil. Later, when ingredient labeling emerged in the European Union, a change was made to follow the Linnaean system for naming plant ingredients, and the English common name was retained in order to harmonize the original names with the new science-based names, e.g., Cocos Nucifera (Coconut) Oil. In the INCI system, the parenthetical English term is historical and only included for plants that were previously identified by the common name. Ingredients produced using plant materials as a feedstock are named based on the English common term for the plant. For example, "coco" is retained as a stem name for ingredients derived from coconut oil, e.g., Coco-Betaine; or "olive" for ingredients derived from olive oil, e.g., Cetyl Olivate. In cases where an ingredient is derived from a plant where an English common name has not been used, the INCI name may be based on the binomial term, e.g., Myristyl Theobroma Grandiflorum Seedate, which describes an ester of myristyl alcohol with the fatty acids derived from the seed oil of *Theobroma grandiflorum*.
- There are certain unique terms that have specific meaning in the INCI nomenclature system. Some examples include the usage of the term "ampho" in the nomenclature for amphoteric surfactants derived from imidazoline

intermediates. In naming these compounds, "ampho" denotes N-hydroxyethyl ethylenediamine and is combined with the names for the other substituents, e.g., Sodium Lauroamphoacetate. "Alkonium" serves as another example, which was borrowed from the drug industry for the antimicrobial, Benzalkonium Chloride. As a root word, "alkonium" denotes N,N-dimethyl N-alkyl benzyl. It has been used in the INCI system to name other cationic surfactants with this grouping, such as Cocoalkonium Chloride and Soyalkonium Chloride. The root word "monium" is used in the names for quaternary ammonium compounds. For example, "dimonium" and "trimonium" describe a dimethyl, or trimethyl substituted quaternary nitrogen, respectively. Ethoxylated alcohols are named by adding the suffix "eth" to the stem name for the fatty alcohol, followed by the average number of moles of ethylene oxide, e.g., Steareth-10.

- In cases where a specific component is isolated from a biological source, or a botanical source, the INCI name is based on the identity of the isolated material when it has been characterized and purified as a substance of well-defined composition. For example, the name "Luteolin" is assigned for a raw material of high purity; if the raw material is derived from the thyme leaf and is not purified, the name would be assigned according to the binomial, *Thymus vulgaris.*
- INCI names for raw materials derived through the application of biotechnology are determined by the purity of the product. Ingredients produced through a bioprocess, like ingredients that are chemically synthesized, are named on the basis of their composition. If the product is of well-defined composition, the name is based on the intended product, or specific entity, as previously mentioned. Ingredients produced through microbial fermentation where the end product is not characterized as a specific component are named according to the starting materials. These INCI names include the identity of the microorganism(s), substrate(s), and any descriptive terms to characterize the downstream processing involved in their production. INCI names for ingredients produced through plant tissue culture are determined in the same way, i.e., according to the plant source in cases where a specific component is not isolated and purified.

## 11.4 BOTANICAL NAMES

Plant extracts are widely used in cosmetic products and their nomenclature deserves special mention in this chapter. As noted previously, INCI names for plant-sourced ingredients were originally based on the common name and later amended to follow the Linnaean binomial system. There are notable differences between INCI names and scientific binomial names. The special punctuation, formatting, and rules set forth by the International Nomenclature Code for algae, fungi, and plants (Melbourne Code) are not utilized in INCI nomenclature in order to facilitate creating finished product labels for cosmetic products. For example, italicized text is not used for the genus and species terms; and in INCI names both the genus and species are capitalized rather than only the genus term. INCI names do not typically include the variety or subspecies or specific cultivars. Also, hybrids that result from the cross-breeding of species are not described by the "x" symbol between each species. In INCI names, hybrids are described by a "slash" symbol, e.g., Citrus Hassaku/Natsudaidai Fruit Extract. Further distinction with INCI names is usage of the slash symbol to separate multiple plant parts within a single source plant.

Plant classification is a dynamic field. Today many of the traditional scientific names for plants are challenged because of the greater understanding of species relationships afforded by new DNA-based methods. Many familiar plant names are being updated, and some of these have a long history of usage in cosmetic products. Name changes are inevitable, but learning new names, changing documents, updating references, and cross-referencing old names impose costs and can cause confusion. To help the process of learning new names, in the 2016 edition of the Dictionary, the currently accepted scientific name is identified for many plants where the INCI name reflects the older plant name. *Butyrospermum parkii* serves as a classic example. The current scientific name for this plant is *Vitellaria paradoxa*. For now, the INCI name will continue to utilize *Butyrospermum parkii* (yet reference *Vitelleria paradoxa* by definition) in order to minimize confusion in the marketplace and disruption to the industry.

## 11.5 INCI NAMES AND CAS

The correlation between INCI names and CAS numbers can be a source of confusion in substance identification. CAS Registry Numbers are assigned by the Chemical Abstracts Service, which is a division of the American Chemical Society, and are unique numerical identifiers of a given chemical substance. CAS numbers serve to track

ingredient information in the literature and provide a link for the various terms used to identify substances throughout the world. CAS numbers are often used for reporting purposes by various regulatory authorities.

Ambiguity arises because the relationship between a CAS number and an INCI name is not always one-to-one. In some cases, more than one INCI name may have the same CAS number, or more than one CAS number may apply to an INCI name. As an example of the latter, INCI names often do not differentiate substances by stereochemistry; whereas a CAS number is assigned to each specific stereoisomer. In the INCI database, a suffix descriptor such as -DL is added to the CAS number to provide clarity in these cases. Conversely, some CAS numbers can be applied to multiple INCI names; an example of this is the CAS numbers for botanical substances. Typically, the description associated with a CAS number from the CAS database for a botanical reads: "Extractives and their physically modified derivatives such as tinctures, concretes, absolutes, essential oils, oleoresins, terpenes, terpene-free fractions, distillates, residues, etc., obtained from …" The CAS number for this description could apply to any INCI name that is associated with the plant material. In the INCI database, the suffix descriptor "generic" is added to the CAS number in these cases to provide clarity.

## 11.6 INCI NAMES AND COSING

CosIng is the database provided by the European Commission (EC) for information on cosmetic ingredients identified in EC Cosmetics Regulation No. 1223/2009. Most of the INCI names contained in CosIng are provided by PCPC on a regular basis through the EC liaison to the Nomenclature Committee. There are some differences between the ingredients included in CosIng and the ingredients in the database maintained by PCPC. For example, ingredients not permitted for use in the EU are not included in CosIng, and some ingredient names specific to the EU are identified by the EU name. An example of the latter is the Color Index name used to describe colorants, and trivial names specific to the EU, such as cera alba. Also, many botanical extract names in CosIng omit the English common name that is often part of the INCI name.

## 11.7 APPLYING FOR AN INCI NAME

The assignment of an INCI name can be made by request through an electronic application process that is available online: https://inci.personalcarecouncil.org/inci-app/. Applications are typically submitted by an ingredient supplier; however, anyone can submit an application for an INCI name. Details of the application include fields that relate to the composition of the ingredient and its manufacturing process. Applicants are also given the opportunity to suggest an INCI name. The application process does not require the submission of safety data because safety determinations are not within the purview of the Nomenclature Committee. Hence, the assignment of an INCI name does not imply that the substance has been approved for use or regarded as safe as a cosmetic ingredient. It also does not mean that the ingredient complies with laws and regulations in various global jurisdictions. The safety of an ingredient and its suitability for use in a cosmetic product is ultimately the responsibility of the finished product manufacturer.

## 11.8 CONCLUSIONS

There are many benefits to a standardized system of ingredient labeling names for cosmetics. In marketing products across different regions, businesses gain efficiency when labeling with standardized terms, consumers are provided with transparency regardless of the origin of the product, and barriers to international trade are minimized. Medical practitioners and scientists are afforded the consistent communication of information about ingredients in products, which is especially important for identifying materials associated with adverse reactions. The safety and regulatory status of ingredients can be tracked on a global basis, which facilitates the marketing of safe products in compliance with national regulations throughout the world. While it is not possible to acknowledge all of the features that distinguish a given ingredient, INCI names provide a universally consistent means to convey the composition of cosmetic products.

CHAPTER

# 12

# Water

*H. Fukui*

**FUKUI Professional Engineer Office, Yokohama, Japan**

## 12.1 INTRODUCTION

We cannot survive without water. In ancient philosophy, water was one of Aristotle's four elements of matter, and regardless of the era, water is a universal element on this planet. Life was born in the sea, and as it evolved and moved its habitat to land, plants and animals kept the environment of the sea inside their bodies.

There are approximately 1.4 billion square kilometers of water on Earth. The vast majority of this water on Earth is seawater and less than 2.5% is fresh water, and when excluding the polar ice the amount of fresh water is only less than 1%. Water on Earth evaporates mainly from the sea and falls back to Earth as rain or snow. Since water circulates in a short period, it has been perceived as an unlimited resource even though it is actually limited. Water molecules are polar, with a slightly negative charge at the oxygen and a slightly positive charge at the hydrogens.

There are three phases of matter as gas, liquid, and solid, and water is an extremely rare substance where all three phases are found on Earth as vapor (gas), water (liquid), and ice (solid). Furthermore, hydrogen bonds make water clusters, which are very important to life.

As a polar molecule water dissolves polar substances. The interaction of water and solute is called hydration, and this interaction also plays an important role in biological reactions as hydration of ions and biological polymers.

Water is vital to life and the skin has an important role of keeping water inside the body.

Additionally, the single-most-used ingredient in cosmetics is water. This is not irrelevant to the fact that water is an essential substance that plays an important role in the human body. There are insoluble cosmetic substances that do not dissolve to water, but they are also evenly mixed in water by solubilization and emulsification.

In this chapter, we will learn the basic properties of water and its roles in the human body.

## 12.2 BASIC PHYSICAL PROPERTIES AND BIOLOGICAL ROLES OF WATER

### 12.2.1 The Structure of Water Molecules

Water molecules are nonlinear three-atom molecules with one oxygen atom sharing its six electrons in its L shell with the electron on the K shell of two hydrogen atoms. As shown in Fig. 12.1, the distance of the O−H bond is 96.8 pm, the bond angle is 104 degree, and the Van der Waals radius is approximately 140 pm.

The bond angle of water is close to the bond angle of a regular tetrahedron, which is approximately 109 degree, so it is thought that the bond angle is mainly caused by the bond of the $sp^3$ hybrid orbit of the oxygen atom. The oxygen atom and hydrogen atoms in a water molecule are bonded by covalent bonds. The electronegativity of the oxygen atom is stronger than hydrogen, so the electrons are drawn to the oxygen atom giving the oxygen atom a negative charge and hydrogen atoms positive charges.

As a result, water molecules have permanent dipole moment with a value of 1.85D. This value is larger than other hydrogen homologues ($H_2S$ 0.97D, $H_2Te < 0.2D$) and the polarity is higher when compared to organic solvents such as hexane (0.00D), chloroform (0.95D), and ethanol (1.69D). The solubility of inorganic salts is strongly influenced by the permanent dipole moment of water.

Water with regular hydrogen and oxygen atoms is not the only kind of water; there is water with D or T hydrogen atoms, which have two or three times larger mass. $D_2O$ and DHO are called heavy water, and only a millionth of 3% exists naturally. Having a stronger hydrogen bond, heavy water is immobile compared to light water and is toxic to organisms.

*Cosmetic Science and Technology: Theoretical Principles and Applications*
http://dx.doi.org/10.1016/B978-0-12-802005-0.00012-4



Copyright © 2017 Elsevier Inc. All rights reserved.

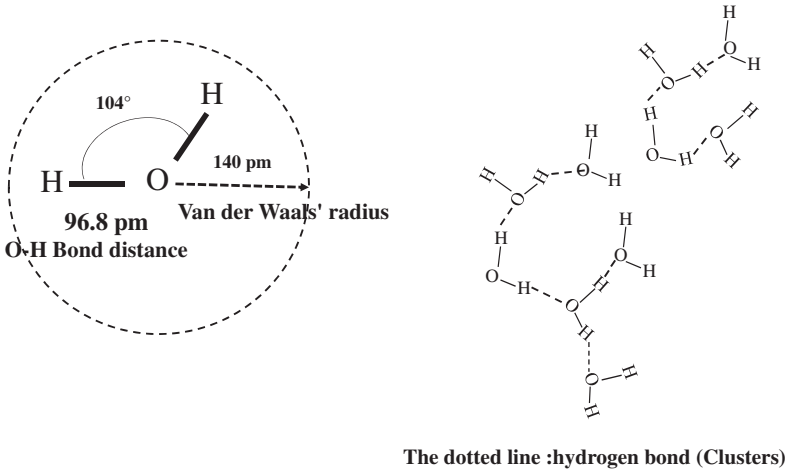



FIGURE 12.1 Molecule structure of water and clusters.

### 12.2.2 Phase Diagram of Water

As shown in Fig. 12.2, water can show three phases of ice (solid), water (liquid), and water vapor (gas) depending on the temperature and pressure. There are only a limited number of substances that show all three phases on Earth. When the temperature and pressure rises along the border of liquid water and water vapor, water reaches its critical point (374 degree, 218 atm) where a distinct difference between liquid water and water vapor does not exist. If the temperature and pressure is higher than the critical point, water becomes supercritical water and shows the properties of both liquid and gas. This phase can dissolve many substances from inorganic substances to organic substances, and is widely used to synthesize or extract new substances. Additionally, water reaches its highest density at 3.98°C and the volume becomes minimal. The density of water is higher than ice at all temperatures between the melting point and boiling point, and as a result, ice floats on water. The reason organisms that live in lakes are able to survive when the lake freezes is directly related to the fact that ice floats on water.

### 12.2.3 The Structure of Water and Hydrogen Bonds

The vibration of water molecules is believed to be caused by a total of three bands, which are two stretching vibration bands of the O—H near 3400 $cm^{-1}$ and one bending vibration band of the H—O—H near 1600 $cm^{-1}$.[1] However, actual measurements of water molecule vibration show more bands than these basic three bands, and it is thought that the hydrogen bonds between the water molecules make the molecules form clusters by bonding to each other (Fig. 12.1). These water molecule clusters have a chronological factor and the order is within only several picoseconds (ps). To illustrate how fast the speed of the cluster's structure change is, light can only advance 30 μm in 1 ps.

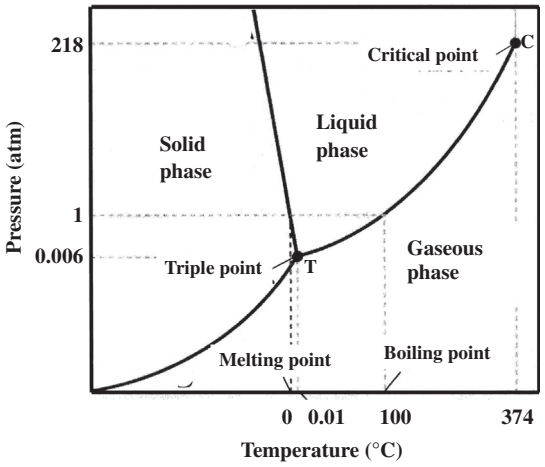



FIGURE 12.2 Phase diagram of water.

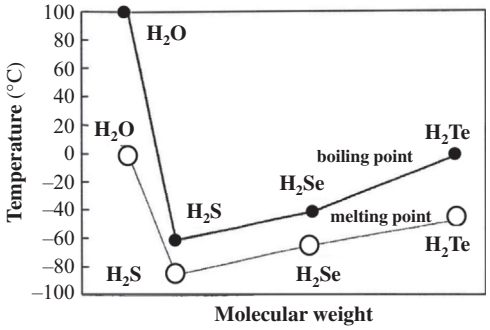



FIGURE 12.3 Boiling point and melting point of oxygen homologue hydrogen compounds.

Since liquid water molecules are bonded to each other by hydrogen bonds, both the melting point and boiling point are higher than the temperature predicted from other homologues without hydrogen bonds. Other unique physicochemical properties of water are also deeply related to the hydrogen bonds of water molecules.

In general, the physical property of similar compounds with atoms from the same homologous series of the periodic table changes depending on the atomic number of the atom that it is bonded to. For example, the boiling point and melting point of hydrogen compound homologues are shown in Fig. 12.3, $H_2S$, $H_2Se$, and $H_2Te$, and they increase linearly with molecular weight. When calculating the boiling point and melting point of water with a molecular weight of 18, the values are approximately $-80°C$ and $-110°C$, respectively. However, the actual values are significantly higher than these calculated values, with a boiling point of 100°C and melting point of 0°C. Additionally, more thermal energy is required to break the hydrogen bonds between the water molecules. The specific heat capacity at constant pressure, or in other words, the calories required to increase the temperature of 1 g of water by 1°C, is higher than that of other substances with a similar molecular weight. This shows that a strong intermolecular force works between the water molecules.

A hydrogen bond is an attractive interaction force where hydrogen atoms covalently bonded to atoms with high electronegativity (electronegative atoms) create a noncovalent bond with independent electron pair of neighboring atoms such as nitrogen or oxygen. There are intermolecular hydrogen bonds that work between separate molecules and intramolecular hydrogen bonds that work between separate groups of a single molecule. Hydrogen bonds become strongest when molecules are linearly aligned. Furthermore, hydrogen bonds do not occur when the distance is greater than or equal to 0.3 nm. The energy of hydrogen bonds is approximately 10–40 kJ/mol and is much weaker than ionic bonds or covalent bonds but stronger than the Van der Waals force.

Hydrogen bonds have been found in water through several methods such as X-ray diffraction, neutron diffraction, and NMR spectroscopy. As mentioned previously, these hydrogen bonds play an important role in the physical properties of water. Radial distribution function using X-ray diffraction has shown that the nearest neighboring water molecule numbers are 4.4[2], slightly larger than 4.0 of ice. This is why water density is higher than ice. X-ray diffraction also showed that the intermolecular distance increased with heat.

Rotation and hydrogen bonds of water molecules form and disappear in a short period of $10^{-12}$ s, so although they are called clusters, it is believed that they dynamically change.

When observing the OH stretching vibration under infrared spectrum at femtosecond levels, it can be found that water structure change that occurs with laser irradiation does not last longer than 50 fs ($5 \times 10^{-14}$). Usually the cluster structures are made from 5 to 10 water molecules, and are believed to be most stable with ringed structures.

Furthermore, hydrogen bond formation also leads to changes in other properties, such as changes in the molecule polarity or absorption of ultraviolet and visible spectra.

## 12.2.4 Thermal Properties of Water

4.2 (kJ/kg·K) is required to raise the temperature of water 1°C from 18°C. As shown in Table 12.1, the specific heat capacity of water is 4.2 and is higher than many other substances such as ethanol. This means that more thermal energy is required to heat water, but also means that water does not easily cool down once it is heated. Water does not easily get warm or cool, and this property is deeply related to preserving life for organisms.

Warm-blooded animals keep their body temperature at 36–37°C. The highest body temperature a human can tolerate is said to be 44–45°C. In this temperature range, enzyme proteins that work as catalysts for many biochemical reactions function stably, but these enzyme proteins change irreversibly at higher temperatures and this leads to

**TABLE 12.1** Specific Heat Capacity of Substances

| Substance | Specific Heat Capacity (kJ/kg· K)[a] |
|---|---|
| Water | 4.19 |
| Ethanol | 2.46 |
| Coconut oil | 2.10 |
| Pentane | 1.66 |
| Aluminum | 0.90 |
| Glass | 0.68 |
| Iron | 0.44 |

[a]*Regular state.*

death. The lowest body temperature the human body can tolerate is said to be 33−34°C; below this temperature consciousness disorder occurs, and can no longer can survive at 25−27°C. More than 60% of the human body mass is water, and the specific heat capacity of water protects the body from temperature changes of the surrounding environment, maintaining the internal body environment with body temperature adjustment.

Body temperature adjustment is strongly related to the vaporization heat of water. Heat is mainly generated in the body at the liver, heart, and muscles, and is distributed to the skin through the circulatory system and released to the air. Heat is released to the outer environment when it reaches the skin through radiation, conduction, and evaporation. Eighty percent of heat is released by radiation and conduction, and the remaining 20% is released by evaporation. Evaporation, including insensible perspiration such as sweating and breathing, is extremely important when the surrounding temperature is higher than body temperature. Even when we are not sweating, approximately 500 mL of the body's water evaporates from the lungs and skin per day. Although insensible perspiration from the lungs and skin cannot be controlled, sweating is controlled and the amount increases when the surrounding temperature is higher than body temperature to increase vaporization heat. The vaporization heat of water is 2250 kJ/kg, which is much larger than the vaporization heat of other substances such as ethanol, which is 393 kJ/kg. Again, water plays an important role from its large vaporization heat.

### 12.2.5 Surface Tension of Water and Wettability

Liquid water has a characteristic where it tries to make its surface area as small as possible, a phenomenon called surface tension. When comparing the intermolecular attraction forces of the surface molecules on the interface between liquid and gas to the intermolecular attraction forces of the molecules in bulk water, the bulk water molecule intermolecular force is larger since they are attracted from every direction with the same force. On the other hand, the intermolecular attraction force from the gas molecules outside of the liquid is weaker so the surface molecules are mainly drawn to other molecules on the surface and to the molecules in the water. Thus, these forces make the liquid surface area smaller. As shown in Table 12.2, the surface tension of water is 72.8 mN/m and is larger than 22.5 of ethanol or 28.9 of benzene. The wettability to a solid surface decreases when the surface tension is larger, and surfactants are used to reduce the tension.

**TABLE 12.2** Surface Tension of Liquids

| Substance | Surface Tension (mN/m) |
|---|---|
| n-Hexane | 18.40 |
| Ethanol | 22.55 |
| Methanol | 22.60 |
| Acetone | 23.30 |
| Benzene | 28.90 |
| Water | 72.75 |

## 12.2.6 Solubility of Water

### *12.2.6.1 Water-Soluble Substances*

Water can dissolve a plethora of substances as a solvent. Water-soluble substances (solutes) are roughly categorized into hydrophilic substances, hydrophobic substances, and amphiphilic substances, and the dissolving property varies depending on the type of solute. Among hydrophilic substances, there are electrolytes and nonelectrolytes.

A common rule that has been long known is that "similar substances have high affinity." Since water is a polar molecule, polar substances easily dissolve to water and nonpolar substances do not easily dissolve to water. Therefore water easily dissolves inorganic salts. Contrarily, organic substances and oils do not easily dissolve to water. The highest possible concentration for a substance to dissolve is called the solubility, and the liquid at this concentration is called a saturated solution. The solubility differs depending on the temperature, and in general the solubility increases when the temperature rises in most cases. With gases, the solubility decreases with temperature increase and increases when the pressure increases.

Hydrophilic substances (electrolytes): Water easily dissolves inorganic salts, and this is related to the large dipole moment of water molecules. Inorganic electrolytes such as sodium chloride and potassium chloride are dissolved into water as inorganic ions, and these ions are surrounded by water molecules and become hydrated. Since water is a polar molecule, the negative area (O: oxygen) of the bipolar molecule is oriented around cations, and the positive area (H: hydrogen) of the bipolar molecule is oriented around anions. This is called ion hydration, and the hydrated liquid is called hydrated water. Ions with small ion radius such as $Li^+$ hydrate more water and the radius of the hydrated ion becomes larger. The number of hydrated water molecules, the symmetry, and the distance from the oxygen in the water molecules have been determined for most metal ions.[3]

In order for substances to dissolve in water, the solute particles must disperse and the dispersed solute particles must dissolve into the water molecules. Looking at the energy of this process, the former is an endothermic reaction and the latter is an exothermal reaction. The heat of dissolution is the difference between the two energy reactions. For solutes to dissolve, it is better if the interaction between the solute particles is weak and the interaction between the solute particles and water molecules is strong.

Hydrophilic substances (nonelectrolytes): Polar substances such as sucrose and alcohols have functional groups like OH groups that can form hydrogen bonds and easily dissolve to water.

Hydrophobic substances (hydrophobes): Hydrocarbons such as methane and ethane are hydrophobic substances and are nonpolar, and are very slightly soluble substances. Water molecules create ice-like cage structure (iceberg) around hydrophobes, which decrease the mobility of water molecules (entropy reduction) resulting in an increase of total free energy of the system. In order to avoid this unfavorable change, hydrophobes aggregate in water in order to minimize contact with water. This phenomena between hydrophobe and water is called hydrophobic interaction. Hydrophobic interaction is deeply related to micellization, structure preservation of proteins, and formation of biomembranes.

Amphiphilic substances: Molecules that have both hydrophilic groups and hydrophobic groups in a single molecule are called amphiphilic substances. When soap is dissolved into water, they start to aggregate above a certain concentration and the hydrophilic groups face outward and the hydrophobic groups face inward, creating aggregations called micelles.

### *12.2.6.2 Ion Hydration Inside the Body*

The interaction between water and solutes is generally called hydration. The main interactions between water and solutes are electrostatic interaction and hydrogen bonding, but Van der Waals force and hydrophobic hydration also interact between water and solutes. The main interaction differs depending on the property of the solute. With inorganic ions, the main interaction is electrostatic interaction, but with most sugars such as sucrose and starch, the main interaction is hydrogen bonding.

The hydration of ions is an important aspect and plays a strong role in understanding life. For example, $Na^+$ or $K^+$, which are seen in many reactions in the body, are distributed unevenly in the body, and the concentration of Na+ is much higher than K+ in extracellular regions but the concentration is opposite inside cells. It is thought that the hydration properties of ions are deeply related to the uneven distribution.

## 12.2.7 The Role of Water in Biological Environments

One of the most important roles of water in the body of organisms is distribution of substances. In order to deliver various nutrients to each tissue, blood or peptic juice with optimal water content is required. Water is also used to

excrete metabolites and biological waste. Carbon dioxide, one of the biological wastes produced in the body, can be vaporized and excreted from the lungs through breathing, or dissolved into water and carried to the kidneys through the blood, excreted as urine. Twenty percent of carbon gas is dissolved and carried by the water portion of blood (blood serum). Such a mechanism is possible since water is an ideal solvent with optimal properties to dissolve various biologically derived substances including metabolites and wastes.

### 12.2.8 Water Used in Cosmetics

In general, normal water or purified water is used for cosmetics. Normal water is tap water or water from wells that meet the water quality standards stipulated by waterworks laws. Purified water is ion-exchanged water or distilled water made from normal water. Colorless and transparent water with no precipitates or smell is used for cosmetics, and additionally impurities such as microbes, metal ions, and organic substances are also removed from the water for safety and sanitary reasons. Recently water with functions, called functional water, is also used in many cases, such as deep-sea water or water from various hot springs.

### 12.2.9 Functional Water

Activated water has gained attention from many fields to add more functionality. However, it is important to know that not all of these waters have a scientifically proven basis to their marketed functions.

There are several methods to activate water, such as (1) add a form of energy, (2) contact or dissolve a substance, (3) penetrate through various filters, and (4) copy information of the desired functions.

Activated water can show changes such as (1) change in the structure of water, (2) formation of activated chemical species, (3) change in the oxidation−reduction potential, (4) change in the energy, and (5) change in the physical property.

Some examples of functional water are electrolyzed water (alkaline ionized water, acidic water), magnetic water, active hydrogen water (reinjected water), radiant wave water, and $\pi$ water. An example of natural functional water is deep-sea water, which is used from its high nutrient content, purity, and low temperature. Examples of purified water are superpurified water that is purified to be as close to 100% as possible, electrolyzed water created by electrolysis, degassed water that has the dissolved gases removed, and supersonic treated water that is activated by supersonic vibration. Ozone water and hydrogen water are waters with a controlled gas content, and fine-bubble water is water with micron or nanolevel gases existing in water.

### 12.2.10 Water Adsorbed to Powder Surfaces

Pigments and other powders used in cosmetics usually have a large amount of water adsorbed to the powder surface. For example, titanium oxide and zinc oxide are metal oxides with hydroxyl groups on the surface, and they have even more water molecules adsorbed to the surface at room temperature. As such, it is important to think about the water when dispersing lipids to powders. Furthermore, the isoelectric point of solids changes the positive charge in low pH areas, and in high pH areas the negative charge changes.

## 12.3 CELL MEMBRANES AND WATER

### 12.3.1 Proteins and Water

#### *12.3.1.1 Primary Structures of Proteins*

Proteins are composed of polypeptides chained in a single direction created by peptide bonds (−NH−CO−) of the carboxyl groups and amino groups of various amino acids. Every organism has amino proteins, with approximately 20 kinds of amino acid residue group side chains, and these have various properties. For example, some of these proteins have electrical charge and have different hydrophilic/hydrophobic properties. The alignment structure between the terminal amino group to the terminal carboxyl group is called the primary structure of proteins. This protein alignment is defined by genetic information.

#### *12.3.1.2 Secondary Structure of Proteins*

Proteins are made from long-chained polypeptides, but the chain is actually folded in a unique three-dimensional structure. This three-dimensional structure is the most stable structure for each protein in their environment, and if

the protein is a water-soluble protein that exists in the intercellular aqueous solution, the hydrophobic side chain faces inward and the hydrophilic groups are on the surface. There are largely two types of three-dimensional structures of proteins. One is the α-helix, where the α carbon atoms in bonded side chains create a patterned spiral structure. This structure is formed when the C═O groups in the peptide bonds bonded to the α carbons create a hydrogen bond with the N−H groups in the peptide bonds bonded to the α carbons four residue groups away. There is also a folded structure called β-sheet. In this structure, α carbons are linearly aligned, and the N−H group in the peptide bonds create a hydrogen bond with the C═O group in the neighboring β adjacent strand as stable structure. These patterned structures like the α-helix and β-sheets are called secondary structures.

#### *12.3.1.3 Tertiary Structures of Proteins*

As seen herein, primary structures are the alignment of amino acids and secondary structures are the unique folded patterns, and there are also tertiary structures that are three-dimensional structures made from secondary structures. Furthermore, there are structures where the entire protein molecule is a combination of various polypeptide chains; this structure is called a quaternary structure. Since proteins form various three-dimensional structures, they have various chemical properties. Although polypeptides are useful and can create stable three-dimensional structures, it is believed that new functions were added without changing their structure much during evolution. Therefore many proteins can be classified into protein families that have similar primary structures or tertiary structures. For example, Aquaporin (AQP) is a water channel that has a unique effect against water and also has its own protein family.

#### *12.3.1.4 Water Molecules and Protein*

Most proteins are made from amino acids connected by peptide bonds, and the hydrated water molecules on the protein surfaces are integral to the stability of the molecular structure of proteins such as random coils and helices. The hydrated surface of proteins is strongly influenced by the amino groups and carboxyl groups on the protein surface. It has been found that many water-soluble proteins have low-mobility water molecules adjacent to their surfaces, and it has been observed that they are not found at further distances from the surface. A similar phenomenon has also been observed with other substances such as polysaccharide and nucleic acids. On hydrophilic interfaces, the water molecules on the interface bond directly to the hydrophilic groups on the interface and are oriented, and do not freeze at −90°C. It is believed that the same occurs with biological polymer surfaces.

### 12.3.2 Cell Membranes and Water

Cells are physically separated from their surroundings by cell membranes that stand between the surroundings and the cytoplasm. This allows the intracellular environment to be independent from the extracellular environment. The main substance of biomembranes is phospholipids, which are amphiphilic substances with both a hydrophilic and hydrophobic group. The outer side of the bilayer membrane of phospholipids is hydrophilic, and the inner side is hydrophobic. The outer hydrophilic area has a negative charge, and they repel proteins that also have negative charge, so they do not easily adsorb. Likewise, ionized electrically charged substances do not easily penetrate the membranes due to electrical interaction.

Water molecules and other extremely small molecules, as well as lipophilic molecules, can penetrate the bilayer membrane of phospholipids. However, electrically charged molecules or polar molecules such as amino acids, sugars, and ions cannot penetrate the membrane. Polar substances form many hydrogen bonds with water molecules and the ions are surrounded by water molecules, so they are unable to penetrate the membrane. Water molecules penetrate the membrane with a diffusive motion called osmosis. This passive motion does not use metabolic energy and the penetration is defined by the concentration of the solute. Besides this simple osmosis, water molecules also penetrate the membrane through ion channels by hydrating ions or through water channels called aquaporins.

### 12.3.3 Cell Membranes and Substance Distribution

The cell membrane is not only a barrier but also has dynamic functions by taking in necessary substances through the membrane and excreting unnecessary substances out of the membrane.

Let's take a look at how the cells can move substances in and out through the membrane. The membrane has a structure where proteins float, and these membranes play an important role to take in substances that cells need. Protein molecules with specific three-dimensional structures can selectively bond to specific molecules with noncovalent bonds such as hydrogen bonds. There are many proteins that work as catalysts that induce chemical reactions by

bonding to specific molecules and stabilizing an intermediate state of a chemical reaction. Such proteins are known as enzymes. Furthermore, there are also receptors that recognize specific molecules and transfer the information. There are also channels that bypass specific molecules and pumps that carry specific molecules. It has been found that some of these proteins can also control their functions by changing their structure. Carrier proteins and ion channels are such proteins that can carry substances through cell membranes. Some unique membrane carrying functions of carrier proteins actively carry substances by consuming energy to carry substances against the concentration gradient.

### 12.3.4 Water Channels

Intracellular water is preserved by osmotic pressure caused within the cells. Cells adjust their osmotic pressure by using substance carrying to quickly maintain the homeostasis of the intracellular environment. Water can move faster when the osmotic pressure gradient between the intracellular and extracellular environment is larger, but energy such as ATP is required for substance carrying that creates this gradient. Cell membranes are bilayer semipermeable membranes, and water can penetrate these membranes relatively easily. Water moves quickly with the osmotic pressure gradient to establish equilibrium, but it is more convenient if there are water-permeable channels that allow water to move even if the osmotic pressure gradient is small.

### 12.3.5 Aquaporin

Aquaporin has six clockwise α-helix structures, and the terminal amino groups and terminal carboxyl groups stick out of the cell membrane surface toward the cytoplasm. There are five looped structures between the helices that connect the inside and outside of the cells. Two of these loops are hydrophobic and have a structure called Asn-Pro-Ala (NPA) motif. The NPA motif overlaps inside the cell membrane and has a three-dimensional hourglass structure. Water passes through this area. Asparagine and oxygen atoms in water molecules create hydrogen bonds, and the water molecules pass through the membranes while spinning through the channel in a single row. Most AQPs only bypass water, but there are some that pass glycerin too. Thirteen types of AQPs have been found in mammals. As shown in Table 12.3, many tissues of the human body have AQPs, and the type of AQP in the skin is AQP3, which selectively passes water and glycerin and preserves the skin moisture.

**TABLE 12.3** Aquaporin in Various Tissues

| Tissue | Aquaporin |
|---|---|
| Skin | AQP3,4 |
| Eyes | AQP0,1,3,4,5 |
| Muscles | AQP4 |
| Red blood cells | AQP1,3 |
| White blood cells | AQP9 |
| Brain | AQP1,3,4,9 |
| Lungs | AQP1,5 |
| Trachea | AQP3,4 |
| Nasal cavity | AQP3,4 |
| Heart | AQP1 |
| Liver | AQP1,8,9 |
| Kidneys | AQP1,2,3,4,6,7,11 |
| Spleen | AQP12 |
| Intestine | AQP1,3,4,7,8 |
| Testicle | AQP1,2,7,8,9 |
| Gallbladder | AQP1 |
| Spinal cord | AQP1,4 |

# 12.4 THE SKIN AND WATER

## 12.4.1 The Mechanism of Moisture Retaining

In order to keep precious water from leaving the body, the horny cell has mechanisms as shown in Fig. 12.4 to prevent dehydration in the dry environment of living on land. Sebum, which is composed of triglyceride, wax, and fatty acids, is on the outermost area of the skin and prevents moisture evaporation. The granular cells in the epidermis slowly divide into corneocytes that overlaps like thin tiles. When these tiles firmly construct about 20 layers, they create a thin membrane of horny cell that surrounds the body surface as a film that does not allow any water to leak. Roughly one layer of horny cells is formed every day, so the outermost layer peels off as waste and a new protective layer is always moved to the surface. There are water-soluble substances in the corneocyte horny cells called natural moisturizing factors (NMFs). As shown in Fig. 12.5, NMF is made from amino acids that are created when proteins, known as filaggrin, move to the horny cell and are decomposed by protease. These amino acids are water soluble and are not produced unless the skin cornifies correctly.

Another important water-preserving barrier is created during cornification. Small particles called lamellar bodies are filled with lipids, which are released just before they move to the horny cell, and the released lipids structure evenly to form intercellular lipids. Intercellular lipids are mainly composed of ceramides, cholesterol, and cholesterol esters, which prevent evaporation and keep the NMF amino acids from leaking. These intercellular lipids are amphiphilic substances, and their hydrophilic groups and hydrophobic groups aggregate to each other to create a layered lamellar structure. This structure does not easily let water pass through. In order to form this important structure, the membrane surrounding the horny cell cells, called cornified envelope (CE), must mature. As CE matures, the protein membranes are covered with lipids, and intercellular lipids are evenly oriented as lamellar structures on top of this membrane to show barrier functions. As such, NMFs, intercellular lipids, and sebum protect the

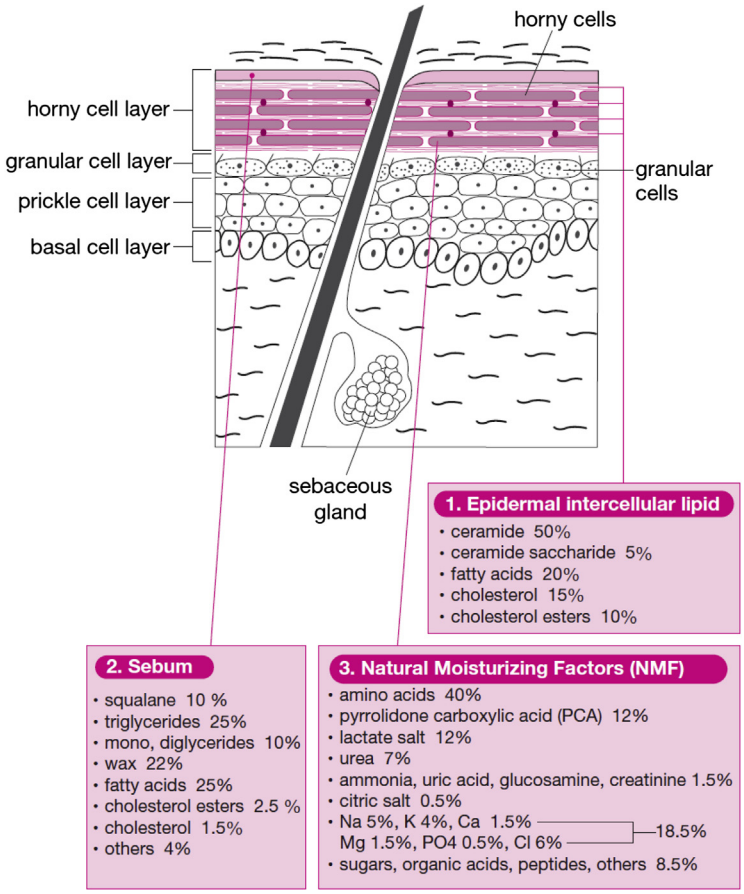



FIGURE 12.4 How the body prevents dehydration.

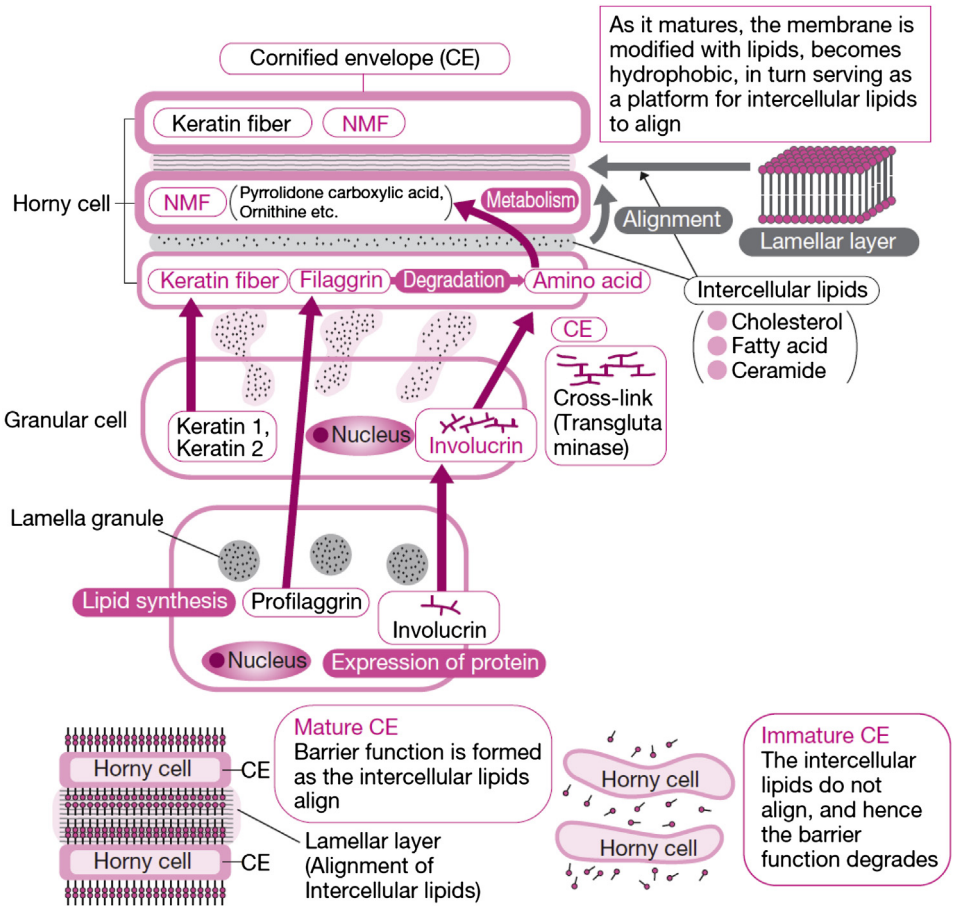



FIGURE 12.5 How a healthy horny cell layer is formed.

skin to keep water in the body, but if any of these conditions are not preserved, water easily leaves the body. Furthermore, foreign substances also penetrate the skin easily if the barrier function is not maintained.

A healthy horny cell has 10–20% water, and the skin shows irritation below this content. In cosmetics, water is formulated with moisturizers in order to prevent the water content of the horny cell from dropping. Similarly, water also plays an important role in hair.

## 12.4.2 The Mechanism of Perspiration

The most prominent mechanism of excreting water from the skin is sweat, which is secreted from gland tissue called sweat glands. Sweat glands are classified into eccrine glands and apocrine glands.

There are three types of perspiration from the eccrine glands.

1. Perspiration to lower the increased body temperature to normal temperature
2. Nervous perspiration at the hands, face, underarms, or groin from mental causes such as anxiety or nervousness.
3. Gustatory perspiration caused by consuming hot or spicy foods.

Ninety-nine percent of the sweat secreted from these sweat glands is water, and substances such as salt, urea, ammonia, and lactic acid account for the remaining 1%.

Apocrine glands are found in specific areas such as the underarms, around the navel, and groin, and they grow during puberty and shrink at senescence. Hardly any salt is found in the sweat secreted from these sweat glands, and they contain protein, lipids, sugars, and ammonium, and is slightly sticky. The sweat itself is odorless but the bacteria on the skin decompose the sweat and as a result this sweat can cause odor. AQP5 expresses at sweat glands.

## 12.4.3 Skin Moisture Measurement

The water content of the horny cell can be measured by measuring the electrical resistance change of the horny cell, with methods such as measuring the impedance or capacitance of the skin. Furthermore, transepidermal water

loss (TEWL) is evaluated by the amount of water evaporated from the skin, and the horny cell barrier function is higher if the TEWL is lower.

The water in the skin is either intracellular water or intercellular water. Furthermore, both of these can have free water that evaporates like bulk water and bonded water that is bonded to biological components, and these do not easily evaporate[4]. Bonded water is also found in the horny cell and it preserves the flexibility of the horny cell. Free water and bonded water content can be determined through methods such as thermal analysis. Healthy skin contains approximately 30% water, and when the content is larger free water increases, leading to proteolysis and the structure of the horny cell is broken, creating swollen skin. The distribution of free water in the skin can be analyzed with dielectric spectroscopy of the entire skin or by wideband measurement with probes contacted to the skin.[5]

Since water absorbs near-infrared regions, near-infrared camera systems are being developed to target the strongest absorption near 1920 $nm^{-1}$ to visualize the water in the skin.[6]

## 12.5 CONCLUSIONS

Water is the single-most-used ingredient in cosmetics and is also the most important substance for life. The skin is delicately designed to keep this important water inside the body. As we have learned in this chapter, although water is very common it actually has extremely unique properties, and it is not extreme to say that this uniqueness created life. We have looked at these unique properties of water and its functions in the body as well as in the skin. The structure or properties of water like the oxidation−reduction property are believed to change with slight amounts of gas and metal ions or delicate energy states, so there is a possibility that water with reactive oxygen species inhibiting or antiaging properties will be discovered. We hope the cosmetics of our dreams will be created through new discoveries in water.

## References

1. Mizushima S, Shimauchi T. *Infrared absorption and Raman effect", Kyouritu Zensho*. 1958.
2. Morgan J, et al. *J Chem Phys* 1938;**6**:3275.
3. Ohtaki H, et al. *Chem Rev* 1993;**93**:1157.
4. Imokawa G, et al. *J Inv Derm* 1991;**96-6**:845.
5. Shirakashi R, et al. *Seisan Kenkyu* 2015;**67**:247.
6. Egawa M, et al. *Appl Spectrosc* 2011;**65**:924.

CHAPTER

# 13

# The Use of Polymers in Cosmetic Products

*R.Y. Lochhead*

**The University of Southern Mississipi, Hattiesburg, MS, United States**

## 13.1 RHEOLOGY MODIFIERS

A whole host of polymers is used in cosmetics to deliver a wide range of attributes.[1,2] In this chapter I will attempt to proceed logically through the properties conferred by polymers in cosmetics and personal care products and the nature of the polymers that deliver particular attributes. I will begin this discussion by considering the use of polymers to modify rheology because the molecular and supramolecular chemistry and physics implicit in rheology modification necessarily requires consideration of fundamental physicochemical aspects that will form a useful intellectual foundation for other polymer applications that are discussed later in the chapter. Thickeners, or rheology modifiers are used in personal care to achieve stability against settling during storage and to confer desired delivery characteristics and perceived sensory cues when consumer products are applied. For example, the rheology modifier should improve body, smoothness, and silkiness, to make a product more aesthetically pleasing.[3]

Rheology modifiers may be natural, semisynthetic, or synthetic. For example, natural rheology modifiers include casein, alginates, guar gum, xanthan gum, and gum tragacanth; semisynthetic thickeners include modified celluloses such as carboxymethyl cellulose, methyl cellulose, hydroxyethyl cellulose, and hydroxypropyl cellulose; and synthetic rheology modifiers include polyelectrolytic acrylic polymers and maleic anhydride copolymers.

In personal care products, the vast majority of rheology modifiers are used to "thicken" aqueous systems. For hydrogels, gel-like suspensions or emulsions, the rheological parameters that can be correlated with sensory perception include: (1) enhanced viscosity, (2) viscoelasticity, (3) yield stress, (4) thixotropy, (5) wall-slip, and (6) shear banding.[4]

The preferred rheological characteristics are usually attained only above the critical overlap concentration of the polymers in the system.[5] The concept of overlap concentration is discussed in Chapter 2. In most cases the dissolved polymers form higher order hierarchical structures that are responsible for the observed rheology.

The simplest of the hierarchical structures are polymers that "thicken" by entanglement of the polymer molecules in solution.[6] Plain vinyl polymers have flexible chains that "wriggle" by means of crankshaft-like rotation around the backbone C—C bonds. The fundamental links of polymer chains correspond to the Kuhn length, which is twice the persistence length (the persistence lengths and Kuhn lengths are discussed in Chapter 2), and this is the smallest unit of the chain that can wriggle. The most flexible polymers have Kuhn lengths that correspond to about three C—C backbone bonds. If there are $n$ links in a given chain, all links could wriggle independently. Simultaneously, there could be cooperative motion between the links. Boltzmann kinetic considerations predict that such cooperative motion of longer parts of the chain would necessarily have a longer relaxation time than independent single-link motion. This is the basis of Rouse—Zimm theories of the movement of polymer chains, which postulates that the chains when perturbed will relax by a distribution of modes, with the fastest mode (the $n$-th mode for a chain consisting of $n$ Kuhn length segments) corresponding to the shortest relaxation time available to a given polymer molecule. The zeroth mode corresponds to the tumbling of the entire molecule. If the molecules are subjected to oscillating stress, as the frequency of the stress increases beyond the possible relaxation frequency of the zeroth mode, the entire molecule will be unable to tumble in the time between oscillations, and relaxation by the zeroth mode will become impossible. As the frequency of oscillation increases beyond the zeroth mode, the first mode (corresponding to a wavelike motion in which one-half of the molecule moves one way and the other half of the molecule moves in the opposite direction) will become impossible, then with further increase in perturbation frequency, higher modes will become successively impossible. Theoretically, the fastest relaxation time available to a polymer molecule will correspond to the relaxation time of the persistence length of the molecule.

*Cosmetic Science and Technology: Theoretical Principles and Applications*
http://dx.doi.org/10.1016/B978-0-12-802005-0.00013-6



Copyright © 2017 Elsevier Inc. All rights reserved.

The Deborah number, De, is defined as the ratio of the relaxation time for a material to adjust to applied stresses or deformations,[7]

$$\mathrm{De} = \frac{time\ of\ relaxation}{time\ of\ observation}$$

When De is much lower than 1, the molecules relax quicker than the applied deformation and Newtonian viscous flow is perceived. For De much greater than 1, the molecules cannot relax at the speed of deformation and elastic solid-like behavior is observed. Thus as the rate of perturbation increases, the material will become less viscous and more elastic, until the frequency of the oscillation corresponds to the rate of relaxation of the persistence length of the molecule, at which point the material becomes completely elastic. This assumes that the magnitude of deformation is less than that required to rupture the material or break the polymer chains. As a result of the Rouse−Zimm modes, there is necessarily a distribution of relaxation times with the slowest being the zeroth mode and the fastest being the "*n*-th" mode for a chain consisting of *n* persistence length segments. The dimensions of wormlike chains are strongly influenced by the shape of the molecules. Wormlike polymer molecules have stiff chains, with longer persistence lengths than flexible molecules. Consequently, these stiff polymer chains have slower *n*-th mode relaxation times than flexible molecules.

In dilute solution in a good solvent, polymer molecules are separate isolated entities and all modes of response to stimuli are available over a range of frequencies from zeroth mode to *n*-th mode.[8] The "correlation length" in dilute solution is the length of the molecule that corresponds to the zeroth mode, that is, end-over-end tumbling of the entire molecule. Properties such as dilute solution viscosity are a manifestation of that correlation length. Above the critical entanglement concentration, the correlation length becomes the distance between entanglements and the rheological properties are a manifestation of this length and the kinetics of disentanglements.[9] As the polymer concentration increases, the distance between entanglements becomes progressively shorter. When the distance between entanglements becomes equal to the Kuhn length for the given polymer, the polymer segments cannot relax and the polymer behaves as an elastic solid. Pure rubbers, which are by definition polymers above their glass transition temperature, can still exhibit viscous flow because they have sufficient excluded volume with their bulk structure to allow relaxation of chain segments. Silicones demonstrate this to an extreme level. The Si−O−Si bond rotates more freely than a C−C bond, and silicones have higher excluded volume and weaker intermolecular interactions that typical hydrocarbon polymer. This explains why high-molecular-weight dimethicones exist as liquids, whereas corresponding hydrocarbon polymers are essentially solids under the same temperature and pressure conditions.

In summary, polymer solutions have some of the viscous flow characteristics of pure Newtonian liquids, but they also show some of the rebound characteristics of elastic solids. Polymer solutions are viscoelastic. This is especially true in the semidilute regime where the polymer molecules are entangled with each other. If the shear rate (or extension rate) is faster than the time required for disentanglement, the polymer molecules will be stretched. This stretching will disturb the equilibrium conformation of the polymer molecules and force them into shapes that are statistically less random than in the system at rest. This results in a decrease in conformational entropy (from the Boltzmann relationship $S = k \ln \Omega$, where $\Omega$ is the number of possible arrangements of the chain). When the shear stress ceases, the polymer molecules relax to their original shape and configuration relative to each other. This relaxation is observed as elastic recovery of some of the energy of deformation and, since the relaxation is driven by entropy, it is termed "entropy spring." Thickening is perceived when the rate of disentanglement is slower than the rate of deformation. The Deborah number describes the threshold for "thickening."

The characteristic that is used to rank the stiffness of semiflexible molecules is the molecular persistence length, which is half of the Kuhn length (see Chapter 2 for more details on persistence length). The persistence length is related to the hydrodynamic volume for polymer molecules.[10] The stiffer the molecule (longer persistence length), the larger the hydrodynamic volume of the molecule. This means that stiff molecules have lower critical overlap concentrations than flexible molecules of the same molecular mass. The values of persistence lengths of many inflexible wormlike molecules,[11,12], such as DNA and poly(alkyl isocyanates) have been determined by analyzing data for the mean square radii of gyration, intrinsic viscosities, sedimentation coefficients, and dielectric and viscoelastic relaxation times.[13−17] Stiff polymer molecules, due to their relatively larger hydrodynamic volume, have lower critical overlap and critical entanglement concentrations than flexible polymer molecules. Moreover, at any given concentration, stiff polymer molecules have fewer Kuhn lengths between entanglements than flexible polymer molecules. This makes soluble stiff polymers useful as thickeners.

### 13.1.1 Thermal Behavior of Polymer Gels

In addition to concentration dependence, the thermal behavior of polymer gels must be considered. Some gels are viscous solutions that maintain most of their viscosity upon heating. These are useful if formulation stability is being sought. Examples of polymers that provide such stable viscous gels are guar gum,[18] xanthan gum,[19] and Carbomer. There are two types of thermoreversible gels: those that "melt" upon heating, and those that transition from a solution to a gel upon heating. Gelatin,[20] pectin,[21,22] and carrageenan[23] produce thermoreversible gels that melt upon heating. Solutions of methylcellulose,[24] hydroxypropyl methylcellulose,[25] hydroxypropylcellulose,[26] and poloxamers[27] all gel upon reaching being heated beyond a certain temperature. Poly(*N*-isopropylacrylamide) solutions exhibit a lower critical solution temperature close to human body temperature.[28] Below this temperature poly(*N*-isopropylacrylamide) forms viscous liquid; in the vicinity of the LCST, the solution gels, and upon heating to higher temperatures, polyisopropylacrylamide separates from solution in the form of an insoluble plastic. Thermally induced gels occur usually only in the semidilute regime (that is, above the critical entanglement concentration). Calcium alginate gels are primarily elastic gels that are thermostable; they persist from 0°C to 100°C.[29]

Hydrophilic polymer powders are sensitive to humidity, and in humid atmospheres they will absorb fairly large amounts of water from the air.[30] This absorbed water must be accounted for in determining the amounts of polymer powder to be added in a given formulation. In extreme circumstances, the capillary forces due to sorbed water will turn the powder into a solid "brick." Therefore, it is essential to store hydrophilic polymer powders in humidity resistant packaging.

### 13.1.2 Practical Considerations

There is a persistent history of experimental and formulating/manufacturing errors caused by improper preparation of solutions of hydrophilic rheology modifiers. Many thickeners are applied as fine powders. When preparing solutions of water-soluble or water-swellable rheology modifiers it is important to ensure that the powder is disaggregated before it begins to swell and dissolve. If disaggregation is not achieved quickly, capillary pressure will drive water into the pores of powder aggregates, and wetting inside the capillary pores will initially drive the fundamental particles closer together. Thereafter, particles can swell into the pores of the aggregate to form gels. The gels act as a barrier to diffusion of water into the aggregates, which results in persistent "fisheyes" of gelled polymer and inhomogeneous solution. Efficient dispersion of hydrophilic polymer powders can be achieved by dispersing via specialized equipment such as eductors or triclover blenders. Alternatively, the powder can be dispersed in a hydrophobic liquid component of the formulation prior to being added to the aqueous phase. Ideally, the hydrophobic "coating" delays hydration of the powder until the powder particles are dispersed in the bulk aqueous liquid.

### 13.1.3 Cellulose and Starches

Cellulose and starches are polymers of glucose. In starch, the glucose units are connected by α-1,4 and α-1,6 units, and in cellulose the glucose units are connected by β-1,4 units. As a result, starch is a semicrystalline polymer and cellulose is a crystalline polymer. Starch exists as a linear form, named amylose, and a branched form, named amylopectin. When heated to high temperature in water under pressure, starch can be gelatinized. In this process, the intermolecular "crystalline" hydrogen bonds of starch are exchanged to make H-bonds with water. This irreversibly dissolves the starch granules in water. Different types of physical and/or chemical modifications can be applied to native starches to change or enhance their properties for specific cosmetic applications. Physical treatments mainly affect the granule structure, allowing the starch to become cold water dispersible for manufacturing ease. This reduces the amount of total energy required to formulate, as starches not modified in this manner would require an extended cook time at 80−100°C to become dispersible in water. Chemical treatments may be used to lower the molecular weight of the starch molecule and/or to add functional substituent groups, such as esters or ethers, to enhance solubility, stability, and aesthetic attributes.

#### *13.1.3.1 Cellulose*

Cellulose is a natural polymer consisting of D-glucose units joined through β(1→4)-glycosidic bonds. This structure confers a certain stiffness on the polymer molecular backbone.[31] Cellulosic thickeners consist of semiflexible molecules with large hydrodynamic diameters in the order of 10−30 nm.[32] As a result, cellulosic derivative reaches the entanglement threshold of the semidilute regime at extremely low concentrations as shown in Fig. 13.1.[33]

Water is not a good solvent for cellulose and amylose derivatives; this is shown by the fact that their expansion factor, $\alpha$, is only slightly larger than unity. Cellulose is insoluble in water. Cellulose derivatives in water show

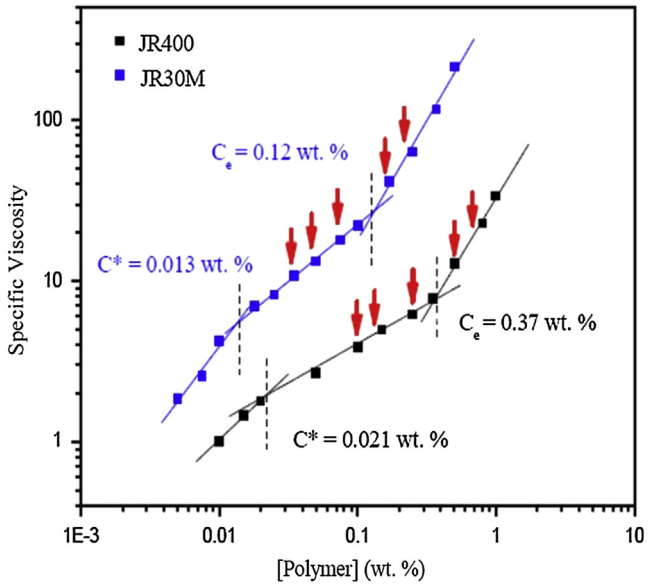



FIGURE 13.1 The dependence of specific viscosity on polymer concentration, showing the location of the critical overlap concentration (C*) and the critical entanglement concentration (Ce) for two cellulosic polymers.

negative values for the second virial coefficient. This means that, even although they are soluble in all proportions, these polymers become thermodynamically less soluble in water as their concentration increases. This could be due to the crystal structure that is formed by cellulose–cellulose intermolecular hydrogen bonding. In spite of the presence of -OH groups, cellulose forms crystals having nonhydrophilic surfaces.[34] Paradoxically, derivatization of cellulose with semihydrophobic substituents leads to increased water solubility because the substituents sterically hinder the intermolecular crystallization of the cellulose chains.

### *13.1.3.2 Cellulosic Rheology Modifiers*

In general, cellulosic thickeners are distinguished by: (1) molecular weight, (2) degree of substitution, and (3) molar substitution.

#### 13.1.3.2.1 The Degree of Substitution

Cellulose consists of glucose units joined end to end. Each glucose unit possesses three free hydroxyl groups. The degree of substitution reports the average number of hydroxyl groups per glucose unit that are substituted on the chain. For example, carboxymethylcellulose can have maximum degree of substitution of 3, which corresponds to complete substitution of all three hydroxyl units on every glucose unit in the cellulose chain. The degree of substitution of carboxymethyl cellulose is demonstrated by Fig. 13.2 in which each anhydroglucose unit has one of the three possible hydroxyl units substituted by a carboxymethyl group, to yield a carboxymethylcellulose with a degree of substitution of 1.

#### 13.1.3.2.2 Molar Substitution

When cellulose is substituted by ethoxylation by ring-opening ethylene oxide, the ethylene oxide can add to hydroxyl sites on the cellulose backbone or to already added ring-opened ethoxy groups. Thus, the molecule of hydroxyethylcellulose that results can have more than one ethoxy group substituted on any one of the original OH groups of

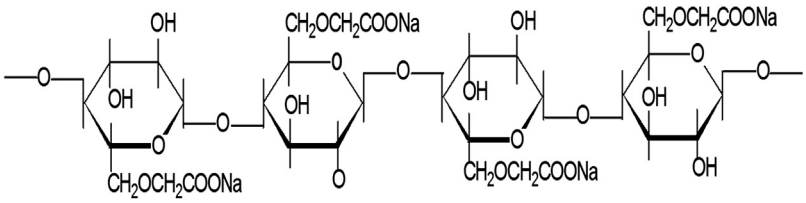



FIGURE 13.2 Sodium carboxymethylcellulose. The degree of substitution is the average number of substituted carboxymethyl groups per anhydroglucose ring. In the schematic structure above, the degree of substitution is 1.

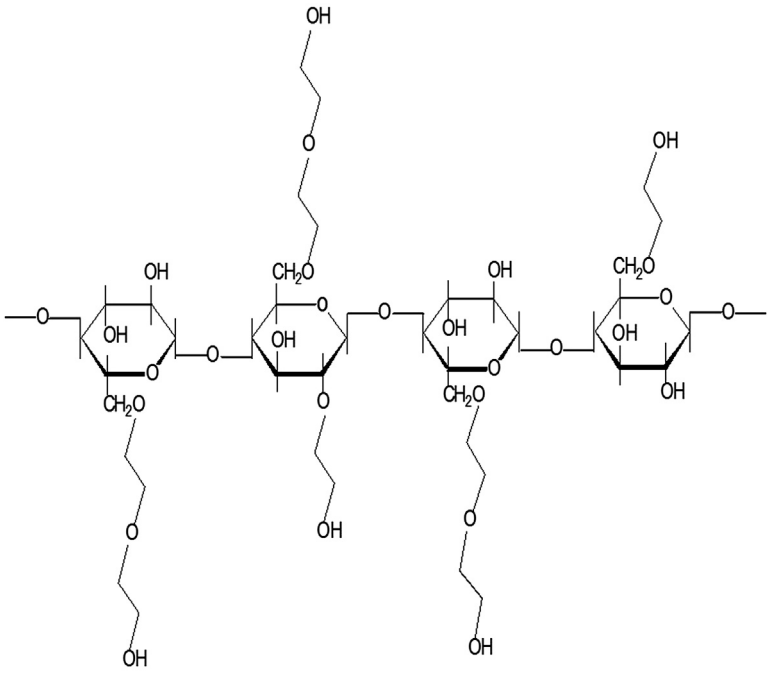


FIGURE 13.3 A schematic representation of the molecular structure of hydroxyethylcellulose. See text for a discussion of the degree of substitution and molar substitution of this schematic molecule.

the cellulose chain. Therefore, merely specifying the degree of substitution is not sufficient to describe the product.[35,36] One must also specify the molar substitution, which is the average number of ethylene oxide molecules that have reacted with each anhydroglucose unit. Thus as shown in Fig. 13.3, three anhydroglucose units are substituted at one position of the ring and one anhydroglucose unit is substituted at two positions. Therefore, the average degree of substitution could be calculated from five substituted positions on four rings to be $5/4 = 1.25$. The total number of ethoxyl groups on all four anhydroglucose rings is 8. Therefore, the molar substitution of this schematic molecule is $8/4 = 2$. There are optimal values of degree of substitution and molar substitution for water solubility determined by the balance of substituents to disrupt cellulose crystallinity and the relatively hydrophobicity of the substituents themselves.

The textural properties of hydroxyethylcellulose solutions can be measured by texture profile analysis.[37,38] Such measurements in vitro relate to the textural properties of formulations in vivo,[39] for example, ease of removal from the container, ease of application to the skin or other substrate, retention of the product to the site of application, and after-feel of the product. Tensile testing by texture profile analysis can measure the strength of adhesion of formulations to a substrate. However, tack is measured if the applied formulation undergoes cohesive rather than adhesive failure. Measurement of the compression required to spread a formulation over a fixed distance provides a measure of the spreadability. This measure, combined with steady-shear rheology and oscillatory-shear measurements give information on the "rub-in" characteristics of creams, lotions, and gels.[40] Hydroxyethylcellulose and carboxymethylcellulose solutions show an increase in storage modulus as the frequency of oscillating shear is increased. This results from an increased "difficulty" of disentanglement of the polymer chains. For sodium carboxymethylcellulose the ratio of viscous to elastic moduli (termed the "loss tangent" by rheologists) is independent of oscillation frequency, whereas hydroxyethylcellulose solutions become more elastic with increased shear. Such variation in response to shear frequency could cause differences in perceived responses between applications and between individual consumers. Beyond certain threshold values of concentration, the adhesive strength plateaus, reflecting a concentration limit for entanglement with polymers in other surfaces. This was reported for interaction with mucin when these polymers were used as mucoadhesives. The plateau in adhesive strength also correlates with the fact that below a threshold concentration, these polymers fail cohesively rather than adhesively under tension. For example, threshold values for cohesive failure have been reported as 5 weight percent for hydroxyethylcellulose and 12 weight percent for sodium carboxymethylcellulose.

Hydroxyethylcellulose is a nonionic thickener that is compatible with most ionic ingredients. It has low-foaming characteristics, good solution clarity, and good viscosity reproducibility if the time and extent of mixing is consistent from batch to batch. It should be noted that irreversible scission of hydroxyethylcellulose molecule will occur under excessive shear. Also, extreme pH values should be avoided because hydroxyethylcellulose is susceptible to acid and

base hydrolysis. Solutions of hydroxyethyl cellulose are shear thinning and thixotropic, and show "stringy" rheology. These characteristics derive from disentangling the entangled network, and the thixotropy is a consequence of the time that it takes for the polymers to recover their entangled configuration.

Hydroxyethylcellulose hydrates quickly at pH values above 7, and this can lead to the presence of fisheyes in the finished composition. Therefore, it is recommended that hydroxyethylcellulose solutions should be prepared at a pH of 7 or less to ensure proper dispersion prior to hydration. Different grades of hydroxyethylcellulose can be blended to achieve the desired product rheology.

#### *13.1.3.3 Hydroxypropylcellulose*

Hydroxypropylcellulose shares many characteristics of hydroxyethylcellulose. One difference is that hydroxypropylcellulose has a lower critical solution temperature (LCST) at relatively low temperatures (e.g., 40−45°C), and it is soluble in a wide range of organic solvents. These are a consequence of semihydrophobic propoxy substituent. The low solubility above the LCST is used to advantage in dispersing hydroxypropylcellulose powder. Good dispersion can be achieved in hot water and then solvation and homogeneous solutions can be realized by cooling with agitation until the temperature drops below the LCST. On the other hand, heating aids the preparation of solutions in organic solvents.

#### *13.1.3.4 Hydroxypropyl Methylcellulose*

Hydroxypropyl methylcellulose is another semihydrophobic substituted cellulose that is useful a silky-feel thickener and foam stabilizer for shampoos and body gels, and as a secondary thickener for creams and lotions.

### 13.1.4 The Galactomannans

The galactomannans (Fig. 13.4) are gums found in seeds and in the cell wall of some molds.[41] Structurally they are polysaccharides consisting of a mannose backbone with regularly spaced galactose side groups.

The galactomannans vary with respect to the frequency of galactose side groups as shown in Table 13.1:

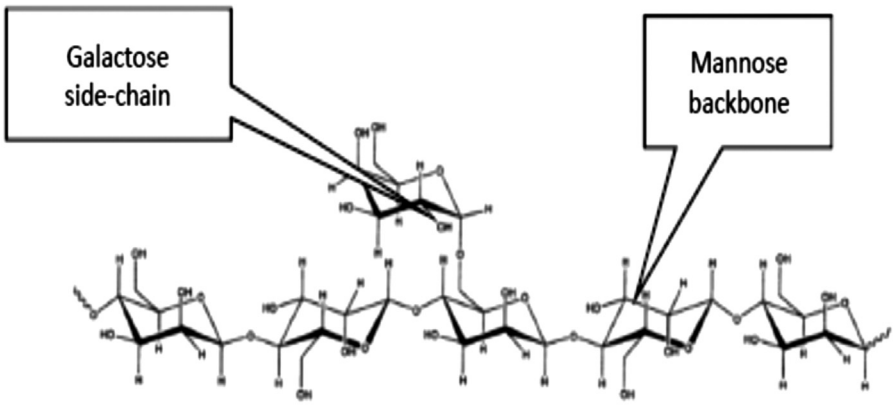



**FIGURE 13.4** A schematic molecular structure for galactomannan.

**TABLE 13.1** Galactomannan Substitution Levels

| | |
|---|---|
| Ivory nut mannan | No galactose |
| Japonica galactomannan | 1galactose/5.75 mannose units |
| Locust bean gum | 1 galactose/4 mannose units |
| Cassia gum | 1 galactose/4 mannose units |
| Tara gum | 1 galactose/3 mannose units |
| Guar gun | 1 galactose/2 mannose units |
| Fenugreek gum | 1 galactose/1 mannose unit |

In concert with the previous discussion on cellulose derivatives, the level of galactose substitution in galactomannans is important to the solubility characteristics of the gum. For example, ivory nut mannan is insoluble in water, whereas, fenugreek gum dissolves and adopts a simple random coil conformation in solution.[42]

### 13.1.5 Guar Gum

Guar is principally grown in Texas and Oklahoma in the United States, India, and Australia.[43] This gum is a nonionic hydrocolloid, which, as a result of more galactose branch points, is more soluble than locust bean gum. In the semidilute regime, guar gum, with two galactose units for every two mannose units, forms viscous solutions with long texture, as expected for an entangled network of stiff chains. Consistent with this mechanism of thickening, solutions of guar gum show strong shear thinning and thixotropy. In common with other galactomannans, guar gum shows viscosity synergy with xanthan gum. Guar is not self-gelling and is marginally affected by monovalent salts, but calcium can "cross-link" guar gum to a gel. Guar gum is not affected by ionic strength and is stable in the pH range 5–7. However, it will hydrolytically degrade at pH extremes and at raised temperatures. Guar gum is insoluble in most organic solvents. One interesting property of guar gum is its capability to retard ice crystal growth by slowing mass transfer across the solid/liquid interface. For this reason, formulations with guar gum often show good freeze–thaw stability, although guar is reported to be inferior to xanthan gum in this respect.[44]

Hydroxypropyl guar has excellent alcohol and salt tolerance, and its compatibility with surfactants makes it suitable for use in pearlescent shampoos and opaque hand and body lotions. Its shear-thinning characteristics that derive from its weak gel structure confer lubricating properties that are useful in applications such as shaving.[45] Hydroxypropyl guar is stable over a pH range of 4–8.

### 13.1.6 Locust Bean Gum

Locust bean gum (also called carob gum) is only partially soluble in cold water. The mannan sections of the polymer chain can bind together to form a crystalline region that is thermodynamically more stable than the solution state. Hence even when in solution at ambient temperature there is a tendency for the polymer chains to aggregate, and this aggregation results in a three-dimensional polymer network that forms a weak gel held together only at the aggregation domains. The advantage of a weak gel is that it does not show the long, stringy rheology of entangled networks and it flows smoothly when sheared.

Although locust bean gum forms viscous shear-thinning weak gels, it readily forms elastic gels by interaction with other hydrocolloids such as carrageenans. It has been suggested that for solutions of locust bean gum and carrageenan, the synergistic gelling originates from stabilization of the K-carrageenan network by the mannan chains of locust bean gum, which results in finer aggregate strands dispersed throughout the entangled network.[46] The synergy with other macromolecules, such as xanthan gum, is used to prevent gel syneresis on storage.[47]

### 13.1.7 Xanthan Gum

Xanthan gum (Fig. 13.5) is a branched polysaccharide produced by fermentation as an exopolysaccharide from the microorganism *Xanthomonas campestris*. It was discovered in the research laboratories of the US Department of Agriculture,[48] and it was thoroughly studied due to its propensity to supplement and improve upon the properties of available natural gums. Xanthan gum is an anionic polyelectrolyte with a β-(1→4)-D-glucopyranose glucan (as cellulose) backbone with side chains of -(3→1)-α-linked D-mannopyranose-(2→1)-β-D-glucuronic acid-(4→1)-β-D-mannopyranose on alternating residues. Each molecule consists of about 7000 pentamers and the gum is less polydisperse than most hydrocolloids. The polymer backbone is identical to cellulose, consisting of β-D, 1,4 anhydroglucose repeat units. This backbone is decorated with trisaccharide side chains attached to C-3 on alternating rings. The trisaccharide side chains consist of a D-glucuronic acid unit between two D-mannose units, and these align with the polymer backbone, thereby stiffening the chain.

The stiff chains are conformed into single, double, or triple helices.[49,50] Xanthan is soluble in water and confers high viscosities at low concentrations. The helical matrix imparts pseudoplasticity, suspending, and instant recovery. It is useful as a thickener, a dispersing agent, and an emulsion stabilizer that has been approved for food use. The viscosity of a xanthan solution depends upon the temperature conditions of dissolution, and the rate of cooling, since temperature affects the formation of the helical network structure. At low dissolution temperatures the conformation is ordered and at high dissolution temperatures the conformation becomes disordered.[51] The viscosity of xanthan solutions declines at low salt concentrations, due to diminished intermolecular ionic repulsion,[52] but above

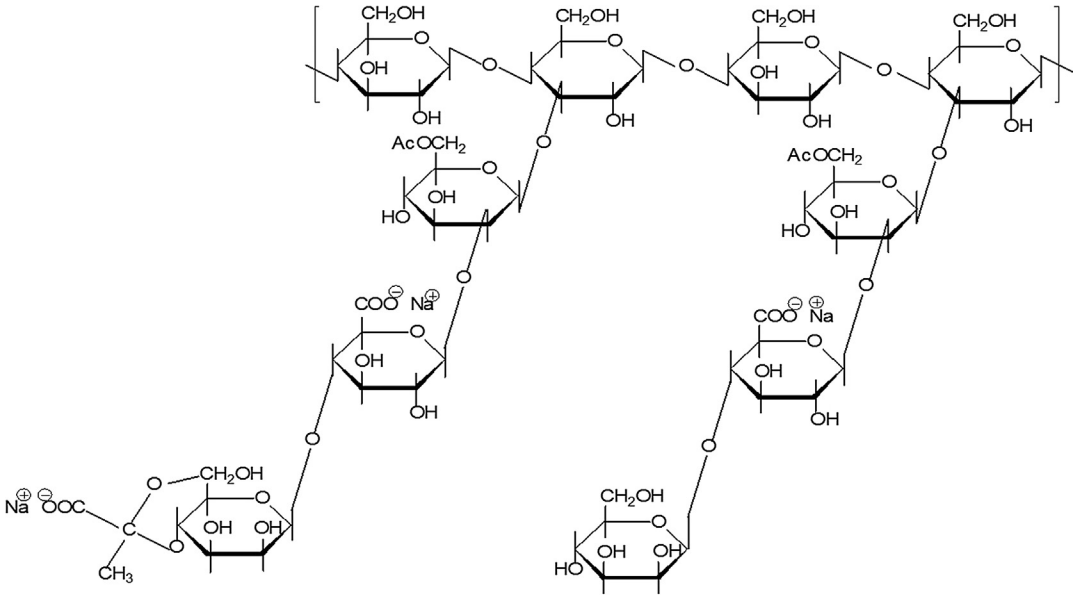


FIGURE 13.5 A schematic molecular structure for xanthan gum.

about 0.1% salt, the viscosity becomes independent of salt concentration.[53] As a consequence, xanthan gum is an especially useful rheology modifier for ion-containing solutions, especially for formulation that needs to be prepared over a large salt concentration range or in cases for which the salt concentration of ingredients shows batch-to-batch variation.

Xanthan gum delivers stable viscosities across the pH range 3–9. Xanthan also confers a yield stress that must be overcome for the system to begin to flow. Yield stress fluids are especially useful for the permanent suspension of particulate solids or emulsion droplets in aqueous compositions.

Gels can be formed by the synergistic interaction between xanthan gum and other polysaccharides, including galactomannans and carrageenans.

### 13.1.8 Pullulan

Pullulan is a polysaccharide polymer consisting of maltotriose units (three glucose units connected by α-1,4 glycosidic bonds) connected to each other by an α-1,6 glycosidic bond. Pullulan is produced from starch by the fungus *Aureobasidium pullulans*. Pullulan differs from most polysaccharides in that it is easily water soluble, as a result of the low degree of hydrogen bonding in its crystal form. An interesting application uses pullulan with up to 35% ethanol in water to provide naturally derived hair fixative agents with enhanced drying times; it was found that drying times decrease with an increase in alcohol.

### 13.1.9 Gellan Gum

Gellan gum is a water-soluble anionic polysaccharide produced by the bacterium *Sphingomonas elodea*.[54] Gellan gum consists of tetrasaccharide repeating units. The tetrasaccharide is made up of two β-1,4,D glucose units, one β-1,4,D-glucuronic acid unit, and one α-L.1,3-rhamnose unit. Gellan gum forms gels at very low concentrations, even as low as 0.1%. They are available in two types: low acyl, which forms hard, brittle gels; and high acyl, which forms soft, elastic gels that are not brittle. Gellan contributes a significant yield stress at low viscosity, which makes it useful for low viscosity suspensions. Gellan can be used at low levels in a wide variety of products that require gelling, texturizing, stabilizing, suspending, film-forming, and structuring.[55]

### 13.1.10 The Carrageenans

The word *carrageenan* is derived from the Irish word *carraigeen* meaning rock moss. In the form of Irish moss, carrageenan has been used as a thickener in foods and medicine for eons. Carrageenan is used primarily for its property of forming strong gels in the presence of certain salts and other gums. The carrageenans are extracted from

seaweed. Irish moss is the common term for the seaweed species *Chondrus crispus*. Present-day sources of carrageenan include *C. crispus* but go well beyond this species of seaweed.[56] Although there is essentially a continuous range of carrageenans according to degree of sulfation,[57] the carrageenans are classified as mu, nu, lambda, kappa, iota, theta, and xi forms according to the extent of sulfate substitution and structural considerations.[58–67] Lambda carrageen is the form that is soluble in 0.25M KCl, while the kappa and iota forms are insoluble in this salt solution.[68,69] Almost half of the sugar units in kappa carrageenan are 3,6-anhydro-D-galactose but lambda carrageenan contains little or none of this sugar.[70] Potassium ions induce gelling in mu, nu, kappa, and iota carrageenans, which typically have their 1,3 units either sulfated or unsulfated. Lambda, xi, and theta carrageenans have both their 1,3 and 1,4 units sulfated at C2 and they viscosify but do not gel. *C. crispus* is largely harvested in the Maritime Provinces of Canada with smaller quantities collected along the coasts of Maine and Massachusetts in the United States. The carrageenan from *C. crispus*, which comprises a mixture of kappa and lambda carrageenan, is useful for applications such as chocolate milk stabilization. *Gigartina acicularis* and *Gigartina pistillata* occur and are harvested together along the coasts of southern France, Spain, Portugal, and Morocco. The latter two species yield a nongelling, predominantly lambda- or xi-type carrageenan. *Eucheuma cottonii* and *Eucheuma spinosum* are harvested in Indonesia and the Philippines. *E. cottonii* contains largely κ carrageenan and μ carrageenan, which may be converted to kappa carrageenan by alkali treatment. *Eucheuma spinosum* contains a similarly high level of ι carrageenan with some ν carrageenan precursor.

*Furcellaria fastigiata* yields furcellaran ("Danish agar"), *F. fastigiata* is found along many coasts of the North Atlantic but is harvested only in Denmark and the Maritime Provinces of Canada. *Furcellaran* contains a strong gelling type carrageenan, which is very much like kappa carrageenan. Other seaweed types, such as *C. crispus* and *Gigartina* types contain not only a mix of κ and λ type carrageenans but also a type of carrageenan polymer that is essentially a block copolymer of different carrageenan types.

Carrageenans are linear polysaccharides consisting of repeating disaccharide units. The disaccharides are α-D-galactopyranose-linked 1,3 and β-D-galactopyranose residues linked through positions 1,4. Carrageenans and agar are similar, except that carrageenans are in the D-form, whereas agars are in the L-form. Ordered substitution of sulfate hemi-ester groups on the polysaccharide backbone confers distinct solubility properties and the ability to interact specifically with certain metal ions.

Carrageenans complex with proteins, especially below the isoelectric point of the protein. Under these conditions the protein is net positively charged and the carrageenan is negatively charged.[71] At high temperatures carrageenan molecules adopt a random coil conformation. Upon cooling, however, the molecules form a helical conformation.[58] The helices aggregate into domains under the influence of certain ions, particularly calcium and potassium ions, and this causes the solution to gel.[23] However, lambda carrageenan does not gel, even in the presence of calcium ions.

Carrageenans are used as rheology modifiers and stabilizers in emulsions, lotions, and pigment dispersions, and as a binder in toothpaste. They are especially useful as gelling agents in hot climates due to their relatively high gel melting temperature.[72,73]

Carrageenans show synergy in thickening with polygalactomannans, such as guar gum and locust bean gum.[74] Similar synergies are found between galactomannans and bacterial exopolysaccharides, such as xanthan gum.[75]

### 13.1.11 Alginates

Alginates (Fig. 13.6) are hydrophilic biopolymers that form heat-stable gels that can develop at room or body temperatures. The alginates are a family of linear blocky copolymers in which the blocks comprise either β, 1-4-D-mannuronic acid (M) or its epimer α-L-guluronic acid (G) units.

Alginate is the structural polymer in marine brown algae such as *Laminaria hyperborea*, *Macrocystis pyrifera*, *Lessonia nigrescens*, and *Ascophyllum nodosum*. Alginic acids extracted from different seaweeds are differentiated by the

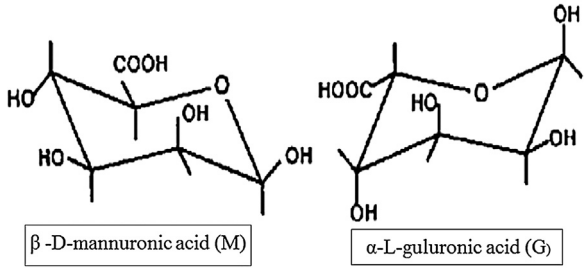



**FIGURE 13.6** Alginates are blocky copolymers of the epimers mannuronic acid and guluronic acid.

relative amount and sequential arrangement of these epimers along the polymer chain.[76] Alginate is also produced by fermentation using certain bacteria such as *Pseudomonas aeruginosa*, *Azotobacter vinelandii*, and *Pseudomonas fluorescens*.[77] Alginate is usually supplied as the salt form sodium alginate.

Alginate gels are produced when a divalent cation interacts with the carboxylate groups on the guluronate units on adjacent chains. The calcium guluronate blocks form junction zones that multiply cross-link the polymers and restrict their relative motion to form an elastic network. Originally the junction zone was assigned a 2/1 zig-zag conformation termed the "egg-box" structure.[78,79] This structure may be accurate for rapidly formed gels but it is now postulated that the junction zones have equilibrium triple helix structure.[80] The junction zones are connected by flexible mannuronic acid chains that imbibe large quantities of water. The resulting structure is a rigid, nonmelting hydrogel that is useful for diffusion-controlled release of ingredients encapsulated within the gel.

The most common method of making alginate gels is the dialysis/diffusion method where the alginate solution is added to a solution of calcium ions that diffuse into the alginate causing it to gel. Rapid gelling can result in an inconsistent product, and for this reason techniques have been adopted to slow the gelation process. The most common technique is to chelate the calcium ions to slow the exchange from solution to alginate. An interesting approach that claims "self-gelling" alginates comprises a two-compartment kit in which one compartment contains a sodium alginate solution and the other contains an alginate gel with an excess of divalent ions. Upon mixing, the ions slowly diffuse into the alginate solution to form a consistent gel.[81]

### 13.1.12 Pectin

Pectin is a complex polysaccharide consisting mainly of methoxy esterified α, D-1, 4-galacturonic acid units. Pectins are categorized according to their methoxy content and whether they form gels quickly or slowly. Approximately, pectins can be categorized as high methoxy pectins (>50% esterified) and low methoxy pectins (<50% esterified). The low methoxy pectins can also be amidated.

High methoxy pectins form gels at low pH and in the presence of sugar. They are classified as rapid set, medium set, or slow set and are used in acidified milk drinks (pH <4.6) to stabilize the proteins. Low methoxy pectins form gels that are partly shear reversible.

### 13.1.13 Larch Galactoarabinan

Galactoarabinan (also called arabinogalactan) was first described by Trimble in 1898 in a report of the examination of the excrescence from the Western larch, *Larix occidentalis*.[82] In 1916, Schorger and Smith identified D-galactose in the hydrolysate of the gum. Subsequent researchers identified the water-soluble gum in larch as an arabinogalactan having a ratio of one L-arabinose to six D-galactose units.

The plant genus *Larix* refers generally to any of the numerous conifers in the family of Pinaceae that have deciduous needlelike leaves. Galactoarabinan is preferentially sourced from four species of larch tree:

- *Larix occidentalis* (Western Larch) found in Montana, Idaho, Washington, and Oregon
- *Larix laricina* (Eastern Larch)
- *Larix decidua* (European Larch)
- *Larix Siberia* (Russian Larch)

Western larch contains the largest amounts of galactoarabinan, ranging from 8% to 25% on a dry weight basis. The gum is aqueously extracted from sawmill residues and butt logs, which are often too deformed or damaged to be useful as lumber. Butt logs are the zone of the tree that is richest in galactoarabinan gum. Repeated precipitation in ethanol serves to purify the galactoarabinan. The gum is decolorized by the use of ion-exchange resin.

In the 1940s, two constituents of galactoarabinan were reported to have molecular weights of 16,000 and 100,000 respectively.[82]

"Ultrarefined arabinogalactan" refers to arabinogalactan isolated from a plant source such as trees of the genus *Larix*, with a purity greater than 95%. In a preferred embodiment, the molecular weight of the ultrarefined arabinogalactan is between 10,000 and 30,000 Da (by size exclusion-chromatography with pullulan reference).[83]

Galactoarabinan has been used as a rheology modifier that confers useful yield stresses at low viscosities. Market use studies prior to 1959 indicated that galactoarabinan conferred lower viscosities but better dispersing properties than gum arabic.[84]

Galactoarabinan is included with xanthan gum and other polysaccharides as a rheology modifier for concentrated emulsions that can be diluted into ready-to-use lotions for application to wet wipes.[85–87] The desired rheology

profile in this case is one that exhibits low initial viscosity and high yield stress. Galactoarabinan is a rheology modifier for the delivery system for water-soluble/water dispersible actives.[88] Arabinogalactans are listed as such in the use of acrylamide/quaternary dimethylaminoethylacrylate copolymers for use in hair conditioning.[89]

Galactoarabinan also serves as a humectant and is listed as a suitable humectant in patents addressed to skin treatment[90]; sunscreen safety and efficacy enhancement[91]; ultraviolet (UV) protecting composition containing polyaminoamide containing 1,3-diimine groups,[92] or water-soluble cationic monomers and polymers[93]; skin care composition containing an anionic polymer[94]; personal care compositions containing *N*,*N* dialkylammonium halide/*N*-vinylpyrrolidine polymer,[95]; in combination with a hydrophobically modified polymer for use with personal care compositions[96]; hair loss prevention by natural amino acid and peptide complexes[97]; skin and hair restoration by natural amino acid peptide complexes[98]; chiral complexes of ascorbic acid with natural antioxidant and antiinflammatory ketones including aloe, citrus, ginger, and mango for skin and hair care[99]; multifunction "crown complexes" from amino acids and peptides for skin and hair restoration[100]; hydroxy acid complexes for antiaging and skin renovation[101]; ascorbic acid—natural sugar lactone esters for comprehensive skin and scalp care[102]; protection of skin from UV and peroxide,[103] topical delivery system for phytosterols[104]; topical delivery system for antiaging and skin whitening agents[105]; artemisinin derivatives with natural amino acids, peptides, and amino sugars for the treatment of infection and topical condition in mammals[106]; artemisinin derivatives with natural amino acids, peptides, and amino sugars for skin imperfections and infection in mammals[107]; prevention of cellular senescence in mammals by natural peptide complexes[108–110]; osmoprotective complexes for prevention of intracellular dehydration in mammals[111]; osmoprotective complexes for prevention of mitochondrial free radical damage-related skin aging[112]; compositions and methods for treating, preventing, and/or ameliorating cancers, the onset of cancers or the symptoms of cancers.[113]

Acetyl, propyl, and bezoyl esters and methyl ether derivatives of galactoarabinan have been reported.[84] Lipidated galactoarabinan comprises galactoarabinan modified by the attachment of long-chain alkyl groups (e.g., decanoate, stearate, oleate) by means of ether- or ester-linking groups. The lipidated galactoarabinan is water soluble and is capable of solubilizing hydrophobic drugs. It has been disclosed as an adjuvant for parenteral formulations.[83]

### 13.1.14 Particulate Thickeners

Systems of colloidal particles can be useful rheology modifiers if they can form network structures or volume-filling structures within a liquid. If the structure breaks down under shear, then the system shows thixotropy and shear thinning characteristics. Dispersions of fumed silica and smectite clays show this behavior. Alternatively, if the structure builds under shear the system shows rheopexy or shear thickening. In extreme cases, such structure building can lead to a jamming fluid that becomes solid under high shear. For example, a concentrated dispersion of corn starch is liquid under conditions of low shear, but becomes a solid under high rates of shear.[114] Dispersions of particulates can also show "avalanche" behavior, in which small perturbations are recovered by the structure, but above a critical level of perturbation, the structure fails catastrophically.

Yield stress fluids are desirable for the homogeneous suspension of particulate dispersions and emulsions. Yield stress fluids are characterized by a solid-like to liquid-like transition when the applied stress exceeds a yield stress. Examples are creams, cosmetic gels, and structured shampoos. Yield stress fluids can be categorized at two extremes: (1) simple yield stress materials,[115] such as foams, emulsions, and Carbomer microgels; and (2) thixotropic yield stress materials,[116] which are avalanche fluids like clay dispersions. Simple yield stress materials have a finite critical shear rate and instantaneous recovery after shear.[117,118] Thixotropic yield stress materials show homogeneous flow at vanishingly small shear rates under controlled stress and relatively long recovery times that correspond to the rebuilding of fluid structure. Yield stress materials are described by the ideal Herschel—Bulkley model,[119] which is depicted graphically in Fig. 13.7.

Measurement of the tiny yield stresses exhibited by flowable consumer products is not trivial and is made more difficult by the need to account for slip at the wall of the rheometer.[120]

Avalanche fluids often show a bifurcation in their rheological behavior; applied stresses below a critical stress actually help to build a stronger structure and the viscoelastic moduli increase with time under stress. However, applied stresses above the critical value cause catastrophic loss of structure and simultaneous dramatic decreases in the viscoelastic moduli of the system. Pseudo-phase diagrams can be constructed for particulate dispersions. This is exemplified for the colloidal clay laponite, which does not gel above a critical temperature (akin to a melting temperature) because Brownian motion prevents self-assembly. Below the critical temperature, gels form at high particle concentrations and phase separation occurs by interparticle attraction at lower concentrations below a

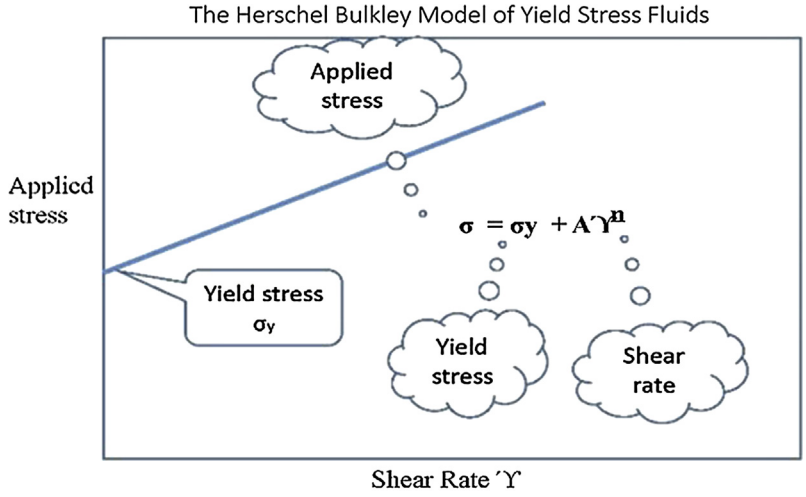



FIGURE 13.7 A graphical representation of the Herschel-Bulkely model for yield stress fluids.

critical percolation threshold.[121] Binary pseudo-phase diagrams can be constructed to map the rheophysical behavior of suspensions and pastes.[122] At low rates of shear, for slightly interacting particles, Brownian motion dominates and the system behaves as a low viscosity liquid. Increase in particle–particle interaction results in systems that are soft gels and finally hard suspensions. Above the yield stress, hydrodynamic effects dominate and the systems flow. An interesting example of the effect of interparticle interaction is shown in the stimuli-responsive thermogelling fluid that can be formed by combining Laponite with poloxamer. Aqueous poloxamer solutions display a lower critical solution temperature (LCST) at accessible temperatures. Separation of poloxamer at its LCST induces self-assembly of a percolating network of Laponite particles and causes the system to gel as the temperature is raised above the LCST.[123]

#### *13.1.14.1 Carbomer*

Carbomers, are a class of cross-linked acrylic acid polymers that function in aqueous formulations to build viscosity, form gels, stabilize emulsions, and suspend particles. When properly dispersed in aqueous media, the Carbomers exist as packed arrays of swollen microgels, which have many of the characteristics of particulate thickeners, e.g., yield stress and avalanche flow. The cross-linkers used for Carbomers are typically allyl ethers of polyalcohols,[124,125] such as tetraallyl pentaerythritol (TAPE) and hexaallyl sucrose. The National Formulary (NF) lists traditional Carbomers individually according to their specific chemistry and properties, e.g., solution viscosity, using numbers associated with the trade names of early Carbomers, e.g., Carbomer 934, 940, and 941. These polymers were made by precipitation polymerization in benzene as solvent.[126,127] Modern Carbomers are synthesized using benzene-free processes.[128–137] For these modern Carbomers, the National Formulary uses the terms Carbomer Homopolymer, Carbomer Copolymer, and Carbomer Interpolymer to describe the various grades of Carbomers employed as excipients in pharmaceuticals and OTC drug formulations. In the European Pharmacopeia the term Carbomer is used across the entire range of grades, and in the Japanese Pharmaceutical Excipient monographs, the name Carboxyvinyl Polymer is used. The INCI Dictionary reserves the name Carbomer for cross-linked homopolymers of acrylic acid, and it names cross-linked copolymers of acrylic acid with other comonomers as acrylate crosspolymers, e.g., Acrylates/C10-C30 Alkyl Acrylate Crosspolymer.

Carbomer molecules lie at the top end of molecular masses for polymers. The molecular masses of Carbomers have been estimated to be on the order of $10^8$–$10^9$ g/mol.[128] Since the Carbomers are cross-linked, they are swellable rather than being truly water soluble. This distinction is crucial to the rheological properties that Carbomers confer on the systems that they thicken. Unlike uncross-linked poly(acrylic acid), which dissolves to form solutions of polymer coils that overlap and entangle above the relevant critical concentrations, Carbomers disperse in water and swell upon neutralization to form dispersions of swollen microgels that pack together to fill the available space with packed microscopic "sponges" with interstitial spaces that are essentially free solvent.[138]

Carbomers are typically supplied as fluffy, white, hydroscopic powders that may have a slight "acetic acid" odor. A variety of Carbomers are available commercially, differing principally by the type of process solvent used, the type and level of cross-linker employed, and the addition of optional additives to improve wetting and

dispersibility.[139–142] Carbomers are considered to be nontoxic and exhibit little or no irritation potential to skin and eyes at the concentrations employed in cosmetics and personal care products.[143,144]

Carbomers are readily dispersible in water and in mixtures of polar organic solvents with water, such as 70% w/w ethanol-water solution. Dispersions of Carbomer powder are hazy, have nominal increase in viscosity, and have pH values of about 2.5–3.5. Upon neutralization of the carboxylic acid groups with a base such as sodium hydroxide, triethanolamine, or 2-aminomethylpropylamine, the Carbomer molecules become ionized and swell to several hundred or even more than a thousand times their original volumes due to electrostatic repulsions between the negatively charged carboxylate groups that stiffen the chains between cross-links,[145,146] or osmotic swelling due to a Donnan equilibrium.[147] The resulting microgel dispersions are crystal-clear flowable with high Brookfield viscosities (10,000–100,000 mPa s are not unusual at Carbomer concentrations below 1%) and high yield values. These yield values enable long-term stable suspension of solid, liquid, and even gas particulates. Yield value is the resistance of a fluid to initial flow when a stress is applied.[148,149] At rest, the closely packed network of Carbomer microgels behaves as an elastic solid that resists deformation and traps particulates as stationary objects in the gel. The network begins to flow only when a critical level of shear stress, i.e., the yield stress, is applied, and a critical level of deformation is reached, at which point the microgels can pass each other, resulting in fluid flow.[149,150] Carbomer-thickened systems exhibit viscoplastic (avalanche) flow when the critical level of deformation is surpassed.[151,152] When heterogeneous phases (e.g., emulsion droplets, pigments, pearlizers, opacifiers, air bubbles, silica abrasives, etc.) are dispersed in Carbomer-thickened formulations, the microgel network entraps and stabilizes them against creaming and/or sedimentation while the fluid is at rest, i.e., below the yield stress.[148] The combination of yield stress and viscoplastic flow provides storage stability and facilitates product dispensing and application. These properties make Carbomers useful rheology modifiers for creams and lotions, hair styling gels, and toothpastes.

Certain precautions must be observed when using Carbomers and most polyelectrolyte rheology modifiers. The thickening performance is restricted to the pH range of about 5–9. Carbomer-thickened systems are susceptible to loss of viscosity upon addition of salt ions to the system. The loss of viscosity results from a salt-induced shift in the Donnan equilibrium between the polyelectrolyte and its counterions that causes contraction of the electrical double layer that leads to deswelling of the microgels. The effect of ions can manifest itself in unanticipated ways. For example, Carbomers must be neutralized with base to cause the microgels to swell. If too much base is added and then the acid added to back-titrate to the desired pH, the excess ions produced will cause deswelling of the microgels and a loss in viscosity and yield value. Multivalent ions (e.g., $Ca^{2+}$, $Mg^{2+}$, etc.), even at low concentrations, will condense on the polyelectrolyte causing collapse of the microgels.[153]

The inherent sensitivity to salt of cross-linked polyelectrolyte thickeners, such as Carbomers, can be used to advantage in Carbomer delivery systems that collapse upon application to the salt on the surface of skin, to effectively deliver benefit agents. During the 1990s hydrophobically modified versions of Carbomers (Acrylates/C10-30 Alkyl Acrylate Crosspolymer) were introduced with both emulsifying and rheology-modifying properties.[154–156] These polymeric emulsifiers offered a route to "surfactant-free" emulsions with triggered oil release upon application to the skin. These new emulsifiers also overcame the tendency of conventionally emulsified products to re-emulsify after the emulsion broke. This led to products such as sports sunscreen that resisted sweat. Now, (meth) acrylic acid/alkyl(meth)acrylate copolymers, cross-linked with allyl ethers of pentaerythritol, have been disclosed as thickening systems that maintain aqueous solution viscosity even in the presence of electrolyte.[157]

### 13.1.15 Acryloyldimethyltaurate Polymeric Rheology Modifiers

Polymeric thickeners based on acryloyldimethytaurine (INCI Acryloyldimethyltaurate) and its salts were introduced into the market in the 1990s,[158] and they were asserted to offer better thickening efficiencies than conventional Carbomers in acid and salt-containing compositions. These polymeric thickeners are cross-linked and it is alleged that triallylamine cross-linkers resist acid hydrolysis better than dimethylacrylamide cross-linkers.[159] It has been reported that, in finished formulations, the concentration of residual acrylamide monomer from such acrylamide copolymers can rise during storage. This problem was addressed by an improved inverse emulsion polymerization process designed to produce acrylamide/acryloyldimethyltaurate copolymers that maintained acrylamide concentrations below 2 ppm upon storage of the final product.[160]

Thickening at neutral pH is well understood and achievable by the use of carboxylate-type thickeners. However, thickening of acid systems is desired. Copolymers obtained from 2-acrylamido-2-methylpropanesulfonic acid or its salt, dialkylacrylide, and cross-linking monomers provide thickening at acid pH ranges with limited or no stickiness. Similarly, copolymers of 2-acrylamido-2-methylpropanesulphonic acid (also known as *N*-acryloyl taurate) and acrylic acid are useful because, unlike conventional acrylic acid thickeners, they can increase the viscosity of

low-pH compositions and they resist significant viscosity loss in the presence of interfering ions. For example, they can thicken compositions containing the UV-A sunscreen1,4-benzene[di(3-methylidene-10-camphorsulfonic)]acid. Acryloyl taurate/Vinyl pyrrolidone copolymer is an efficient thickener and stabilizer for emulsion compositions containing alpha- and beta-hydroxyacids.[161,162] A measurable yield stress with desirable shear thinning characteristics can be achieved with such polymers if the molecular weight is higher than 6,000,000 and if the polymers contain greater than 20% 2-acrylamido-2-methylpropanesulphonate. However, copolymers of 2-acrylamido-2-methylpropanesulphonic acid and acrylic acid exhibit a sticky feel upon drying. This stickiness can be alleviated by cross-linking copolymers of 2-acrylamido-2-methylpropanesulphonic acid and hydroxyethylacrylamide.[163] The sticky feel can also be ameliorated by copolymerizing acrylamidomethylpropane sulfonate with hydroxyethyl methacrylate and an appropriate cross-linker.[164]

Comb copolymers of *N*-acryloyl taurate with commercially available macromonomers also exhibit good thickening, emulsifying properties, and clarity.[165,166]

### 13.1.16 Associative Thickeners

The term "associative" thickener is defined as water-soluble or water-swellable polymer that has chemically attached hydrophobic groups that are capable of hydrophobic associations similar to those of conventional surfactants. The most usually encountered attached "hydrophobes" are alkyl or aralkyl groups containing from about four to about 30 carbon atoms. It is common for these hydrophobes to be linked to the chain by means of polyoxyethylene spacer groups. Commercially available associative thickeners are usually classified as one of three types:

1. Naturally derived nonionic thickeners such as hydrophobically modified hydroxyethyl cellulose (HMHEC). Water-soluble cellulose derivatives are modified with hydrophobic groups usually by functionalizing some portion of the free hydroxyl groups in the cellulose polymer. An example of an HMHEC is cetyl hydroxyethylcellulose.
2. Synthetically derived nonionic thickeners such as hydrophobically modified ethoxylated urethanes (HEUR) and hydrophobically modified aminoplast technology (HEAT) copolymers.[167] Generally, these compounds are prepared by joining bis-hydroxyl polyethers with isocyanates or aminoplast couplers. Commonly, the hydrophilic polyether polyol adduct is a polyalkylene glycol such as polyethylene glycol, polypropylene glycol, or polybutylene glycol, having a molecular weight in the range of 200 to about 20,000 Da. Alkyl isocyanates or aminoplasts are used to attach hydrophobic moieties to the hydrophilic chains. The polymer may be blocky,[168] comb-like,[169] or star-like.
3. Synthetically derived anionic thickeners such as hydrophobically modified alkali-swellable emulsion polymers (HASE). HASE polymers are prepared as emulsion copolymers.[170] The acrylic carboxylate emulsion polymers are water-insoluble colloidal dispersions that are provided in the form of emulsion polymers at low pH and become soluble or swellable in water and confer thickening when the pH is adjusted above about 6. A typical HASE thickener would be a *ter*polymer of methacrylic acid, an acrylate such as ethyl acrylate, and a (meth)acrylic ester of an alkoxylated long-chain (C8-C30) alcohol, and sometimes a small quantity of a cross-linking agent.

These are high-molecular-weight polymers, having molecular weights in the range 50,000 to 500,000 Da. Typical HASE thickeners are those described by the INCI names Acrylates copolymer, Acrylates/Steareth-20-Methacrylate copolymer or Acrylates/Beheneth-25 − Methacrylate copolymer, Polyacrylate-X or Acrylates Crosspolymer-X, where X is a definite number.[171] For example, the Acrylates/Beheneth-25 − Methacrylate copolymer is a random copolymer of alkyl (probably ethyl) acrylate, acrylic acid, methacrylic acid, and the methacrylate ester of behenyl polyethoxylate, with an average ethylene oxide degree of polymerization of 25. Hydrophobic association between the polyelectrolyte chains results in the formation of an intermolecular network that significantly enhances the viscosity of the system.

HASE thickeners do display a number of attributes that make them appropriate for rheology modification of some personal care products:

- They are available in a liquid form, at about 20% solids. They are easily cold processed in comparison with powder products that require special dispersion techniques to avoid clumping or the formation of "fisheyes" in the finished formulation.
- They show some electrolyte tolerance.[172]
- They interact synergistically with surfactants and with hydrophobic particles to enhance the viscosity and stability of liquid products.

- They confer yield stress and shear thin above the yield stress for ease of dispensing and application. That is, they display Ellis-type rheology. Consequently, they can stably suspend particles and liquid droplets in aqueous-based formulations.
- They are usually effective in the pH range 5.5–9.
- Acrylates/Beneneth-25-Methacrylate is one of only a few copolymers that is capable of adequately thickening peroxide formulations for application in consumer products.
- Unlike the natural thickeners, these associative thickeners are resistant to enzymatic or microbiological degradation.

Careful formulation of associative thickeners with surfactants can provide enhancement of the rheology of aqueous detergent systems.[173–179] For nonionic surfactants, enhanced thickening is usually observed only for relatively hydrophobic surfactants. The thickening efficiency peaks at the surfactant critical micelle concentration (CMC) but is also useful in compositions with wormlike micelles if the ratio of polymer to micelles is appropriate. Thickening is lost if there are many more micelles than polymer molecules. Depletion-type separation into a surfactant-rich phase and a polymer-rich phase may occur at high surfactant and polymer loadings. Depletion phase separation of this type is driven by osmotic competition between the polymer and surfactants for the available water in a system in which the large micelles and polymer molecules contribute little to the configurational entropy of mixing.

The product types that rely on associative thickener polymer/surfactant interaction for synergistic thickening include (1) hair conditioners in which the quaternary ammonium salt surfactants are compatible with the associative thickener; (2) dandruff shampoos, astringents, and sunscreens containing zinc compounds (such as zinc pyrithione, zinc phenol, and zinc oxide, respectively) as active ingredient and mixed surfactant/associative thickener to maintain the insoluble zinc pyridine thiol −*N*- oxide particles in homogeneous suspension[180]; (3) shampoos with high ionic content from ionic surfactants and added salts; (4) facial makeup emulsions, especially pigmented emulsions containing sunscreens; (5) hand creams and hand lotions to maintain emulsion homogeneity and to provide appropriate rheology for the desired feel upon application; and (6) acidic personal care products such as alpha hydroxy acids containing cationic surfactants, mild organic acids (such as lactic acid, citric acid, glycolic acid, and fruit acids).

For HASE thickeners it has been taught that the particular structure of the polymeric backbone that generates the water solubility is not critical to the performance of the polymer in the thickening operation other than providing hydrophilic quality to the molecule. What is critical is the placement of the complex hydrophobic groups in the polymer chain that confer enhanced thickening by hydrophobic association in the aqueous system.[181] These hydrophobic groups associations are dynamic, molecular, hydrophobic associations that occur in aqueous solution. The duration of time that an individual hydrophobic association exists is related to (1) the chemical potential of the hydrophobe in its associated state compared to its molecular isolation in the aqueous environment and (2) steric factors. The chemical potential of the hydrophobe, $\Delta\mu$, can be roughly estimated by the equation[182]

$$\Delta\mu = 2RT - \frac{V_s + V_p}{2}(\delta_s - \delta_p)^2 x^2$$

where, R is the universal gas constant; T is the temperature in degrees Kelvin; $V_s$ and $V_p$ are the molar volumes of the solvent (water) and hydrophobe, respectively; $\delta_s$ and $\delta_p$ are the solubility parameters of the solvent (water) and hydrophobe, respectively; and x is the volume fraction concentration of hydrophobe present. The more negative the value of $\Delta\mu$, the stronger the propensity to form and maintain hydrophobic associations. The molar volumes are a linear function of alkyl chain length. Thus, strong hydrophobic associations are possible where there is a large disparity between the molar volumes of the solvent (water) and the hydrophobe as well as a large difference between the solubility parameters. When the chemical potential is zero or positive, aggregation by hydrophobic association is not expected. The number of hydrophobic groups required to provide optimum thickening efficiency can be decreased by either increasing the molar volume of the hydrophobe or by reducing its contribution to the solubility parameter. For the steady shear responses of the various n-alkyl HASE polymers at a polymer concentration of 10 g/L it is found that there is a progressive increase in viscosity building as the size of the hydrophobe is increased. There are no major qualitative differences with varying hydrophobe size, except that with longer n-alkyl chains, the magnitude of the storage modulus G′ begins to exceed that of the loss modulus G″. Each of the polymers shows a power law relationship of the form $G' \sim c^n$, with the power law exponent "n" increasing with hydrophobe size.[183]

The hydrophobicity of the macromonomer strongly influences the diffusion coefficient of the network cluster. With increasing carbon number on the hydrophobic macromonomer, the diffusion coefficient of the cluster decreases and the hydrodynamic correlation length increases due to the reduction in the number of hydrophobic junctions

inside the cluster.[184] Large, complex hydrophobic groups are recommended to achieve the highest performance in associative thickening.[185,186] There is also an optimum length for the hydrophilic spacing group,[187] which is commonly polyoxyethylene.

There are three concentration regimes that can be explained by different modes of hydrophobic association.[188] In the most dilute regime, the polymer chains are isolated and the hydrophobes interact intramolecularly. There is an intermediate regime, in which the steady shear viscosity and the elastic modulus increase dramatically with polymer concentration. This increase is attributed to the polymer chains becoming overlapped and the intramolecular interactions becoming substituted for intermolecular interactions with increasing polymer concentration. In the third regime, the hydrophobes are engaged in intermolecular interaction and a weaker dependence of viscosity with polymer concentration is observed. It is also noted that there is an optimum level of macromonomer substitution for the highest viscosity. In this case that level is about 1 mol % of macromonomers.

The use of HASE polymers is limited in aqueous formulations because they have little thickening ability at less than 1% and high concentrations are not economically desirable, and high viscous HASE polymers are difficult to handle during manufacturing. Consequently, additional rheological modifiers are sometimes used to offset these disadvantages of HASE copolymers. For example, HASE properties have been enhanced by the following: adding surfactants to the composition; using macromonomer-derived associative polymers as cothickeners; adding a mixture of multiphobe and monophobe compounds; or suppressing the viscosity of HASE polymers by complexation of the hydrophobic moieties of the polymer with cyclodextrin. It has also been shown that mixtures of certain cationic polysaccharides and anionic HASE polymers can give systems with enhanced viscosity stability with respect to increased ionic strength and also to elevated temperatures.[189] HASE thickeners with improved clarity and improved resistance to salt are based upon the conventional methacrylic acid/ethylacetate system with "associative" monomers that are bicycloheptyl polyethers and long-chain polyethers.[190]

The challenge of thickening surfactant compositions at the isoelectric point of hair has been met by introducing an acrylates copolymer that contains semihydrophobic monomers such as hydroxypropyl acrylate, showing a reverse behavior in surfactant systems. Upon initial neutralization with base, the viscosity increases only above pH 6 to 6.5. If acid is then added to this thickened system, the viscosity increases once more even down to a pH of 5, which is desirable for pH-balanced shampoos.[179,191]

Hydrophobically modified cationic or amphoteric thickeners offer improved compatibility with cationic and low-pH formulations.[192]

### 13.1.17 Rheology Modifiers With Film-Forming Capability

There are many rheology modifiers available to the personal care formulator, but a recent trend has been directed toward multifunctional polymers, especially to rheology modifiers with film-forming fixative properties, for example, copolymers of acrylic acid, *N*-vinylpyrrolidone, a cationic monomer (preferably *N*-vinylimidazole), and a hydrophobic monomer that may be a long-chain ester of methacrylic acid having an ethoxylated spacer chain, preferably PEG-25 methacrylate.[193] Such rheology modifiers disperse rapidly in aqueous systems at pH 6–8 to yield gels with hair fixative properties.

### 13.1.18 Stimuli-Responsive Rheology Modifiers

For decades, the personal care industry has sought stimuli-responsive systems that exhibit one set of properties during storage and a triggered change to different properties during dispersing and application to the desired substrate. Thermal transitions are useful triggers for systems that are soluble at low temperatures and that show gelling or phase separation when the temperature is raised above a critical temperature (the lower critical solution temperature) that is usually called the cloud point. The very name "cloud point" conveys the impression that these systems become translucent or opaque above the critical temperature. In some cosmetic compositions it is desirable to form clear gels when the critical temperature is reached, and this has been achieved by grafting random PEG/PPG copolymers to a poly(methacrylic) acid backbone.[194] These polymers could be tailored to gel within a few degrees over a desired temperature range and the transition temperature could be tailored within a range of about 20–60°C.

### 13.1.19 Thickening Oil

The vast majority of polymeric thickeners in personal care are used to thicken aqueous systems. There are needs to thicken oil-continuous formulations, which are not addressed by the hydrophilic polymers discussed before. One

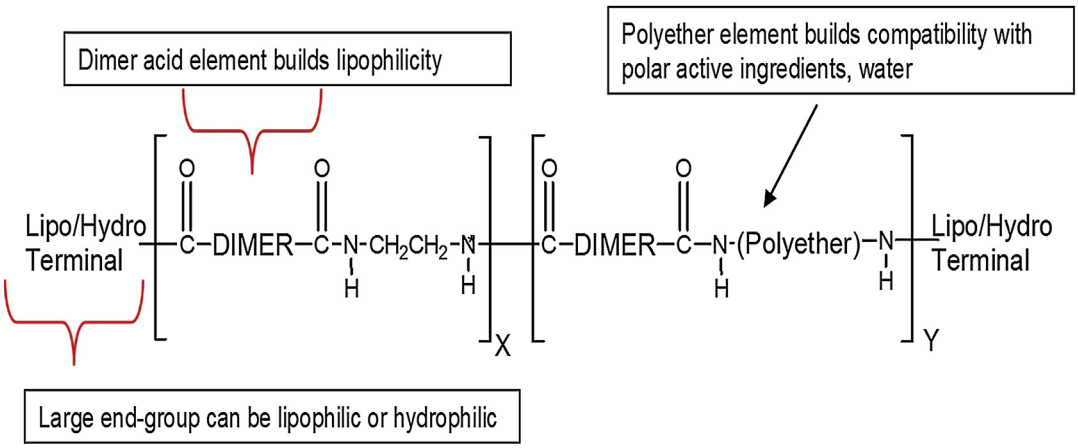



FIGURE 13.8 A schematic molecular structure of the oil-gelling dimer acid amides that are derived from pine oils.

class of useful oil gellants are derived from the plentiful resource of pine tree extracts (Fig. 13.8). These are offered under the INCI names Ethylenediamine/Stearyl Dimer Dilinoleate Copolymer, Ethylenediamine/Hydrogenated Dimer Dilinoleate Copolymer Bis-Di-C14-18 Alkyl Amide, Bis-stearyl Ethylenediamine/Neopentyl Glycol/Stearyl Hydrogenated Dimer Dilinoleate Copolymer, Polyamide-3, Polyamide-4, and Polyamide-6. These vegetable-derived polyamides, produced using naturally occurring fatty acids, offer a broad range of functionality to personal care formulations as film formers, water-repellent agents, emulsion stabilizers, structuring agents, wetting agents, and compatiblizers of actives (specifically in sunscreen formulations). The versatility of these polymers is demonstrated by their ability to produce personal care products in many different product forms, ranging from sprays to gels to aqueous emulsions and crystal-clear sticks. Ethylenediamine/Stearyl Dimer Dilinoleate and Tallate Copolymers telechelic polymers that self-assemble to form clear gel-oil phases. Traditionally, waxes have been used for this purpose, but the wax-gelled systems tend to be translucent or hazy. The clear gels convey more intense and brighter colors than the traditional wax gellants. Variants of this chemistry have been introduced by linking internal polyether blocks and internal fatty blocks into the polyamides.[195] These polymers have higher molecular weights and they are effective as gellants at low concentrations. They are viscoelastic thickeners in some solvents and soft or hard gels can be tailored by judicious selection of solvents. The higher molecular weights favor the formation of tough flexible films upon evaporation of the solvents.

The properties depend upon the selection of diamines and terminators used in the condensation reaction.[196–206] These polyamides can stretch across the range from relatively nonpolar to nearly water soluble. When formulating, polymer selection can be made based on its solubility parameter relative to the other ingredients in the personal care formulation. It is important in this respect to consider all three components of the Hansen solubility parameter to optimize for best compatibility (solubility parameter is discussed in Chapter 3). These polymers have the ability to form shear thinning oil-based gels (Fig. 13.9). The modulus of the gel (from deformable gel up to clear, hard stick form) is proportional to the concentration of polyamide used. The gelation mechanism is postulated to arise from a supramolecular hydrogen-bonded network.[207]

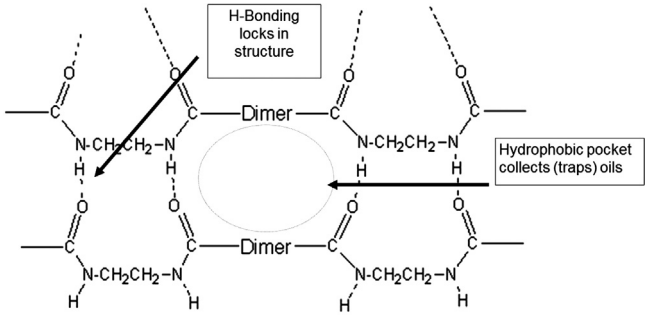



FIGURE 13.9 A depiction of the mechanism of gelation of ethylenediamine/stearyl dimer dilinoleate copolymer.

## 13.2 PRECISE MOLECULAR TAILORING FOR SIMULTANEOUS ENABLEMENT OF CONTRASTING QUALITIES

Since the 1970s it has been understood that conflicting properties can be achieved by incorporating copolymer blocks within the same polymer molecule. Thus, glassy blocks combined with elastomeric blocks enable thermoplastic elastomers, and amphipathic block copolymers offer the similar surface active and aggregation properties as surfactants at a larger scale and with slower kinetics.[208] Precise molecular block structures were first realized by anionic living polymerization, but such anionic synthesis could only be conducted in aprotic media and this severely limited the choice of monomers and solvents. Free radical living polymerization greatly diversified the range of block and graft copolymers that could be precisely synthesized.[209,210] The advent of these new polymers is allowing formulators to overcome the frustrating challenge of blending dissimilar polymers to try to achieve conflicting properties within the same formulation. It is well known that the low entropy of mixing disfavors compatibility between different polymers. Examples of conflicting properties in skin makeup properties are gloss or matteness, good adhesion to the support, and resistance to mechanical transfer or removal by secreted sweat or sebum but easy removability after use. Block, graft, and gradient copolymers serve to compatibilize such compositions and gradient polymers have been proposed for this purpose.[211] Block copolymers of styrene and butadiene or isoprene can thicken oils to give clear gels.[212]

Amphipathic block copolymers are a subset of polymers that can be synthesized by living polymerization. These polymers self-assemble to form complex, well-defined mesomorphic structures, which allows these polymers to thicken aqueous solutions to form viscoelastic gels.[213,214] Hydrogels can be formed without covalent cross-links from such amphipathic block copolymers because the aggregated hydrophobic blocks can act as junction zones within the structure. Such hydrogels can offer advantages in processing and in "self-healing" properties whereby junction zones that are disrupted by shear or extension may reform in the quiescent state. Moreover, these amphipathic block copolymers can allow tailoring of physical and mechanical properties, and also control of water adsorption and transmission. This is done by adjusting the size and number of blocks. Copolymers consisting of hydrophobic blocks, hydrophilic blocks such as acrylic acid, and middle blocks, for example, of short alkyl chain methacrylate such as butyl methacrylate[215] are stimuli responsive insofar as the water content of their hydrogels can be adjusted by changing the pH.

### 13.2.1 Side-Chain Crystalline Copolymers

An interesting class of amphipathic polymers are the so-called side-chain crystalline polymers, which have hydrophilic backbones and a plethora of closely spaced hydrophobic linear alkyl side chains. These are usually copolymers of short- and long-chain alkyl (meth)acrylates. They exhibit the interesting property of being hydrophobic below the melting point of the side chains but they become hydrophilic when the side chains melt. The triggered transition from hydrophobic to hydrophilic can be tightly controlled to within a degree or two, and that property has made them useful as stimuli-responsive seed-protective polymers.[216] These copolymers have now been shown to be useful oil thickeners for cosmetic compositions that have continuous oil phases.[217,218] The mechanism of thickening depends upon the crystalline chains forming a gel network in nonpolar oils when cooled below their melting point. The melting point of the side chains is adjusted to confer good flow and deposition at skin temperature when the gel is applied to the skin and can be adjusted to give a nongreasy, nontacky sensory profile to oil-based products.

### 13.2.2 Foam Enhancement by Amphipathic Block Copolymers

Amphipathic block copolymers can enhance foam in detergent systems.[219] These are block copolymers comprising a cationic block and a nonionic block. Polymers comprising diblocks of dimethylaminoethyl methacrylate and hydroxyethylmethacrylate and triblock copolymers that also contain acrylic or methacrylic acids have been reported for this purpose (Figs. 13.10 and 13.11).

Block copolymers offer the amphipathic properties of surfactants but on a larger scale. We can expect an increase in the prominence and diversity of block copolymers as a direct result of the introduction of living free radical polymerization techniques. It might be interesting to speculate on the mechanism whereby these polymers enhance foam. Foams are formed when surfactant molecules diffuse to and adsorb at an expanding liquid/air interface. Polymer molecules diffuse slowly—too slowly to adsorb at the expanding interface in the instant before it collapses. Therefore, it is reasonable to deduce that these polymers stabilize foam that is initially formed by adsorption of

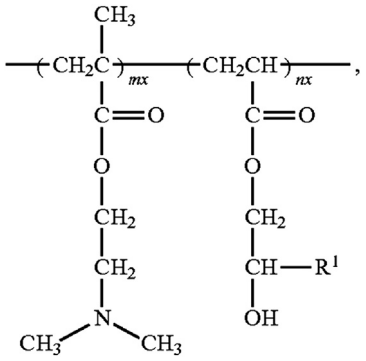


**FIGURE 13.10** Diblock copolymer of dimethylaminoethyl methacrylate and hydroxyethylmethacrylate.

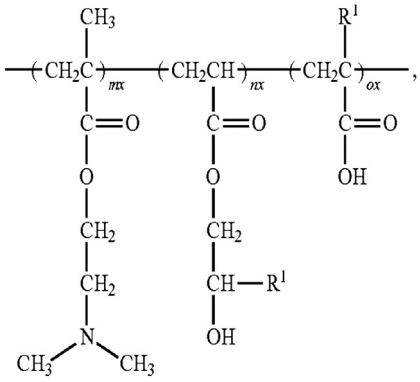


**FIGURE 13.11** Triblock copolymer of dimethylaminoethyl methacrylate, hydroxyethylmethacrylate, and (meth)acrylic acid.

surfactant at the interface. Foams collapse by two main mechanisms: draining of the liquid and puncture of the lamellae. (The physics of foam stability, drainage, and rupture are discussed in Chapter 2). The foam lamellae are the junctions between two foam bubble cells and the Plateau border that is situated at the triple-cell junction. The Laplace pressure in the liquid components of the foam is inversely proportional to the curvature of the interface. The higher curvature of the Plateau border results in a lower pressure in that region and this causes the liquid in the foam to drain preferentially from the lamellae to the Plateau borders. Based upon this reasoning, it can be understood that drainage can be hindered in two ways, namely by blockage of the lamellae or by blockage at the Plateau border. About two decades ago, Goddard carefully measured the drainage from foam films and deduced that Polyquaternium-24 adsorbed across the lamellar interface and hindered the drainage of liquid from the foam. In addition, about 30 years ago Friberg concluded that certain liquid crystals blocked the Plateau border region and thus delayed foam drainage and conferred longer-term stability on surfactant foams. In the case of the amphipathic block copolymers, hindered drainage of the lamellar liquid could be caused by adsorption of the cationic entities at the lamellar surface with the nonionic and/or anionic blocks in the lamellar liquid. Alternatively, formation of phase-separated coacervates between the cationic polymer and the anionic surfactant could result in blockage of the Plateau border. Of course, if the interaction of the cationic polymer was strong enough to form "inverse micellar" structures, then there would be a possibility that the phase-separated particles could cause a local reversal of the curvature in the lamellae and this in turn would result in breakage of the lamellar film and subsequent foam destabilization. This limit could be a reason for the specified maximum cationic charge density in the written description and in claims of the patent application for these polymers.

### 13.2.3 Solid Foams

The concept of polymer stabilization of liquid foams can be extended to the preparation of products in the form of polymer-enabled solid foams. Easily dissolvable porous solid shampoos could be useful to reduce the weight of water being transported in consumer goods and, thereby, to lower their carbon footprint. An extension of this type of innovation is to provide delivery of cationic conditioners that would normally be incompatible with liquid

shampoos and enhanced delivery of these actives to the keratin substrate. Another claimed advantage of porous solids is the ability to have one scent for the solid and then to allow a second different fragrance to bloom when the solid is wetted by water.[220–224] The porous solids are made by mixing the surfactants, glycerin as plasticizer and water in the presence of a water-soluble polymer. Poly(vinyl alcohol) is exemplified as this water-soluble polymer, but a wide range of synthetic and natural polymers could be used to achieve the same objective. After a heating and mixing cycle, the solid foam is formed by aeration.

## 13.3 POLYMERS THAT MODIFY SURFACES

Some natural polymers have the propensity to precisely tailor the free energies of a wide range of surfaces to fall within a narrow window. Biomimetic imitation of such polymers could enhance the ways in which surfaces could be modified to precisely meet consumer requirements. For example, hydrophobins are small proteins formed by filamentous fungi such as *Schizophyllum commune*.[225] The purpose of these proteins seems to be to adjust the free energy of multifarious surfaces to the optimum surface free energy for invasion by the fungus. Thus, hydrophobins are known that spontaneously raise the surface free energy of poly(tetrafluoroethylene) and lower the surface free energy of glass to an optimal range for the benefit of the fungus. Hydrophobins form relatively nonviscous aqueous solutions at low concentrations (less than 3%) but gels at higher concentrations. Surfaces coated with hydrophobins have been suggested for use as waterproofers,[226] phase stabilizers,[227] demulsifiers, evaporation retardants, soiling inhibitors,[228] and to prevent the formation of ice on surfaces.[229]

Apparently, hydrophobins interact synergistically with a wide range of water-soluble polymers to confer synergistic thickening, and this could be used to advantage in cosmetic gels, conditioners, and cleansing compositions such as shampoos.

The ability of the lotus leaf to repel water and soiling from its surface has been promulgated in the scientific literature. The term "lotus effect" has been coined from the observation that water droplets ball up on the leaf surface of the lotus flower (*Nelumbo*). Nanoscale roughening of a hydrophobic surface enhances the contact angle and renders the surface more hydrophobic than a chemically identical smooth surface. Superhydrophobicity results when the surface possesses arrays of nanosize protrusions.[230–232] The small particles in the coating impart a surface roughness to the coating, and this enhances its hydrophobicity. The droplets roll off the leaves, taking with them any dirt that may have been deposited and conferring the property of self-cleaning on the leaf surfaces. This superhydrophobicity is realized as a result of the regular periodic hydrophobic nanostructure on the surface of the lotus leaf.[233] In recent years, there has been a fairly large effort to mimic the lotus leaf and to produce regular nanostructured superhydrophobic surfaces that could be self-cleaning. Hair and skin can be rendered superhydrophobic by applying a water-in-silicone emulsion containing a hydrophobic particulate polymer and octyl-silyl-functionalized fumed silica.[234] A hydrophobic film-forming polymer such acrylates/dimethicone copolymer with hydrophobic particles iron oxide and triethoxycaprylsilane is optionally included in these compositions. Such films could possibly shield the hair from sweat, rain, and dirt, and it is suggested that treatment with such a composition could possibly allow swimmers to spontaneously dry their hair by merely shaking their heads.

Superhydrophobic coatings have been postulated as a means of controlling frizzy hair.[235] Hair becomes frizzy when it is exposed to high humidity, and previous technologies for controlling frizz were based upon coating the hair with silicones. Superhydrophobicity concepts are offered to the control of frizz for an extended period of time without adversely affecting other properties such as appearance, feel, volume, shine, and softness.

One approach is to hydrophobically coat the hair with a composite that includes a hydrophobically surface-modified aluminum oxide (ranging from nanometer to micron size), a silicone acrylate film-former and a silicone fluid.[236]

## 13.4 TRANSFER-RESISTANT COLOR COSMETICS[237]

Many wearers of lipstick desire a product that is delivered easily and uniformly to the lips, but once applied, it should not transfer to other surfaces. This paradox was addressed by the introduction of "transfer-resistant" lipstick by Revlon in the 1990s,[238–240] and since that time silicone resins have been a preferred ingredient to achieve transfer resistance in color cosmetics.[241,242] Complex silicones including dilauroyl trimethylolpropane siloxy silicate or diisostearoyl trimethylolpropane siloxy silicate were used to enable transfer-resistant properties in Revlon's lipsticks.[238] These were introduced to the formulations as a mixture with volatile oils. The volatile oils aided the

spreading of the compositions on the skin and, once the volatiles evaporated on contact with skin, transfer-resistant properties and durable wear were realized. It should be noted that packaging had to be designed to prevent evaporation of the volatile oil from the product during storage and between uses. In 1993, it was disclosed that silicone pressure-sensitive adhesives provided improved adherence to skin and they were used to impart wash-off resistance to mascara formulations.[243] The pressure-sensitive adhesive included a trimethylsilyl end-blocked resin, a silanol-terminated dimethicone, and a phenyltrimethicone. Trimethylated silica in lipstick conferred transfer-resistant properties to the film that was deposited on the lips.[244] Trimethylated silica was initially prepared by dispersing fine-grained silica in a solvent mixture of low-viscosity silicone oil in a volatile hydrocarbon. When the volatile hydrocarbon was distilled away, a smooth transparent paste or grease was obtained.[245] This inspired the exploration of volatile/nonvolatile mixtures in makeup products. The volatile silicones enabled spreading of the product on the skin or lips, and, once dried, the trimethylated silica conferred transfer resistance.[246–248] This technology was extended to mascaras, concealers, foundations, eyeshadows, and sunblocks by incorporation of film-forming polyamide or acrylate copolymers.[249]

Silicone resins that were used early in the development of transfer-resistant cosmetics are known as " MQ" or "MT" resins to signify that they consist of polymers constructed from monofunctional (M), trifunctional (T), and/or quatrifunctional (Q) silane functional groups.[250] A wide range of cosmetic compositions containing high-molecular-weight, particulate MQ resin have been claimed.[251] It has been found that the finish of cosmetic compositions can be improved by tailoring the properties of MQ and MT resins by adjusting the ratio of M:Q or M:T units in the resin. In particular, improved finish is achieved when the rate of M units is up to three times greater than the number of Q units.[252] However, one drawback of the MQ and MT resins is that they are not compatible with polar media, and this poses difficulties for formulation in aqueous compositions. Thus, organopolysilsesquioxanes of the MQ type conferred good water repellency and long wear on cosmetic compositions.[253] However, the resins were soluble in the same phase as cosmetic pigments, and the oil in that phase caused swelling and discontinuity of the silicone films of such resins on the skin. Consequently, the pigment became detached and the pigment ran. The water repellency was improved and oil resistance conferred on the cosmetics by replacing the oils with volatile silicones and volatile oils.[254] Liquid lip makeup was developed that was nontransferable to surfaces such as drinking glasses. This composition contained 40% MQ resin, 20% volatile hydrocarbon oil, 20% powder, 10% glyceryl triisostearate, and 10% red dye.[255] The incorporation of volatile low-molecular-weight cyclosiloxanes resulted in a desirable silky feel.

The formulation limits and testing protocols for silicone fluid viscosity, polymer/pigment, and organosilicone resin/silicone fluid concentrations were laid down in a patent that coincided with the introduction of a transfer-resistant lipstick that included MQ resin, dimethicone gum, isododecane or cyclomethicone as volatile carrier, and pigments for color.[256]

Durability and transfer resistance of a lipstick are desirable. However, durability should not mean that the lipstick should not be capable of easy removal when desired. Removal products were developed, some consisting of petrolatum or dimethicone-based compositions and others comprised of cross-linked silicone elastomers and solvents suitable for application to skin.[257] In this instance, the cross-linked siloxanes were dimethicone/vinyl dimethicone crosspolymers. The importance of particle size on skin feel was included in the invention of these removers. Particle sizes smaller than 10 μm produce a reduction in skin feel and viscosity benefits whereas particle sizes exceeding 200 μm form silicon elastomer gel balls on the skin. The preferred liquid carriers were those having Hildebrand solubility parameters of less than about 9.[258,259] Another remover composition was based on Nylon-611/Dimethicone copolymer and dimethicone or phenylmethicone.[260]

Since the introduction of the original transfer-resistant color cosmetics, innovation has been rapid, to improve durability and to address perceived sensory drawbacks. The model of MQ resin plus volatile oil was essentially a "film-former plus plasticizer" combination. Since the MQ resin is essentially a tackifier, the compositions were essentially a compromise between high tack with good skin adhesion and low tack with poor adhesion. Moreover, the original transfer-resistant lipsticks gave a dry feel and a matte finish to the lips at a time when glossy lipsticks were preferred.[261] Unfortunately, high amounts of gloss oils compromised properties such as stick structure, nontacky feel on the lips, and transfer resistance. This drawback was overcome by the discovery that shiny lipsticks could be achieved by adding poly(isobutyl methacrylate-co-methyl FOSEA-g-polydimethylsiloxane), or polydimethylsiloxane -g- poly(isobutyl methacrylate) to transfer-resistant stick formulations,[262] or by adding the liquid polyester dilinoleic acid/butanediol copolymer, which effectively structures the oil phase, increases adhesion, and, thereby, lowers tack at relatively low concentrations. It was also discovered that the common silicone phenyldimethicone gives high gloss, and the silicone resins continued to confer improved durability of color with little or no migration on keratin surfaces.[263–265]

Shiny lipsticks provide an intense youthful look, which is not considered to be appropriate for older women. Therefore, a luster finish was sought to provide enough shine and "dewy look" to convey the appearance of good health without being obviously shiny. It was known that mattifying properties could be achieved by the addition of appropriate fillers, but the use of these fillers brought back tacky, discomfort during wear.[266] Eventually the desired luster finish was achieved by including low surface tension spreading agents that were poor solvents for the siloxysilicate resins, Examples of these agents are fluoro-guerbet esters, such as fluorooctyldecyl meadowfoamate.[267,268] An alternative approach was to emulsify the "glossy" silicones by including silicone emulsifiers such as cetyl dimethicone copolyol (and) polyglyceryl 4-isostearate (and) hexyl laurate, or cetyl dimethicone copolyol (and) polyglyceryl-3 oleate (and) hexyl laurate, or silicone superwetting polymers.[269,270] Stick integrity was improved by incorporating glassy methacrylate copolymers.[271,272] The glass transition indicates the ability of polymer molecules to move relative to each other. Polymer molecules move by rotation around the covalent bonds of the chain backbone and side groups in a motion that resembles the rotation of a crankshaft. At temperatures below the glass transition temperature (commonly abbreviated to Tg), there is insufficient energy for the units on adjacent chains to "wriggle" past each other and the units are trapped in local space. Above the Tg, the macromolecular chains have enough energy to wriggle past each other and to exhibit long-range motion over a reasonable period of time. Thus, below the glass transition temperature, polymeric materials behave like "glasses" and above the Tg they behave like "rubbers." The glassy methacrylate polymers added just enough structure to give good stick integrity but not enough to impact the desired "payout" on application to the lips.

The next challenge was to develop lipsticks with reduced permeability to oil and water to allow wearers to eat and drink, and blot away perspiration or exuded sebum without affecting the products' transfer resistance or the wearer's made-up appearance. To achieve this, the low surface tension, high-gloss, easy-spreading perfluoropolyether liquids were included as ingredients to act as barriers to the dissolution of the lipstick from the lips.[273,274] The special properties of the polyfluorocarbons arise from the strength of the C−F bond, which, at 485 kJ/mol, is much stronger than C−H (413 kJ/mole) or C−C bonds (348 kJ/mol). When all of the hydrogen atoms of hydrocarbon chain are replaced by fluorine atoms, the molecule is effectively covered in an impermeable sheath that resists acids, alkalies, enzymes, oils, solvents, and aqueous solutions—hot or cold.[275] Polyperfluoromethylisopropyl ether has a very low surface tension that enables it to spread quickly and evenly over surfaces. An additional advantage is that polyperfluoromethylisopropyl ether is not greasy and is not flushed from the skin by perspiration. It does not impregnate silicones or other polymers; it cannot even wet an adsorbed layer of itself; it rather forms a thin coating, often a monolayer, over these other materials to render them nonwettable by most common liquids.[276]

Eventually, two-part lip compositions were reintroduced. These consisted of a base coat, comprising MQ resin, and a top coat of oil that was delivered from a volatile solvent such as isododecane.[277] The idea is the first layer provides long-wearing, transfer-resistance while the second layer contributes shine/gloss and feel benefits without compromising the first layer. For example, the desired attributes were achieved by applying a film of a silicone resin and a polyamide-silicone copolymer over the lipstick color layer on the keratin.[278] Later products combined the two layers into one stick in which the protective layer was suspended as discrete unemulsified droplets.[279] The dispersed phase had a critical surface tension that was lower than that of the layer on the skin, and this allowed the dispersed phase to spontaneously spread on top of the color layer and thereby to confer desirable feel attributes and gloss.[280]

More recently, it has been recognized that the surface energy of skin is variable and to obtain a natural-looking distribution of color over the skin, variable surface energy particles with both hydrophobic and hydrophilic surfaces have been introduced. For example, an inorganic particle can be selectively coated with hydrophilic cationic polyethylenimine and hydrophobic aminopropyl terminated polydimethylsiloxane in such a way that the polymers are located on mutually exclusive locations on the particle surface.[281] The variation in surface energy causes the particles to adhere to the variable skin surface and to provide a natural-looking distribution of color over the skin surface.

Transfer-resistant color cosmetics can be uncomfortable to wear. The challenges in this realm stemmed from the fact that transfer-resistant compositions could be difficult to spread, tacky during application, and they could convey a tautness or mask-effect during wear. Moreover, upon drying out the films could become brittle and "flake off." Therefore, the next technical hurdle was to provide transfer-resistant color cosmetics that were comfortable to wear. This goal was achieved in different ways:

- By including polypropylenesilsesquioxane waxes in transfer-resistant formulations based on silsesquioxanes and siloxysilicate resins. Silsesquioxane wax alkyl substitution exceeding 30 carbons yielded stable color cosmetic formulations. C30-45 alkyldimethylsilyl polypropylenesilsesquioxane was preferred in this instance.[282]

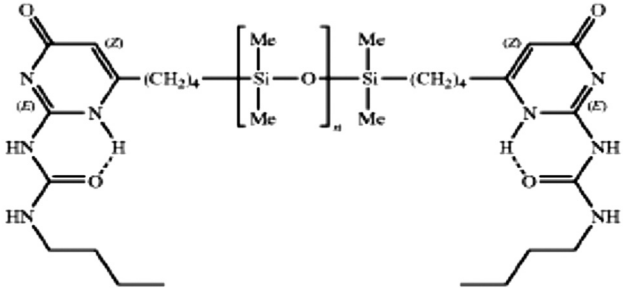
- By incorporating highly branched liquid polyesters and hyperbranched polyols to generate a network film by interweaving the polymer chains to confer durable transfer resistance and shine. The branched polyesters were formed from the reaction of pentaerythritol with benzoic, isophthalic, and isostearic acids.[283]

The paradoxical requirements of durable shine, transfer resistance, and comfortable wear then led to the development of color cosmetic formulations that incorporated block copolymers[284] and then included tackifiers and modified silicones[285–288] with the block copolymers. Triblock copolymers comprising hard, glassy polystyrene end segments and soft, rubbery poly(ethylene/butylene) middle segments were preferred. These were the principal structure formers in the formula and they enabled the formation of transparent, translucent, or opaque gels. The block copolymers also enhanced the integrity of the film that was formed on the skin and held the tackifing MQ resin within its soft microdomains. The hard segment could be dissolved by nonvolatile esters such as isopropyl myristate or isopropylpalmitate. The soft segments could be dissolved by volatile solvents such as isododecane and/or dissolved by nonvolatile solvents such as hydrogenated polydecene. The next stage was to replace the nonvolatile oil with a thermoplastic elastomer that was compatible with MQ resin or other solid tackifier resins. The tackifier essentially functioned as a pressure-sensitive adhesive. Tackifiers generally fall into four different chemical classes: hydrocarbon resins, terpenes, amorphous rosins and rosin esters, and pure monomer resins. It was necessary to ensure that the tackifiers were compatible with the block copolymer at the microlevel. Hansen's three-component solubility parameters were used to identify the needed compatibilities. The particularly preferred tackifier in this case was a hydrogenated styrene/methylstyrene/indene copolymer. Modified silicones (such as polyether/alkyl comodified silicones) were added to improve the texture and comfort. Rheology measurements were conducted to help specify the properties of the lip-gloss compositions as a function of the storage and loss moduli of the composition. It was discovered that the mixture of the solid resin with the solid polymeric material resulted in a softer material with good adhesion and less tack on the skin.[289]

The successful use of the microdomain-segregated structures of block copolymers led to a quest for other higher-order structures that promised transfer-resistant makeups that were comfortable to wear. Coincidentally, during this period, capabilities to build useful supramolecular structures emerged. These supramolecular structures were constructed by tailoring intermolecular forces like hydrogen bonding, dipole−dipole interaction, or the attraction of oppositely charged ionic moieties to arrange the constituent molecules in extensive three-dimensional networks.[290] Such supramolecular structures opened the door to tough materials that could be cleaved at will and then allowed to self-heal spontaneously by the reformation of hydrogen bonds to reconnect the cleaved structures.[291] These concepts were utilized to design durable, tough, comfortable skin cosmetics that could be applied and removed as required. Such materials for color cosmetics were constructed from:[292]

- Polymers that can self-assemble into hydrogen-bonded networks as the film dries out on the keratin surface. Examples of such polymers are:[292]
  - α -ω di(4-benzyloxy-6-butyl-2-butylueidopyrimidinyl) poly(dimethyl siloxane) and polyesters with bis-hydroxyls with ureidopyrimione groups, such as the sebacate/terephthalate copolymer of neopentylglycol (Figs. 13.12 and 13.13).
- By including a copolymer formed from an ionizable amine monomer with a (thio)urethane/(thio)urea monomer having the structure shown in Fig. 13.14.[293]
- By the formation films comprising of hydrogen-bonded networks. For example, these films were laid down from emulsions that contained maleinized polypropylene or polyethylene and a hyperbranched polyol[294] and/or a sugar silicone surfactant.[295,296]

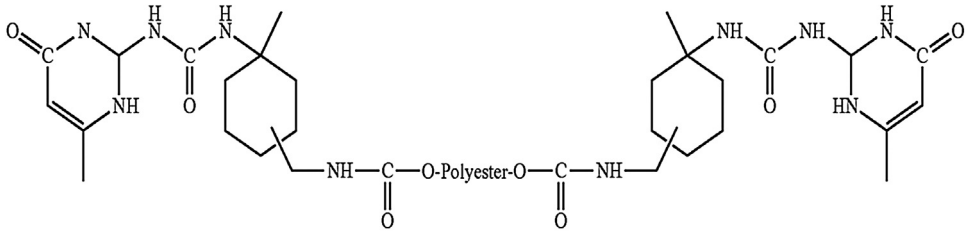
α -ω di(4-benzyloxy-6-butyl-2-butylueidopyrimidinyl) poly(dimethyl siloxane)




Reproduced from Mougin et al. U.S. Patent 8,354,097

FIGURE 13.12 The molecular structure of α -ω di(4-benzyloxy-6-butyl-2-butylueidopyrimidinyl) poly(dimethyl siloxane).

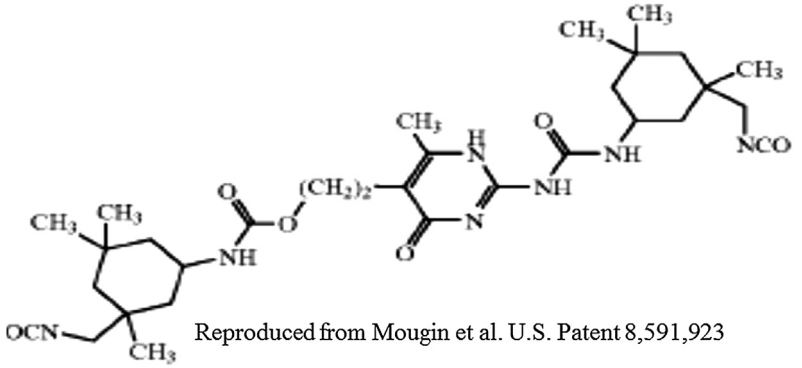
Polyesters with bis-hydroxyls with ureidopyrimione groups




Reproduced from Mougin et al.
U.S. Patent 8,354,097

FIGURE 13.13 The molecular structure of a polyester with bis-hydroxyls with ureidopyrimione groups.

Copolymer formed from an ionizable amine monomer
with a (thio)urethane/(thio)urea (II)



Reproduced from Mougin et al. U.S. Patent 8,591,923

FIGURE 13.14 The molecular structure of a copolymer formed from an ionizable amine monomer with a (thio)urethane/(thio)urea.

- By combining silicone-amide copolymers with a volatile alcohol and oil and a thickener. The silicone-amide (for example Nylon-611/dimethicone copolymer) forms a pliable film as a result of hydrogen bonding between the very flexible silicone macromolecules and the composition was structured by "thickening" with block copolymers to produce a basecoat that is comfortable for long-term wear.[297,298]
- Emulsions formed by combining a polar-modified polymer and an alkoxysilane produce bouncy gels that impart good adhesion, long wear, and transfer-resistant properties to cosmetic compositions applied to keratin.[299]

The use of controlled extensive hydrogen bonding to form structured films is shown by compositions that include supramolecular polymers with a hyperbranched functional polymer, a light silicone fluid, and a copolymer containing a silicone resin segment and a fluid silicone segment.[300]

The supramolecular polymer was prepared by reacting hydroxyl terminated poly-1,2- butadiene with a ureidopyrimidine to obtain a polymer having the structure shown in Fig. 13.15:

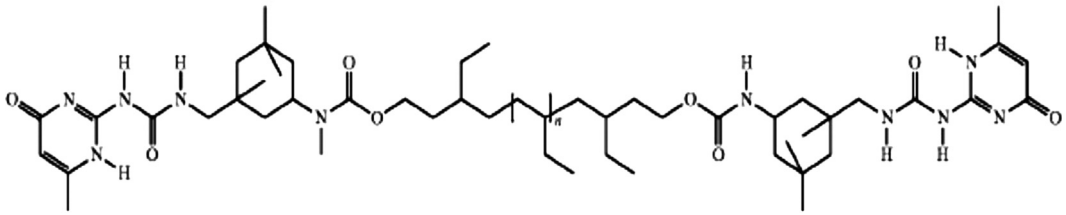
The hydroxyl-terminated precursor is made by anionic living polymerization. This process gives polymers having a narrow molecular weight distribution and the selection of polymerization solvent allows control of 1,2 versus 1,4 addition of the butadiene. The properties derived from this polymer arise from the end groups' ability to form multiple hydrogen bonds between neighboring hyperbranched polymers and thereby to build up a supramolecular structure. Such supramolecular structures are found in shape-memory copolymers.

The hyperbranched functional polymer, which confers detackifying properties, is a C30 + olefin/undecylenic acid metallocene copolymer. Polymerization using a metallocene catalyst allows precise control of the polymer structure.

A light silicone, phenyltrimethicone or trimethyl pentaphenyl trisiloxane, confers gloss and slip to the formulation.

The transfer-resistant properties are conferred by the silicone copolymer, which is prepared by reacting an MQ resin with a bis-hydroxydimethicone.

Supramolecular polymer prepared by reacting hydroxyl terminated poly-1,2- butadiene with a ureidopyrimidine



Reproduced from Tong et al. U.S Patent 8,709,388

FIGURE 13.15 A depiction of the molecular structure of a supramolecular polymer prepared by reacting hydroxyl terminated poly-1,2-butadiene with a ureidopyrimidine.

The tackiness was evaluated by measuring the work of adhesion with a texture analyzer (as in the previous discussion of hydroxyethylcellulose). The addition of the silicone copolymer and light silicone fluid conferred improved high, long-lasting shine, duration of wear, and less removability during eating.

## 13.5 FILM-FORMING POLYMERS IN COSMETICS AND PERSONAL CARE PRODUCTS

The subject of hair fixatives is covered by Colleen Rocafort in Chapter 21. The contents of this chapter, therefore, will be directed to complementing rather than duplicating the excellent review by Ms. Rocafort.

### 13.5.1 Hair Fixatives

Hair fixatives that allow temporary retention of hair style were introduced in the middle of the 20th century. Shellac was the preferred film-forming polymer in those early products. However, shellac is essentially a varnish that resists removal by water and shampoo, and, therefore, it suffers from the drawback of building up on hair with repeated use. Water-soluble and shampoo-dispersible synthetic polymers were introduced to overcome this deficiency. The first of these polymers was poly(*N*-vinyl -2-pyrrolidine) (PVP). It was soluble in water in all proportions and also showed excellent substantivity to hair. However, PVP was plasticized in humid atmospheres and this caused the hairstyle to "droop." Subsequently, copolymers were developed to improve on this shortcoming. These polymers were designed to exhibit a duality of purpose: to hold the hair in its desired shape, even under conditions of high humidity, but after use to be completely removed by shampoo. In conventional random copolymers there is usually a compromise between these paradoxical properties, and many conventional fixative polymers are sensitive to moisture from humidity, rain, or sweat and this reduces the durability of the hairstyle. Today's hair-styling formulations should be capable of being applied to dampened hair after shampooing and/or conditioning, or to dry hair. These products should be readily removed by water or shampoo. The performance required by hairsprays was raised even in the face of regulations that eliminated chlorofluorocarbon propellants and limited the amount of volatile organic compounds in hair fixatives making it desirable to use largely aqueous-based formulations to deliver humidity-resisting polymers with facile removal by shampoo. Today, hair fixative polymers can be chemically complex. For example, fixation with less susceptibility to moisture was achieved by including polyacrylate-14, which is a fixative polymer having an acidic vinyl monomer, a hydrophobic nonionic vinyl monomer, two associative monomers, and a semihydrophobic monomer; and a second copolymer comprising a C3-C8 ethylenically unsaturated monocarboxylic acid monomer, a nonionic vinyl monomer, and a hydroxy-substituted nonionic vinyl monomer.[301] Acrylates/hydroxyesters acrylates copolymer may also be used for the same purpose. These polymers exhibit the dual advantages of being a hair gel thickener and a film-forming hair fixative.[302]

The cross-linked derivative, Polyacrylate-2 Crosspolymer,[303] is a branched acrylate copolymer of C1-C4 alkyl (meth)acrylate, (meth)acrylic acid, and an amphipathic moiety that contains silicone side chains and associative hydrophobic chains.[304] Soft, hydrophobic domains are randomly combined with hard, hydrophilic domains to form the backbone of this polymer, and this results in the simultaneous achievement of the paradoxical properties of

stiffness and humidity resistance, with resistance to flaking, combined with the sensory attributes of shine enhancement and ease of distribution through hair.

Another rheology modifier/hair styling resin for delivery from aqueous systems[305] is a cross-linked linear poly(-vinyl amide/polymerizable carboxylic acid) copolymer, in which the vinyl amide is selected from vinylpyrrolidone, vinylcaprolactam, *N*-vinylformamide, or *N*-vinyl acetamide. The polymerizable carboxylic acid can be (meth)acrylic acid.

### 13.5.2 Macromolecular Compatibility and Controlled Segregation to Confer Multifunctionality

Controlling structures at the nanoscale can lead to the development of innovative properties for materials used in hairstyling, and this opens the door to new styling opportunities. Arrays of hydrophobic nanoparticles on the surface of hair have been developed to prevent the intrusion of water into the hair and thereby to prevent frizz. Genetically engineered silk analogs are already being used to create styling with smooth feel, and as this technology advances, there can be hope for paradoxical properties of hair fixatives, such as strengthening in the presence of moisture to counteract the drooping of hairstyles on humid days. Polymer blends are increasingly being utilized to confer high hold with good aesthetics. In this instance, it should be noted that polymers are often incompatible due to their low entropy of mixing, and the enhancement of properties by polymer blending is not a straightforward exercise in formulation. Supramolecular assemblies of oppositely charged polymers and particles may lead to the introduction of hair set with soft feel. Nanostructuring of materials offers the promise of revolutionary new products that could overcome the compromise in benefit delivery that is often accepted with conventional materials. For example, multifunctional clear gels that are probably supramolecular micro- or nanocomposites can be formed by combining the particulate film-former anionic polyester-5 with the cationic polysaccharide Polyquaternium-10. Clear hair gels are obtained that deliver styling with a soft feel.[306]

The styling hold of strong-holding hairstyles is determined primarily from the type and amount of styling polymer that is used. For strong hold, humidity resistance, low stickiness and excellent manageability are necessary. A reasonable degree of conditioning is also desirable. There is a trend to move toward fixative polymer blends to achieve the high hold without compromising other aesthetics. For example, these properties have been achieved by combining amphipathic cationic polymers with chitosan as a stabilizer to maintain homogeneity in the formulation and to produce the desired rheology for application.[307] If compatibility is to be realized, the low entropy of mixing of polymers must be compensated by strong enthalpic interactions. This is especially the case for stiff-backboned polymers. Moreover, stiff polymers tend to have a limited range of solubility that limits the degree of formulation freedom to prepare a blend of water-soluble fixative macromolecules that will resist moisture.

However, stable high-hold formulations containing two distinct copolymers have been created. For example, blends of Acrylates/$C_{1-2}$ succinate/hydroxyacrylates copolymer and Octylacrylamide/acrylates/butylaminoethyl methacrylate copolymer are compatible and they retain flexibility, elasticity, and plasticity.

The entropic demixing of polymers is used to create precisely organized microdomain separated materials utilizing block copolymers. In this case the dissimilar blocks are covalently bound to each other and this forbids macrophase separation. The micro/nanophases can be self-assembled into a variety of precise structures, each with distinct mechanical, optical, and solubility characteristics.[308] Until recently, the application of this technology to personal care was limited because anionic polymerization was the only available production technology. Anionic polymerization is limited to few monomers, and this severely limited the possible diversity of block copolymers that could be produced for personal care applications. This situation was changed with the introduction of living free radical polymerization, which has broadened the variety of possible block copolymers that can be produced. Block copolymeric, stimuli responsive emulsifiers with film-forming capability are being created for the personal care industry.[309] Soft hold can be achieved by combining certain microdomain-separated polyurethanes with PVP homopolymers or copolymers.[310]

Demand for natural ingredients has led to the introduction of natural or naturally derived macromolecular fixatives. The limitation of natural styling polymers includes issues such as viscosities that are too high to spray and limitations in compatibility with other common formulation ingredients. Also, synthetic polymer options cover a wider variety of properties than available naturally derived options, making some synthetic polymers currently irreplaceable in styling product formulations.

For example, chitosan derivatives are being applied to enhance long-term hold. Thus, compositions containing chitosan derivatives and elastomeric silicones improve the fullness and long-term hold of hair.[311] Long-lasting hold is also achieved by combining chitosan derivatives with a polymer comprising an amino-substituted vinyl unit, a hydrophobic nonionic vinyl unit, an associative vinyl unit, and a semihydrophobic vinyl surfactant unit.[312]

Biopolymer latex may be produced by cross-linking starch with glyoxal (for example, in an extruder) followed by cryogenic grinding. Such biopolymer latexes are disclosed as being suitable hair fixatives with the benefit that the polymers are derived from natural and sustainable resources.[313]

Biomimicry is an understandable extension of the use of natural ingredients. In this context, inspiration has been taken from the proteins that allow mussels to adhere tenaciously to surfaces even when they are underwater. Blue marine mussel (*Mytilus edulis*) secretes adhesive proteins containing the amino acid, L-3, 4-dihydroxy-L-phenylalanine (DOPA). There is an ample supply of these proteins at the interface between adhesive pads of the mussels and the surfaces to which they adhere.[314,315] The *o*-dihydroxyphenyl (catechol) functional group of DOPA has strong affinity for many surfaces.[316] Under oxidizing conditions, the catechol group transforms its chemical structure into a quinone. Indeed, aqueous gelling agents have been produced by reacting DOPA with thiol end-capped poloxamer.[317] Copolymers containing a group similar to catechol adhere tenaciously to surfaces. However, the mussel proteins and these copolymers do not confer styling on hair, but the copolymer readily coats polysilicic acids and this forms a particulate material that adheres to hair and allows recovery of style even when it has been altered by wind or water.[318]

### 13.5.3 Temporary Style With Easy Restylability

Simple hair fixatives allow the hair to be set in a style once. Improved versions allow the hair to be styled and then restyled at will. For example, a person could have one style for the day, a restyle for afternoon, and another restyle for evening, without having to reapply a fixative composition. There have been several approaches to achieve restyling. For example, systems based upon polymers with a glass transition temperature less than 10°C and a minimum defined separation force are useful as restylable fixatives. One such system is based on branched sulfonic polyesters, (INCI Polyester-5).[319] If these polymers are applied from alcohol solutions, the hair feels dry after brushing and they are not homogeneously distributed over the hair. This drawback can be overcome by including a polysaccharide thickener in the composition.[320] Suitable polysaccharides for this purpose are cellulose derivatives or Gellan gums. These compositions can be manipulated to confer conditioning as well as restylable hold, if cationic cellulose ethers could be included in the formulation. However, the interaction between cationic polysaccharides and anionic Polyester-5 commonly results in precipitated complexes rather than gels. Still, compatible gels containing both Polyquaternium-10 and Polyester-5 have been reported.[321]

Restylable hair fixatives and mascaras are possible with elastomeric particulate microspheres.[322] The microspheres are particles of diameter between 10 and 250 μm, and they contain cross-linked silicone elastomer, preferably dimethicone/vinyl dimethicone crosspolymer,[323] poly(2- ethylhexyl acrylate) or poly (butyl acrylate), having glass transition temperatures of less than −20°C. The relatively large particle size limits the extent of adhesion and allows the hairs to be easily peeled and re-adhered.[324]

### 13.5.4 Polymers for the Delivery of Long-Lasting, Quick-Change Styles

Temporary hair styling is achieved by combining hair fixative polymers with heating devices. However, these styles rarely last for more than one day and the styles tend to be unchangeable once set in place. In this respect, an interesting advance has been disclosed for the long-term styling of hair with the option of changing the shape anytime at will.[325] This is achieved by placing a polysiloxane/urea block copolymer to the hair and applying heat. The block copolymer is substantive to the hair and the treatment is durable. Moreover, because the polymer is thermoplastic, the style can be changed at any time by the reapplication of heat sufficient to melt the polymer. The polymers are synthesized by chain-extending polyether and polyester polyols or *bis*-hydroxyalkylsilicones and/or alpha, omega aminosilicone with an appropriate diisocyanate coupler. The polymer formulation is applied to the hair and heated with a curling iron to 200°C to produce a ringlet that can be easily straightened with a flat iron and then recurled with a curling iron as desired.

### 13.5.5 Hair Grooming With Whipping

Whipped emulsions provide all the benefits of a pomade but with improved elasticity.[326] The products are formed by using two polysaccharide emulsifiers and a gelling agent. One of the emulsifiers is xanthan gum and the other is a mannan polymer (this includes a wide range of polymers including guar, locust bean gum, and pectin). This is a good example of the utilization of the synergistic structuring between xanthan gum and galactomannans. The gellant may be Carbomer or an acryloyl taurate thickener.

## 13.6 HAIR-CONDITIONING POLYMERS

In its pristine state hair has a hydrophobic surface, but oxidation and/or treatment with surfactants causes the hair surface to become hydrophilic and to lose its natural conditioning. Conditioning of damaged hair is commonly achieved by treatment with aqueous formulations that contain fatty alcohols, cationic surfactants, and optionally silicones. These components are considered to adsorb in a hydrophilic head-down hydrophobic tail-up conformation that confers hydrophobicity on the damaged hydrophilic hair surface. Cationic conditioning polymers are used to enhance the conditioning properties, especially to mitigate the effects of extreme processing that are experienced during hair straightening.

Early synthetic conditioning polymers included poly(diallyldimethylammonium chloride) [Polyquaternium-6] and its copolymer with acrylamide [Polyquaternium-7], PVP copolymerized with dimethylaminoethylmethacrylate [Polyquaternium-11] (Fig. 13.16), Polyvinylimidazolines [Polyquaternium-16],[1,327,328] and their copolymers and terpolymers.

These polymers are still being used today and they have been supplemented by a variety of copolymers and terpolymers. In order to improve spreadability on hair to enhance disentangling and feel benefits, polyols are formulated with an aminosilicone and a cationic.polyvinyllactam.[329,330] A preferred polymer for this purpose is Polyquaternium-55, which is the polymeric quaternary ammonium chloride formed from vinylpyrrolidone, dimethylaminopropyl methacrylate, and methacryloyl-aminopropyl-lauryldimonium chloride.

Polyampholytes have been commercially available as conditioning polymers for a considerable time. A prominent example is Polyquaternium-39, which is a copolymer of diallyldimethylammonium chloride, acrylamide, and acrylic acid. However, these monomers do not polymerize well together and early versions were mixtures of copolymers with different compositions. Now, a more uniform terpolymer of diallyldimethylammonium chloride, acrylamide, and acrylic acid has been made by a monomer feed method for better control of molecular weight and composition.[331]

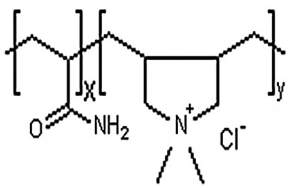
Copolymers comprising a diallylamine (typically diallyldimethyl ammonium chloride) and vinyllactam monomers (typically polyvinylpyrrolidone) are useful film formers that confer conditioning properties such as good wet and dry combability feel, volume, and handle ability.[332]

An interesting stimuli-responsive system is formed from responsive particles with two contrasting polymers adsorbed to the particle core.[333] These moieties adsorb to the hydrophilic hair surface and render it hydrophobic, thereby conferring conditioning attributes to the hair. For example, grafting of aminopropyl-terminated dimethicone and polyethylenimine on titanium dioxide particles produces responsive particles. These particles form stable dispersions in water and aqueous solutions because they are sterically stabilized by expansion of the polyethylenimine into the aqueous medium. When they are deposited on hair and dried, the polyethylenimine layer collapses and the dimethicone layer expands to change the sterically stabilized hydrophilic surface to a hydrophobic surface, which is perceived as conditioned hair.

Freeze-thaw stability can still be a problem for concentrated or vesicular phases. The subject of freeze-thaw stability in this context is addressed by researchers who have developed new hydrophobically modified alkali swellable (HASE) in which the hydrophobes are specially designed macromonomers (Fig. 13.17).[334]

Two-in-one shampoos based upon complex coacervation were introduced in the 1970s and this mode of deposition continues to be improved. Early two-in-one shampoos were based upon the cationic cellulose derivative Polyquaternium-10 (Fig. 13.18) and the cationic galactomannan guar hydroxypropyltrimonium chloride.

Complexes of these cationic polymers with anionic surfactant were solubilized in excess surfactant and were induced to phase separate as a coacervate liquid phase upon dilution during the rinsing cycle. Thus, upon dilution with water, complex coacervate (formed from the cationic polymer and anionic surfactant) separates from solution as the shampoo is rinsed from the hair.[335] This triggered phase separation has also been used to deposit conditioning agents such as silicones and therapeutics such as the antidandruff agent zinc pyridinethiol *N*- oxide.




Polyquaternium-7

**FIGURE 13.16** Polyquaternium-11 is a copolymer of acrylamide and diallyldimethylammonium chloride.

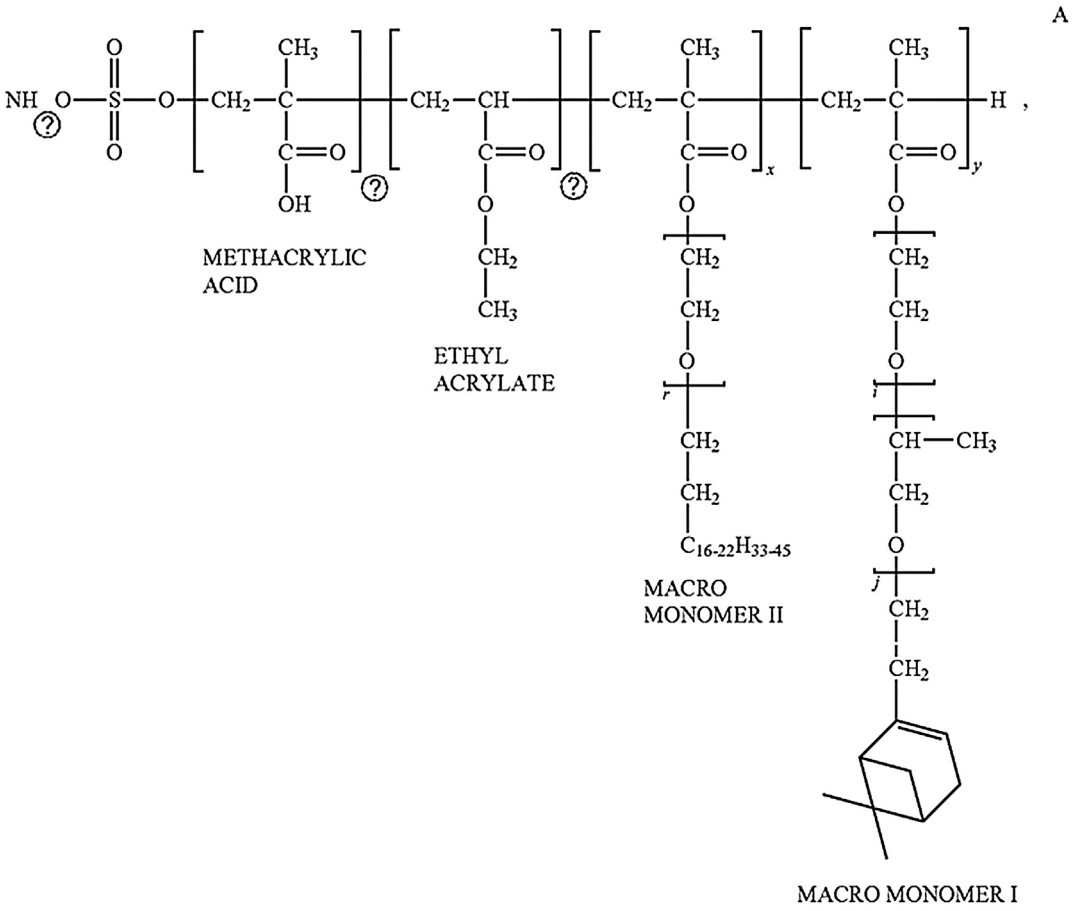



FIGURE 13.17 An example of a HASE thickener with two specifically designed macromonomers.

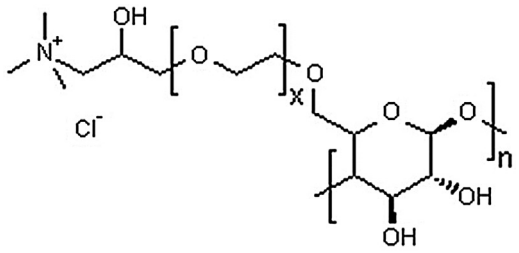



FIGURE 13.18 Polyquaternium-10 is a cationic derivative of hydroxyethylcellulose.

Guar hydroxypropyltrimonium chloride is a cationic polygalactomannan that has been used for three decades as a hair-conditioning polymer that dilution-deposits coacervate phases from anionic surfactant compositions.

The aggregation process of coacervate formation between oppositely charged polyelectrolytes and surfactants has been explained by Dubin and coworkers[336] as electrostatic interactions between the oppositely charged polymer molecules and surfactant micelles in which there are two distinct regions of coacervate formation at different micelle charge densities. The Dubin model indicates that micelle charge density controls coacervate formation. For oppositely charged polyelectrolyte and surfactant molecules, the surfactant binds to the polyelectrolyte due to electrostatic attractive forces. As the complex neutralizes, coacervation occurs as the intrapolymer complexes develop into interpolymer aggregates. At higher micelle charge density, coacervate precipitation occurs due to strong electrostatic interactions. Polyquaternium-7 and Polyquaternium-10 have been used in formulations over the last

30 years. They have large differences in charge density.[337] According to the Dubin model, these differences of charge densities explain the different interactions these polymers have with surfactants in a system.

On the other hand, Goddard[338–340] has proposed that the coacervate formation process is a site-specific ion–ion interaction. Here, the cooperative process between the electrostatic interaction and hydrophobic association/segregation governs complex formation. The association between the surfactant anion and the polymer cations is driven by the resultant loss of free energy. Thus, a loss of enthalpy accrues from the ionic attraction between polyions and surfactant ions of opposite charge, and the release of soluble counterions into the surrounding media results in a gain in configurational entropy. The formation process is also driven by hydrophobic interaction between tail groups of the bound surfactant molecules, resulting in intramolecular and intermolecular association of these groups.

Goddard[338,341] observed that complexes formed between the oppositely charged polyelectrolyte and surfactant system depend on the surfactant concentration and involve surfactant binding, phase separation, and resolubilization.

Goddard'[342,343] demonstrated that above the critical concentration of the surfactant, known as the critical aggregation concentration (CAC), site-specific interactions occur between anionic surfactant molecules and cationic sites along the polymer backbone. Increased interactions between the polymer and surfactant molecules are driven by increasing the surfactant concentration. However, a threshold occurs where the polymer-surfactant complex phase separates from the aqueous solution to form a polymer-surfactant coacervate. As the concentration of the surfactant is increased above the CMC of the polymer-surfactant system, the coacervate can become soluble to form a single-phase system.

The basic, yet unresolved, difference between Goddard's hypothesis and Dubin's hypothesis derives from Goddard's explanation that coacervation results from single ion–ion interaction whereas Dubin's explains the phenomenon as arising from a colloidal interaction between the polyelectrolyte and the surfactant micelles.

Conditioning shampoos commonly contain dispersed silicone droplets that are expected to deposit on the hair surface during shampooing to confer conditioning benefits. If the silicone is not removed by subsequent shampoos, it can build up on the hair causing "droop" and flatness. Moreover, the relatively large silicone droplets scatter light and the resultant lack of product clarity is often hidden by adding opacifiers to the shampoo or packaging in an opaque bottle. If pregelatinized starch, such as hydroxypropyl distarch phosphate, is included with Polyquaternium-10, transparent conditioning shampoos can be obtained.[344]

Another way to minimize buildup is to treat the hair with water-in-water emulsions that can be prepared by including cationic polymers with soluble salts in surfactant compositions.[345] These water-in-water emulsions provide conditioning benefits with good spread of the conditioning phase on the hair and less chance of buildup.

Coacervates formed from certain cationic starches (having molecular weights in the range of about 850,000 to 15 million, and charge densities in the range 0.2–5 milliequivalents/gram) and anionic surfactants in the presence of zinc pyrithione (antidandruff shampoos), do offer enhanced deposition of conditioning agents on hair without undesirable "buildup" on repeated shampoo applications.[346]

More recently, non-guar galactomannans have been introduced to two-in-one shampoos and also to conditioners.[347–353] One cationic galactomannan that was highlighted for rheology modification and deposition is cationic cassia.[354,355] Guar gum has a galactose side group approximately for every two mannose backbone units, whereas cassia has only one galactose for every five mannose backbone units, and the galactose units are bonded to the C-6 position of the mannose unit. These galactose groups sterically hinder the substitutable C-6 hydroxyl unit and this limits the extent of possible cationic substitution on guar gum. In cassia, however, there is less steric hindrance of the C-6 hydroxyl group and, consequently, higher degrees of cationic substitution are possible with cassia (60% for cassia relative to 30% for guar). Higher galactose substitution leads to better water solubility. Consequently, guar gum is soluble in cold water but cassia gum is only sparingly soluble in cold and hot water.

These cationic polymers operate by depositing a polymer-surfactant complex coacervate that separates as a distinct phase during the rinsing step of the shampoo process. Maximum coacervate deposition occurs at precise ratios of cationic polymer:anionic surfactant but the optimum ratio for coacervation might not coincide with the best ratios for cleaning and foaming.

Hydrophobic modification of cationic hydroxyethylcellulose is claimed to endow better efficacy. Polyquaternium-24 is a hydrophobically modified cationic hydroxyethylcellulose. The polymer provides enhanced depositions of cosmetic oil from a bodywash formulation[356] and it also improves upon the performance of higher substituted versions that give good foaming but poor substantivity and impractical high viscosities.

Polyquaternium-24 is also a preferable thickener for zinc-depositing compositions. Anionic thickeners are not appropriate for this purpose because they bind with the metal. Therefore, cationic or nonionic thickeners are preferable and Polyquaternium-24 is appropriate for this purpose.

Cationic guar has been a known additive for two-in-one shampoos for more than three decades. It has now been shown that improved post-shampoo detangling times are achieved by including a small degree of hydrophobic

substitution in the cationic guar derivatives.[357] The hydrophobe is added by the well-known ring opening of the appropriate glycidyl ether. Cationic hydrophobically modified galactomannan ethers (specifically guars) are water soluble when the degree of cationic substitution is from 0.01 to 0.5 and the degree of C12–C32 alkyl substitution is below 0.001. If the hydrophobic substitution is raised from this tiny amount, the solubility in water is compromised.[358]

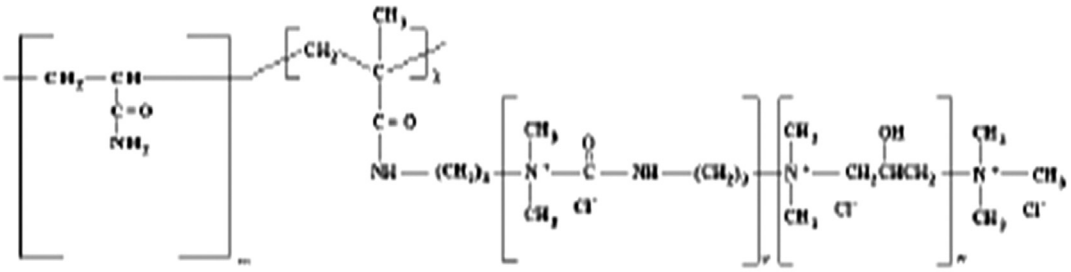
Synthetic copolymers of acrylamide with a monomer having three quaternary groups (Polyquaternium-76) (Fig. 13.19) are postulated to provide improved deposition on hair and improved conditioning performance with respect to wet combing.[359]

To date much of the study of coacervate deposition on hair has been focused on liquid systems. However, in real application, the shampoo is foamed on hair prior to rinsing. This raises the question of the significance of the surfactant foam on the delivery of coacervate to the hair surface. This is a reasonable question because, in processes such as mineral froth flotation, hydrophobic particles are readily separated from hydrophilic particles and concentrated in the froth. In shampoos, lather is believed to give the consumer a perception of cleansing as they use the product. To achieve this rich lather, surfactant concentrations are typically greater than those needed to cleanse even the most soiled hair.[360]

### 13.6.1 Coacervate in the Foam

Upon foam formation, surfactant molecules adsorb at the air–water interface of the foam film (Fig. 13.20).

At certain concentrations of polymer and surfactant, coacervates form in the solution. As foaming/lather formation occurs, it has been postulated that the coacervate present in the solution is adsorbed into the crust of the foam



Polyquaternium -76

FIGURE 13.19 Polyquaternium-76 has three quaternary nitrogen groups in each side chain.

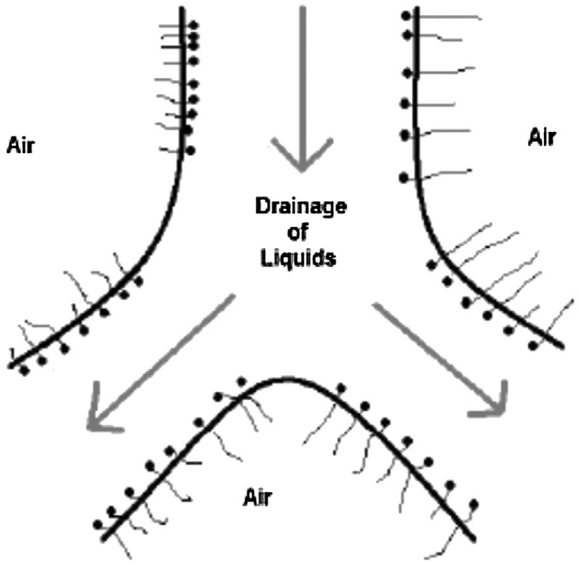



FIGURE 13.20 Schematic of surfactant alignment during foam formation.

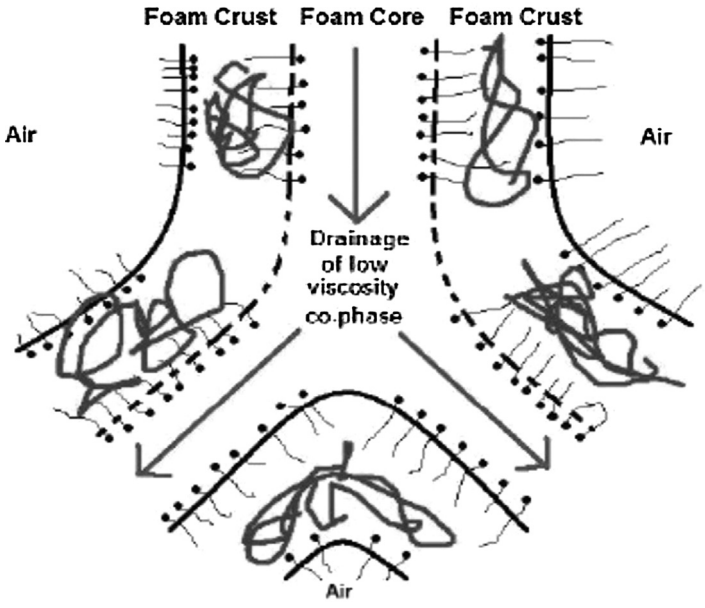



FIGURE 13.21 Schematic of coacervate presence in foam.

lamella as shown in Fig. 13.21. The high viscosity coacervate gel is present in the lamella crust, while the low viscosity phase is present in the lamellar core.[361]

Chitin is a polysaccharide comprised of β-1→4 linked *N*-acetylglucosamine units, and is found in many places throughout the natural world as the main component of the cell walls of fungi, exoskeletons of crustaceans (crabs, lobsters, shrimps) and insects. Chitin is one of the most abundant naturally derived materials in the world. However, chitin is generally insoluble in most cosmetic solvents.

Chitosan is a polysaccharide comprised of β-1→4 linked D-glucosamine units. Chitosan is produced commercially by deacetylation of chitin (the degree of deacetylation (%DA) ranges from 60% to 100%), but can be found naturally, particularly in the cell walls of some fungi. The amino group in chitosan has a p*K*a value of ~6.5, thus, chitosan is positively charged and soluble in acidic to neutral solution, and will bind with negatively charged surfaces.

Although the naturally derived polymers discussed herein have potential in hair-styling applications, none are a perfect replacement for synthetic polymers. There is an opportunity in the industry in identifying new chemical approaches to add cosmetic functionality to naturally derived polymers. There are many areas where no naturally derived polymer alternative for styling formulations has been found. The big opportunity is to develop naturally derived hair care polymers that can be considered not only as commodity formulation ingredients but as truly functional materials.

### 13.6.2 Enhancing Mildness

Isethionates are surfactants that have been noted for their mildness to skin and for at least three decades they have been the basis of non-soap detergent bars. The mildness can be enhanced even further by including mildness benefit agents that can be flocculated by cationic polymers present in the formulation and delivered as flocs upon dilution of the formulation.[362] The preferred benefit agent in this case is petrolatum and the cationic polymers are well-known polymers like Polyquaternium-10 and guar hydroxypropyltrimonium chloride.

### 13.6.3 Polymers That Mitigate Hair Damage[363]

There are continuing efforts to understand the mechanisms of hair degradation and to devise means to protect or repair the hair from the damage caused from environmental and cosmetic treatments.

It is well known that hair has three structural elements: the cortex, which resides in the interior of the fiber; the cuticle, which is wrapped around the exterior; and the medulla, which is a tubular region of low density that resides within the cortex region. It is also well known that hair can be damaged by exposure to mechanical stress and abrasion from combing and brushing, oxidative stress due to UV irradiation in our oxygen-rich environment, and chemical treatments designed to perm, color, straighten, relax, or bleach the hair.

For example, perming causes hair to lose about 58% of its protein of molecular weight 48 and 60 kDa.[364] After such damaging treatments, it is standard protocol to use conditioners to screen the damage by improving wet and dry combing attributes, conferring soft feel and alleviating static flyaway. However, conventional conditioners do little to restore the hair strength.

Synthetic copolymers of styrene and acrylates can be utilized to coat damaged hair for improved shine. An advantage of using polymers as hair fixatives is to minimize the use of the more commonly employed silicones, which can compromise fixative properties.[365] This method does not repair damaged hair but relies on the high refractive index of latex polymers as the means of attaining gloss/luster of the polymer-treated hair.

Aminofunctional silicones have been shown to offer protection from the damage incurred from bleaching and oxidative dyeing and they do confer effective conditioning and visual shine and smoothness to the hair.[366] Multisequenced cationic polydimethylsiloxane-polyether copolymers are claimed to improve combability, softness, volume, shapeability, manageability, disentangleability, and shine of hair, both damaged and undamaged.[367]

MQ resins are highly branched silicone resins that have been used extensively to confer transfer-resistance to color cosmetics. These resins are useful materials for the repair of split ends.[368] Stable emulsions of MQ resins that matched the surface energy of hair facilitated spreading of the emulsion on the hair surface, to uniformly distribute the deposited MQ resin on the hair. The surface energy of healthy hair and damaged hair is reported to be 24−28 dyn/cm and 20 to about 50 dyn/cm, respectively. The intent in this case is to ensure that the external phase of the emulsion has such an affinity for the hair that it spontaneously spreads along the hair shaft, thereby causing the emulsion to break and coat the hair with a film of coalesced, plasticized MQ resin that is sufficiently strong to resist removal through many wash, blow dry, and styling cycles. The appropriate emulsion is achieved by emulsifying the plasticized MQ by sequential addition of emulsifiers. The emulsion was applied to the split ends of a hair tress, then washed, rinsed, and blown dry and subjected to two passes with a hot iron at a temperature of approximately 425°C. This cycle was repeated multiple times without reapplication of the MQ resin emulsion. After the first cycle, all of the split ends were mended. After the sixth cycle, 75% of the split ends remained intact.

Hair is photodegraded by both UVA and UVB radiation. UVB radiation (280−320 nm) is mostly absorbed by the cuticle where it is responsible for protein loss by breaking disulfide bonds on the surface of the cuticle, while UVA radiation (320−400 nm) is able to penetrate the cuticle layers where it produces reactive oxygen species and causes oxidation of amino acids, sterols, and fatty acids, decomposition of lipids, and a decrease of melanin within the cortex.[369,370] Tyrosine and tryptophan residues in hair proteins absorb strongly in the ultraviolet region, and they act as photosensitizers for photochemical damage.[371] The melanin pigment in hair protects hair against photodamage by absorbing across the visible and UV spectrum and acting as a free radical scavenger, thus preventing the radicals from entering into the keratin matrix.[372,373] However, even melanin is photodegraded and this is manifested by a fading of the color of hair upon UVA exposure.[374] For this reason Kojic acid (5-hydroxy-2-hydroxymethyl-4-pyranone) has been used for hair lightening because it is a tyrosinase inhibitor that operates by chelating the copper atoms in the enzyme. However, exogenous copper actually increases UV damage of hair.[375] It is proposed that copper acts as catalyst with photoproduced hydrogen peroxide to form reactive alkoxy radicals that degrade tryptophan and similar amino acid components of the hair protein. Menthyl carbamate compounds have been developed to lighten hair and skin without tyranosinase inhibition.[376]

Keratins are a group of more than 30 cytoskeletal proteins that are intertwined and linked through covalent disulfide bonds, coulombic salt bonds, hydrogen bonds, and dispersion forces to form microfibrils in the hair cortex. They are divided into two subsets: type I keratins that are acidic and have molecular weights in the range of 40−48 kD; and type II keratins that are basic to neutral and have molecular weights from 58 to 65 kD.[377] UV radiation causes structural changes within keratin by oxidation of amino acids, resulting in the rupture of sulfur linkages.[378] These types of damage result in decreased shine, color fading, weakened structural integrity, and breakage. Many approaches have been implemented to use polymers to prevent, repair, or mask the damage to UV-exposed hair. Protein hydrolysates have been incorporated into hair products for decades, and soluble keratin has been offered as a hair strengthener/protectant/conditioner,[379] and peptides with strong affinity to hair and nails have been bioengineered.[380] Sulfonated wool keratin applied to the hair in a conditioner formulation with stearyl amidopropyl dimethyldiamine has been shown to condition and strengthen bleached hair.[381] A suggested mechanism for the binding of the sulfonated keratin to the surfaces of the damaged hair is that the anionic sulfonated keratin forms a complex with the cationic surfactant and this complex has an affinity for the negatively charged damaged hair.

Amphipathic self-associating peptides form gels that are triggerable by pH, and they can be triggered to self-assemble into Beta sheet tapes, ribbons, or fibrils.[382] The fibrils can be spun into high-tensile-strength fibers. These self-assembled structures can be seeded with cells, and in this capacity they can serve as scaffolds for tissue engineering. Such structure-building peptides may offer the potential of strengthening damaged hair by adsorption

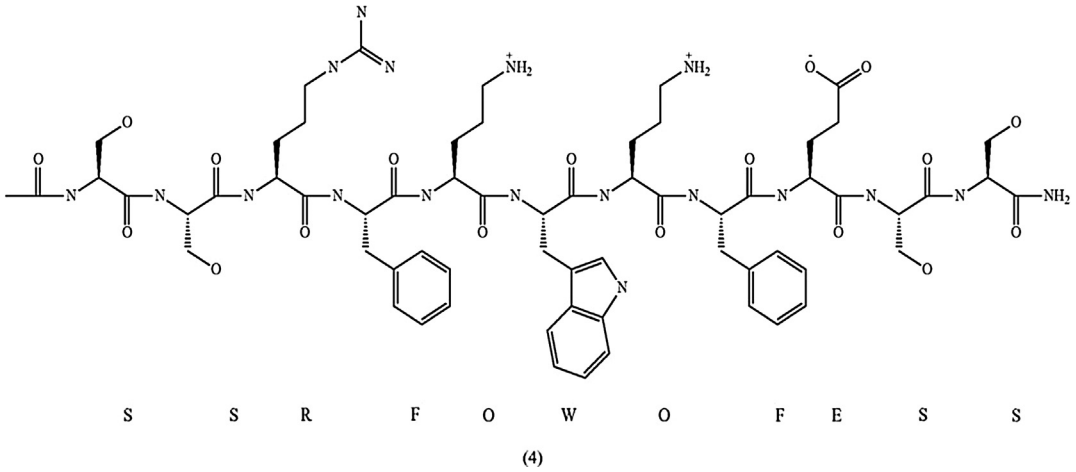



FIGURE 13.22 Amphipathic self-assembling peptide carrying a net 2+ charge at physiological pH. *Reproduced from U.S. Patent Application 20140044649.*

thereto. It is especially of interest that the peptides can be constructed to have selectively negative or positive charge at physiological pH values and thus they can be designed to adhere to negatively charged hair keratin. Examples of such positively charged peptides are shown in Fig. 13.22 and examples of the self-assembled structures attainable from such peptides are shown in Fig. 13.23.

Polyglycerol partial esters with an average degree of polymerization from two to eight have been disclosed as additives that enhance the grip and elasticity of hair and also protect the hair against heat damage.[383] They are also disclosed as hair-repair and hair-strengthening agents. The mechanism by which these compounds achieve their results is not specifically disclosed but it is unlikely that such large entities could penetrate into the cortex of undamaged hair, but they could possibly reach the cortex of damaged hair from which the cuticle was stripped.

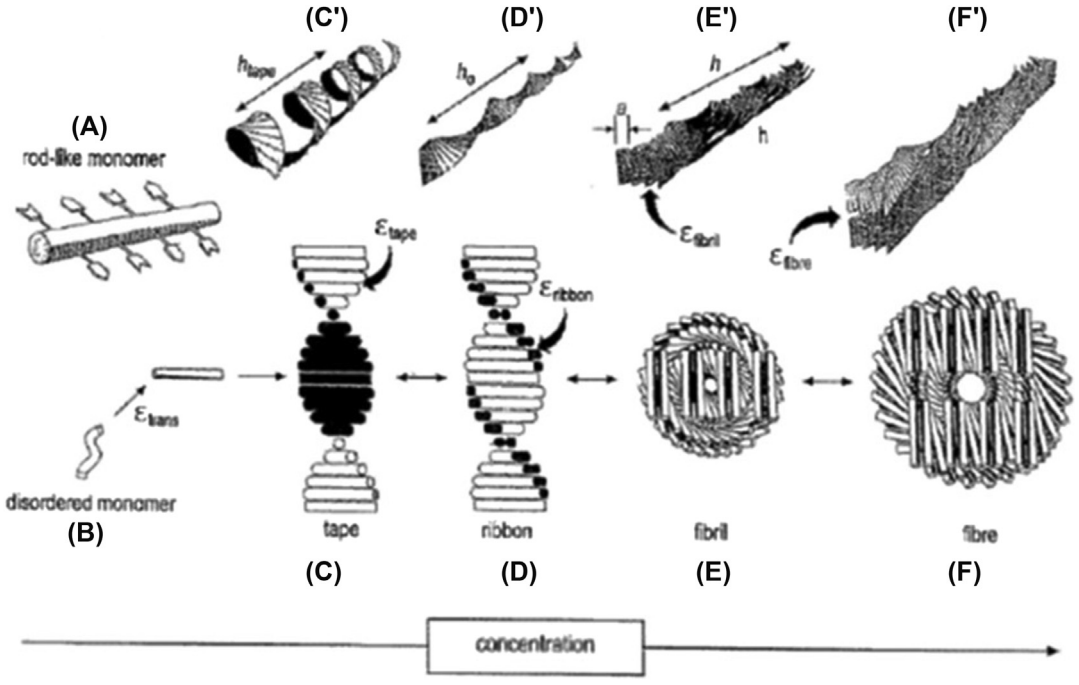



FIGURE 13.23 Amphipathic peptides can self-assemble to fibrils, tapes, helices, and rods. *Reproduced from U.S. Patent Application 20140044649.*

### 13.6.4 Polymers to Strengthen Permed Hair

Permanent waving involves a first step of reducing the cystine bonds within the hair fiber followed by shaping the hair into the desired style, then reoxidation to restore the S−S bonds into their new configuration. This process is known to damage the hair, and the damage is exacerbated by the common practice of heating the hair with perming irons. Many treatments have been applied to mitigate the damage. The application of cationic polymers to the hair surface during the perming process can lessen the damage.[384] Examples of such an approach include:

1. A reducing treatment with cysteine and protection from an amodimethicone;
2. Reduction of the hair in the presence of a fixing polymer that is precipitated by the reducing agent restrengthens the hair.[385] The precipitated polymer holds the hair in shape during the reduction and fixing steps, which alleviates the need for mechanical tensioning. Moreover, the set lasts twice as long as the conventional treatment. Crotonic acid/vinyl acetate/vinyl t-butyl benzoate terpolymer is known for this treatment.

### 13.6.5 Polymers for Improvements in Hair Coloring

Conventional conditioning agents are incompatible with hair dye formulations but there is a need to simultaneously color and condition the hair. This is achieved by the addition of ethylene acrylic acid copolymers optionally in combination with a metallocene polymerized polyolefin.[386] The addition of just 1% of these polymers led to advantages in wet combing benefits.

The oxidizing agents used in hair colorants do damage the hair fibers. Moreover, the rapid kinetics of oxidation can cause uneven coloring of the hair, especially when long preparation procedures are involved such as in selective highlighting. Encapsulation of the oxidation precursors with polymethacrylates, poly(vinylacetate)s, or shellac allows the coloring process to be more uniform.[387]

## 13.7 POLYMERS FOR THE TREATMENT OF SKIN

### 13.7.1 Hyaluronic Acid for Antiwrinkle Treatment

The skin is the largest organ in the body. It is a complex organ with an active metabolism, and it simultaneously functions as the body's protective barrier against loss of moisture, the intrusion of environmental toxins, and harmful electromagnetic radiation. The skin undergoes natural, or *intrinsic* aging, which leads to fine lines and wrinkling that are prominent signs of senescence. In aged skin intercellular substances are degraded and the skin's ability to retard moisture loss is impaired. Alternatively, *extrinsic* aging of the skin occurs due to repeated exposure to UV light and environmental pollutants such as cigarette smoke. Actinic aging due to UV exposure manifests itself as pronounced and obvious wrinkling. Such deep wrinkling is due to the loss of elasticity of the skin as a consequence of the destruction of elastic fibers in the reticular dermis. Hyaluronic acid is a high-molecular-weight polysaccharide that exists naturally within the dermis and contributes to the hydration and elasticity of the skin. Hyaluronic acid has been included in skin treatment compositions for several decades. However, hyaluronic acid, whether injected or topically applied, is rapidly degraded. Consequently, a method for treating skin defects, including wrinkles, embraces creams that should contain both hyaluronic acid and an inhibitor of hyaluronic acid degradation.[388] Glycyrrhetinic acid is a suitable inhibitor for this purpose.

Topically applied high-molecular-weight hyaluronic acid (500,000 to 3 million Da) forms films on the skin, which act as barriers against moisture loss. Low-molecular-weight hyaluronic acid (500−50,000 Da), on the other hand, is claimed to permeate and moisturize the skin. Topical compositions containing high- and low-molecular-weight hyaluronic acids in combination with antiinflammatory polysaccharides are claimed to have antiaging effects on skin.[389]

### 13.7.2 Mitigation of Skin Irritation and Inflammation

The conventional way of treating skin irritation or inflammation is to apply topical products that contain ingredients that are believed to have antiirritant or antiinflammatory properties. However, there are many biologically reactive pathways that lead to these adverse skin conditions, and these ingredients often do not address all of the pathways. Pathways that contribute to skin inflammation include the Adhesion pathway, the Chemotaxis pathway, the Collagenase pathway, the COX pathway, the Elastase pathway, the Histamine pathway, the Histamine Receptor

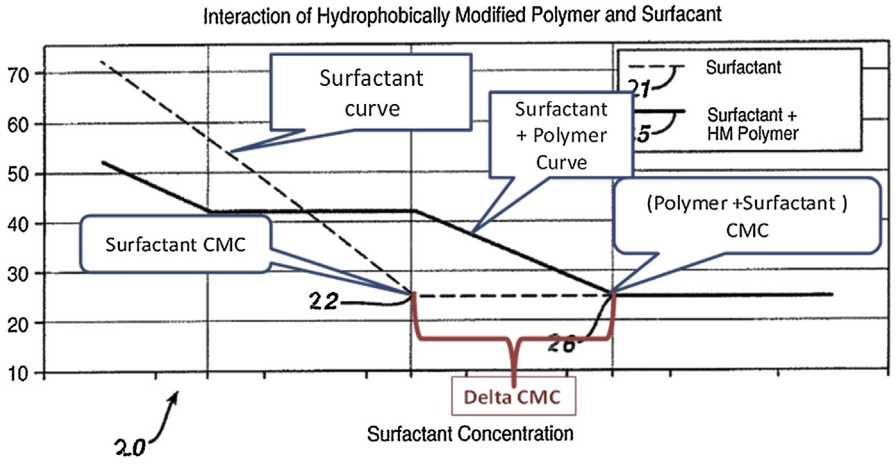



FIGURE 13.24 Delta CMC is defined as the difference between the measured CMC for the surfactant + polymer composition and the surfactant composition alone.

pathway, the LO pathway, the PDE pathway, the PLA-2 pathway, and the VEGF pathway, and ingredients can be selected that inhibit each pathway to be included in a composition for normalizing skin.[390]

Skin cleansing usually involves detergents. However, detergents have a tendency to cause skin irritation and there is a need to mitigate the effects of these known irritants. Certain non-cross-linked linear acrylic copolymers can lower the irritation potential of surfactants and provide products that are both clear and highly foaming.[391] The preferred polymers interact with the surfactant and effectively shift the CMC to higher concentrations, while lowering the critical aggregation concentration—the latter being the concentration at which the surfactant selectively interacts with the polymer rather than adsorbing at the liquid surface. It is postulated that free surfactant molecules and free surfactant micelles are responsible for irritation of skin and eyes and that binding of the surfactant to the polymer effectively reduces the concentration of free micelles. In order to assess the potential efficacy of polymers to interact with surfactants in this way, measurements are taken of the difference between the CMC of the surfactant alone and the higher concentration of the surfactant in the presence of polymer. The difference between these two values is termed delta CMC. Larger values of delta CMC for a particular surfactant indicate a lowering of the irritation potential. The delta CMC provides a measure that is useful for selecting, comparing, and optimizing polymers that reduce the irritation potential of selected surfactant systems. A particular acrylates copolymer that also effectively provides "back-acid" thickening has been identified as a polymer that exhibited a satisfactory "delta CMC"[392] (Fig. 13.24).

### 13.7.3 Multicomponent Complexes for Cleansing and Treatment of Skin

Skin hygiene traditionally involves the use of soap and water, and thorough cleansing with abrasive soaps entails exfoliation of the skin surface. The inclusion of fibers, filaments, and/or particles having core-sheath structures provided improved products for exfoliating while cleansing the skin.[393] However, these dispersed elements tended to trap hair and debris with continued use and this gave the product an unsanitary appearance. This problem has been tackled by introducing discrete elements constructed from a water-soluble core and an erodible shell[394] such as a core of poly(ethylene oxide) and a shell of stearyl alcohol. As these discrete elements are exposed at the surface of a soap bar, the erodible shells are abraded or dissolved and the water-soluble cores readily detach from the surface.

Controlled release of actives, such as ascorbic acid, to the skin may be accomplished by including the active in a multicomponent layer that partially coats a pigment, such as titanium dioxide. Incomplete coverage of a pigment particle by a hydrophilic coating and a hydrophobic deposit and finish can individually tailor the release of actives to the needs of the skin of the user by the action of the stratum corneum proteases.[395] Hydrophobic actives are contained within the hydrophobic deposit, and hydrophilic actives are included in the hydrophilic coating. Exemplary hydrophobic deposits are dimethicone and trimethysiloxysilicate, and hydrophilic deposits can be selected from water, glycols, glycerin, water-based gums, Carbomer/water-based gels, acrylates copolymers, quaternary amine compounds, and/or carbohydrates.

### 13.7.4 Removing Wrinkles by External Tensioning and "Playing Tricks With Light"

The appearance of wrinkles can be mitigated by mechanical means that depend upon the formation of a tensioning film on the skin to temporarily overcome the sagging of the wrinkled skin underneath. This effect can be achieved by application of a film-forming anionic or amphoteric polyurethane[396] or by the application of an interpolymer of a polyurethane and a polvinylpyrrolidone/silicone copolymer[397] (INCI PVP/Dimethiconylacrylate/Polycarbamyl).

Cosmetic artists have long used concealing makeups to hide wrinkles and skin defects, but these products are opacifiers that give the wearer a matte "made-up" look. In recent years there has been a move to foundations that "play tricks" with light to conceal skin blemishes. These products give a more natural look to the skin of the wearer. In this vein, compositions containing a number of distinct particulates have been advanced for the purpose of filling and hiding fine lines and wrinkles.[398] The particulates are chosen to have complementary size ranges and this is forwarded as a reason for them to pack closely within facial lines. The particulates may be chosen polyethylenes, polymethylsilsesquioxanes, siloxanes, polyamides, polyolefins, polystyrenes, polytetrafluoroethylenes, polyurethanes, polymethacrylates, starch and starch derivatives, and composite particles. For example, the first particulate is a polyethylene having a median particle size from 10 to about 30 μm and the second particulate is a starch with a median particle size from 0.5 to 15 μm, while the third particulate is polymethylsilsesquioxane with a median particle size from 0.5 to about 15 μm, and the fourth particulate is a polyamide with a median particle size from 3 to 20 μm. These particles are delivered in silicone-in-water emulsions that provide a desirable feel to encourage frequent usage, especially to provide chronic or long-term benefit. Silicone elastomers provide the silky, nongreasy feel. The silicone-in-water emulsions are preferred in this case over water-in-silicone emulsions in order to overcome stability problems and processing complexities.

## 13.8 POLYMERS AS CONTROLLED RELEASE MATRICES

Encapsulation is useful for adding stability to ingredients that could lose efficacy by reacting with other formulation ingredients during storage. Encapsulation is also useful to protect ingredients against degradation by light, oxidation, heat, or extremes of pH. The beneficial agents protected could be sunscreens, skin lighteners, moisturizers, emollients, perfumes, flavors, and oils. Microencapsulation can also be employed as a route to controlled delivery for cosmetics and dermatological therapeutics.

Differential solubility with respect to pH can also be used to encapsulate oils. For example, alkali metal salts prepared from ethylene/maleic anhydride copolymer are soluble in solutions of high pH but insoluble at low pH. Microcapsules can be formed by dispersing oils in aqueous solutions of ethylene/maleic anhydride at high pH and then reducing the pH to the region of 5–8 to allow the polymer to precipitate and coat the surface of the dispersed oil droplets.[399]

Complex coacervates prepared by the interaction of cationic and anionic polyelectrolytes can be employed as encapsulants.[400] Simple coacervates can also be formed by the addition of polymers like polyethylene to solutions of ethylcellulose in cyclohexane, and this process has been applied to the formation of microencapsulation of pharmaceutical actives for the purpose of taste masking.[401]

Polycaprolactone oligomers are insoluble in water and in shea butter. When heated, however, the polymer dissolves up to 10 wt% in the shea butter. This preferential solubility behavior allows the preparation of nanocapsules by heating homogenized dispersions of mixtures of shea butter, water, and polycaprolactone oligomers to 80°C then cooling to 20°C to allow coacervate to form at the oil–water interfaces.[402]

Polysaccharide-zein complexes are appropriate for the delivery of shear sensitive microparticles containing active agents.[403] Zein is a water-insoluble/alcohol soluble prolamine from corn gluten that is highly resistant to bacterial attack. The advantage of this system is exemplified by an herbal essence/agar–zein complex in a skin cream. The skin cream conferred a distinctive and lingering herbal odor, and it was reported to be nonirritable. Films formed by combining a water-soluble polymer with a water-insoluble polymer can be used as controlled release delivery systems for therapeutics, fragrances, flavorings, colorants, or other cosmetic materials.[404] The polymers and the functional active agents are prepared in the form of a slurry that is cast into a film. Preferably, the film is cut into pieces such as flakes and the flakes are then incorporated into a liquid vehicle to make the final product. For skin care applications, the functional materials can be surfactants, sunscreens, conditioners, moisturizers, antioxidants, enzymes, antibacterial agents, occlusive agents, exfoliants, lighteners, and antiaging ingredients. In an example of a bodywash, the film is formed by mixing PVP and PVP/VA copolymer, a dispersion of poly(ethyl methacrylate)

in ethanol and a functional ingredient in ethanol. A film was cast from the resulting polymer solution/slurry and the film was cut into flakes that were suspended in a bodywash formulation that contained sufficient acrylates copolymer to stably suspend the flakes.

Conjugates of drug molecules with polymer is an approach that has been used to circumvent the difficulties of delivering "problem" actives. Polymers such as poly(hydroxypropylmethacrylate), poly(ethylene glycol), and poly (-L-glutamic acid) have been used for this purpose. These approaches have been combined by covalently attaching cyclodextrin moieties to polymers by covalent attachment to polyvinyl alcohol or cellulose, or by copolymerization with vinyl acetate or methyl methacrylate.[405] There have even been polymers made in which the polymer backbone is threaded though the cyclodextrin rings.[406] Biocompatible, water-soluble polymers containing covalently attached cyclodextrin moieties can be used for the purpose of conjugating guest molecules by attachment that can be cleaved under biological conditions.[407] These cyclodextrin-containing polymers improve actives stability and solubility, and reduce toxicity of small molecule therapeutics when used in vivo. Moreover, by selecting from a variety of linker groups and targeting ligands the polymers can provide controlled delivery of a wide variety of therapeutic ingredients.

### 13.8.1 Enhanced Delivery

Perfume can be the costliest ingredient in a formulation, and economic benefit can be realized by enhancing the deposition of fragrance on target substrates and prolonging the duration of release of the desirable fragrance. There are also consumer perception benefits that can be derived from controlling the release of the different perfume components with respect to time. For example, "freshness" attributes are usually associated with "top notes" and "middle notes." However, "top notes" can be quickly lost due to evaporation and they tend to dissolve easily in aqueous media and be rinsed away. This challenge has been addressed by polymer particles that selectively adsorb/absorb top notes and middle notes of perfume and enhance deposition from rinse-off personal care products.[408] The polymeric particle contains a cationic polymer and a perfume with a C log P value that indicates that partitioning of the substance is one thousand-fold preferentially into the octanol phase rather than the water phase. The Kovats index system is an accurate method of reporting gas chromatographic data for interlaboratory substance identification. The efficacy of the polymer particles in depositing and releasing the different perfume raw materials can be rated by their Kovats index. Possible "cationic" monomers for synthesis of the selective perfume-releasing polymers are dimethylamino alkyl acrylates, vinyl pyrrolidones, vinyl imidazoyls, vinyl ethers with diethylamino groups, vinylpyridines, alkyl acrylamides, and dialkylaminoalkyl acrylamides. A preferable copolymer is made from methyl methacrylate and dimethyl aminoethyl methacrylate cross-linked with ethylene glycol dimethacrylate.

## 13.9 DENDRITIC POLYMERS

Iontophoresis is a process whereby an electrical potential is applied across the skin to enhance transdermal delivery. The intrusion is controlled by containing the active ingredients in a gel within a small reservoir to which the potential is applied. Dendrimer gels have been recommended for this purpose.[409] The words *dendrimer*[410] (coined by Tomalia) and *arborol* (coined by Newkome) are derived from the Greek *dendro* (meaning treelike) and the Latin *arbor*[411] (meaning tree to describe the fractal-like branched structures of these molecules). Dendrimers and arborols are prepared by a series of iterative steps, each designed to add one sequence of successive segmental units to the outside of the molecule. Each sequence is called a "generation." Dendrimers can be constructed by a divergent synthesis or a convergent synthesis. Divergent construction starts with the cone of the molecule and builds out generation by generation. In convergent construction the branches are assembled first, and then they are brought together and bound by the core. Dendrimers and arborols are more precise branched molecules than hyperbranched polymers. Hyperbranched polymers, first patented by Kim in 1987,[412–414] are prepared in a single pot process and, as a consequence, the individual molecules within the product vary in molecular weight and structure.

Amphipathic arborols are capable of self-assembling into micelles.[411] The solubility of one-directional arborols in water decreases dramatically with increasing length of the alkane hydrophobic group, from 13.0 mmol/L when $n$ is 6, to 1.4 mmol/L when $n$ is 8, to less than 0.017 mmol/L when $n$ is 9, for [9]-$n$ arborols.[415] At concentrations significantly higher than the critical micelle concentration, there is a possibility that amphipathic arborols would form gels by hydrophobic association and these gels might be expected to have a more uniform pore size than conventional

polymer gels. This could be the reason that these interesting treelike molecules are being proposed for use in iontophoresis reservoirs to enhance the selectivity of delivery of active substances across the skin.

Cationic hyperbranched copolymers are used in shampoos to confer a volumizing effect on the hair.[416]

## 13.10 POLYMERIC ANTIMICROBIALS AND BACTERIOSTATS

One aspect of sustainability is to enhance the sustainability of the human being who is the customer, by mitigating or eradicating the presence of harmful or perceived harmful ingredients. One subject of such perceived concern is the use of antimicrobial ingredients. Small-molecule preservatives are coming under increasing scrutiny, especially in Europe, and polymeric antimicrobials are being investigated with the hope that they will function effectively in the product but will not permeate the skin barrier. There is an apparent dilemma here—because antimicrobials must be active biocides against living microorganisms but should not be harmful to humans, their animals, or their plants. It has been argued that polymeric antimicrobials could be designed to be effective against a broad spectrum of harmful microorganisms, but the polymeric agent itself would be too big to penetrate the skin, and this would add an element of safety to the use of broad-spectrum antibacterials. A geographically diverse group of researchers have approached this challenge by substituting polyethylenimine with alkaryl groups.[417] The expectation is that, in addition to being less able to penetrate the skin, these materials would be more substantive to skin, which would provide antimicrobial protection for a longer duration and reduce the amount of these compounds that would be released to the environment. Moreover, functionalization with other functional groups could allow the solubility of the antimicrobial agent to be designed, and incorporation of several antimicrobial groups into one polymeric molecule could allow the formulation of "broad-spectrum antimicrobial cocktails" without the worry of the incompatibilities that are encountered when one tries to add more than one antimicrobial compound to a formulation. The polymeric antimicrobial approach is interesting and is one to be watched as it emerges to, hopefully, make our products even safer than the present exceptionally high level of safety.

In an interesting application, University of Florida researchers have pointed to silanols as antibacterial agents.[418] The silanols are identified as trialkylsilanols, siloxanediols, and siloxanols. These all contain OH groups attached to a Si atom. It is well known that such a bond is unstable with respect to condensation, which converts it to an Si-O-Si group. The latter group is the backbone of silicones, and this reaction is used to prepare silicones and also to drive sol−gel reactions. One way that the researchers overcome this inherent instability is to attach the silanols to polymers that contain hydroxyl groups to "silylated" polymers that release the silanols by hydrolysis "in situ" when the silylated polymer is applied to the appropriate substrate, such as topical application to the skin surface. The silylated polymers include polysaccharides, proteins, poly(alkylene glycol(s)), and amine and hydroxyl terminated polymers. It is also interesting that one embodiment is described in which the silanol is attached to filaments of, for example, cotton especially for use as dental floss.

Antimicrobial agents, such as silver, have been combined with a cross-linked hydrogel to create a hydrophilic polymer antimicrobial system that has potential application in the personal care industry, including cosmetics, skin treatment, diapers, and bandages.[419]

Polymers with antimicrobial properties have been proclaimed. For example, chitosan is readily converted to 3-trimethylammonium-2-hydroxypropyl-*N*-chitosan, *N*-carboxy-methyl chitosan can be converted to an *N*′,*N*′-dimethylammonium propyl carbamoyl derivative and further modified by quaternization to produce a series of chitosan aminoamide quats. The antimicrobial activity of 3-trimethylammonium-2-hydroxypropyl-*N*-chitosan against *Escherichia coli*, *Staphylococcus aureus*, and *Pseudomonas aeruginosa* was demonstrated using the minimum inhibitory concentration test. The derivative exhibited biocidal activity at least an order of magnitude higher than previously reported chitosan antimicrobial agents.[420]

Polyethylenenimine polymers have also been utilized as polymeric antimicrobial agents. For example, an antimicrobial polymer derived from polyethylenenimine was effective against pathogenic gram-positive and gram-negative bacteria, yeasts and molds, and skin flora bacteria.[421] Copolymers and derivatives of polyethylenimine with broad-spectrum antimicrobial properties are active against microbes on contact. It is believed that the large molecular size of these compounds enables them to resist removal from substrates and also prevents their ingress into the lower layers of skin of humans and animals.[422]

Polymeric antimicrobials can also be effective against yeasts. Poly(methylmethacrylate-co-vinylbenzoylchloride) and linear poly(chloroethylvinylether-co-vinylbenzoylchloride) are active against *Candida albicans* and *Candida tropicalis*. The poly(methylmethacrylate-co-vinylbenzoylchloride) proved more active against both *C. albicans* and

*C. tropicalis* because of its increased cytotoxicity on bacteria and its interference with the cell walls. Poly(chloroethylvinylether-co-vinylbenzoylchloride) also proved effective by increasing the permeability of yeast cell walls.

## 13.11 ENVIRONMENTAL AND ECOLOGICAL CONSIDERATIONS

### 13.11.1 Polymers in Skin Products for Ecological Sustainability

The consumer goods sector is driving hard toward providing the products and logistics trains for a sustainable planet.[423–425]

Emulsions are applied to nonwoven substrates to make wipes for application to skin. An interesting innovative concept is to actually make the nonwoven substrate serve the purposes of the emulsion. Commercialization of such products would help to reduce the amount of waste going to landfills. In this context, nonwoven filaments containing an active ingredient have been prototyped to deliver materials to skin, hair, dishes, and laundry.[426] The products are made of fibrous webs of dissolvable fibers that can be quickly and easily dissolved in the palm of the consumer's hand.[427] Moreover, fibers are made of a surfactant, a structuring polymer, plasticizer, an extensional rheology modifier, and other additives that confer the desired attributes of the finished article that could eliminate the water from a formulation and printing, which could radically reduce the amount of packaging material. In a particular prototype, the surfactants are classified into foaming and nonfoaming types. Formulators would recognize the foaming type to be similar to shampoos and cleansers, and the nonfoaming type to be more like conditioners. The structuring polymer is a water-soluble polymer such as poly(vinyl alcohol), poly(acrylate), PVP, PEO, starch, pullulan, or cellulose ethers. When the fiber is spun, these extensional rheology modifiers function to enable the formation of thin fibers rather than a spray of droplets that would be expected from a liquid as a result of Plateau–Rayleigh instability. For the production of sprays, one seeks conditions that favor Plateau–Rayleigh instability, but for the production of fine fibers it is important to try to avoid such instability. Plateau–Rayleigh instability results from perturbations that are always present in a thin liquid tube. Some of the perturbations can grow until they pinch the fiber into drops (this is discussed in Chapter 3). The thinner the liquid tube, the more likely it is to be unstable. If a liquid is viscous or it contains an associating solute or an entangled polymer solution, then the liquid can be spun into much finer filaments. This is directly attributable to the increase in extensional viscosity of the system. Thus the extensional rheology modifiers are required to enable spinning of extremely fine fibers. The finer the fiber, the more quickly it dissolves in the palm of the hand. Extensional rheology modifiers are usually high-molecular-weight soluble polymers. In this case high-molecular-weight poly(ethylene oxide) is preferred. Very fine fibers can be made by several processes such as spunbonding, electrospinning, melt blowing, or melt fibrillation. Spunbonded fibers are produced by extruding a "melt" through a series of fine capillaries, and the filaments are progressively reduced in diameter. Melt film fibrillation was developed Torobin and by Dale Reneker's group at the University of Akron and it involves the formation of a small concentric film by extrusion through an annulus. Simultaneously, high-velocity air is forced through the annulus and, as the film emerges, the air causes it to fibrillate into many small-diameter fibers. The fibers are then formed into a nonwoven mat on a conveyor or on a drum. With this technology, it is possible to homogeneously mix different fibers or filaments within a single nonwoven mat. Thus, multifunctional products are possible in which one fiber functions initially in the process and another fiber functions separately in a next stage, and so on—like a shampoo and post-shampoo conditioner in one product without the problems of compatibility and storage stability that are associated with combination liquid compositions.

Du Pont has moved toward naturally derived products by revealing micronized polyester beads that are synthesized using plant-derived diols. The beads are targeted toward exfoliation of skin, and the advantages that they are perceived to offer are "naturally" derived rather than petrochemically sourced and less coarse and irritating to skin than the natural kernel powders that are stated to cause microcuts on the skin surface. Paradoxically, in December 2015, the Microbeads Free Waters Act was signed into law in the United States. Pressure is now mounting to enact a ban on many polymers that are included as ingredients in personal care products. The reasoning behind such bans derives from the concern that polymeric ingredients go "down the drain" and enter the environment.

Cosmetics and personal care products became a target of criticism when New Zealand researchers observed that polyethylene microbeads were listed on the ingredient labels of some products.[428] Despite the lack of direct evidence and contradictory data and opinions, concerns were escalated across the world by nongovernmental organizations and by some marine scientists[429,430] who engaged in a "Ban the Microbead" campaign that began on the Internet and was magnified and escalated through popular media. The cosmetic industry, via the Personal Care Products Council, responded quickly by voluntarily offering to phase out plastic microparticulate ingredients within a few years.

Despite this voluntary response, legislation was enacted in several states and in some countries to ban plastic microbeads from cosmetic products. It is notable that the provisions of the act are more lenient than the conditions of voluntary withdrawal that were offered by the industry.

A recent United Nations Environmental Program fact sheet entitled "Plastic in Cosmetics"[431] seeks to expand the definition of microplastic to many polymers used in formulation, such as polyethylene waxes, polyurethanes, polyacrylate thickeners, acrylates copolymers, and silicone resins. The Netherlands' National Institute for Public Health and the Environment (RIVM) acknowledges that microplastics have been identified as a global environmental problem and have been shown to affect aquatic life. In a letter report, RIVM attempted to define microplastics by specifying their physicochemical properties and addressing three questions:

- Is the material a microplastic?
- Is it a microplastic that persists in the environment?
- Is it likely that aquatic organisms are exposed?

The Canadian government is proposing to list plastic microbeads as toxic under the Toxic Substances Act, and the Australian government is being encouraged to follow the lead of the United States. The evidence for the ban on microbeads is controversial and contradictory. Nevertheless, it is clear that merely sourcing materials from nature is not sufficient. In the future, polymer suppliers will be expected to clearly define the fate of their product when it goes down the drain after use.

## 13.12 SUMMARY

Today, several thousand different polymers are used as ingredients in personal care products. In many cases these polymers are used to deliver desired attributes to skin and hair, and this polymer technology can be the harbinger of polymers that later appear as delivery agents for therapeutic drugs. This review is directed to disclosing the physical principles for the use of polymers in cosmetics and personal care products from rheology modifiers to structured phases to polymers that modify surfaces and finally to polymers in an age of environmental and ecological awareness. The advent of living free radical polymerization has opened the door to synthesis of a wide range of block and graft copolymers, and cosmetic formulators have utilized these new materials to simultaneously introduce apparently contradictory mechanical properties and to resolve formulation incompatibilities. Stimuli-responsive polymers have been introduced that are hydrophobic below a trigger temperature and hydrophilic above it. Transfer-resistant cosmetics depend upon the detailed molecular structures of silicone resins. Rheology modifiers for polar and nonpolar systems are more precise due to the ability of polymer scientists to control molecular structure, molecular weight, and polydispersity. The structure/property relationships of associative thickeners continue to be unraveled with a few surprises in recent years with the introduction of semihydrophobic monomers to the polymer backbone. Gelling agents have been derived with film-forming properties that confer on them the dual characteristics of thickener and hair fixative. These polymers are complemented by thermoplastic elastomers that provide durable styles that are changeable at will and polymers that strengthen permed, dyed, and relaxed hair. Complex coacervates continue to be the preferred modus operandi for stimuli-responsive two-in-one shampoos but delivery by complexes has been extended to fragrances, colors, and therapeutic agents such as the antidandruff agent zinc pyridinethiol-*N*-oxide. Encapsulation and microencapsulation are being utilized to protect ingredients and to deliver them to the desired target substrates.

Polymeric antimicrobials are being introduced with the promise of product preservation without the worry of skin permeation.

The review finalizes by looking at the attempts of the industry to become good stewards of human, environmental, and ecological safety.

## References

1. Lochhead RY. The history of polymers in hair care (1940–present). *Cosmet Toilet* 1988;**103**(12):25.
2. Lochhead RY. *Trends in polymers for personal care*, **49(2)**. Polymer Preprints of the American Chemical Society; 2008. p. 675.
3. Jones CE, Reeve P. [U.S. Patent 5,916,967]. Assignee: Rohm and Haas Company; June 29, 1999.
4. Ozkan S, Gillece TW, Senak L, Moore DJ. Characterization of yield stress and slip behaviour of skin/hair care gels using steady flow and LAOS measurements and their correlation with sensorial attributes. *Int J Cosmet Sci* 2012;**34**:193–201.
5. Doi M, Edwards SF. *The theory of polymer dynamics, Chapters 8 and 9*. Oxford: Clarendon Press; 1988.
6. Klein J. The onset of entangled behavior in semidilute and concentrated polymer solutions. *Macromolecules* 1978;**11**:852–8.

7. Reiner M. *The Deborah number*, **17**. Physics Today; 1964. p. 62.
8. De Gennes PG. *Scaling concepts in polymer physics*. Ithaca (NY): Cornell University Press; 1979.
9. De Gennes PG. *Macromolecules* 1976;**9**(4):594–8.
10. Benoit H, Doty PM. *J Phys Chem* 1953;**57**:958.
11. Kratky O, Porod G. Röntgenuntersuchung gelöster Fadenmoleküle. *Rec Trav Chim Pays-Bas* 1949;**68**:1106–23.
12. Rubinstein M, Colby RH. *Polymer physics*. Oxford University Press; 2003.
13. Ullman R. *J Chem Phys* 1968;**49**:5486.
14. Yamakawa H, Norisuye T, Fujita H. *Macromolecules* 1980;**13**:345.
15. Yamakawa H, Fujii M. *Macromolecules* 1974;**7**:128.
16. Lochhead RY, Dev SB, North AM. Dielectric and viscoelastic relaxation in dilute solutions of some non-gaussian chains. *Discuss Faraday Soc* 1970;**49**:244.
17. Lochhead RY, North AM. Dielectric relaxation in solutions of two poly(alkyl isocyanates)s. *J Chem Soc, Faraday Trans 2* 1972;**68**(7):1089.
18. Wang Q, Ellis PR, Ross-Murphy SB. The stability of guar gum in an aqueous system under acidic conditions. *Food Hydrocolloids* 2000;**14**: 129–34.
19. Urlacher B, Noble O. Xanthan gum. In: Imeson AP, editor. *Thickening and gelling agents for food*. Springer; 1997. p. 284–311.
20. Petrie SEB, Becker R. Thermal behavior of aqueous gelatin solutions. In: Porter RS, Johnson JJ, editors. *Analytical calorimetry*. Springer; 1970. p. 225–38.
21. Evagelioua V, Richardsona RK, Morris ER. Effect of pH, sugar type and thermal annealing on high-methoxy pectin gels. *Carbohydr Polym* 2000;**42**:245–59.
22. Fu J-T, Rao MA. Rheology and structure development during gelation of low-methoxyl pectin gels: the effect of sucrose. *Food Hydrocolloids* 2001;**15**:93–100.
23. Morris ER, Rees DA, Robinson G. Cation-specific aggregation of carrageenan helices: Domain model of polymer gel structure. *J Mol Biol* 1980; **138**:349–62.
24. Kobayashi K, Huang C-i, Lodge TP. Thermoreversible gelation of aqueous methylcellulose solutions. *Macromolecules* 1999;**32**:7070–7.
25. Sarkar N. Kinetics of thermal gelation of methylcellulose and hydroxypropylmethylcellulose in aqueous solutions. *Carbohydr Polym* 1995;**26**: 195–203.
26. Sarkar N. Thermal gelation properties of methyl and hydroxypropyl methylcellulose. *J Appl Polym Sci* 1979;**24**:1073–87.
27. Escobar-Chávez JJ, López-Cervantes M, Naïk A, Kalia YN, Quintanar-Guerrero D, Ganem-Quintanar A. Applications of thermoreversible pluronic F127 gels in pharmaceutical formulations. *J Pharm Pharm Sci* 2006;**9**:339–58.
28. Inomata H, Goto S, Saito S. Phase transition of N-substituted acrylamide gels. *Macromolecules* 1990;**23**:4887–8.
29. Onsøyen E. In: Imeson AP, editor. *Alginates, thickening and gelling agents for food*. Springer; 1997. p. 22–44.
30. Brochure D. *Hydroxyethyl cellulose, thickener, binder, stabilizer, film former, protective colloid*. [Form No. 325-00001-0805 AMS]. http://www.ashland.com/Ashland/Static/Documents/ASI/Paints%20and%20Coatings/PDS_4756_Natrosol_Performax_1325.pdf.
31. Kamide K, Miyazai Y. The partial free draining effect and unperturbed chain dimensions of cellulose, amylose, and their derivatives. *Polym J* 1978;**10**:409–31.
32. Saito M. Wormlike chain parameters of cellulose and cellulose derivatives. *Polym J* 1983;**15**:213–23.
33. Padman V. [Ph.D. dissertation]. The University of Southern Mississippi; 2013.
34. Biermann O, Hädicke E, Koltzenburg S, Müller-Plathe F. *Angew Chem Int Ed* 2001;**40**:3822–4825.
35. Parfondry A, Perlin AS. *Carbohydr Res* 1977;**57**:39–49.
36. Reuben J, Casti TE. *Carbohydr Res* 1987;**163**:9l–8.
37. Jones DS, Woolfson AD, Brown AF. Textural, viscoelastic and mucoadhesive properties of pharmaceutical gels composed of cellulose polymers. *Int J Pharm* 1997;**151**:223–33.
38. Schwartz NO. Adaptation of the sensory textile profile method to skin care products. *J Text Studies* 1975;**42**:33–42.
39. Szczesniak AS, Brandt MA, Friedman HH. Development of standard rating scales for mechanical parameters of texture and correlation between the objective and sensory methods of texture evaluation. *J Food Sci* 1963;**28**:397–403.
40. Lucero MJ, Vigo J, Leon MJ. The influence of antioxidants on the spreadability of α-tocopherol gels. *Drug Dev Ind Pharm* 1994b;**20**:2315–22.
41. Wielinga MW. *Production and application of seed gums, Gums and stabilizers for the food industry 5*. 1990.
42. http://www.cybercolloids.net/information/technical-articles/carob-and-locust-bean-gum-structure.
43. Guar and Guar derivatives. *Aqualon Brochure*. http://www.ashland.com/Ashland/Static/Documents/AAFI/PRO_250-61_Guar.pdf.
44. Muadklay J, Charoenrein S. Effects of hydrocolloids and freezing rates on freeze–thaw stability of tapioca starch gels. *Food Hydrocolloids* 2008; **22**:1268–72.
45. *Ashland product data sheet number 4037-7*. https://www.ulprospector.com/documents/12353.pdf?bs=305&b=11609&st=20.
46. Lundin L, Hermansson A-M. Influence of locust bean gum on the rheological behavior and microstructure of κ-carrageenan. *Carbohydr Polym* 1995;**28**:91–9.
47. http://www.cybercolloids.net/information/technical-articles/carob-and-locust-bean-gum-lbg-properties.
48. Margaritis A, Zajic JE. Biotechnology review: mixing mass transfer and scale-up of polysaccharide fermentations. *Biotechnol Bioeng* 1978;**20**: 939–1001.
49. Morris ER. *Molecular origin of xanthan solution properties. Extracellular microbial polysaccharides*, **45**. Washington, DC: ACS Symp Series; 1997. p. 81–9.
50. Milas M, Rinaudo M. Conformational investigation on the bacterial polysaccharide xanthan. *Carbohydr Res* 1979;**76**:189–96.
51. Garcia-Ochoa F, Santos VE, Casas JA, Gomez E. Xanthan gum: production, recovery, and properties. *Biotechnol Adv* 2000;**18**:549–79.
52. Smith JH, Pace GW. Recovery of microbial polysaccharides. *J Chem Technol Biotechnol* 1982;**32**:119–29.
53. Kang KS, Pettit DJ. Xanthan, gellan, wellan, and rhamsan. In: Whistler RL, BeMiller JN, editors. *Industrial gums*. New York: Academic Press; 1993. p. 341–98.
54. Kang KS, Veeder GT, Mirrasoul PJ, Kaneko T, Cottrell IW. Agar-like polysaccharide produced by a *Pseudomonas* species: Production and basic properties. *Appl Environ Microbiol* 1982;**43**:1086–91.

55. https://www.cpkelco.com/markets-served/household-products/products/kelcogel-gellan-gum/.
56. Stanley N. Production, properties and uses of carrageenan. Chapter 3. In: McHugh DJ, editor. *Production and utilization of products from commercial seaweeds. FAO Fish.Tech.Pap., (288)*; 1987. Available at, http://www.fao.org/3/a-x5822e/x5822e05.htm#TopOfPage.
57. Pernas AJ, et al. Chemical heterogeneity of carrageenans as shown by fractional precipitation with potassium chloride. *Acta Chem Scand* 1967; **21**:98–110.
58. Rees DA. Mechanism of gelation in polysaccharide systems. In: *Gelation and gelling agents*, **13**. London: British Food Manufacturing Research Association; 1972. p. 7–12. Symposium proceedings.
59. Dolan TCS, Rees DA. The carrageenans. Part 2. The positions of the glycosidic linkages and sulphate esters in lambda carragennan. *J Chem Soc* 1965:3534–9.
60. Anderson NS, Dolan TCS, Rees DA. Carrageenans. Part 3. Oxidative hydrolysis of methylated kappa-carrageenan and evidence for a masked repeating structure. *J Chem Soc (C)* 1968:596–601.
61. Anderson NS, et al. Carrageenans. Part 4. Variations in the structure and gel properties of kappa-carrageenan, and the characterization of sulphate esters by infrared spectroscopy. *J Chem Soc (C)* 1968:602–6.
62. Anderson NS, et al. Carrageenans. Part 5. The masked repeating structures of lambda- and mu-carrageenans. *Carbohydr Res* 1968;**7**:468–73.
63. Lawson CJ, Rees DA. Carrageenans. Part 6. Reinvestigation of acetolysis products of lambda-carrageenan. Revision of the structure of a -1,3-galactotriose, and a further example of the reverse specificities of glycoside hydrolysis and acetolysis. *J Chem Soc (C)* 1968:1301–4.
64. Lawson CJ, et al. Carrageenans. Part 8. Repeating structures of galactan sulphates from *Furcellaria fastigiata*,*Gigartina canaliculata*, *Gigartina atropurpurea*, *Ahnfeltia durvillaei*, *Gymnogongrus furcellatus*, *Eucheuma cottonii*, *Eucheuma spinosum*, *Eucheuma isiforme*, *Eucheuma uncinatum*, *Agardhiella tenera*, *Pachymenia hymantophora and Gloiopeltis cervicornis*. *J Chem Soc Lond Perkins Trans 1* 1973:2177–82. 1973.
65. Penman A, Rees DA. Carrageenans. Part 9. Methylation analysis of galactan sulphates from *Furcellaria fastigiata*, *Gigartina canaliculata*, *Gigartina chamissoi*, *Gigartina atropurpurea*, *Ahnfeltia durvillaei*, *Gymnogongrus furcellatus*, *Eucheuma isiforme*, *Eucheuma uncinatum*, *Aghardhiella tenera*, *Pachymenia hymantophora and Gloiopeltis cervicornis*. Structure of xi-carrageenan. *J Chem Soc Lond Perkins Trans 1* 1973:2182–7.
66. Penman A, Rees DA. Carrageenans. Part 10. Synthesis of 3,6-di-0-methyl-D-galactose, a new sugar from the methylation analysis of polysaccharides related to xi-carrageenan. *J Chem Soc Lond Perkins Trans 1* 1973:2188–91.
67. Penman A, Rees DA. Carrageenans. Part 11. Mild oxidative hydrolysis of kappa- and lambda-carrageenans and the characterization of oligosaccharide sulphates. *J Chem Soc Lond Perkins Trans 1* 1973:2191–6.
68. Smith DB, Cook WH. Fractionation of carrageenan. *Arch Biochem Biophys* 1953;**45**:232–3.
69. Rees DA. The carrageenan system of polysaccharides. Part 1. The relation between the kappa- and lambda-components. *J Chem Soc* 1963;**18**: 21–32.
70. Smith DB, Cook WH, Neal JL. Physical studies on carrageenan and carrageenan fractions. *Arch Biochem Biophys* 1954;**53**:192–204.
71. MacMullan EA, Eirich F. The precipitation reaction of carrageenan with gelatin. *J Colloid Sci* 1963;**18**:526–37.
72. Graham HD, editor. *Food colloids*. Westport (Connecticut): AVI Publishing Co., Inc.; 1977.
73. Davidson RL, editor. *Handbook of water-soluble gums*. New York: McGraw-Hill Book Co.; 1980.
74. Dea ICM, Mckinnon AA, Rees DA. *J Mol Biol* 1972;**68**:153–72.
75. Dea ICM, Morris ER, Rees DA, Welsh EJ, Barnes HA, Price J. Associations of like and unlike polysaccharides: mechanism and specificity in galactomannans, interacting bacterial polysaccharides, and related systems. *Carbohydr Res* 1977;**57**:249–72.
76. Hjelland F. *Process for the production of alginate having a high mannuronic acid-content*. United States Patent 7,838,641. November 23, 2010.
77. Martin G, Haavard S, Karunakaran KP, Bakkevig K, Ertesvaag H, Ellingsen T, et al. *New mutant strains of Pseudomonas fluorescens and variants thereof, methods for their production, and uses thereof in alginate production* [WO 2004011628 (A1)], 2004. [Priority Date July 26, 2002].
78. Grant GT, Morris ER, Rees DA, Smith PJC, Thom D. *FEBS Lett* 1973;**32**:195.
79. Morris ER, Rees DA, Thom D, Boyd J. *J Carbohydr Res* 1978;**66**:145.
80. Li L, Fang Y, Vreeker R, Appelqvist I. Reexamining the egg-box model in calcium-alginate gels with X-ray diffraction. *Biomacromolecules* 2007; **8**:464–8.
81. Melvik JE, Dornish M, Onsoyen E, Berge AB, Svendsen T. *Self-gelling alginate systems and uses thereof*. United States Patent 8,481,695. July 9, 2013.
82. Stout AW. Larch arabogalactan. In: Whistler RL, BeMiller JN, editors. *Industrial Gums*. New York and London: Academic Press; 1959. p. 307–10. Chapter XII.
83. Richards GN. *Water soluble lipidated arabinogalactan*. European Patent Application 0 939 771 B1, filed. Proprietor The University of Montana; November 20, 1997.
84. Stout AW. Larch arabogalactan. In: Whistler RL, BeMiller JN, editors. *Industrial gums*. New York and London: Academic Press; 1959. p. 309. Chapter XII.
85. Chamba S, Deckner GE, Herrlein MK, Martinez-Campoy A. *Process for making a wet wipe using a concentrated emulsion*. United States Patent 7,365,030 B2. Cincinnati (OH): Assigned to The Procter & Gamble Company; April 29, 2008.
86. Marsh RG, Drechsler LE, Herrlein MK, Martinez Campoy A, Zimnawoda MR, Sawin PA. *Wet wipe lotions comprising particulate material*. United States Patent 7,666,827 B2. Cincinnati (OH): Assigned to The Procter & Gamble Company; February 23, 2010.
87. Sheehan AA, Sawin PA. *One-dimensional continuous molded element*. United States Patent 7,771,648 B2. Cincinnati (OH): Assigned to The Procter & Gamble Company; August 10, 2010.
88. Bertini I, Fragai M, Conte ML, Luchinat C, Nativi C, Venturi C. *Derivatives of arylsulfonamido-substituted hydroxamic acid as matrix metalloproteinases inhibitors*. United States Patent 7, 772,430 B2. August 10, 2010. Assigned to Protera S.R.L., Sesto Fiorentino (IT).
89. Brandt LM, Betts DE, Johnson CC. *Cosmetic compositions containing dispersion polymers*. United States Patent 6,696,067 B2. Naperville (IL, US): Assigned to Ondeo Nalco Company; February 24, 2004.
90. Shibuya T, Miyake A, Ishihara T, Miyake M, Wake H. *External dermal composition for anti-ageing and method for producing the same*. United States Patent Application 2015/0342854 Al. Assignee: Hayashibara Co., Ltd; December 3, 2015.
91. Gupta SK. *Sunscreen safety and efficacy enhancement*. United States Patent 7,597,879 B2. Scottsdale (AZ): Assigned to Bioderm Research; October 6, 2009.
92. Wei M, Hessefort YZ, Carlson WM. *Water-soluble polyaminoamides comprising 1,3-diimines as sunscreen agents*. United States Patent 6,887,400 Bl. Naperville (IL, US): Assigned to Ondeo Nalco Company; May 3, 2005.

93. Hessefort YZ, Morris JD, Carlson WM, Wei M, Quadir M, Brammer Jr LE. *Water soluble monomers and polymers for protecting substrates from ultraviolet light*. United States Patent 7,008,618 Bl. March 7, 2006.
94. Hessefort YZ, Betts DE, Brandt LM, Carlson WM, Smith JL. *Skin care compositions containing an anionic polymer*. United States Patent 7,455,848 B2. November 25, 2008.
95. Brandt LM, Cramm JR. *Personal care compositions containing N,N-diallyldialkylammonium halide/N-vinylpyrrolidone polymers*. United States Patent 7,115,254 Bl. October 3, 2006.
96. Brandt L, Cramm J, Patel DJ, Hessefort YZ, Carlson WM. *Process for producing a hydrophobically modified polymer for use with personal care compositions*. United States Patent 8,241,618 B2. August 14, 2012.
97. Gupta SK. *Hair loss prevention by natural amino acid and peptide complexes*. United States Patent 7,834,210 B2. November 16, 2010.
98. Gupta SK. *Skin and hair restoration by natural amino acid peptide complexes*. United States Patent 7,572,933 B2. August 11, 2009.
99. Gupta SK, Walker L. *Chiral complexes of ascorbic acid with natural antioxidant and anti-inflammatory ketones including aloe, citrus, ginger, and mango for skin and hair care*. United States Patent 8,227,426 B2. July 24, 2012.
100. Gupta SK. *Multifunction "crown complexes" from amino acids and peptides for skin and hair restoration*. United States Patent 7,427,690 B2. September 23, 2008.
101. Gupta SK. *Hydroxy acid complexes for antiaging and skin renovation*. United States Patent 7,547,454 B2. June 16, 2009.
102. Gupta SK. *Ascorbic acid-natural sugar lactone esters for comprehensive skin and scalp care*. United States Patent 7,842,723 B2. November 30, 2010.
103. Gupta SK. *Protection of skin from UV and peroxide*. United States Patent 7 ,993,630 B2. Scottsdale (AZ): Assigned to Bioderm Research; August 9, 2011.
104. Gupta SK. *Topical delivery system for phytosterols*. United States Patent 7,615,546 B2. Scottsdale (AZ): Assigned to Bioderm Research; November 10, 2009.
105. Gupta SK. *Topical delivery system for antiaging and skin whitening agents*. United States Patent 7,777,073 B2. Scottsdale (AZ): Assigned to Bioderm Research; August 17, 2010.
106. Gupta SK. *Artemisinin derivatives with natural amino acids, peptides, and amino sugars for the treatment of infection and topical condition in mammals*. United States Patent 8,193,376 B2. June 5, 2012.
107. Gupta SK. *Artemisinin derivatives with natural amino acids, peptides, and amino sugars for skin imperfections and infection in mammals*. United States Patent 8,232,417 B2. July 31, 2012.
108. Gupta SK, Walker L. *Prevention of cellular senescence in mammals by natural peptide complexes*. United States Patent 8,212,076 B2. Chandler (AZ): Assigned to Covalence, Inc.; July 3, 2012.
109. Gupta SK, Walker L. *Prevention of cellular senescence in mammals by natural peptide complexes*. United States Patent 8,258,343 B1. Chandler (AZ): Assigned to Island Kinetics, Inc.; September 4, 2012.
110. Gupta SK, Walker L. *Prevention of cellular senescence in mammals by natural peptide complexes*. United States Patent 8,293,943 B1. Chandler (AZ): Assigned to Island Kinetics, Inc.; October 23, 2012.
111. Gupta SK, Walker L. *Osmoprotective complexes for prevention of intra-cellular dehydration in mammals*. United States Patent 8,314,070 B2. Chandler (AZ): Assigned to Island Kinetics, Inc.; November 20, 2012.
112. Gupta SK, Walker L. *Osmoprotective complexes for prevention of mitochondrial free radical damage related skin aging*. United States Patent 8,394,851 B2. Chandler (AZ): Assigned to Island Kinetics, Inc.; March 12, 2013.
113. Lichtenberger LM, Dial EJ. *Compositions and methods for treating, preventing and/or ameliorating cancers, the onset of cancers or the symptoms of cancers*. United States Patent 7,838,511 B2. Assigned to The Board of Regents of the University of Texas System; November 23, 2010.
114. http://www.youtube.com/watch?v=f2XQ97XHjVw.
115. Coussot P, Tabuteau H, Chateau X, Tocquer L, Ovarlez G. *J Rheol* 2006;**50**:975–94.
116. Møller PCF, Fall A, Chikkadi V, Derks D, Bonn D. *Phil Trans R Soc Lond A* 2009;**367**:5139–55.
117. Becu L, Manneville S, Colin A. *Phys Rev Lett* 2006;**96**:138302.
118. Ragouilliaux A, Ovarlez G, Shahidzadeh-Bonn N, Herzhaft B, Palermo T, Coussot P. *Phys Rev E* 2007;**76**(051408).
119. Herschel WH, Bulkley R. Konsistenzmessungen von Gummi-Benzollösungen. *Kolloid Zeitschrift* 1926;**39**:291–300.
120. Tang HS, Kalyon DM. Estimation of the parameters of Herschel–Bulkley fluid under wall slip using a combination of capillary and squeeze flow viscometers. *Rheologica Acta* 2004;**43**(1):80–8.
121. Ruzicka B, Zaccarelli E, Zulian L, Angelini R, Sztucki M, Moussaïd A, et al. Observation of empty liquids and equilibrium gels in a colloidal clay. *Nat Mater* 2011;**10**:56–60.
122. Coussot P, Ancey C. Rheophysical classification of concentrated suspensions and granulated pastes. *Phys Rev E* 1999;**59**.
123. Sun K, Raghavan SR. Thermogelling fluids containing low concentrations of Pluronic F127 and laponite nanoparticles. *Langmuir* 2010;**26**:8015.
124. *Carbomer, official monographs, in the United States pharmacopeia 34-National Formulary 29*. Baltimore (MD): United Book Press, Inc.; 2011. p. 1465–73.
125. Carbomer, Monograph ID 5092. In: *the International cosmetic ingredient dictionary and handbook*. 13th ed. Washington, DC: Personal Care Products Council; 2010.
126. Brown HP. *Carboxylic polymers*. United States Patent 2,798,053. July 2, 1957.
127. Ackerman JF, Jones JF. *Mucilaginous composition comprising salt of crosslinked carboxylic polymer and method of preparing the same U.S. Patent 2923692*. February 2, 1960.
128. *Molecular weight of carbopol and pemulen polymers, Lubrizol Technical Data Sheet, TDS-222*. Cleveland (OH): Lubrizol Advanced Materials; July 10, 2008.
129. Hsu CC. *Polycarboxylic acids with higher thickening capacity and better clarity*. U.S. Patent 4,923,940. May 8, 1990.
130. Glass JA, Jones JF. *Polymerization process*. U.S. Patent 2,980,655. April 18, 1961.
131. Lochhead RY, George TR, Banks WL. *Stable carboxylic acid polymers in mineral spirits*. United States Patent 4,668,731. May 26, 1987. European Patent EP 214460 A1; March 18, 1987.
132. Lochhead RY, Garcia JC. *Improved process for polymerizing unsaturated acids in mineral spirits*. European Patent EP0107062B1. October 22, 1986.
133. George TR, Lochhead RY. *Stable mineral spirit dispersions of carboxyl-containing polymers*. U.S. Patent 4,536,628. August 20, 1985.
134. Lochhead RY, Garcia JC. *Polymerizing unsaturated acids in mineral spirits*. U.S. Patent 4,420,596. December 13, 1983.

135. Hsu CC, Koebel RF, Lochhead RY, Nagarajan MK, Sauer CE, Masler WF. *Oxidation-resistant polymeric thickeners*. European Patent 435066 A2. July 3, 1991.
136. Hsu CC, Lochhead RY, Masler WF, Sehm EJ. *Bioadhesive carboxylic polymers*. European Patent 459373 A2. December 4, 1991.
137. Kim NS, Jahnel W. *Method for producing cross-linked acrylic acid polymers*. U.S. Patent Application 20110158929. June 30, 2011. Assignee BASF SE.
138. Lochhead RY, Davidson JA, Thomas GM. Poly(acrylic acid) thickeners: the importance of gel microrheology and evaluation of hydrophobically modified derivatives as emulsifiers. In: Glass JE, editor. *Polymers in aqueous media: performance through association, advances in chemistry series #223*. Washington, DC: American Chemical Society; 1989. p. 113.
139. Long II CJ, Amjad Z, Masler III WF, Wingo WH. *Easy to disperse polycarboxylic acid thickeners*. U.S. Patent 5,288,814. February 22, 1994.
140. Long II CJ, Amjad Z, Masler III WF, Wingo WH. *Easy to disperse polycarboxylic acid thickeners*. U.S. Patent 5,349,040. September 20, 1994.
141. J Adams D, Amjad Z, Lemma S, Carl II JL. *Polycarboxylic acid thickeners, emulsifiers, and suspending aids having improved wettability characteristics*. U.S. Patent 5,373,044. December 13, 1994.
142. Adams JD, Amjad Z, Lemma S, Long II CJ. *Polycarboxylic acid thickeners, emulsifiers, and suspending aids having improved wettability characteristics*. U.S. Patent 5,468,797. November 21, 1995.
143. Cosmetic Ingredient Review Expert Panel. Annual review of cosmetic ingredient safety assessments − 2001/2002. *Int J Toxicol* 2003;**22**(Suppl. 1): 1−35.
144. Elder RL, editor. Final report on the safety assessment of Carbomers-934, -910, -934P, -940, 941, and -962. *J Am Coll Toxicol* 1982;**1**(2):109−41.
145. Sasaki S, Ojima H, Yataki K, Maeda H. Flory exponent of the chain of the expanding polyion gel. *J Chem Phys* 1995;**102**:9694−9.
146. Takahashi A, Nagasa M. Excluded volume of polyelectrolyte in salt solutions. *J Am Chem Soc* 1964;**86**:543−8.
147. Katchalsky A, Michaeli I. Polyelectrolyte gels in salt solutions. *J Polym Sc* 1955;**15**:69−86.
148. *Measurement and understanding of yield value in personal care formulations, Lubrizol Technical Data Sheet, TDS-244*. Cleveland (OH): Lubrizol Advanced Materials; January 2002.
149. Cloitre M. Yielding, flow, and slip in microgel suspensions: from microstructure to macroscopic rheology. In: Fernandez-Nieves A, Wyss H, Mattsson J, Weitz DA, editors. *Microgel suspensions, fundamentals and applications*. Weinheim (Germany): Wiley-VCH Verlag GmbH & Co.; 2011. p. 285−310. Chapter 11.
150. Ketz Jr RJ, Prud'homme RK, Graessley WW. Rheology of concentrated microgel solutions. *Rheologica Acta* 1988;**27**:531−9.
151. Cocharda S, Ancey C. Experimental investigation of the spreading of viscoplastic fluids on inclined planes. *J Non-Newtonian Fluid Mech* 2009; **158**:73−84.
152. Chambon G, Ghemmour A, Naaim M. Experimental investigation of viscoplastic free-surface flows in a steady uniform regime. *J Fluid Mech* 2014;**754**:332−6.
153. Manning GS. Limiting laws and counterion condensation in polyelectrolyte solutions i. colligative properties. *J Chem Phys* 1969;**51**(3):924.
154. Lochhead RY, Castaneda JY, Hemker WJ. *Stable and quick-breaking topical skin compositions from oil-in-water emulsions containing acrylic polymers*. European Patent 268164 A2. May 25, 1988. U.S. Patent 5,004,598, April 2, 1991.
155. Castaneda JY, Lochhead RY. *Emulsions comprising a high molecular weight anionic emulsifying agent*. European Patent 482417 A1. April 29, 1992.
156. Lochhead RY. Electrosteric stabilization of oil-in-water emulsions by hydrophobically modified Poly(acrylic acid) thickeners. In: Schulz DN, Glass JE, editors. *Chapter in polymers as rheology modifiers, ACS Symposium Series #462*. Washington, DC: American Chemical Society; 1991. p. 101.
157. Yoshinaka M, Morimitsu Y, Kobayashi S, Kosugi M. *Meth(acrylic acid/alkyl (meth)acrylate ester copolymer and cosmetic preparation containing the same*. U.S. Patent Application 20100267845. Assigned to Sumitomo Seika Chemicals Co.; October 21, 2010.
158. DuPuis C, Hansenne I, Maubru M, Sebillotte-Arnaud L, Lorant R. *Use in cosmetics of a cross-linked and at least 90% neutralized poly(2-acrylamido-2-propane sulfonic acid) and topical compositions containing same*. WO 98/00094; Published. Assigned to L'Oreal; January 8, 1998.
159. Blondel F. *Polymeric thickening composition*. U.S. Patent 8,936,797. January 20, 2015.
160. Mallo P, Braun O, Guy F, Bonnardel A. *Process for the preparation of inverse latex of acrylamide-based polymers and composition comprising said latex*. U.S. Patent 8,668,915. March 11, 2014. 8,512,684 August 20, 2013.
161. Suares AJ, Zhang JH. [United States Patent 6,986,895]; January 17, 2006.
162. Ito K, Mori Y. [United States Patent Application 20060046949]; March 2, 2006.
163. Sogabe A, Kaneda I. [U.S. Patent Application 20070231354]; October 4, 2007.
164. Sogabe A, Kaneda I. *Water soluble thickener and cosmetic preparation containing same*. U.S. Patent Application 20110237752. September 29, 2011.
165. Morschhauser R, Löffler M, Maier I. [United States Patent 6,964,995]; November 15, 2005.
166. Morschhäuser R, Glauder J, Löffler M, Kayser C, Tardi A. [United States Patent 6,891,011]; May 10, 2005.
167. Emmons WD, Stevens TE. *Polyurethane thickeners in latex compositions*. U.S. Pat. No. 4,079,028. March 14, 1978.
168. Eisenhart EK, Howard PR, Randow RL, Aviles RG. *Polyurethane mixture*. U.S. Pat. No. 5,281,654. January 25, 1994.
169. Hoy KL, Hoy RC. *Polymers with hydrophobe bunches*. U.S. Pat. Nos. 4,426,485. January 17, 1984. Dehm DC, Hoy KL, Hoy RC. Water soluble polyurethane comb polymer [4,496,708]; January 29, 1985.
170. Sonnabend LF. *Liquid emulsion polymers useful as pH responsive thickeners for aqueous systems*. U.S. Pat. No. 4,384,096. May 17, 1983.
171. *Aculyn−28; A cost-effective versatile rheology modifier*. International Specialty Products Technical Brochure.
172. Marchant N, Simon Y. *Rheology modifying copolymer composition*. United States Patent 6,433,061. August 13, 2002.
173. Hulden M. *Colloids Surf A: Physicochem Eng Aspects* 1996;**82**:263−77.
174. Jones CE. In: *Proceedings of the 4th World Surfactants Congress, CESIO, Barcelona*, **2**; 1996. p. 439−50.
175. Reeve P. In: *Proceedings of International Federation of Society of Cosmetic Chemists*. Budapest: IFSCC; 1997.
176. Jenkins RD, Bassett DR, Shay GD. *Polymers containing macromonomers*. U.S. Pat. No. 5,292,843. March 8, 1994.
177. Schmucker-Castner JF, Ambuter H, Snyder M, Weaver AA, Kotian S. *Stable aqueous surfactant compositions*. United States Patent 6,635,702. October 21, 2003.
178. Schmucker-Castner JF, Ambuter H, Snyder M, Weaver AA, Kotian S. *Stable aqueous surfactant compositions*. United States Patent 6,897,253. May 24, 2005.
179. Schmucker-Castner JF, Ambuter H, Snyder M, Weaver AA, Kotian S. *Stable aqueous surfactant compositions*. United States Patent 7,217,752. May 15, 2007.

180. Lochhead RY, Warfield DSS. *Suspension composition for aqueous surfactant systems*. U.S. Patent 4,686,254. August 11, 1987.
181. Jenkins RD, Bassett DR, Shay GD. *Polymers containing macromonomers*. U.S. Patent 5,292,843. March 8, 1994.
182. Hoy KL, Hoy RC. *Polymers with hydrophobe bunches*. U.S. Patent 4,426,485. January 17, 1984.
183. English RJ, Raghavan SR, Jenkins RD, Khan SA. Associative polymers bearing n-alkyl hydrophobes: Rheological evidence for microgel-like behavior. *J Rheol* 1999;**43**:1175–94.
184. Dai S, Tam KC, Jenkins RD. Dynamic light scattering of semi-dilute hydrophobically modified alkali-soluble emulsion solutions with varying length of hydrophobic alkyl chains. *Macromol Chem Phys* 2002;**203**:2312–21.
185. Jenkins RD, Bassett DR, Shay GD. *Polymers containing complex hydrophobic groups*. U.S. Patent 5,292,828. March 8, 1994.
186. Ng WK, Tam KC, Jenkins RD. Rheological properties of methacrylic acid/ethyl acrylate co-polymer: comparison between an unmodified and hydrophobically modified system. *Polymer* 2001;**42**:249–59.
187. Dai S, Tam KC, Jenkins RD. Dynamic light scattering of semidilute hydrophobically modified alkali-soluble emulsion solutions with different lengths of poly(ethylene oxide) spacer chain. *J Polym Sci Part B, Polym Phys* 2005;**43**:3288–98.
188. Abdala AA, Wu W, Olesen KR, Jenkins RD, Tonelli AE, Khan SA. Solution rheology of hydrophobically modified associative polymers: effects of backbone composition and hydrophobe concentration. *J Rheol* 2004;**48**:979–94.
189. Pabalan TR, Martinez-Castro N, Kesavan S, Labeau MP. *Rheology modifier compositions and methods of use*. U.S. Patent 8,969,261. March 3, 2015.
190. Houg L, Bzducha W, Herve P, Hennaux P, Douglass A, Adamy M, et al. *Rheology modifier polymer*. U.S. Patents 8,784,786, July 22, 2014 and 9090727. July 28, 2015.
191. *Carbopol® Aqua SF-1 Polymer Technical Data Sheet TDS -294, Edition*. July 2007. http://www.personalcare.noveon.com/TechnicalDataSheets/TDS-294_Carbopol_Aqua_SF-1.pdf.
192. Loffler M, Morschhauser R. *Cosmetic, pharmaceutical and dermatological products*. United States Patent 7,493,157. May 17, 2011.
193. Nguyen KS, Fast I, Werner R. *Anionic associative rheology modifiers*. U.S. Patent Application 20110218295, U.S. Patent Application 20110218296. September 8, 2011. Assignee BASF SE.
194. L'Alloret F. *Polymer compositions comprising water-soluble units and LCST units, and aqueous composition comprising them*. U.S. Patent 7,883,692. February 8, 2011.
195. Pavlin MS. *Polyamide-polyether block copolymer*. U.S. Patent Application 20090082460. March 26, 2009.
196. Pavlin M, MacQueen R. *Ester-terminated polyamides of polymerized fatty acids useful in formulating transparent gels in low polarity liquids*. U.S. Patent 5,783,657. July 21, 1998.
197. Berger, et al. *Gels including bioactive components*. U.S. Patent 6,242,509. June 5, 2001.
198. MacQueen R, Pavlin M. *Tertiary amide terminated polyamides and uses thereof U.S. Patent 6,268,466*. July 31, 2001.
199. Ferrari V. *Composition containing a liquid fatty phase gelled with a polyamide containing ester end groups*. U.S. Patent 6,402,408. June 11, 2002.
200. Mendolia M. *Cosmetic composition containing silicon-modified amides as thickening agents and method of forming same*. U.S. Patent 5,874,069. February 23, 1999.
201. Barr M, et al. *Cosmetic composition containing thickening agent of siloxane polymer with hydrogen-bonding groups*. U.S. Patent 5,919,441. July 6, 1999.
202. Barr M, et al. *Cosmetic composition containing siloxane based polyamides as thickening agents U.S. Patent 6,051,216*. April 18, 2000.
203. Pavlin M, O'Brien R. *Aqueous suspensions containing polymerized fatty acid-based polyamides*. U.S. Patent 6,864,349. March 08, 2005.
204. Pavlin M, MacQueen R. *Hydrocarbon-terminated polyether-polyamide block copolymers and uses thereof*. U.S. Patent 6,399,713. June 4, 2002.
205. Pavlin M, MacQueen R. *Hydrocarbon-terminated polyether-polyamide block copolymers and uses thereof*. U.S. Patent 6,870,011. March 22, 2005.
206. Pavlin M. *Polyamide-polyether block copolymer*. U.S. Patent 6,956,099. October 18, 2005.
207. Pavlin MS, Lai KTG, Peterson MD, Gupta S. Nature-based specialty polyamides for personal care. *HAPPI* 2008;**45**(2):62–5.
208. Matsen MW, Bates FS. Origins of complex self-assembly in block copolymer. *Macromolecules* 1996;**29**:7641–4.
209. Wang J-S, Matyjaszewski K. *Macromolecules* 1995;**28**:7901–10.
210. Chiefari J, (Bill) Chong YK, Ercole F, Krstina J, Jeffery J, Le TPT, et al. Living free-radical polymerization by reversible addition-fragmentation chain transfer: the RAFT process. *Macromolecules* 1998;**31**:5559–62.
211. Farcet C. *Gradient copolymer, composition including same and cosmetic make-up or care method*. U.S. Patent Application 20090047308. February 19, 2009. Assigned to L'Oreal.
212. Gina Butuc S. *Gel compositions*. United States Patent 6,881,776. April 19, 2005.
213. Destarac M, Joanicot M, Reeb R. *Gelled aqueous composition comprising a block copolymer containing at least one water-soluble block and one hydrophobic block*. U.S. Patent 6,506,837. January 14, 2003. Assigned to Rhodia Chimie, http://patft.uspto.gov/netacgi/nph-Parser?Sect1=PTO1&Sect2=HITOFF&d=PALL&p=1&u=%2Fnetahtml%2FPTO%2Fsrchnum.htm&r=1&f=G&l=50&s1=6506837.PN.&OS=PN/6506837&RS=PN/6506837-h0#h0. http://patft.uspto.gov/netacgi/nph-Parser?Sect1=PTO1&Sect2=HITOFF&d=PALL&p=1&u=%2Fnetahtml%2FPTO%2Fsrchnum.htm&r=1&f=G&l=50&s1=6506837.PN.&OS=PN/6506837&RS=PN/6506837-h2#h2.
214. Anthony O, Bonnet-Gonnet C, Destarac M, Farhoosh R, Joanicot M, Lizarraga G, et al. *Water-soluble block copolymers comprising a hydrophilic block and a hydrophobic block*. U.S. Patent 6,437,040. August 20, 2002. Assigned to Rhodia Chimie, http://patft.uspto.gov/netacgi/nph-Parser?Sect1=PTO1&Sect2=HITOFF&d=PALL&p=1&u=%2Fnetahtml%2FPTO%2Fsrchnum.htm&r=1&f=G&l=50&s1=6437040.PN.&OS=PN/6437040&RS=PN/6437040-h0#h0. http://patft.uspto.gov/netacgi/nph-Parser?Sect1=PTO1&Sect2=HITOFF&d=PALL&p=1&u=%2Fnetahtml%2FPTO%2Fsrchnum.htm&r=1&f=G&l=50&s1=6437040.PN.&OS=PN/6437040&RS=PN/6437040-h2#h2.
215. Schmidt S, Callais P, Macy N, Mendolia M. *Amphiphilic block copolymers*. U.S. Patent 8,541,511. September 24, 2013.
216. Stewart RF, Balachander N, Bitler SP, Phan L, Yoon VY. *Aqueous emulsions of crystalline polymers for coating seeds*. U.S. Patent 6,199,318. March 13, 2001.
217. Bitler SP, Taft DD. *Polymeric thickeners for oil-containing compositions*. U.S. Patent 7,449,511. November 11, 2008. Composition containing a liquid fatty phase gelled with a semi-crystalline copolymer; U.S. Patent Application 20090068133; March 12, 2009.
218. Mondet J, Blin X. *Composition containing a liquid fatty phase gelled with a semi-crystalline copolymer*. U.S. Patent Application 20090068133. March 12, 2009.
219. Yeung DW-K, Bergeron V, Bodet J-F, Sivik MR, Kluesener BW, Scheper WM. *Polymers, compositions and methods for use for foams, laundry detergents, shower rinses and coagulants*. U.S. Patent 8,188,204. May 29, 2012.

220. Glenn Jr RW, Kaufman KM, Dunbar JC, Gardlik JM, Murphy BP. *Porous, dissolvable solid substrate and surface resident coating comprising water sensitive actives*. U.S. Patent 9,198,838. December 1, 2015. U.S. Patent 8,349,787 January 8, 2013; U.S. Patent Application 20110189246, August 4, 2011, U.S. Patent Application 20110182956, July 28, 2011.
221. Glenn RW, Kaufman KM. *Porous, dissolvable solid substrate and a surface resident coating of cationic surfactant conditioner*. U.S. Patent 8,349,341. January 8, 2013.
222. Glenn RW, Kaufman KM. *Porous, dissolvable solid substrate and a cationic surfactant conditioner material*. U.S. Patent 8,349,787. January 8, 2013.
223. Glenn RW, Kaufman MK, Willman JR. *Porous, dissolvable solid substrate and surface resident coating comprising matrix microspheres*. U.S. Patent 9,295,859. March 29, 2016.
224. Glenn RW, Kaufman MK, Willman JR. *Porous, dissolvable solid substrate and surface resident coating comprising matrix microspheres*. U.S. Patent Application 20110182956. July 28, 2011.
225. Schonherr M, Faust T, Richter U, Subkowski T, Karos M. *Method for the production of dry free-flowing hydrophobin preparations*. United States Patent 8,096,484. January 17, 2012.
226. Gabor E, Buthe A, Eck J, Kaufmann F, Koch H-J, Meurer G. *Method of treating cellulosic materials with hydrophobins*. United States Patent 8,455,107. June 4, 2013.
227. Guzmann M, Eck P, Baus U. *Use of hydrophobin as a phase stabilizer*. United States Patent 8,535,535. September 17, 2013.
228. Becker H, Bollschweiler C, Subkowski T, Baus U, Lemaire H-G, Karos M. *Use of hydrophobin for hard surface soil-repellent treatment*. United States Patent Application 20090305930. December 10, 2009.
229. Baus U, Montag T, Subkowski T, Bollschweiler C, Grunwald I, Rischka K. *Use of hydrophobins to prevent ice from forming on surfaces*. United States Patent 7,981,313. July 19, 2011.
230. Barthlott W, Ehler N. *Raster-Elektronenmikroskopie der Epidermis-Oberflächen von Spermatophyten, Tropische und subtropische Pflanzenwelt (Akad. Wiss Lit Mainz)*, **19**; 1977. p. 110.
231. Brown JF. *Laboratory vessel having hydrophobic coating and process for manufacturing same*. U.S. Patent 5,853,894. December 29, 1998.
232. Werner O, Wagberg L. The influence of geometry on superhydrophobicity. In: Provder T, Baghdachi J, editors. *Smart coatings II*. ACS Symposium Series 1002 13 250–273; 2009.
233. Lafuma A, Quéré D. Superhydrophobic states. *Nat Mater* 2003;**2**:457–60.
234. Ranade RA, Garrison MS, Robinson F, Sandstrom G. *Cosmetic compositions for imparting hydrophobicity and water repellency to hair*. U.S. Patent 9,005,591. April 14, 2015.
235. Advance techniques frizz control lotus shield anti-frizz treatment. http://shop.avon.com/shop/search.aspx?department=search7find_spec=frizz.
236. Garrison MS, Robinson FE, Sandstrom GA, Buckridge KA, Yang S, Luo X. *Methods and compositions for preventing or reducing frizzy appearance of hair*. U.S. Patent Application 8,932,569. January 13, 2015.
237. Lochhead R, Lochhead M. Two decades of transfer-resistant lipstick. *Cosmet Toilet* January 2015;**130**(1).
238. Castrogiovanni A, Barone SJ, Krog A, McCulley ML, Callelo JF. *Cosmetic compositions with improved transfer resistance*. U.S. Patent 5,505,937. 1996.
239. Brieva H, Russ JG, Sandewicz IM. *Cosmetic compositions*. U.S. Patent 5,911,974. June 15, 1999.
240. Revlon Inc.. - Company profile, information, business description, history, background information on Revlon Inc., reference for business, company index http://www.referenceforbusiness.com/history2/10/Revlon-Inc.html#ixzz3HBYTVvXH.
241. Herman V. Hopes for truly long-lasting lipstick must no longer simply be kissed off fashion: cosmetics companies say they have discovered the secrets to colors that stay on at least a full workday. *Dallas Morning News* July 11, 1996.
242. De Gennes P-G. Ultradivided matter. *Nature* 2001;**412**:385.
243. Kryzsik D. *Cosmetics with enhanced durability.* U.S. Patent 5,330,747. July 19, 1994.
244. Brieva H, Russ JG, Sandewicz IM. *Cosmetic compositions*. U.S. Patent5,800,816. September 1, 1998. U.S. Patent 5,911,974; June 15, 1999.
245. Kuwata S, Goi T, Shimizu T, Ogihara T. *Process of preparing silicone composition, and cosmetic and lustering materials containing silicone composition obtained*. U.S. Patent 4,983,388. January 8, 1991.
246. Brieva H, Russ JG, Sandewicz IM. *Cosmetic compositions*. U.S. Patent 6,274,152. August 14, 2001.
247. Brieva H, Russ JG, Sandewicz IM. *Cosmetic compositions*. U.S. Patent 6,464.964. Assigned to Revlon Consumer Products Corporation; October 15, 2002.
248. Brieva H, Russ JG, Sandewicz IM. *Cosmetic compositions*. U.S. Patent 6,562,322. May 13, 2003.
249. Brieva H, Russ JG, Sandewicz IM. *Cosmetic compositions*. U.S. Patent 6,780,422. August 24, 2004.
250. Jose M, Ureneck AM. *Color cosmetic compositions containing organic oil and silicone mixture* [U.S. Patent 6,620,417]; September 16, 2003. Jose M, Ureneck AM. *Color cosmetic compositions containing organic oil and silicone mixture* [U.S. Patent 6,908,621]; June 21, 2005.
251. Brieva H, Russ JG, Sandewicz IM. [Manalapan (NJ), Westfield, NJ]. U.S. Patent 5,800,816. http://patft.uspto.gov/netacgi/nph-Parser?Sect1=PTO1&Sect2=HITOFF&d=PALL&p=1&u=%2Fnetahtml%2FPTO%2Fsrchnum.htm&r=1&f=G&l=50&s1=5,800,816.PN.&OS=PN/5,800,816&RS=PN/5,800,816-h0#h0; http://patft.uspto.gov/netacgi/nph-Parser?Sect1=PTO1&Sect2=HITOFF&d=PALL&p=1&u=%2Fnetahtml%2FPTO%2Fsrchnum.htm&r=1&f=G&l=50&s1=5,800,816.PN.&OS=PN/5,800,816&RS=PN/5,800,816-h2#h2; 1998.
252. Patil AA, Calello JF, Sandewicz RW. [U.S. Patent Application 20080050328]; 2008.
253. Kimura H, Horei Y, Sato Y. *Cosmetic composition*. U.S. Patent 5,676,938. October 14, 1997.
254. Tomomasa S, Takada H, Soyama Y. *Make-up cosmetic composition*. U.S. Patent 5,948,393. September 7, 1999.
255. Shiseido. Japanese Patent Application 61-158913; July 18, 1986.
256. Drechsler LE, Rabe TE, Smith ED. *Transfer resistant cosmetic compositions*. U.S. Patent 6,071,503. June 6, 2000. U.S. Patent 6,074,654; June 13, 2000; U.S. Patent 6,139,823; October 31, 2000; U.S. Patent 6,340,466; January 22, 2001; U.S. Patent 6,406,683; June 18, 2002.
257. Vatter ML. *Transfer-resistant makeup removing compositions* [U.S. Patent 7,404,966], July 29, 2008.
258. Vaughan CD. Solubility effects in product, package, penetration and preservation. *Cosmet Toilet* October 1988;**103**:47–69.
259. Vaughan CD. Using solubility parameters in cosmetics formulation. *J Soc Cosmet Chem* September/October, 1988;**36**:319–33.
260. Chen M, Chou V, McDermott P. *Methods for removing make-up compositions from keratin materials*. U.S. Patent 8,241,617. August 14, 2012.
261. Calello JF, Patil AA, Barone SJ, Krog AM. *Glossy transfer resistant cosmetic compositions*. U.S. Patent 6,033,650. March 7, 2000.

262. Calello JF, Patil AA, Barone SJ, Krog AM. *Glossy transfer resistant cosmetic compositions*. U.S. Patent 5,849,275. December 15, 1998.
263. Ilekti P, Guillard S. *Composition containing a tackifying resin and a combination of particular oils*. U.S. Patent 8,357,354. January 22, 2013.
264. Barba C, Cavazzuti R. *Cosmetic makeup and/or care method using a siloxane resin and a phenyl silicone oil*. U.S. Patent 8,367,083. February 5, 2013. Assigned to L'Oreal.
265. Barba C, Ricard A. *Compositions based on polyester in an oily phase and uses thereof*. U.S. Patent 8, 734, 765. May 27, 2014.
266. Dop F. *Cosmetic method using a composition containing siloxane resins and specific non-ionic surfactant*. U.S. Patent 8,747,828. June 10, 2014.
267. Barone SJ, Krog AM, Jose N, Ordino RJ. *Transfer resistant high lustre cosmetic stick compositions*. U.S. Patent 5,836,223. November 17, 1998.
268. Barone SJ, Krog AM, Jose N, Ordino RJ. *Transfer resistant high lustre cosmetic stick compositions*. U.S. Patent 6,036,947. March 14, 2000.
269. Krog AM, Barone SJ, Jose NR, McLaughlin GA. *Transfer resistant cosmetic stick compositions with semi-matte finish*. U.S. Patent 5,945,092. August 31, 1999. U.S. Patent 5,849,275, December 15, 1998.
270. Krog AM, Barone SJ, Jose NR, McLaughlin GA. *Transfer resistant cosmetic stick compositions with semi-matte finish*. U.S. Patent 6,045,782. April 4, 2000.
271. Anton WL, Bednarek MB, Calello JF, Jose N, Patil AA, Russ JG, et al. *Cosmetic compositions*. U.S. Patent 6,066,313. Assigned to Revlon Consumer Products Corporation; May 23, 2000.
272. Anton WL, Bednarek MB, Calello JF, Jose N, Patil AA, Russ JG, et al. *Cosmetic compositions*. U.S. Patent 6,153,206. November 28, 2000.
273. Brieva H, Russ JG, Sandevicz IM. *Cosmetic compositions*. U.S. Patent 5,985,298. November 16, 1999.
274. Brieva H, Russ JG, Sandevicz IM. *Cosmetic compositions*. U.S. Patent 7,005,134. February 28, 2006.
275. *New scientist*. April 22, 1989. p. 48–50.
276. Kim HI, Mate CM, Hannibal KA, Perry SS. How disjoining pressure drives the dewetting of a polymer film on a silicone surface. *Phys Rev Lett* 1999;**82**(17):3496.
277. Luo D, Brieva H, Susak M, Wang T, Mu W, Nazar S, et al. *Transfer resistant cosmetic*. U.S. Patent 7,261,877. August 28, 2007.
278. Thevenet L. *Liquid foundation, a makeup method, and a kit for implementing such a method*. U.S. Patent 20090081261. March 26, 2009.
279. Sabino MC, Glen MA, Rabe TE. *Long-wearing cosmetic compositions with improved shine*. U.S. Patent 8,318,187. November 20, 2012.
280. Fox HW, Zisman WA. *J Colloid Sci* 1950;**5**:514. Fox HW, Zisman WA. *J. Colloid Sci* 1952;**7**:109. Fox HW, Zisman WA. *J Colloid Sci* 1952;**7**:428.
281. Constantinides IC, Willicut RJ, Baker ES, Hutton III HD, Felts TJ, Schechtman LA, et al. *Personal care compositions comprising responsive particles*. U.S. Patent 8,865,144. October 21, 2014.
282. Bradshaw K, Bui H. *Comfortable long-wearing transfer-resistant colored cosmetic compositions having a non-tacky feel*. U.S. Patent 8,586.013. November 19, 2013.
283. Kawaratani Y, Bui HS. *Cosmetic compositions having long lasting shine*. U.S. Patent 8,658,142. February 25, 2014.
284. Jacques V, Schwartz V, Blin X. *Composition for making-up the skin comprising at least one resin, at least one block copolymer and at least one solid fatty substance, free from volatile oil*. U.S. Patent 8,252,270. August 28, 2012.
285. Bui Hy S, Lu S, Pradier F, Mercado R, Blin X. *Cosmetic compositions containing block copolymers, tackifiers and shine enhancing agents*. U.S. Patent 8,557,230. October 15, 2013.
286. Bui HS, Rohmeyer AM, McDermott P. *Cosmetic composition containing a block copolymer, a tackifier, a silsesquioxane wax and/or resin*. U.S. Patent 8,658.141. February 25, 2014. Assigned to L'Oreal.
287. Bui Hy S, Lu S, Pradier F, Mercado R. *Cosmetic compositions containing block copolymers, tackifiers and a selective solvent for hard blocks*. U.S. Patents 8,673,282; 8,673,283; 8,673,284. March 18, 2014.
288. Bui Hy S, Lu S, Pradier F, Mercado R, Blin X, Arnaud P. *Cosmetic compositions containing block copolymers, tackifiers and modified silicones*. U.S. Patent 8,758,739. June 24, 2014. U.S. Patent 8,778,323, July 15, 2014.
289. www.scconline.org_wp-content_uploads_2014_10_lu.pdf.
290. Lehn J-M. Toward complex matter: supramolecular chemistry and self-organization. *Proc Natl Acad Sci USA* April 16, 2002;**99**(8):4763.
291. Roosma J, Mes T, Leclere P, Palmans ARA, Meijer EW. Supramolecular materials from benzene-1,3,5,-tricarboxamide-based nanorods. *J Am Chem Soc* 2008;**130**(4):1120.
292. Mougin N, Livoreil A, Mondet J. *Cosmetic composition forming after application a supramolecular polymer*. U.S. Patent 8,354,097. January 15, 2013.
293. Mougin N, Schultze X, Chodorowski-Kimmes S. *Cosmetic compositon comprising a (thio)urethane/(thio)urea copolymer capable of forming at least 3 hydrogen bonds, and a method of cosmetic treatment*. U.S. Patent 8,591,923. November 26, 2013.
294. Bui HS, Kanji M, Li C, Tong AC, Halpern S, Bavouzet B. *Composition comprising a polyol and a reaction product*. U.S. Patent 8,647,611. February 11, 2014.
295. Bui HS, Kanji M, Li C, Tong AC, Halpern S. *Composition comprising a polyol, and a oil-soluble polar modified polymer* [U.S. Patent 8,551,459], October 8, 2013.
296. Bui HS, Kanji M, Li C, Tong AC, Halpern S, Bavouzet B. *Composition comprising a polyol, a sugar silicone surfactant and a oil-soluble polar modified polymer*. U.S. Patent 8,652,451. February 18, 2014. U.S. Patent 8,663,609, March 4, 2014.
297. Bui Hy S, Lu SX, Yu WH, Pradier F. *Compositions containing silicone polymer, wax and volatile solvent*. U.S. Patent 8,697,039. April 15, 2014. Assigned to L'Oreal.
298. McDermott P, Chen M, Kawaratani Y, Ilekti P, Levy F, Blin X. *Composition containing a polyorganosiloxane polymer, a thickening agent and at least one volatile alcohol*. U.S. Patent 8,728,500. May 20, 2014.
299. Bui Hy S, Tong AC, Rossi MP. *Reaction product of a polar modified polymer and an alkoxysilane and a composition containing the reaction product*. U.S. Patent 8,747,868; June 10 2014; U.S. Patent 8,846,062. September 30, 2014.
300. Tong AC, Bui HS. *Cosmetic compositions based on a supramolecular polymer, a hyperbranched functional polymer, a light silicone fluid and a copolymer of a silicone resin and a fluid silicone*. U.S. Patent 8,709,388. April 29, 2014. 8,846,015; September 30, 2014; assigned to L'Oreal.
301. Water A, Birkel S, Franzke M, Schmitt K. *Moisture resistant hair styling composition containing two polymers*. United States Patent 20070197704. August 23, 2007.
302. *Fixate™ plus Polymer, TDS-331*. October 23, 2007. http://www.personalcare.noveon.com/TechnicalDataSheets/TDS-331_Fixate_PLUS.pdf.
303. *Fixate™ superhold polymer, technical data sheet TDS 5565 2007093K*. The Lubrizol Corporation. https://www.lubrizol.com/PersonalCare/Products/Fixate/FixateSuperhold.html.

304. Krysik D, Rafferty DW, Tamareselvy K, Zellia J, Liu X, Shlepr J. *Advancements in styling technology — Fixate™ superhold polymer provides stiff hold and superior humidity resistance to styling products*. Cosmetics and Toiletries Manufacture Worldwide; 2007. p. 11.
305. Drezwinski M, Albanese J, Yap E, Shih JS. *Rheology modifier/hairstyling resin United States Patent Application 2007020264*. August 30, 2007.
306. www.eastman.com/Literature_Center/C/CB67.pdf.
307. Mueller B, Kaftcan P. *Agent for fibers containing keratin, comprising at least one specific amphiphilic cationic polymer and at least one additional film-forming and/or stabilizing polymer selected from chitosan and derivates thereof U.S. Patent Application 20110165109*. July 7, 2011.
308. Bates FS, Fredrickson GH. *Block copolymers—Designer soft materials*, **52**. Physics Today; 1999. p. 32.
309. McCarthy P. *Designed polymers with well-defined polymeric arches: a novel approach to achieving high performance skin sensorics, HBA Expo*. 2011. www.hbaexpo.com/technical-track-12.
310. Dorr S, Hofacker S, Viala S. *Hair setting composition*. U.S. Patent Application 2010/0215608. August 26, 2010.
311. Van Flodrop H, Hentrich D. *Cosmetic compositions with chitosan and silicone elastomers*. U.S. Patent Application 2010/0215604. August 26, 2010.
312. Loifenfeld M, Birkel S. *Cosmetic composition*. U.S. Patent Application 2010/0215607. August 26, 2010.
313. Wheeler MR, Orawski P, Higuera M, Mores L. *Hair fixatives comprising cross linked starches*. U.S. Patent Application 20110212145. September 1, 2011.
314. Lee H, Scherer NF, Messersmith PB. *Proc Natl Acad Sci USA* 2006;**103**:12999–3003.
315. Lee H, Dellatore SM, Miller WM, Messersmith PB. *Science* 2007;**318**:426–30.
316. Waite JH, Tanzer ML. *Science* 1981;**212**:1038–40.
317. Lee Y, Chung HJ, Yeo S, Ahn C-H, Lee H, Messersmith PB, et al. *Soft Matter* 2010;**6**:977–83.
318. Knappe T. *Styling agent*. U.S. Patent 8,182,797. May 22, 2012.
319. Rollat-Corvol I, Samain H. *Cosmetic composition comprising at least one branched sulphonic polyester and at least one conditioning agent*. United States Patent Application 20050002887. January 6, 2005.
320. Gawtrey J, Bebot C, Pasquet D. *Cosmetic composition comprising a branched sulphonic acid polyester and a thickener and uses in hairstyling*. U.S. Patent Application 2010/0236569. September 23, 2010.
321. *Clear conditioning gels with Eastman AQTM 48 polymer and UCARE polymers JR*: Eastman Technical Bulletin. http://www.eastman.com/Products/Pages/ProductHome.aspx?Product=71001940&list=products.
322. Quadir M, Burakov D, Rollat-Corvol I. *Cosmetic and dermatologic compositions containing mesosphere*. U.S. Patent Application 20070224140. September 27, 2007.
323. Singer JM, Baek J. *Hair styling compositions containing a silicone elastomer and a non-aqueous polar solvent*. U.S. Patent Application 20070204871. September 6, 2007. Assigned to L'Oreal.
324. Quadir M, Burakov D, Rollat- Corvol I. *Cosmetic and dermatologic compositions containing mesosphere*. U.S. Patent Application 20070224140. September 27, 2007. Assigned to L'Oreal.
325. Vic G, Brun G, Gourlaouen L. *Process for treating hair fibers using polysiloxane/urea*. United States Patent 9,125,838. September 8, 2015.
326. Hunter N. *Whipped composition for the treatment of keratin fibers*. U.S. Patent 9,125,838. September 8, 2015.
327. Lochhead RY. Encyclopedia of polymers and thickeners for cosmetics. *Cosmet Toilet* 1988;**103**:99.
328. Lochhead RY, Fron WR. The encyclopedia of polymers and thickeners for cosmetics. *Cosmet Toilet* 1993;**108**(5):95.
329. Bebot C. *Cosmetic composition comprising at least one cationic poly (vinyllactam), at least one fatty alcohol, and at least polyol, cosmetic process for treating keratin fibers and use of the composition*. United States Patent 8,940,283. January 27, 2015.
330. Pasquet D, Bebot C. *Cosmetic composition comprising at least one cationic poly (vinyllactam), at least one fatty alcohol, and at least one amino silicone, cosmetic process and use of the composition*. United States Patent 8,936,779. January 20, 2015.
331. Sabelko JJ, Cramm JR, Damyanti J. *Low molecular weight ampholytic polymers for personal care applications*. U.S. Patent Application 20070207106. September 6, 2007.
332. Chrisstoffels L, Becker S, Volkel L. *Polymers comprising diallylamines*. United States Patent Application 20070191548. August 16, 2007.
333. Constantinides IC, Willicut RJ, Baker ES, Hutton HD, Felts TJ, Schechtman LA, et al. *Personal care compositions comprising responsive particles*. United States Patent 8,865,144. October 21, 2014.
334. Hough LA, Bzducha W, Herve P, Hennaux P, O'Rourke M, Ericka P. *Compositions with freeze thaw stability*. U.S. Patent Application 20110223125. September 15, 2011.
335. Goddard ED, Gruber JV. *Principles of polymer science and technology in cosmetics and personal care*. 1999. p. 181–5.
336. Wang Y, Kimura K, Huang Q, Dubin PL, Jaeger W. *Macromolecules* 1999;**32**:7128.
337. Robbins C. *Chemical and physical behavior of human hair*. 4th ed. 2002. p. 352–60.
338. Goddard ED, Phillips TS, Hannan RB. *J Soc Cosmet Chem* 1975;**26**:461.
339. Goddard ED, Hannan RB. *J Am Oil Chem Soc* 1977;**54**:561.
340. Goddard ED, Ananthapadmanabhan KP. *Interactions of surfactants with polymers and proteins*. Boca Raton (FL): CRC Press; 1993. Chapter 2–4.
341. Knox WJ, Parshall TO. *J Colloid Interface Sci* 1970;**33**:16.
342. Holmberg K, Jonsson B, Kronberg B, Lindman B. *Surfactants and polymers in aqueous solution*. 2nd ed. West Sussex (England): John Wiley & Sons Ltd.; 2003.
343. Wang C, Tam KC. *Langmuir* 2002;**18**:6484–90.
344. Albrecht H, Heitmann B, Ruppert S. *Hair shampoo containing pregelatinized, cross-linked starch derivatives*. United States Patent 7,279,449. October 9, 2007.
345. Simonet F, Nicolas-Morgantini L. *Cosmetic composition of water-in-water emulsion type based on surfactants and cationic polymers*. United States Patent 20070237733. October 11, 2007.
346. Peffly MM, Yee JE, Renock SM, Hughes KJ. *Personal care compositions containing cationically modified starch and an anionic surfactant system*. U.S. Patent Application 20090176675. July 9, 2009.
347. Staudigel JA, Peffly MM, Pliego S, Deckner GE. *Personal care composition containing a non-guar galactomannan polymer derivative*. U.S. Patent Application 20060099167. May 11, 2006.
348. Staudigel JA, Peffly MM. *Personal care composition containing a non-guar galactomannan polymer derivative and an anionic surfactant system*. U.S. Patent Application 20070027051. February 1, 2007.

349. Staudigel JA, Peffly MM. *Hair conditioning composition containing a non-guar galactomannan polymer derivative*. U.S. Patent Application 20070292380. December 20, 2007.
350. Peffly MM, Staudigel JA, Pliego S, Deckner GE. *Personal care composition containing a non-guar galactomannan polymer derivative and an anionic surfactant system*. U.S. Patent 9,198,847. December 1, 2015.
351. Peffly MM, Johnson ES, Staudigel JA. *Personal care composition comprising aminosilicone and naturally derived cationic polymers*. U.S. Patent Application 20080206176. August 28, 2008.
352. Peffly MM, Hall NA. *Personal care composition comprising a silicone elastomer*. U.S. Patent 8,147,812. April 3, 2012.
353. Utz F, Lepilleur CA, Tamareselvy K, Chiarelli JA, Schmucker-Castner JF, Myers MP, et al. *Cationic cassia derivatives and applications therefor*. United States Patent 7,262,157. August 28, 2007.
354. Lepilleur CA. *Cationic cassia derivatives and applications therefor*. U.S. Patent 7,923,422. April 12, 2011.
355. Lepilleur CA, Mullay J, Li W, Krzysik D. Cationic cassia polymers as naturally-derived polymers for providing enhanced deposition from shampoo systems. In: *Programs and preprints of the Society of Cosmetic Chemists, Annual Scientific Seminar*; June 2–3, 2011.
356. Kreeger RL, Zhou S. *Cellulose ethers*. U.S. Patent 7,868,164. January 11, 2011.
357. Baldaro E, Bouzeloc S, Postiaux S, Schirosi E, Soontjens D, Ugazio S. *Home and personal care compositions*. U.S. Patent Application 20110189248. August 4, 2011.
358. Langella V, Baldaro E, Bassi GL. *Modified galactomannan ethers*. U.S. Patent 8,546,549. October 1, 2013.
359. Peffly MM, Brown MA, Staudigel JA. *Personal care compositions containing cationic synthetic copolymer and a detersive surfactant*. U.S. Patent Application 20070207109. September 6, 2007.
360. Klein K. *Cosmet Toilet* October 2004:32–4.
361. Rosen MR. *Delivery system handbook for personal care and cosmetic products*. 2005. p. 501–10.
362. Tsaur LS, Ananthapadmanabhan KP. *Personal wash cleanser comprising defined alkanoyl compounds, defined fatty acyl isethionate surfactant product and skin or hair benefit agent delivered in flocs upon dilution*. U.S. Patent 8,105,994. January 31, 2012.
363. Lochhead R, Pearson H. What's happening in hair damage, protection and repair. *Cosmet Toilet* June 2014;**129**(5):28–33.
364. Han Mi-O. *J Cosmet Sci* 2008;**59**(3):203–15.
365. Zeng F, et al. In: Patil A, et al., editors. *Polymers for personal care and cosmetics*. ACS Symposium Series; 2013.
366. Berthiaume MD. *J Soc Cosmet Chem* 1995;**46**(5).
367. Schubert F, Knott W, Ferenz M, Klein K-D, Maurer T, Scheurmann R, et al. *Novel linear polydimethylsiloxane-polyether copolymers having amino and/or quaternary ammonium groups and use thereof*. U.S. Patent 8,957,009. February 17, 2015.
368. Lee WA, Hawkins G. *Emulsified MQ resins: composition and methods*. U.S. Patent Application 20130295028. November 7, 2013.
369. Fernandez E, et al. *J Photochem Photobiol B: Biol* 2012;**117**:146–56.
370. Dario MF, et al. *J Photochem Photobiol B: Biol* 2013;**120**:142–7.
371. Davies MJ. Reactive species formed on proteins exposed to singlet oxygen. *Photochem Photobiol Sci* 2004;**3**:533–7.
372. Sebetic K, et al. *Coll Antropol* 2008;**32**(Suppl. 2):163–5.
373. Korytowski W, et al. Photo-induced generation of hydrogen peroxide and hydroxyl radicals in melanins. *Photochem Photobiol Sci* 1987;**45**: 185–90.
374. Santos N, et al. Hair color changes and protein damage caused by ultraviolet radiation. *J Photochem Photobiol Sci* 2004;**B74**:109–17.
375. Marsh JM, Iveson R, Flagler MJ, Davis MG, Newland AB, Greis KD, et al. Role of copper in photochemical damage of hair. *Int J Cosmet Sci* 2014;**36**:32–8.
376. Vielhaber G, Oertling H, Schaper K, Gomann C, Brodhage R. *Menthyl carbamate compounds as skin and/or hair lightening actives*. U.S. Patent 9,060,949. June 23, 2015.
377. Miranda-Vilela AL, Botelho AJ, Muehlmann LA. An overview of chemical straightening of human hair: technical aspects, potential risks to hair fibre and health and legal issues. *Int J Cosmet Sci* 2014;**36**:2–11.
378. Herrling T, Jung K, Fuchs J. *SOFW-J* 2007;**133**:2–11.
379. https://pc.crodadirect.com/home.aspx?d=content&s=158&r=280.
380. Huang X, Wang H, Wu Y. *Peptide-based conditioners and colorants for hair, skin, and nails*. U.S. Patent 7,544,353. June 9, 2009.
381. Cardamone JM, Erazo-Majewicz P, Naouli N. *Compositions and methods for treating a keratin-based substrate*. U.S. Patent 8,747,823. June 10, 2014.
382. Boden N, Aggeli A, Ingham E, Kirkham J. *Beta sheet tapes ribbons in tissue engineering*. U.S. Patent Application 9,193,764. November 24, 2015.
383. Wenk HH, Lersch P. *Cosmetic composition containing polyglycerol partial ester*. U.S. Patent Application 20120308503. December 6, 2012.
384. Dutheil-Gouret K, Pallanchard M, Livoreil A. *Method for shaping the hair using at least one reducing composition, at least one care composition, and heating*. U.S. Patent 9,005,593. April 14, 2015.
385. Campain C, Devin-Baudoin P. *Process for permanently reshaping the hair*. United States Patent Application 2007019008. August 16, 2007.
386. Jordan SL, Schwartz C. *Personal care compositions for coloring hair*. U.S. Patent 8,133,285. March 13, 2012.
387. Welz C, Manneck H, Kleen A, Akram M. *Coated coloring agents*. U.S. Patent 8,110,010. February 7, 2012.
388. Moutet M, Yadan J-C. *Pharmaceutical or cosmetic preparations for topical and/or parenteral application, preparation methods thereof and use of same*. U.S. Patent Application 20100323985. December 23, 2010.
389. Kim KH, Kim KS, Kim YH, Kim JG, Kim KT, Han CS, et al. *Anti-aging composition for external use comprising low and high molecular weight hyaluronic acids and the polysaccharides extracted from root bark of* Ulmus davidiana. U.S. Patent 8,426,383. April 23, 2013.
390. Collins DF, Maes DH, Muizzuddin N. *Methods and compositions for treating skin*. U.S. Patent Application 20100323042. December 23, 2010.
391. Librizzi JJ, Walters RM, Fevola M, Tamareselvy K. *Low-irritation compositions and methods of making the same*. U.S. Patent 8,025,902. September 27, 2011.
392. Walters RM, Gunn ET, Gandolfi L, Johnson D, Anim-Danso E, Lahey K. *Low-irritating, clear cleansing compositions with relatively low pH*. U.S. Patent Applications 2011/0319306, and 2011/0319307, 2011/0319308. December 29, 2011.
393. Aleles M, Burwell D, Ip R. *Cleansing bar containing discrete elements*. U.S. Patent 6,818,603. November 16, 2004.
394. Eknoian MW, Brennan Jr RA, Ip R, Poccia III JF. *Cosmetic device comprising discrete elements*. U.S. Patent 7,901,696. March 8, 2011.
395. Friel FM, Lee WA-T, Shidara A, Mercado CG, Leaver EJ. *Discontinuous surface coating for particles*. U.S. Patent Application 2011001298. January 20, 2011.

396. Omura T, Yokoo M. *Skin cosmetic*. U.S. Patent Application 8,642,023. February 4, 2014.
397. Brault D, Quevauviller F, Frick R. *Cosmetic method for smoothing wrinkles and fine lines*. U.S. Patent Application 20110014150. January 20, 2011.
398. Griffiths-Brophy SA, Elsbrock RJ. *Personal care composition*. U.S. Patent Application 20100322983. December 23, 2010.
399. Allart PJ, May HB. *Encapsulation process and resulting aqueous dispersion of encapsulated droplets*. U.S. Patent 4,124,526. November 7, 1978. http://patft.uspto.gov/netacgi/nph-Parser?Sect1=PTO1&Sect2=HITOFF&d=PALL&p=1&u=%2Fnetahtml%2FPTO%2Fsrchnum.htm&r=1&f=G&l=50&s1=4124526.PN.&OS=PN/4124526&RS=PN/4124526-h0. http://patft.uspto.gov/netacgi/nph-Parser?Sect1=PTO1&Sect2=HITOFF&d=PALL&p=1&u=%2Fnetahtml%2FPTO%2Fsrchnum.htm&r=1&f=G&l=50&s1=4124526.PN.&OS=PN/4124526&RS=PN/4124526-h2.
400. Petit J-LV. *Mikrokapsein*. EU Patent application 1 462 157. March 24, 2003.
401. Percel PJ, Vishnupad KS, Venkatesh GM. *Functional coating of linezolid microcapsules for taste-masking and associated formulation for oral administration*. U.S. Patent 6,451,345. September 17, 2002. http://patft.uspto.gov/netacgi/nph-Parser?Sect1=PTO1&Sect2=HITOFF&d=PALL&p=1&u=%2Fnetahtml%2FPTO%2Fsrchnum.htm&r=1&f=G&l=50&s1=6451345.PN.&OS=PN/6451345&RS=PN/6451345-h0. http://patft.uspto.gov/netacgi/nph-Parser?Sect1=PTO1&Sect2=HITOFF&d=PALL&p=1&u=%2Fnetahtml%2FPTO%2Fsrchnum.htm&r=1&f=G&l=50&s1=6451345.PN.&OS=PN/6451345&RS=PN/6451345-h2.
402. Simmonet J-T, Biatry B, Prigent F. *Capsules of core/shell type and preparation process*. U.S. Patent Application 20090047. February 19, 2009.
403. Baviskar RJ, Kini M, Pradhan RR, Surianarayanan R. *Cosmetic delivery system and process for manufacture thereof*. U.S. Patent Application 20090041685. February 12, 2009.
404. Ibrahim S, Omer M, Wisnieski KL, Salko D, Haskel A, Connor K. *Film containing compositions*. U.S. Patent Application 2011/0293539. December 1, 2011.
405. Yoshinaga M. *Method of synthesizing cyclodextrin polymers*. U.S. Patent 5,276,088 http://patft.uspto.gov/netacgi/nph-Parser?Sect1=PTO1&Sect2=HITOFF&d=PALL&p=1&u=%2Fnetahtml%2FPTO%2Fsrchnum.htm&r=1&f=G&l=50&s1=5276088.PN.&OS=PN/5276088&RS=PN/5276088-h0#h0. January 4, 1994. http://patft.uspto.gov/netacgi/nph-Parser?Sect1=PTO1&Sect2=HITOFF&d=PALL&p=1&u=%2Fnetahtml%2FPTO%2Fsrchnum.htm&r=1&f=G&l=50&s1=5276088.PN.&OS=PN/5276088&RS=PN/5276088-h2#h2.
406. Yui N. *Supramolecular-structured biodegradable polymeric assembly for drug delivery*. U.S. Patent 5,855,900. January 5, 1999. http://patft.uspto.gov/netacgi/nph-Parser?Sect1=PTO1&Sect2=HITOFF&d=PALL&p=1&u=%2Fnetahtml%2FPTO%2Fsrchnum.htm&r=1&f=G&l=50&s1=5855900.PN.&OS=PN/5855900&RS=PN/5855900-h0#h0. http://patft.uspto.gov/netacgi/nph-Parser?Sect1=PTO1&Sect2=HITOFF&d=PALL&p=1&u=%2Fnetahtml%2FPTO%2Fsrchnum.htm&r=1&f=G&l=50&s1=5855900.PN.&OS=PN/5855900&RS=PN/5855900-h2#h2.
407. Cheng J, Davis ME, Khin KT. *Cyclodextrin-based polymers for therapeutics delivery*. U.S. Patent Application 20080058427. Assigned to Insert Therapeutics, Inc.; March 6, 2008.
408. Dykstra RR, Gallon LS, Clapp ML, Deckner GE. *Rinse-off personal care compositions comprising cationic perfume polymeric particles*. U.S. Patent Application 20080057021. March 6, 2008.
409. Smith GA. *Delivery device having self-assembling dendrite polymer and method of use thereof*. United States Patent Application 2008/0058701 A1. March 6, 2008.
410. Tomalia DA, Baker H, Dewald JR, Hall M, Kallos G, Martin S, et al. A new class of polymers: starburst-dendritic macromolecules. *Polym J (Tokyo)* 1985;**17**:117–32.
411. Newkome GR, Yao Z, Baker GR, Gupta VK. Cascade molecules: a new approach to micelles. A [27]-arborol. *J Org Chem* 1985;**50**:2003–4.
412. Kim YH, Webster OW. Hyperbranched polyphenylenes. *Polym Prepr* 1988;**29**:310–1.
413. Kim YH. Hyperbranched polymers 10 years after. *J Polym Sci Part A: Polym Chem* 1998;**36**:1685–98.
414. Newkome GR, He E, Moorefield CN. Suprasupermolecules with novel properties: metallodendrimers. *Chem Rev* 1999;**99**:1689–746.
415. Sun J, Ramanathan M, Dorman D, Newkome GR, Moorefield CN, Russo PS. Surface properties of a series of amphiphilic dendrimers with short hydrophobic chains. *Langmuir* 2008;**24**:1858–62.
416. Derks F, Foster S, Lochhead R, Maini A, Weber D. *Volume up shampoos II, preparation*. U.S. Patent 8,597,625. December 3, 2013.
417. Huang X, Diesenroth T, Preuss A, Marquais-Bienewald S, Hendricks-Guy C, Jennings J. *Polymeric antimicrobial agents*. U.S. Patent Application 20110318280. December 29, 2011.
418. Jin L, Baney RH. *Antimicrobial compositions, methods of manufacture thereof and articles comprising the same*. U.S. Patent Application 2011/0287074. November 24, 2011.
419. Chandra NS, McNally WF, Furey JM, Robb GJ, Harriton ML. *Hydrogel having antimicrobial properties*. U.S. Patent Application 20060062854. Noble Fiber Technologies; March 23, 2006.
420. http://chemistry.lsu.edu/chem/facultypages/Faculty.php?chemID=59.
421. Huang X, Deisenroth T, et al. *Polymeric anti-microbial agents* [WO 2007085552]. March 27, 2008 [Priority date January 27, 2006].
422. Huang X, Deisenroth T, Preuss A, Marquis- Bienewald S, Hendricks-Guy C, Jennings J. *Polymeric anti-microbial agents*. U.S. Patent Application 20070231291. October 4, 2007.
423. http://www.basf.com/group/sustainability_en/index.
424. http://www.pg.com/en_us/sustainability/environmental_sustainability/index.shtm.
425. http://www.unilever.com/sustainability/.
426. Glenn Jr RW, Gordon GC, Sivik MR, Richards MR, Heinzman SW, James MD, et al. *Filaments comprising an active agent nonwoven webs and methods for making same*. U.S. Patent Applications 2012/0027838. February 2, 2012. 2012/0048769, March 1, 2012; 2012/0052036, March 1, 2012; 2012/0052037, March 1, 2012; 2012/0058166, March 8, 2012, U.S. Patent 9,163,205. October 20, 2015.
427. Glenn Jr RW, Chhabra R, Allen Jr WM, Brennan JP, Paul J. *Dissolvable fibrous web structure article comprising active agents* [U.S. Patent Application 2012/0021026, 20012/January 26, 2012].
428. Fendall LS, Sewell MA. Contributing to marine pollution by washing your face; microplastics in facial cleansers. *Mar Pollut Bull* 2009;**58**:1225–8.
429. http://5gyres.org/posts/2014/08/19/plastic-microbeads-campaign-update/.
430. Abrams R. *Fighting pollution from microbeads used in soaps and creams*. The New York Times; May 22, 2015.
431. http://unep.org/gpa/documents/publications/PlasticinCosmetics2015Factsheet.pdf.

CHAPTER

# 14

# Powders and Inorganic Materials

*Y. Nonomura*

**Yamagata University Graduate School of Science and Engineering, Yonezawa, Japan**

## 14.1 HISTORY OF POWDERS IN COSMETICS

In 1930, a chemist at the Cairo Museum named Alfred Lucas introduced cosmetics of Ancient Egypt on an archaeological journal. It appears that cosmetics of ancient people was an interesting topic to many archaeologists, and in this report Lucas described that the most common pigment in eye makeup and face painting was malachite $Cu_2(CO_3)(OH)_2$ and galenite PbS.[1] Analytic technology has evolved since, and now all the components of cosmetics in the slight remainders of jars can be identified. An especially revolutionary analysis technique was using synchrotron in an electronic field to analyze the synchrotron radiation with accelerated electrons, which revealed the composition and even the crystal structures of slight impurities in the remainders of powder makeup.[2] With this technology, small amounts of laurionite (PbOHCl) and phosgenite ($Pb_2Cl_2CO_3$) were found from the makeup remainders in the jars used in 2000−1200 BC, revealing that advanced wet processes were used to formulate cosmetic pigments in these ancient times.[3] In other words, our ancestors had desires for delicate and beautiful cosmetics for thousands of years, and learned chemical synthesis techniques to achieve their demands.[4]

The history of cosmetics dates back far before Ancient Egypt. In 1966, a campsite of Terra Amata hominids who lived 350,000 years ago was discovered in Nice, France, and remains of red ochre, which is believed to be for body decoration, was also found at this site. This discovery has led to an hypothesis that a mixture of red ochre and fat was used not only for hunting rituals but also to prevent sunburns.[5] As such, clay, yellow ochre, and red ochre were the first cosmetics used by man, followed by a long age of makeup using lead-based pigments for white and color pigments made from iron oxide or botanical derivatives.

The foundation of modern makeup was established in the mid-20th century. Titanium oxide, which is now essential for cosmetic pigments, was first discovered from the sand of a brook in 1789.[6] Industrial production began in the early 20th century, replacing the highly toxic lead as white pigment. This inorganic powder not only scatters ultraviolet (UV) rays but also has a semiconductor band gap and absorbs short-waved UV rays, thus showing a high UV-blocking property.[7] As such, powders and inorganic materials are not only used as pigments in cosmetics for decoration but can also protect the skin from UV rays, and they are now considered an important material for skin care.

Furthermore, recent cosmetics combine various materials and also use powders with special functions from their unique structures. A prominent example is interference pearls, which are titanium dioxide-coated mica or other layered particles that show a brilliant pearl-like interference light.[8] This unique pigment has made the color of makeup cosmetics such as lipstick and nail polish more vivid, and has also been applied to base makeup and opened the doors to natural makeup. This is just one example of how powder materials play an important role in cosmetics today in terms of functionality. In this chapter, we will study powders that are widely used in cosmetics along with their characteristics.

*Cosmetic Science and Technology: Theoretical Principles and Applications*
http://dx.doi.org/10.1016/B978-0-12-802005-0.00014-8



Copyright © 2017 Elsevier Inc. All rights reserved.

# 14.2 POWDERS USED IN COSMETICS

## 14.2.1 Inorganic Pigments

### *14.2.1.1 Extender Pigments*

#### 14.2.1.1.1 Clay Minerals

Like our ancestors tens of thousands of years ago, clay minerals are used for cosmetics with the most advanced functions. Clay minerals are powders that are especially essential for formulating makeup cosmetics. Among these minerals, talc, $Mg_3Si_4O_{10}(OH)_2$, composed from magnesium hydroxide and silicate, has a layered structure and easily fractures into thin planar crystals, and is known to reduce friction.[9] From this property, talc is used to improve the flowability and spreadability of foundations and face powders on the skin. Mica is a planar powder composed mainly of hydrous silicate of aluminum and potassium, and it not only has lubricity from its smooth surface but is also known to make the skin brighter, as well as improve the adhesion of cosmetics. Depending on the ore, there are muscovite, $KAl_2(AlSi_3)O_{10}(OH)_2$, or phlogopite, $KMg_3(AlSi_3)O_{10}(OH)_2$, in the mica family. Additionally, artificially synthesized phlogopite, $KMg_3AlSi_3O_{10}F_2$, is formulated with methods of melting and crystallizing silica, magnesium oxide, aluminum oxide, and potassium fluorosilicate, or with solid phase reaction synthesis where talc and alkali fluorosilicates are mixed and treated with heat. These synthesized phlogopites have high affinity with the skin and are highly translucent, and are used as extender pigments for foundations to make natural-looking skin, and also as base materials for interference pearls.[10]

#### 14.2.1.1.2 Silica

Silica is a substance composed of silicon dioxide, $SiO_2$, and is also known as silicic acid anhydride. Silica is the main component of quartz and silica sand, but it is also found in large amounts in biominerals that make the skeletal structure of ferns, grasses, and diatoms. However, most of the silica used in cosmetics is formulated with wet methods such as dehydrating sodium silicate, hydrolysis of alkoxysilane, or acidic reaction of calcium silicate, or with dry methods such as high-temperature hydrolysis of silicon halide or using electric arc methods with quartz.[11] Siloxane, $\equiv Si-O-Si\equiv$, and four types of silanols, $\equiv Si-OH$, are found on the surface of silica, and the physical property of the silica surface changes depending on the content of these groups.[12] Additionally, surface-modified silica is made by reacting the silanol groups on the silica surface with alkoxysilane, silazane, and/or siloxane, and is widely used to control the surface's hydrophilic (hydrophobic) property.[13] Since they make cosmetics smoother and more transparent, they are used as extender pigments for makeup cosmetics. They also absorb or thicken water and/or oils and are also used for skin care cosmetics.[14]

#### 14.2.1.1.3 Boron Nitride

Boron nitride (BN) is a hexagonal crystal that is made by mixing and heating boron and urea, and has a layered crystal structure similar to graphite.[15] The bonds between the layers are weak, and BN is believed to have a lubricant effect.[16,17] BN also has a smooth application feeling on the skin and adds gloss, and is formulated in foundations and face powders.

#### 14.2.1.1.4 Alumina

Alumina, also known as aluminum oxide, $Al_2O_3$, is produced from crystal corundum or their hydrates, bauxite. Alumina is used as white pigments and also as scrubbing agents for granulated substances.

#### 14.2.1.1.5 Barium Sulfate

Barium sulfate, $BaSO_4$, is made by reacting barium hydroxide and other barium sources with sulfuric acid and has a long history as a translucent white pigment. Barium sulfate can be formed in various shapes such as planar, starred, or spherical structures depending on the formulation condition, especially the supersaturation of its barium source, and the internal pore size also changes.[18] Planar barium sulfate shows especially high lubricity, and when applied to the skin it not only has a smooth feeling but also has a high light-scattering property, showing a soft-focus effect that makes small wrinkles and pores less visible.[19]

### *14.2.1.2 Colored Pigments*

#### 14.2.1.2.1 Iron Oxide

The skin colors of foundations and many makeup cosmetics are often created by mixing red iron oxide, $Fe_2O_3$, yellow iron oxide, $Fe_2O_3 \cdot H_2O$, and black iron oxide, $Fe_3O_4$. Our ancestors tens of thousands of years ago used red ochre as a red paint to decorate their skin, but modern wet, dry, and hydrothermal methods of iron sulfide and iron chloride have allowed us to formulate more vivid colors with a wider range of hues.[20] Red iron oxide and yellow iron oxide show their colors from the d−d transition of electrons in the iron atoms. In other words, the electrons on the outermost shell of the iron ion $Fe^{3+}$ are excited with photoexcitation, and when they transition to a high-energy state they absorb light, showing their red or yellow color[21] (Fig. 14.1). On the other hand, black iron oxide absorbs light in the visible range when the electrons of $Fe^{2+}$ move from the $Fe^{3+}$ in the neighboring crystal from the $Fe^{2+}$ with photoexcitation, showing its black color. Since the shape and size of iron oxide can influence the texture and application feeling, scale-like iron oxides and transparent iron oxide with primary particles smaller than light waves are being developed.

#### 14.2.1.2.2 Ultramarine

Ultramarine is a blue to violet pigment that is made of aluminum and silicon with sulfur, and is a complex of yellow-colored sodium silicate, $Na_{8-10}Al_6Si_6O_{24}S_{2-4}$. The blue in the pigment is believed to be shown by radical anion $S^{3-}$ that has an unpaired electron, but the mechanism of its color is still under discussion.[22] Previously, ground lapis lazuli was used for ultramarine, but currently synthesized ultramarine is formulated by mixing and melting silica, alumina, anhydrous sodium carbonate, sulfur powder, and activated carbon. Ultramarine has high thermal resistance property and high light stability, and is used for eyeliners and other makeup cosmetics but cannot be used under acidic environments.

#### 14.2.1.2.3 Chromium Hydroxide

Chromium hydroxide is a green inorganic substance with a chemical formula $Cr_2O_3$. Chromium hydroxide is synthesized from chromite and is used for coloring products such as eye shadows.

#### 14.2.1.2.4 Manganese Violet

Manganese violet is a violet pigment that is made by reacting manganese dioxide with ammonium phosphate and potassium phosphate. The main component is ammonium manganese pyrophosphate complex, $Mn(III)NH_4P_2O_7$.[23] Manganese violet has high concealing property and high light stability, and is used for coloring in point makeup.

#### 14.2.1.2.5 Carbon Black

Soot from fire has been collected for pigment use, and the main component of soot is carbon black.[24] Currently, carbon black used for pigments is mainly formulated by thermal decomposition or incomplete combustion of natural gas, acetylene, tar, or aromatic oils. The black color of these pigments is made from crystals with graphite-like

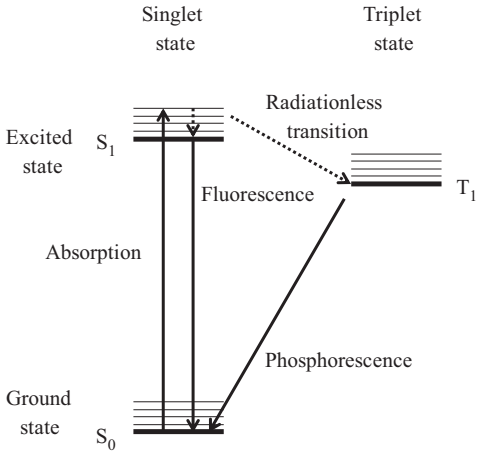



FIGURE 14.1 The coloring mechanism of pigments. In addition to absorbing light, they show colors with light-emitting phenomena known as fluorescence and phosphorescence.

layered structures forming primary particles, and these particles condensate to form aggregates.[25] Furthermore, there are polar groups such as carboxyl groups and quinone-type oxygen atoms on the surface, and there are cases where they can disperse in water.[26] Usually the primary particle is small in tens of nm and shows high adhesion properties.

#### *14.2.1.3 White Pigments*

##### 14.2.1.3.1 Titanium Oxide

In 1966, a photocatalysis effect called the Honda–Fujishima effect was discovered, where water was decomposed into oxygen and hydrogen and electricity was generated when strong light was irradiated to a titanium dioxide electrode set with a platinum electrode in water.[27] Since this effect has many similarities to the photosynthesis of plants, it led to expectations on energy development with artificial photosynthesis. After the discovery, it was found that this photocatalysis effect can also decompose organic compounds and can make the surface of solids superhydrophilic, thus making titanium oxide one of the most focused-on inorganic substances in materials science.[28,29]

This pigment has also gained much attention as a cosmetic ingredient since titanium oxide has the highest refractive index among white pigments and also has a high concealing property. There are three crystal forms of titanium oxide, namely anatase, rutile, and brookite, and in cosmetics rutile is used for its highest refractive index and stability. In particular, titanium oxide with a particle size of approximately 200 nm has the highest light-scattering property and is expected to have a high concealing property, and is widely used as pigment[30] (Fig. 14.2). Furthermore, fine titanium oxide has been long known to be effective for protecting the skin from sunburns caused by UV rays.[31] Many researchers have confirmed that ultrafine titanium oxides with particle sizes in the tens of nm have UV-blocking property.[32]

When adding titanium oxide to cosmetics, it is important to prevent skin irritation and formulation degradation caused by photocatalysis. In order to prevent such effects, the surface of titanium oxide is treated with oxidized metals such as alumina or zirconia, or organic compounds such as silicone, and it is known that inorganic coatings are more effective for inhibiting photocatalysis.[33] Additionally, it is important to remember that even when the surface is treated with silane coupling, the inhibition of photocatalysis can differ depending on the treatment degree.[34]

As such, titanium oxide is a very effective material, but there have also been many discussions among researchers regarding its safety. There were especially strong concerns that the superfine titanium oxide used for UV blocking would be absorbed into the body beyond the stratum corneum barrier, and most research results denied this concern.[32,35] However, there have been reports that when superfine titanium oxide was applied to pigs' ears for weeks, it was absorbed into the body beyond each barrier and stored in each tissue, and caution must be taken when considering this material.[36]

##### 14.2.1.3.2 Zinc Oxide

Zinc oxide, ZnO, is a hexagonal crystal–structured white powder that has a long history as a white pigment. However, the concealing property is smaller than titanium oxide due to a smaller refractive index of 2.03, and the optimal particle diameter as white pigment is said to be around 300–500 nm.[37] Since zinc oxide is an n-type semiconductor like titanium oxide, it not only absorbs UV rays with wave lengths shorter than 380 nm effectively but also has high transparency and does not easily show white powder residue, so it is believed to be an effective anti-UV agent for blocking UV-A rays with wave lengths 320–400 nm, which are believed to cause wrinkles.[38,39]

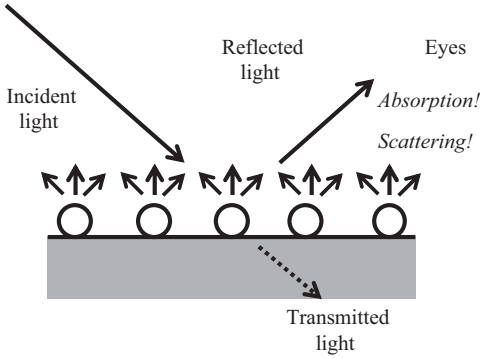



FIGURE 14.2 The concealing and UV-blocking mechanism of titanium oxide and zinc oxide.

Zinc oxide is also known to have skin care effects. For example, zinc oxide is reported to have convergence effects that tighten the skin to make pores less visible,[40] antibacterial effects that kill skin irritation and infection-causing *Staphylococcus aureus/Pseudomonas aeruginosa*,[41] and antiacne effects.[42] Furthermore, zinc oxide selectively adsorbs free fatty acids, and this characteristic has been applied to products such as foundations through development of techniques to prevent makeup smears by adding zinc oxide to cosmetics in order to improve the stability of the cosmetic layer on the skin.[43]

#### 14.2.1.3.3 Calcium Carbonate

Calcium carbonate, $CaCO_3$, is a white to light gray powder found in shells, corals, eggshells, and limestone. Calcium carbonate is usually porous[44] and by filling these pores with medical agents or aromatic agents, they are formulated in pharmaceutical drugs and cosmetics.[45,46] When used for foundation or face powders, they can absorb sebum and increase the sustainability of the cosmetic effects, providing a clear finish.

### *14.2.1.4 Pearlescent Pigments*

The clear and soft shine of pearls has allured us throughout history. Pearlescent pigments are artificial replications of this naturally borne mechanism. The unique gloss of natural pearls is thought to be made by light interference of the parallel layers of multiple overlapping calcium carbonate crystal layers and protein layers, and the light interference of the scattering light of crystals in the crystal layers[47] (Fig. 14.3). Scale-like particles with planar or needle-shaped structures and a relatively high refractive index have been used to replicate this pearly gloss in cosmetics.[8] Furthermore, a method was developed to replicate the colors with interference light by coating the surface of planar mica with titanium oxide or iron oxide, and has been applied to cosmetics.[48] Especially in the 1980s, technology to control the thickness of the coating was established and made it possible to formulate various colors such as red, blue, yellow, and green, and this was applied not only to makeup cosmetics but also for foundation to make the finish more natural.[49,50]

## 14.2.2 Organic Pigments

### *14.2.2.1 Extender Pigments*

#### 14.2.2.1.1 Polymer Resin

Methyl methacrylate crosspolymers, silicone resin, nylons, urethane resin, and various other polymer resins have been used to preserve the shape of formulations and improve the application touch or to control the gloss as extender pigments. Most polymer resins are spherical particles sized from several hundred nm to tens of μm, but nylon can be supplied in various shapes, ranging from spherical to fibers. Spherical polymers scatter light and can provide a soft focus effect where the pores are less visible,[51] and fiber-shaped polymers are added to mascaras to make the eyebrows thicker and longer, and are even used for base makeup to create a younger-looking skin texture.[52]

#### 14.2.2.1.2 Surfactants and Metal Salt

Crystals of surfactant metal salts such as magnesium myristate, zinc myristate, and calcium lauroyl taurate, or surfactants such as lauroyl lysine, are sometimes used as extender pigments or surface treatment agents for makeup cosmetics. These crystals are white and smooth powders, and they have high hydrophobic properties as well as

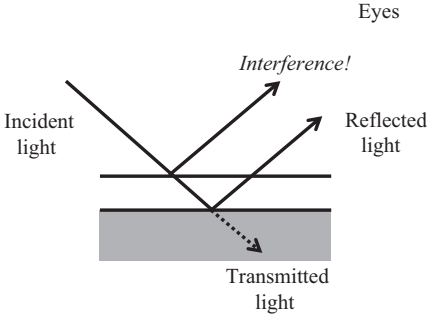



FIGURE 14.3 The coloring mechanism of interference pearls.

lubricity and improve the application touch of cosmetic powders. They also have effect to prevent caking where the powders aggregate and solidify.[53,54]

#### *14.2.2.2 Colored Pigments*

β carotene, gardenia, safflower, and shikonin have been used as naturally derived pigments for cosmetics. These coloring materials often have unstable physical properties and tend to have low optical and thermal stability. On the other hand, only governmentally approved synthetic tar pigments can be used in cosmetics. Generally, these coloring materials have more vivid saturation compared to inorganic materials, and are used for eye shadows, lipstick, and other makeup cosmetics.

## 14.3 CONCLUSIONS

Many cosmetic powders have been developed both from organic and inorganic materials. Recently these materials have been combined to develop organic-inorganic composite materials or capsule-type composite materials, leading to more optical and chemical functions. A prominent example is controlling the interference light of pearlescent pigments by covering the extender pigment's surface with superfine particles that have high light-scattering properties. These pigments with controlled optical properties are applied to cosmetics aiming for functions such as making small wrinkles and pores less visible, and enhancing the face's dynamism to hide sagginess.[55] Another method that has been recently proposed is covering powders with high stimulant-response polymers that show different hydrophilic-hydrophobic properties depending on the pH, and this can be applied to sunscreen cosmetics with water-resistant properties that are resistant to sweat but can easily wash off with water.[56] Nanosized materials are often used in these new cosmetic powders and are often targets of various discussions regarding their safety. Cosmetic manufacturers in the Japan Cosmetic Industry Association are currently cooperating to discuss the safety of these materials systematically.[57] Development and discovery of such materials and functions are expected to expand further to offer more possibilities in beauty.

## References


1. Lucas A. Cosmetics, perfumes and incense in ancient Egypt. *J Egyptian Archaeol* 1930;**16**(1/2):41–53.
2. Martinetto P, Anne M, Dooryhée E, Drakopoulos M, Dubus M, Salomon J, et al. Synchrotron X-ray micro-beam studies of ancient Egyptian make-up. *Nucl Instrum Methods Phys Res B* 2001;**181**(1–4):744–8.
3. Walter P, Martinetto P, Tsoucaris G, Bréniaux R, Lefebvre MA, Richard G, et al. Making make-up in Ancient Egypt. *Nature* 1999;**397**(6719):483–4.
4. Dooryhée E, Martinetto P, Walter P, Anne M. Synchrotron X-ray analyses in art and archaeology. *Radiat Phys Chem* 2004;**71**(3–4):863–8.
5. Suzuki M. A consideration on the roots of cosmetics from the viewpoint of cosmetic chemists. *J Soc Cosmet Chem Jpn* 1988;**22**(2):103–8.
6. Thorpe TE. On the atomic weight of titanium. *J Chem Soc Trans* 1885;**47**:108–32.
7. Sayre RM, Kollias N, Roberts RL, Baqer A, Sadiq I. Physical sunscreens. *J Soc Cosmet Chem* 1990;**41**(2):103–9.
8. Bolomey RA, Greenstein LM. An instrumental study of the optical characteristics of nacreous and interference pigments. *J Soc Cosmet Chem* 1971;**22**(2):161–77.
9. Deacon RF, Goodman JF. Lubrication by lamellar solids. *Proc Roy Soc Lond A* 1958;**243**(1235):464–82.
10. Ohta S. Synthetic mica and its application. *J Clay Sci Soc Jpn* 2004-2005;**44**(1):31–6.
11. Bergna HE, Roberts WO. *Colloidal silica: Fundamentals and applications*. CRC Press; 2005.
12. McDonald RS. Study of the interaction between hydroxyl groups of aerosil silica and adsorbed non-polar molecules by infrared spectrometry. *J Am Chem Soc* 1957;**79**(4):850–4.
13. Sterman S, Marsden JG. Silane coupling agents. *Ind Eng Chem* 1966;**58**(3):33–7.
14. Wason SK. Cosmetic properties and structure of fine particle synthetic precipitated silicas. *J Soc Cosmet Chem* 1978;**29**(8):497–521.
15. O'Connor TE. Synthesis of boron nitride. *J Am Chem Soc* 1962;**84**(9):1753–4.
16. Rowe GW. Some observations on the frictional behaviour of boron nitride and of graphite. *Wear* 1960;**3**(4):274–85.
17. Kimura Y, Wakabayashi T, Okada K, Wada T, Nishikawa H. Boron nitride as a lubricant additive. *Wear* 1999;**232**(2):199–206.
18. Judat B, Kind M. Morphology and internal structure of barium sulfate—derivation of a new growth mechanism. *J Colloid Interface Sci* 2004;**269**(2):341–53.
19. Emmert R. Quantification of the soft-focus effect: Measuring light-diffusing characteristics of cosmetic pigments and powders. *Cosmet Toilet* 1996;**111**(7):57–61.
20. Uchida H, Sugihara N. Iron oxide system pigments for cosmetics. *J Jpn Soc Colour Mater* 2011;**84**(10):351–7.
21. Tsugita A. Optical properties of pigments and their applications. *J Soc Cosmet Chem Jpn* 1993-1994;**27**(2):119–29.
22. Federico ED, Shöfberger W, Schelvis J, Kapetanaki S, Tyne L, Jerschow A. Insight into frame work destruction in ultramarine pigments. *Inorg Chem* 2006;**45**(3):1270–6.
23. Lee JD, Browne LS. The nature and properties of manganese violet. *J Chem Soc A* 1968:59–561.
24. Hattori T. Carbon black. *J Jpn Soc Colour Mater* 2010;**83**(9):387–93.

25. Biscoe J, Warren BE. An X-ray study of carbon black. *J Appl Phys* 1942;**13**(6):364.
26. Studebaker ML, Huffman EWD, Wolfe AC, Nabors LG. Oxygen-containing groups on the surface of carbon black. *Ind Eng Chem* 1956;**48**(1): 162–6.
27. Fujishima A, Honda K. Electrochemical photolysis of water at a semiconductor electrode. *Nature* 1972;**238**(5358):37–8.
28. Wang R, Hashimoto K, Fujishima A, Chikuni M, Kojima E, Kitamura A, et al. Light-induced amphiphilic surfaces. *Nature* 1997;**388**(6641): 431–2.
29. Sopyan I, Watanabe M, Murasawa S, Hashimoto K, Fujishima A. An efficient $TiO_2$ thin-film photocatalyst: photocatalytic properties in gas-phase acetaldehyde degradation. *J Photochem Photobiol A* 1996;**98**(1–2):79–86.
30. Bruehlman RJ, Thomas LW, Gonick E. Effect of particle size and pigment volume concentration on hiding power of titanium dioxide. *Off Dig* 1961;**3**(433):252–67.
31. Luckiesh M, Taylor AH, Cole HN, Sollmann T. Protective skin coatings for the prevention of sunburn. *J Am Med Assoc* 1946;**130**(1):1–6.
32. Turkoglu M, Yener S. Design and in vivo evaluation of ultrafine inorganic oxide containing sunscreen formulations. *Int J Cosmet Sci* 1997;**19**(4): 193–201.
33. Kobayashi M, Kalriess W. Photocatalytic activity of titanium dioxide and zinc oxide. *Cosmet Toilet* 1997;**112**(6):83–5.
34. Ukaji E, Furusawa T, Sato M, Suzuki N. The effect of surface modification with silane coupling agent on suppressing the photocatalytic activity of fine $TiO_2$ particles as inorganic UV filter. *Appl Surf Sci* 2007;**254**(2):563–9.
35. Gamer AO, Leibold E, van Ravenzwaay B. The in vitro absorption of microfine zinc oxide and titanium dioxide through porcine skin. *Toxicol In Vitro* 2006;**20**(3):301–7.
36. Wu J, Liu W, Xue C, Zhou S, Lan F, Bi L, et al. Toxicity and penetration of $TiO_2$ nanoparticles in hairless mice and porcine skin after subchronic dermal exposure. *Toxicol Lett* 2009;**191**(1):1–8.
37. Moezzi A, McDonagh AM, Cortie MB. Zinc oxide particles: synthesis, properties and applications. *Chem Eng J* 2012;**185–186**:1–22.
38. Mitchnick MA, Fairhurst D, Pinnell SR. Microfine zinc oxide (Z-Cote) as a photostable UVA/UVB sunblock agent. *J Am Acad Dermatol* 1999; **40**(1):85–90.
39. Pinnell SR, Fairhurst D, Gillies R, Mitchnick MA, Kollias N. Microfine zinc oxide is a superior sunscreen ingredient to microfine titanium dioxide. *Dermat Surg* 2000;**26**(4):309–14.
40. Lansdown ABG, Mirastschijski U, Stubbs N, Scanlon E, Ågren MS. Zinc in wound healing: theoretical, experimental, and clinical aspects. *Wound Rep Reg* 2007;**15**(1):2–16.
41. Pasquet J, Chevalier Y, Couval E, Bouvier D, Noizet G, Morlière C, et al. Contents lists antimicrobial activity of zinc oxide particles on five micro-organisms of the challenge tests related to their physicochemical properties. *Int J Pharm* 2014;**460**(1–2):92–100.
42. Petit L, Piérard-Franchimont C, Uhoda E, Vroome V, Cauwenbergh G, Piérard GE. Coping with mild inflammatory catamenial acne A clinical and bioinstrumental split-face assessment. *Skin Res Technol* 2004;**10**(4):278–82.
43. Nomura K, Takasuka Y, Nishimura H, Motoyoshi K, Yamanaka S. Selective adsorption of fatty acids for the prevention of foundation makeup deterioration. *J Soc Cosmet Chem* 1999;**33**(3):254–66.
44. Wei SH, Mahuli SK, Agnihotri R, Fan LS. High surface area calcium carbonate: pore structural properties and sulfation characteristics. *Ind Eng Chem Res* 1997;**36**(6):2141–8.
45. Ueno Y, Futagawa H, Takagi Y, Ueno A, Mizushima Y. Drug-incorporating calcium carbonate nanoparticles for a new delivery system. *J Control Rel* 2005;**103**(1):93–8.
46. Matoba I, Yamazaki H. Adsorption of limonene on inorganic powders. *J Jpn Cosmet Chem Assoc* 1970;**6**(1):12–4.
47. Grégoire C. Topography of the organic components in mother-of-pearl. *J Cell Biol* 1957;**3**(5):797–808.
48. Bolomey RA, Greenstein LM. Pearlescence: The optical behavior of "white" nacreous pigments as an interference effect. *J Soc Cosmet Chem* 1972;**23**(2):77–87.
49. Kimura A, Suzuki F. Development of new type colored nacreous pigment. *J Jpn Soc Powder Powder Metall* 1987;**34**(9):497–501.
50. Shiomi H, Misaki E, Adachi M, Suzuki F. High chroma pearlescent pigments designed by optical simulation. *J Coat Technol Res* 2008;**5**(4): 455–64.
51. Nakamura N. Application of plastic powder materials for cosmetics. *J Jpn Soc Colour Mater* 1988;**61**(8):438–46.
52. Sakazaki Y. Application of powdered fiber for make-up products. *J Jpn Soc Colour Mater* 2007;**80**(3):123–8.
53. Takehara M. Properties and applications of amino acid based surfactants. *Colloids Surf* 1989;**38**(1):149–67.
54. Nonomura Y, Kurita K, Kashimoto A, Hotta H, Kaneko Y, Iitaka K. The internal structure and tribology of calcium lauroyl taurate. *Chem Lett* 2002;**31**(2):216–7.
55. Sato F. New innovative powders with remarkable functions for cosmetic applications. *J Jpn Soc Colour Mater* 2006;**79**(9):397–403.
56. Osawa Y. Powder surface treatment to provide pH-responsiveness. *J Jpn Soc Colour Mater* 2015;**88**(6):171–4.
57. Masunaga T. Safety assessment of nanomaterials in cosmetics. *J Jpn Soc Colour Mater* 2012;**85**(9):384–8.

CHAPTER

# 15

# Surfactants

*Y. Nakama*
**Kishi Kasei Co., Ltd, Kanagawa, Japan**

## 15.1 INTRODUCTION

Dating back to soap used for cleansing in Ancient Rome before the birth of Christ, surfactants today are no longer used just as cleansers but are now used for various functions such as for solubilizing agents, emulsifiers, antifogging agents, defoaming agents, and deinking agents in many fields. Surfactants are more than just cleansers and are used for their numerous functions, and the world of cosmetics is no exception.

In cosmetics, surfactants play important roles, such as keeping immiscible liquids like oil and water evenly mixed, or to help the mixture to penetrate skin and hair, and even keep the mixture stable for years. Additionally, surfactants change their functions with different concentrations, and this makes them essential to cosmetics since they can be utilized to control a product's feeling and functions during the development process.

In this chapter, we will learn the fundamental properties of surfactants that are essential when utilizing their applications in actual cosmetics development. One important thing to know about surfactants in cosmetic formulation is that it is rare to use single surfactants, and usually several are mixed. By mixing several surfactants, they show synergistic effects creating added value when formulating a product. We will look into the basic properties of surfactants, namely solubility (micellization, cloud point, Krafft point) and adsorptivity, which are essential in formulation development. Additionally, we will focus on the unique properties of mixed systems to deepen our understanding of formulation development in Chapter 20.

## 15.2 CHARACTERISTICS AND CLASSIFICATION OF SURFACTANTS

Surfactants are substances that create self-assembled molecular clusters called micelles in a solution (water or oil phase) and adsorb to the interface between a solution and a different phase (gases/solids). To show these two physical properties, a surfactant must have a chemical structure with two different functional groups with different affinity within the same molecule. Usually the molecules of the substances called surfactants have both an alkyl chain with 8−22 carbons. This chain is called a hydrophobic group, which does not show affinity to water (they are called hydrophobic groups since surfactants are often used in water systems, but when used in lipid systems they are called lipophilic groups). The surfactant molecules also have a functional group called the hydrophilic group that has affinity to water. This kind of structure with two opposing functions is called an amphiphilic structure.

Surfactants are classified into ionic surfactants and nonionic surfactants. Ionic surfactants are subclassified into anionic surfactants where the hydrophilic group dissociates into anions in aqueous solutions, cationic surfactants that dissociate into cations, and amphoteric surfactants that dissociate into anions and cations often depending on the pH. Nonionic surfactants are surfactants that do not dissociate into ions in aqueous solutions, and they are subclassified depending on the type of their hydrophilic group (Fig. 15.1). Common hydrophilic groups of ionic surfactants are carboxylate ($-COO^-$), sulfate ($-OSO_3^-$), sulfonate ($SO_3^-$), carboxybetaine ($-NR_2CH_2COO^-$), sulfobetaine ($-N(CH_3)_2C_3H_6SO_3^-$), and quaternary ammonium ($-R_4N^+$). As an example, a soap molecule has a hydrocarbon chain as its lipophilic functional group that has affinity to lipids (the lipophilic group) and a carboxylate anion as its functional group that has affinity to water (the hydrophilic group). In an aqueous solution, the

*Cosmetic Science and Technology: Theoretical Principles and Applications*
http://dx.doi.org/10.1016/B978-0-12-802005-0.00015-X

Copyright © 2017 Elsevier Inc. All rights reserved.

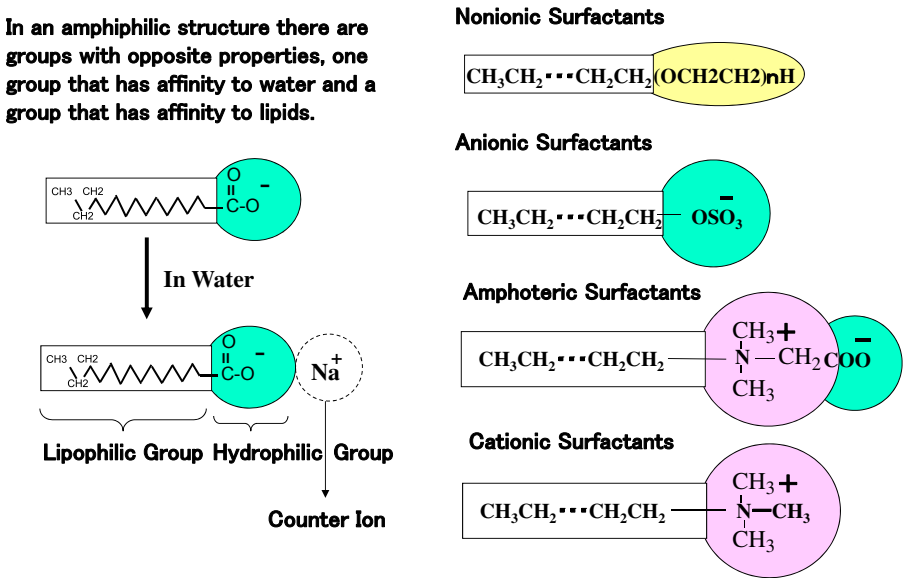



FIGURE 15.1 Structure and classification of surfactants.

carboxylate anion forms a structure with counterions such as $Na^+$, $K^+$, or $Mg^{2+}$ (Fig. 15.1). The hydrophilic group of nonionic surfactants is usually a polyoxyethylene group, but there are also nonionic surfactants with glyceryl groups or sorbitol groups, and nonionic surfactants with these different hydrophilic groups are also used depending on the application.

Surfactants are also classified depending on their solubility, such as hydrophilic surfactants that are soluble in water or hydrophobic (lipophilic) surfactants that are soluble in lipids. Ionic surfactants are generally hydrophilic surfactants, but nonionic surfactants can be either hydrophilic or lipophilic, depending on the balance of the hydrophilic group and lipophilic group. In other words, the solubility of nonionic surfactants depends on the balance between the hydrophilic group's capacity of attracting water and the lipophilic group's capacity of attracting oil. Hydrophilic-lipophilic balance (HLB) is an indicator that quantifies this relative balance. HLB was first proposed by Griffin[1] and currently several formulas to calculate HLB have been reported.[2,3] Since HLB indicates the characteristics of nonionic surfactants, it is commonly used as an indicator for choosing a surfactant for specific applications, such as emulsifiers or cleansers, which are both mentioned later in this chapter (Fig. 15.2). However, since HLB is merely an indicator based on experience, it can be used as a reference to choose a surfactant for an application but this is not enough in formulation development and that can lead to many challenges. Knowing the characteristics of surfactants efficiently and quickly is vital in formulation development. In addition to the HLB, there are two indicators that subjectively show these characteristics: the cloud point for nonionic surfactants and the Krafft point for ionic surfactants.

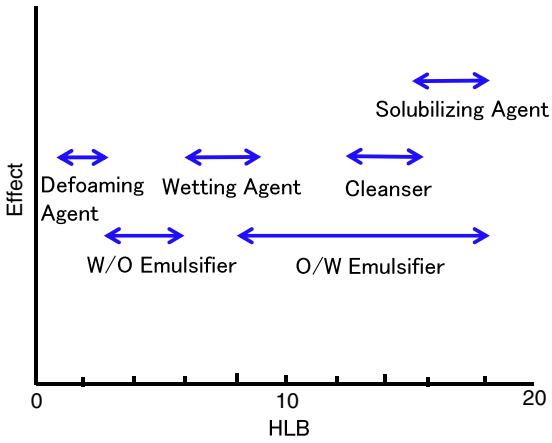



FIGURE 15.2 Index for choosing surfactants.

## 15.3 MICELLIZATION OF SURFACTANTS

One of the most prominent characteristics of surfactants is that when they reach a certain concentration, the surfactant molecules associate and create a micelle (in most cases a spherical micelle), a self-assembled molecular cluster. The critical micelle concentration (CMC) is the concentration where surfactants form micelles.

So, how do these micelles form in aqueous solutions? The key to understanding this phenomenon is in the hydrophobic interaction caused by the increase of entropy in the water molecules that interact with these surfactant molecules.[4] When surfactants are added into water, the water molecules around the hydrophobic groups create an iceberg structure, causing the entropy of the water molecules to decrease. As the concentration rises and the number of surfactant molecules increases, the hydrophobic groups encounter each other and start to associate, causing the iceberg structure to collapse and release free water. When free water is released, the entropy of water molecules increases (the decrease of entropy caused by the association of hydrocarbons is significantly smaller than the entropy increase of water), and this energy triggers micellization.

A surfactant shows different properties in aqueous solutions when it exists as single molecules and when they reach their micellization concentration, so the CMC can be determined by observing the solution's surface tension, conductance, and/or osmotic pressure.[5]

### 15.3.1 The Properties of Micelles

When the concentration of a solution is higher than the CMC, micelles and monomolecular surfactants (monomers) coexist in the aqueous solution, and in the solution they keep a dynamic equilibrium as they associate and dissociate. The exchange rate of the dynamic equilibrium is reported to be of the order of microseconds. Simple micelles are often depicted as being spherical, with disorderly aligned alkyl chains filling the core and with a rough surface with a liquid property. To understand the size of micelles, let's look at the size of the micelle of sodium dodecyl sulfate (SDS) as an example. SDS is known to be a spherical micelle with a diameter of approximately 100 A.[6] In recent molecular dynamics simulation, there are studies that report that the micelles are most energetically stable when approximately 60 SDS molecules are in the cluster.[7] The number of associated molecules in a micelle can be calculated by using common light-scattering method to measure the micellar weight (the size of the micelle) and then dividing the micellar weight with the molecular weight of the surfactant molecule. The number of molecules in this association depends on the molecular shape of the surfactant, and although it does not change with the concentration in low-concentration areas, it changes depending on the environment. For example, nonionic surfactants micelles grow larger when the temperature increases, and ionic surfactant micelles grow larger when the concentration of counterions increases. The most common type of surfactant, with one alkyl group bonded to one hydrophilic group, forms a spherical micelle. However, two-chained surfactants are known to form planar micelles rather than spherical micelles when the monomer concentration increases. Since one-chained surfactants form spherical micelles and two-chained surfactants form planar micelles, the geometrical balance of both the hydrophilic group and lipophilic group's packing space can be estimated. Critical packing parameter (CPP)[8] is a parameter that quantifies the packing space and is used to estimate the micelle structure.

Surfactants show different associated forms when the surfactant concentration increases and form liquid crystals that have shapes, structures, or optical properties different from micelles. Fig. 15.3 shows a conceptual model of a surfactant solution and how the phase conditions change with the temperature and concentration. Usually when the temperature is lower than Tc (the phase transition temperature line between hydrated solids and a solute state in a concentration higher than the CMC), surfactants are insoluble hydrated solids (or crystal hydrates) that have a bilayer structure and are not concentration dependent. When the temperature is higher than Tc, the solute state starts to change from spherical micelles to rodlike micelles as the concentration increases, and in higher concentrations the surfactant molecules start to align and orient, forming liquid crystals (lyotropic liquid crystals). In general, hexagonal liquid crystals are first formed by the alignment of rodlike micelles, and in higher concentrations lamellar liquid crystals start to form. These liquid crystals show optical anisotropy, but sometimes they form cubic liquid crystals that show an isotropic property similar to the property of spherical and rodlike micelles. The rheological property also changes drastically when they transition from micelles to liquid crystals, and this characteristic is utilized in formulation for various applications from cleansers to emulsifiers.

The state of the solute changes at Tc, and Fig. 15.4 shows how the state of bilayer structures changes from hydrated solids to lamellar liquid crystals at Tc. Strictly speaking, hydrated solids can be coagel or gels.[9] Coagel are found at lower temperatures and have a bilayer structure. There is hardly any water between the layers of their hydrophilic

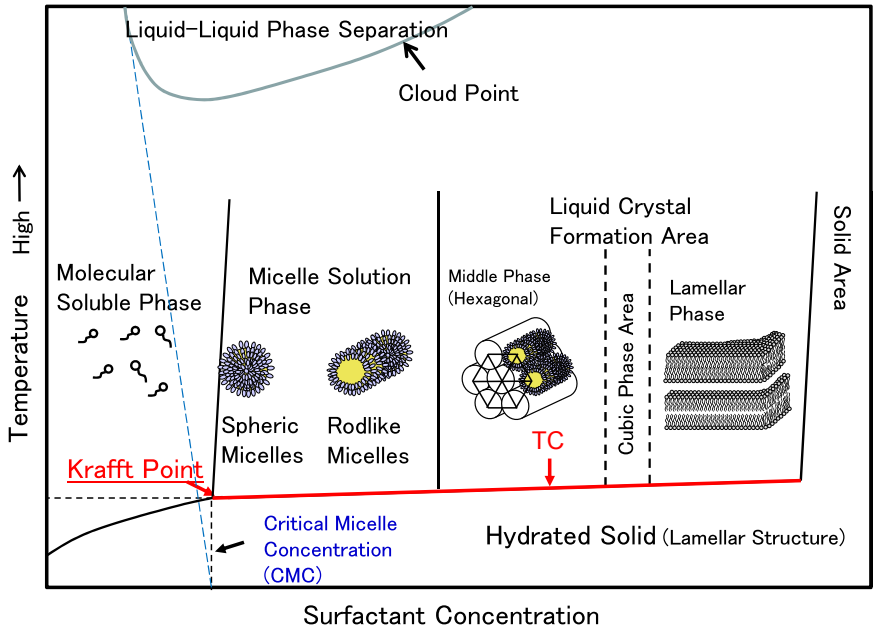



FIGURE 15.3 The concentration and temperature dependency of the phase conditions of a surfactant aqueous solution.

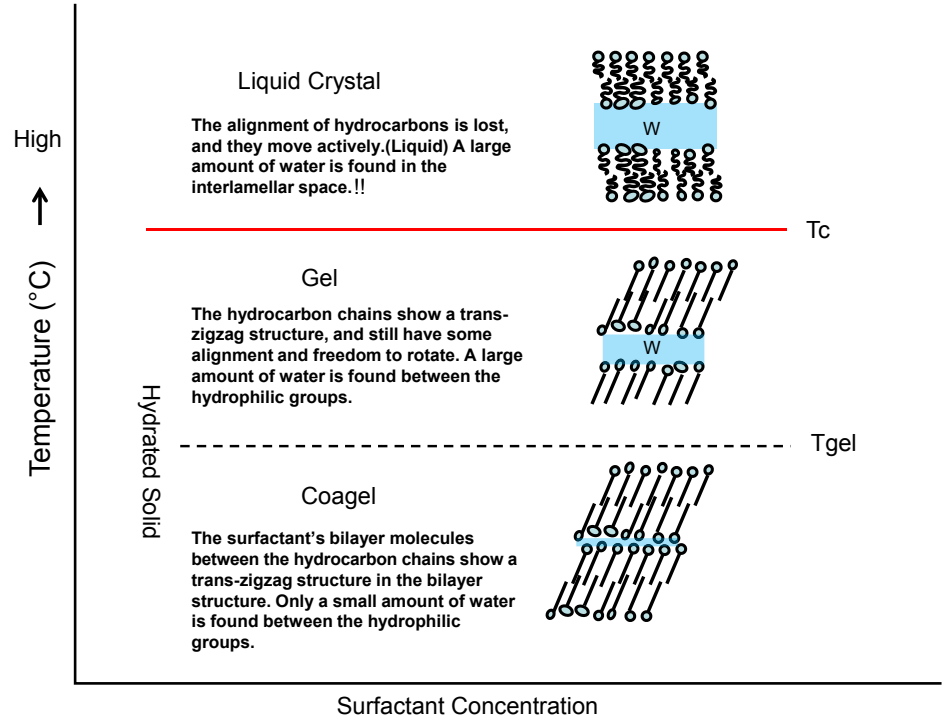



FIGURE 15.4 The structure of surfactants in high concentrations.

groups, and the alkyl chains are aligned with a *trans*-zigzag structure. When the temperature of coagels rises, they start to form gels (or alpha-gels), and this gel phase transition temperature is called Tgel. Like coagels, gels too have bilayer structures, but more water is found between the layers of the hydrophilic groups. Although the alkyl chains in gels are aligned to a certain degree, they have enough freedom to rotate. When the temperature rises even higher, they reach the phase transition temperature Tc and form lamellar liquid crystals. The interlamellar space between the hydrophilic groups contains a large amount of water, and the alkyl chains lose their alignment and become liquid state. The state of the solute can be identified by using wide-angle X-ray diffraction measurement to confirm if it is hydrated solids or lamellar liquid crystals.[10,11]

### 15.3.2 Solubilization

When surfactants are added to aqueous solutions, they can make insoluble lipids and slightly soluble materials soluble, a phenomenon called solubilization. Solubilization occurs in a thermodynamically stable solution where the slightly soluble substances dissolve to the lipophilic group inside the micelles, so solubilization occurs only when the surfactant concentration is higher than the CMC. With spherical micelles, the solubilizing position changes depending on the solubilized substance's polarity. For example, nonpolar substances such as hydrocarbons solubilize to the core of the micelle, a type of solubilization called core shell−type solubilization. On the other hand, substances with strong polarity, such as organic compounds, solubilize to the surface of the micelle's hydrophilic group, like higher alcohols and higher fatty acids that are known to solubilize between surfactants. This type of solubilization is called palisade-type solubilization. The solubilization potential of a surfactant varies with factors such as structure, additive inorganic salts, and temperature. Usually the solubilization potential is higher with longer lipophilic groups since they create larger cores. When inorganic salt is added to ionic surfactant solutions, the electrostatic repulsive force between the hydrophilic groups of the surfactants is suppressed and this lowers the CMC, making the micellar weight larger, leading to a higher solubilization potential. With hydrophilic nonionic surfactants, the molecular aggregation number increases when the aqueous solution's temperature rises, making the micelles grow larger and allowing a significantly greater amount of oil to solubilize.[12]

## 15.4 SOLUBILITY OF SURFACTANTS

### 15.4.1 Cloud Point

Nonionic surfactant solutions tend to cloud when the temperature rises. The water molecules bonded to the ether oxygen of a nonionic surfactant's polyoxyethylene group separate as the temperature rises (dehydration) and the solubility against water decreases, causing a liquid-liquid detachment that makes the liquid cloud. The cloud point refers to the temperature at which this transition occurs. Since a nonionic surfactant with a higher cloud point has a higher hydrophilic property, the cloud point is used as an indicator for the solubility of nonionic surfactants. Polyoxyethylene nonionic surfactants show a significant hydrophilic property in an aqueous solution with its coil-shaped meander structure formation. This meander structure is formed when oxygen atoms in ethylene oxide (EO), the hydrophilic group of polyoxyethylene nonionic surfactants, wrap water molecules into the lipophilic group -CH2- to contact water molecules more efficiently. If the temperature rises, the ether-bonded oxygen atoms and the hydrogen-bonded water molecules start to separate, stretching the coil and decreasing the hydrophilic property, until it finally reaches its cloud point where it can no longer dissolve in water (Fig. 15.5).

Let's see how the molecular aggregation number of micelles changes when the temperature rises.

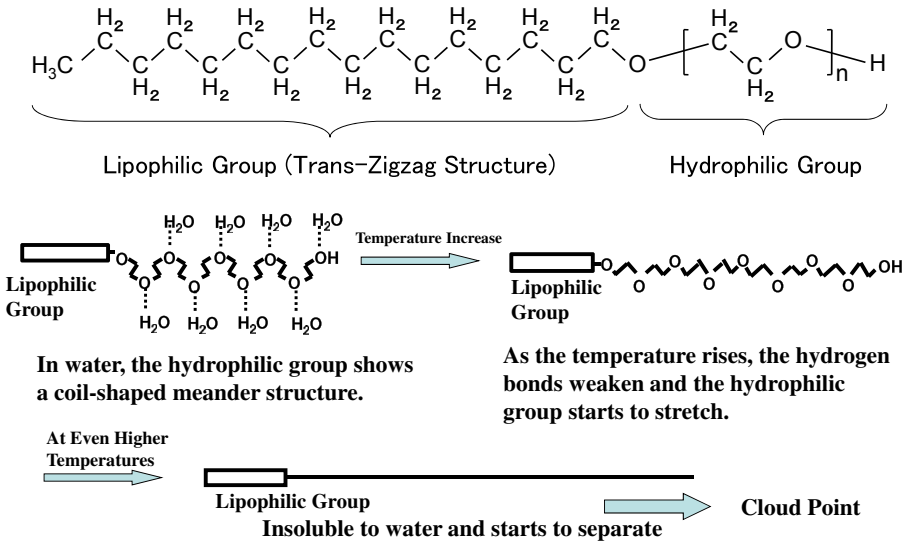



FIGURE 15.5 The clouding phenomenon of polyoxyethylene surfactants.

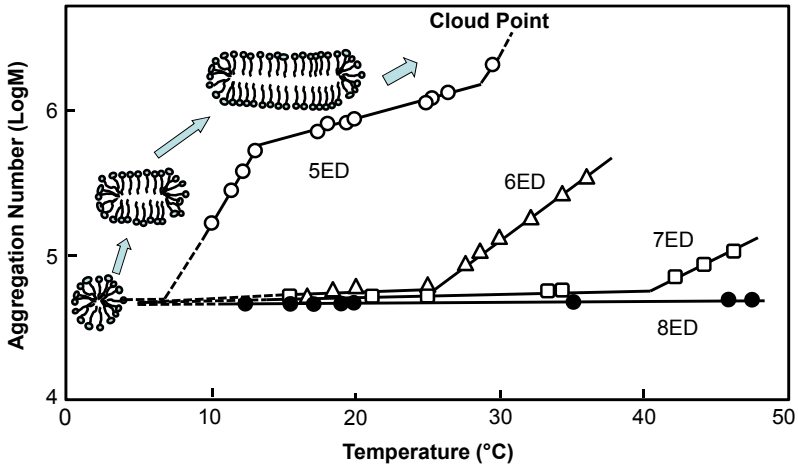



FIGURE 15.6 The effect of temperature on the aggregation number of polyoxyethylene (5, 6, 7, 8) dodecyl Ether.

Fig. 15.6[13] shows the change of the molecular aggregation number against the temperature of nonionic surfactants with 5, 6, 7, and 8 mol of EO added to dodecyl ether. As shown in the graph, the molecular aggregation number increases as the temperature rises for each surfactant. Now let's focus on the dodecyl ether with 5 mol added to the ethylene oxide group (5ED). The cloud point of this surfactant is at 30°C, and at a low temperatures near 5°C the aggregation number is estimated as approximately 100 molecules, with a spherical micelle form similar to other surfactants. However, the molecular aggregation number increases drastically at around 7°C. Presumably, the hydrogen bonds in the hydrophilic groups start to break near this temperature, causing the hydrophilic groups to show hydrophobic properties and stretching the coil-shaped meander structure. This means that steric hindrance is removed and this leads to lowering the packing property, and as a result the molecular aggregation number increases and the micelles grow extremely large. When looking at higher temperatures, the inflection point is around 12°C and at this point the micelles are thought to show a greater structure change. At even higher temperatures, near 30°C the surfactant shows a lipophilic property and can no longer dissolve to water, causing phase separation. The key to this phenomenon is in the extremely large micelle seen at around 10−25°C, where the solubilization potential reaches its maximum. Since this range is just below the cloud point, the liquid is a thermodynamically stable one-phase liquid and has potential for application in formulation development. The temperature where the spherical micelles start to transition with temperature increase is called the threshold temperature (Tt)[14] and is known to be about 20−30°C lower than the cloud point. In recent years, Tt can be determined easily and accurately with differential scanning calorimetry (DSC).[13] The cloud point is usually measured using a 1−2% concentrate surfactant solution, but caution is required when measuring the cloud point since the cloud point significantly increases as the surfactant concentration rises (Fig. 15.7). The cloud point can be explained as the temperature change of the HLB, and it is affected by both the hydrophilic group and lipophilic group. For example, when the lipophilic group is identical, the solubility and the cloud point increase with the number of moles added in the ethylene oxide group. Furthermore, a hydrophilic group that is hydrogen bonded to water molecules can easily be affected by water-soluble salts and polyols, and this factor is not negligible when considering the solubility of nonionic surfactants. This also means that the understanding of these effects can be applied to formulation development. Let's look at the cloud point of polyols, which are frequently used as moisturizers. Fig. 15.8 shows the effect of polyols on polyoxyethylene (6) dodecyl ethers (6ED). As shown in Fig. 15.8, 1,3-butanediol (1,3BG) and propylene glycol (PG) increase the cloud point of 6ED, but glycerol lowers the cloud point. This means that the HLB of nonionic surfactants can be controlled with different polyols, and this method is used in emulsification and in formulation development.[15,16]

## 15.4.2 Krafft Point

The Krafft point is the temperature at which the solubility of ionic surfactants in water increases drastically. To be more precise, the Krafft point is defined as the triple point of the surfactant monomer's solubility curve, the CMC temperature curve, and the phase transition line (Tc) of hydrated solids to micelles and/or liquid crystal (Fig. 15.9). When the surfactant solution is lower than its Krafft point and higher than the CMC, it forms a bilayer structure hydrated solid, and if it is higher than its Krafft point and higher than the CMC, it forms micelles.

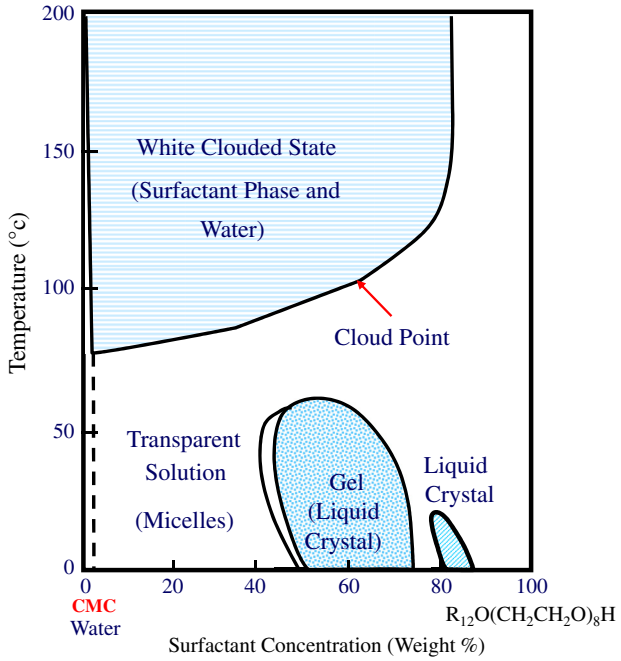



FIGURE 15.7 The concentration dependency of the clouding point.

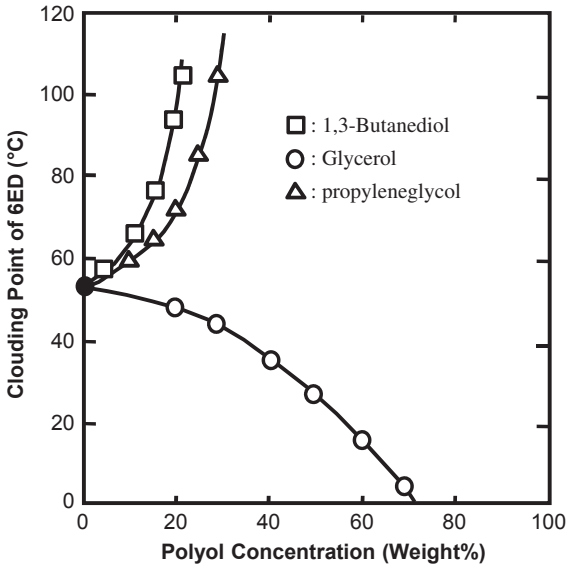



FIGURE 15.8 The effect of polyols on the cloud point of polyoxyethylene (6) dodecyl ether.

Since surfactants do not function unless they are dissolved, knowing the Krafft point of a surfactant is essential to formulation development. Determination of the CMC of a surfactant requires hard and demanding processes such as evaluating the solubility and temperature dependency. However, the Krafft point is thought of as the melting point of a surfactant's hydrated solid,[17] and this concept is often used to determine the Krafft point. Like the cloud point, the Krafft point also is affected by both the hydrophilic and lipophilic groups. For example, when the hydrophilic group is identical, the Krafft point increases and the solubility to water decreases when carbons in the alkyl chain increase. Furthermore, the solubility to water increases and the Krafft point decreases when polar groups are added to the unsaturated group. If the lipophilic group is identical, the solubility changes with the number and position of hydrophilic groups, and when the hydrophilic group is closer to the center of the alkyl chain, the solubility tends to increase. The Krafft point is also largely affected by counterions. In general, the Krafft point decreases and the solubility increases if the hydration degree of the counterion is higher. In formulation development, it is vital to

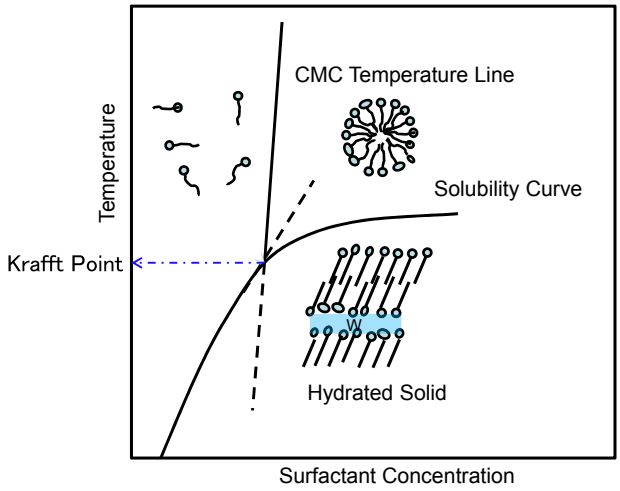



FIGURE 15.9 Conceptual chart of the Krafft point.

lower the Krafft point in order to maintain a low-temperature stability of a formula, essentially meaning that minimizing the crystallization of the surfactant is important.[18]

## 15.5 ADSORPTION OF SURFACTANTS

Like micellization, adsorption to interfaces is another fundamental and vital characteristic of surfactants that gives them their various functions (Table 15.1). Although there are many types of interfaces, the interfaces most commonly seen in cosmetics are air–water, oil–water, and solid (e.g., skin, hair, powder)–water interfaces.

### 15.5.1 Air–Water Interface Adsorption

As seen in skin toners, air–water interfaces are commonly seen in cosmetics. Since water molecules that contact air have fewer neighboring water molecules compared to those in bulk water, they have excess energy and are constantly in a higher energy state compared to the molecules inside the bulk water. Due to this energy difference, the water surface tries to lower its energy by reducing the surface area, creating what we call surface tension. Likewise, this phenomenon is called interfacial tension with oil–water interfaces. When a surfactant is applied to an oil–water interface, the lipophilic and hydrophilic groups of the surfactant molecule attract to oil and water, respectively,

TABLE 15.1 Functions of Surfactants and Applications in Cosmetics

| Interface | Function | Application in Cosmetics |
|---|---|---|
| Air/Water | Foaming/defoaming | Shampoos, facial cleansers, soaps |
| Oil/Water | Emulsification | Skin lotions, creams |
| Solid/Water | Wet | Skin toners, skin lotions, beauty lotions |
| | Scattering | Foundation, lipstick, mascara, sunscreen lotion |
| | Condensation | – |
| | Lubricity | Hair conditioners |
| Solid/Oil | Antistatic properties | Hair conditioners |

aligning the molecules and adsorbing to each phase. Both groups receive cohesive energy from the oil and water molecules through the surfactant's covalent bonds, and at the interfacial area they start to level, decreasing the energy difference and interfacial tension.[19] Therefore, adsorption continues until the surface energy and internal energy become equal. Adsorption changes the characteristics of a surface dramatically and is widely studied in academics and also applied in formulation development.

Knowing how and how much a surfactant is adsorbed to an interface is essential in formulation development. The adsorption at air–water and oil–water interfaces can be calculated by creating a surface (interfacial) tension–concentration curve and applying the Gibbs–Helmholtz equation.[20] This equation shows that the surface adsorption of a surfactant can be determined by the gradient of the surface (interfacial) tension–concentration curve. For example, when the alkyl chain length of a surfactant is longer, the surface tension decreases even at a lower concentration, showing that the surface adsorption amount is higher. Furthermore, the surface area per surfactant molecule can be estimated from the adsorption amount, indicating that this can be applied for development and evaluation of new surfactants.

### 15.5.2 Solid–Water Interface Adsorption

The adsorption isotherm is an effective method to understand the adsorption of surfactants on solid (skin, hair, powder–water interfaces. The adsorption isotherm is a graph that shows the surfactant concentration against the amount of surfactants adsorbed onto unit mass solid, when the solid (skin, hair, powder) is applied with a surfactant solution at a fixed temperature and reaches the equilibrium concentration. Adsorption can be either physical adsorption caused by Van der Waals force or chemical adsorption that is caused by chemical bonds such as covalent bond or ionic interaction. Physical adsorption is relatively weak and is reversible, and the heat of adsorption is only a few kcal/mol. Multilayer adsorption is also a characteristic of physical adsorption, and Langmuir type is a commonly known type of physical adsorption. With chemical adsorption, electrons are transferred between the molecules on the surface and the surfactant, and the adsorption is irreversible. The heat of adsorption is relatively high at 10–100 kcal/mol, and usually the adsorption is monomolecular. The Brunaue–Emmett–Teller isotherm, or BET type, is a common example of chemical adsorption. The type of adsorption can be determined by creating an adsorption isotherm to determine if it is physical adsorption, chemical adsorption, or both. Fig. 15.10 shows the adsorption isotherm on keratin powder, which is used as an alternative for hair, of *N*-lauroyl-*N*-methyl-β-alanine sodium (NaLMA), an anionic surfactant, and stearyl trimethyl ammonium chloride (STAC), a cationic surfactant, at 40°C.[21] The dotted line shows the individual CMC for each surfactant. The adsorption of NaLMA becomes saturated below its CMC, meaning that the majority is adsorbed as a monomer, and the adsorption isotherm pattern shows that its interaction with keratin powder is low, indicating that the adsorption is a Langmuir-type physical

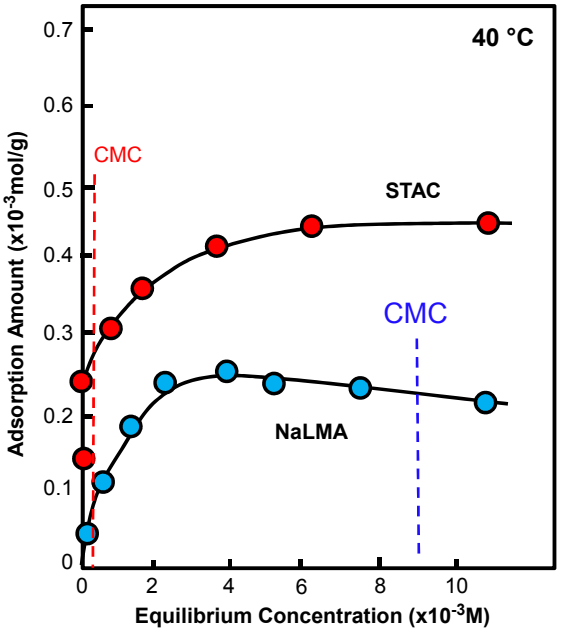



FIGURE 15.10 The adsorption isotherm of STAC and NaLMA with keratin powder.

adsorption. On the contrary, STAC shows a high-adsorption amount at a low-equilibrium concentration indicating that it has a strong chemical adsorption with keratin powder, but the adsorption is saturated just above the CMC, indicating that the surfactant molecules also adsorb when they are monomers or molecular associations of several molecules. The zeta potential of keratin powder is approximately −30 mV, and in an aqueous solution it is electrostatically charged with anions like hair. This explains the adsorption behavior of surfactants against keratin powder through electrical charge.

## 15.6 MIXED SURFACTANT SYSTEMS

### 15.6.1 Interaction of Surfactants

Hypotheses of micellization such as the mass action model[22] and the pseudophase separation model[23] have been proposed. The mass action model perceives micellization as a reversible equilibrium reaction and uses the molecular aggregation number as a variant, and the pseudophase separation model treats the molecular aggregation number as infinite. However, since the pseudophase separation model is easy to apply and directly shows the characteristic of solutions, most theories regarding mixed surfactant system micellization are based on this model, and there is ongoing discussion on different combinations of mixed surfactant systems.[24]

Based on this pseudophase separation model, interaction parameter β has been proposed to relatively evaluate the interaction of surfactants in two-component mixed systems, by using the concept of regular solution that applies nonideality to the micelle phase.[25] Parameter β is calculated from the components' individual CMC and the CMC of the mixed system with their mixed ratio. The parameter shows a negative value if the intermolecular interaction attracts and a higher absolute value if the interaction is stronger. Interaction parameter β has been set for various combinations of surfactant mixtures[25] in real-life applications, and these results show that the interaction tends to be strongest with anionic/cationic mixed systems, followed by anionic/amphoteric, anion or cation/nonionic, and amphoteric/nonionic mixed systems as the weakest. There have been multiple reports on these mixed systems, and according to these reports mixed systems with stronger interaction show a larger difference from the ideal systems, offering interesting phenomena that could lead to additional value in formulation development. For example, most mixed systems show that their CMC is lower than each of the components' individual CMCs[26] and the surfactant efficiency increases, meaning that if used as a cleanser, the required amount can be reduced. There is ongoing debate on the synergy effects of surface tension with cationic/nonionic mixed surfactant systems.[27] Anionic/amphoteric mixed surfactant systems create an intermolecular compound in the solution and make a high-viscosity solution, reducing skin irritation.[28,29] Amphoteric/fatty acid mixed surfactant systems can be utilized for liquid crystals and interfacial membranes to make a stable emulsion against coalescence.[30,31] There are also reports on natural emulsification of anionic/nonionic mixed surfactant systems[32] and low-energy formulation of microemulsions with nonionic/nonionic mixed surfactant systems.[33] Anionic/cationic mixed surfactant systems show the strongest interaction, and there are reports that the micelles of this mixture show unique solution properties and rheological properties, such as rodlike micelle formation[34] and vesicle formation.[35] The synergy effect of the interaction in mixed surfactant systems is currently in discussion from a tribological point of view, both in theory and with experiments.[36]

Focusing on the mixed system with the strongest opposing electrical charge, anionic/cationic mixed surfactant systems, we will learn about the solubility (cloud point, Krafft point) and adsorption to utilize them in formulation development.

### 15.6.2 Solubility of Mixed Surfactant Systems

Although the cloud point is defined as the dehydration of polyoxyethylene-type nonionic surfactants, anionic/cationic mixed surfactant systems are also reported to show clouding.[37,38] Fig. 15.11 shows the phase equilibrium diagram of a three-component mixed system of NaLMA/STAC/water at total concentration 100 mM. The solution shows clouding-like nonionic surfactants above 25°C and near the equimolar point. In a mixed solution, both surfactants stoichiometrically exist as 1:1 ionic-bonded ion pairs (Fig. 15.12). These results suggest that the ion pairs form a structure similar to nonionic surfactant, with oxygen atoms of the NaLMA's amide groups and the carboxyl residue as the hydrophilic group, showing a clouding phenomenon. This suggests that surfactants can show a clouding phenomenon even if they do not have ethylene oxide groups. Since the ion pairs show a clouding phenomenon, these mixed systems can potentially be applied as emulsifiers. The curve below the cloud point curve is the Krafft

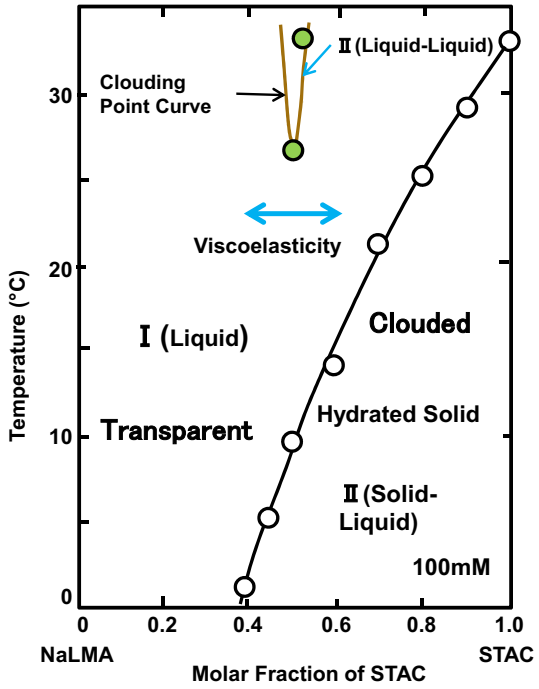



FIGURE 15.11 Phase equilibrium diagram of NaLMA/STAC/water three-component mixed system.

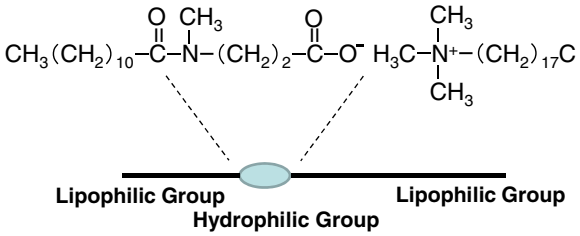



FIGURE 15.12 Schematic diagram of ion pairs.

point−composition curve. As mentioned earlier in this chapter, lowering the Krafft point is vital in formulation development. However, many surfactants show a eutectic point when they are mixed, indicating that the Krafft point can be lowered. The lowered Krafft point can be confirmed by using a Krafft point−composition curve. There are three types of Krafft point−composition curves with two-component mixed systems.[39] The first is when the crystal phase (hydrated solid phase) does not change with the activity of the composition (i.e., only crystals of pure substances exist), and the phase diagram shows a eutectic point. This means that both surfactants exist independently in the hydrated solid phase. The second type is when the activity of the compositions changes continuously in the crystal phase (i.e., all compositions make a solid solution), and the Krafft point is seen between the Krafft points of both surfactants and change continuously. The third is when intermolecular compounds of both surfactants form in the crystal phase, and with this type the Krafft point−composition curve reaches a maximum. The Krafft point of NaLMA is too small to confirm in an STAC/NaLMA mixed system, but the composition curve pattern shows that the mixed system is either a eutectic point type or the type where the Krafft point changes continuously, and if it is the former type, the Krafft point is predicted to be near the molar fraction at around 0.2.

### 15.6.3 The Adsorption Behavior of Mixed Surfactant Systems

In cosmetic formulation, a subject of surfactant adsorption is oils and lipids. Surfactants adsorb to these surfaces and change the characteristics of the surface, and improve the dispersion in the oil and water phase. Surfactants that show these effects are called emulsifiers and surface treatment agents, respectively. In cosmetics, the subject of surfactant adsorption is skin and hair, and with skin, the irritation is studied,[40,41] and with the latter, the conditioning

effect is studied,[42–44] both focusing on their absorptivity. Most of the research on adsorption is about independent surfactants, and there are few studies on the adsorption of mixed surfactant systems. However, there are interesting reports on their adsorption behavior from times when surfactants were used as treatment agents for fibers, and these reports show that anionic/cationic mixed surfactant systems show unique adsorption behavior.[45,46]

Fig. 15.13[21,47] shows the adsorption isotherm of NaLMA, STAC, and the mixed system of these two surfactants on keratin powder at 40°C. When the mixture ratio of STAC against NaLMA increases, the adsorption amount tends to increase. The mixed systems of STAC:NaLMA = 6:4 and 7:3 show that the adsorption amount is higher compared to when STAC is used alone, and shows the highest adsorption amount at 7:3. Additionally, the adsorption isotherm pattern shows that a mixed system with a higher ratio of cation has a stronger irreversible interaction with keratin powder.

Fig. 15.14 shows the adsorption curve of both STAC and NaLMA when mixed at STAC:NaLMA = 7:3, which showed the highest adsorption amount. The dotted lines show the adsorption isotherm for each substance. The adsorption amount of STAC was higher when used with NaLMA than when used alone (Fig. 15.14). The adsorption

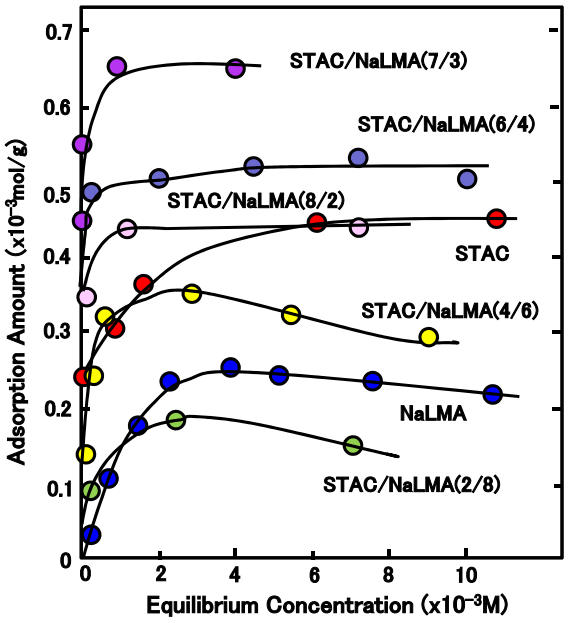



FIGURE 15.13 The adsorption isotherm of STAC/NaLMA mixed system against keratin powder.

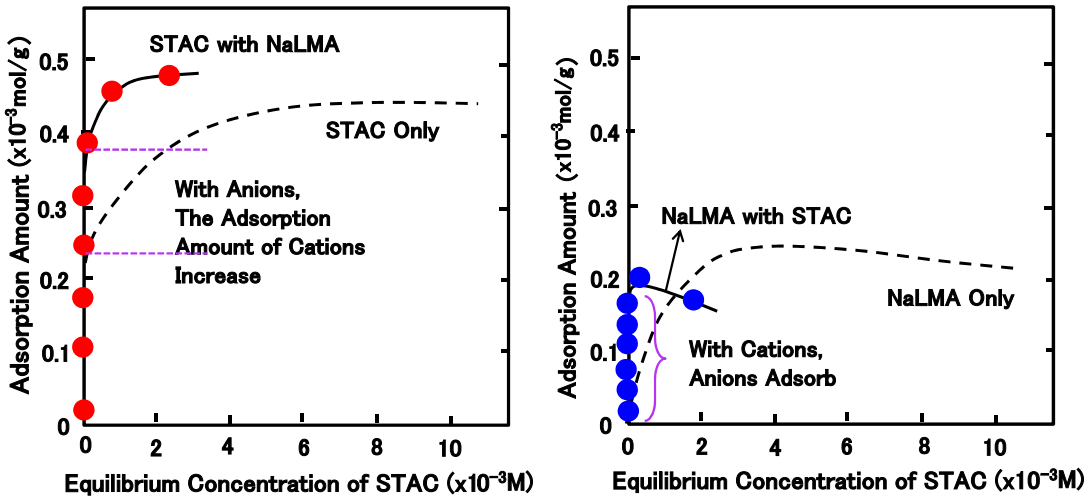



FIGURE 15.14 The adsorption isotherm of STAC and NaLMA against keratin powder in an STAC/NaLMA (7/3) mixed system.

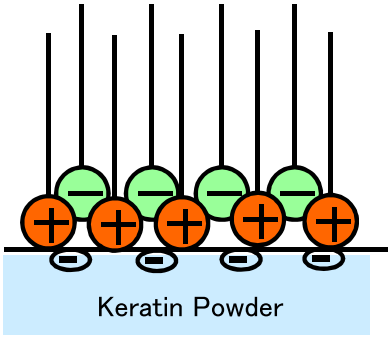



**FIGURE 15.15** The adsorption state of anion/cation mixed system.

of NaLMA was predicted to be a Langmuir-type equilibrium adsorption, but the mixed system with STAC showed that it was an irreversible adsorption behavior.

Let's look at this unique behavior by focusing on the STAC molecule adsorbed on keratin powder. In an aqueous solution, the ion head group of STAC molecules adsorb to electrostatically charged keratin powder, where the electrostatic attracting force and the repelling force between the molecules are balanced Fig. 15.15. However, with STAC: NaLMA = 7:3 mixed aqueous solution system, the mixture that showed the largest adsorption amount, the ion pairs and the excess STAC molecule adsorbed to keratin powder. This behavior indicates that when these molecules adsorb to keratin powder, the repelling force of the STAC molecules is counterbalanced with the NaLMA in the mixture, and as a result the adsorption amount increases compared to when STAC is used alone, and the NaLMA molecules adsorb as ion pairs, showing an irreversible adsorption behavior. This phenomenon can also be seen in real-life application with hair[48] and has been used as conditioning agents in two-in-one shampoos. These results can be explained in general that when the amount of surfactants is increased to adsorb electrostatically to an electrically charged surface; mixing it with a surfactant with the opposite charge is especially effective.

## 15.7 CONCLUSIONS

In this chapter, we have learned the basic functions of surfactants that are essential in cosmetics, especially through the fundamental properties that are vital in formulation development, namely their solubility (micellization, cloud point, and Krafft point) and adsorption, and also learned about the mixed systems that can be directly applied to formulation development. The surfactants introduced in this chapter were hydrocarbon surfactants, which have been used since ancient times, but in recent years the demand for more environmentally friendly surfactants is growing stronger. Today many new surfactants that focus on biodegradation, natural ingredients, and/or botanical ingredients are being developed. On the other hand, the demand for oils that strongly influence the feeling and function of formulas has changed over time and has evolved from hydrocarbon-based to silicone-based to fluorine-based. The surfactants that emulsify these oils are yet to follow this trend with the small exception of occasionally used silicone-based surfactants, and this trend of evolution is also expected.

The roles of surfactants in cosmetics have been mainly for maintaining the form, stabilizing, or adding functionality to products, but development of surfactants that actively function on skin and hair is anticipated. For example, if a surfactant in creams or lotions is an emulsifier but also decomposes into moisturizers on the skin under a certain condition, it would be gentle to the body and can be a new application for surfactants, and such possibilities to explore and develop remain.

## References

1. Griffin WC. *J Cosmet Chem* 1949;**1**:309.
2. Kawakami Y. *Kagaku* 1953;**23**:546.
3. Davies JT, Ridal EK. *Interface phenomena*. NY: Academic Press; 1961. p. 359.
4. Seo M, Araki K, Ootuki J. Supramolecular chemistry. *Tokyokagakudoujin* 1998:99.
5. McDonald. Micelle formation by surfactants. In: *Surfactants and interfacial phenomena*, vol. 3. Wiley-Interscience Publication; 1978. p. 85.
6. Abe M, Ogino K. *Yukagaku* 1982;**31**:569.
7. Yoshii N, Iwahashi K, Okazaki S. *J Chem Phys* 2006;**124**:184901.

8. Israelachvili JN. *Intermolecular and surface forces* [Kondo T, Ooshima H, Trans.] (分子間力と表面力): McGraw-Hill Publication; 1991. p. 256.
9. Seo M, Tujii K. *Surface active chemistry and application*. 1995. p. 67. Dainipontosyo.
10. Tomomasa S, Harusawa F, Machida Y. *Yukagaku* 1987;**36**:938.
11. Mizushima H, Fukasawa J, suzuki T. *Yukagaku* 1994;**43**:656.
12. Shinoda K. *Solution and solubility.* Maruzen; 1991. p. 168.
13. Unpublished.
14. Elworthy PH, McDonald C. *Kolloid-Z.Z. Polym* 1964;**196**:16.
15. Sagitani H, Hirai Y, Nabeta K. *Yukagaku* 1986;**35**:102.
16. Suzuki T, Takei H, Yamazaki S. *J Colloid Interface Sci* 1989;**129**:491.
17. Tujii K. *Yukagaku* 1982;**31**:981.
18. Takeuchi T. *Solution and solubility.* Yoneda Publication; 1999. p. 29.
19. Tajima K. *Oleo Sci* 2001;**1**:83.
20. Rosen MJ. Adsorption of surface-active agents at Interfaces. In: *Surfactants and interfacial phenomena*, vol. 2. Wiley-Interscience Publication; 1978. p. 56.
21. Nakama Y, Yamaguchi M. *Yukagaku* 1993;**42**:366.
22. Mukerjee P. *Adv Colloid Interface Sci* 1967;**1**:241.
23. Shinoda K. *Bull Chem Soc Jpn* 1953;**26**:101.
24. Graciaa A, Lachaise J, Schechter RS. The thermodynamics of mixed micelle formation. In: Abe M, Ogino K, editors. *Mixed surfactant system*: Surfactant Science Series 46, Marcel Dekker.
25. Rubingh DN. Mixed micelles solutions. In: Mittal KL, editor. *Solution chemistry of surfactants*, vol. 1. New York: Pleenum Press; 1979. p. 337.
26. Kawakami K, Kurano K, Kitagawa Y, Yamamura S, Nakamura M, Takeda T. *Yukagaku* 1993;**42**:111.
27. Kakehashi R. *Kagakutokogyo* 2006;**80**:380.
28. Miyazawa K, Ogawa M, Mitui T. *Int J Cosmet Sci* 1984;**6**:33.
29. Moriyama Y, Razali A, Tanaka M, Takeda K. *J Oleo Sci* 2011;**60**:229.
30. Nakama Y, Shiojima Y, Harusawa F. *Yukagaku* 1998;**47**:585.
31. Nakama Y, Shiojima Y, Harusawa F. *Yukagaku* 1998;**47**:1331.
32. Endo C, Ito Y, Akabane C, Kaneko Y, Sakai H. *J Oleo Sci* 2015;**64**:953.
33. Wakisaka S, Nishimura T, Gohtani S. *J Oleo Sci* 2015;**64**:405.
34. Aramaki K, Lemoto S, Ikeda N, Saito K. *J Oleo Sci* 2010;**59**:203.
35. Nakanishi H, Tsuchiya K, Ohkubo T, Sakai H, Abe M. *J Oleo Sci* 2005;**54**:443.
36. Negm NA. Theoretical and practical treatments of surface and bulk properties of aqueous mixed surfactant systems: mixed monolayers, mixed micelles formation, and synergism. In: Girma B, Kashmiri Lal M, editors. *Surfactants in tribology*, vol. 3; 2013. p. 379.
37. Nakama Y, Harusawa F, Murotani I. *J Am Oil Chem Soc* 1990;**67**:717.
38. Mehreteab A, Loprest FJ. *J Colloid Interface Sci* 1988;**125**:602.
39. Tujii K. *Netsusokutei* 1983;**10**(2):57.
40. Hashimoto F, Haruyama M, Yamashita T, Iso T. *J Soc Cosmet Chem Jpn* 1989;**23**:126.
41. Fujiwara N, Toyooka I, Ohnishi K, Onohara E. *J Soc Cosmet Chem Jpn* 1992;**26**:107.
42. Yahagi K, et al. *J Soc Cosmet Chem Jpn* 1990;**23**:301.
43. Mitamura J, et al. 18th IFSCC Congress Venezia Preprint (Poster presentation).
44. Okawa H, Hanabusa K, Suzuki M, Sekine Y, Fukui H. *J Soc Cosmet Chem Jpn* 2014;**38**:9.
45. Muller H, Krempl E. *Tenside* 1968;**5**:333.
46. Tokiwa F. *Yukagaku* 1979;**28**:578.
47. Harusawa F, Nakama Y, Tanaka M. *J Soc Cosmet Chem Jpn* 1991;**25**:110.
48. Harusawa F, Nakama Y, Tanaka M. Anionic-cationic ion-pairs as conditioning agents in shampoos. *Cosmet Toilet* 1991;**106**:35.

CHAPTER

# 16

# Emollients

*R. Miyahara*

**Shiseido Global Innovation Center, Yokohama, Japan**

## 16.1 INTRODUCTION

### 16.1.1 What Are Emollients?

The surface area of the human body is approximately 1.7 $m^2$, and the skin controls evaporation to control the body temperature and prevent the body's dehydration. Natural moisturizing factors (NMFs), stratum corneum intercellular lipids, and sebum are substances that protect the skin's moisture from evaporation. Thanks to these substances, healthy corneocyte contains approximately 25% water and maintains its softness. In cosmetics, substances that act as the sebum and lipids in the skin are called emollients. The physiological effect of creating a thin layer on the skin surface to prevent moisture evaporation to maintain the moisture and the skin's flexible feeling is called the emollient effect, and substances that cause an emollient effect are called emollients. The ideal emollients for the skin are sebum and lipids, which protect moisture by creating a sebum film on the skin surface. Table 16.1 shows the typical components of sebum.[1] Many substances used as emollients have components similar to the ones found in sebum.

Pharmaceutical products that contain emollients preserve the moisture in the stratum corneum and are used as basic skin care products to keep the skin soft (or supple). Emollient creams are the most common types of these products. Emollient creams are also called moisturizers, night creams, or moisturizing creams. Most emollient creams use water-in-oil (w/o)-type emollients that hold a relatively high amount of oil for a high-occlusion effect. In addition to emollients, emollient creams contain moisturizers such as glycerin, 1,3−butylene glycol, propylene glycol, and hyaluronate and are formulated using basic cream production methods. To prevent symptoms that are highly related to dehydration such as small wrinkles and roughness, active chemicals such as retinols, α-hydroxy acids, various vitamins, and astaxanthin are also added to increase the products' efficacy.[1]

### 16.1.2 A Brief History of Emollients

The first emollient recorded in human history is the cold cream invented by Galenus, a Greek doctor who worked in the Roman Empire during 129−199 AD. This cold cream was made mostly of natural oils and wax, and was used as surgical ointment rather than as a basic skin care product. In medieval Europe, applying beeswax and white powder was a popular makeup. Formulation of soap emulsion began in the late 19th century using creams with fatty acids from oils such as beef tallow or cerotic acids from beeswax with borax. During this era, as petroleum mining began, paraffins such as petroleum jelly were also used as emollients. From the 20th century people started to use soap to remove makeup, and basic skin care products evolved in order to supply lost NMF and moisturize and soften the skin. The use of lanolin dates back before World War II, and after the war the industrialization of cosmetic ingredients and emollients spread, leading to the development of a wide variety of synthetic oils and semisynthetic oils made from natural oils. Today progress in chemical technology such as asymmetric synthesis has allowed the synthesis of a plethora of oils with different molecular weights using ceramides and other natural oils. The progress also led to discovery of oils that dissolve in both water and polar oils, unlike surfactants that create micelles, and the variety of emollients has also grown in terms of polarity. Additionally, the variety of natural oils like organic certified oils are more commonly used, and this has become an alternative trend today.

*Cosmetic Science and Technology: Theoretical Principles and Applications*
http://dx.doi.org/10.1016/B978-0-12-802005-0.00016-1



Copyright © 2017 Elsevier Inc. All rights reserved.

**TABLE 16.1** Average Sebum Composition of Human

| | Composition ( % ) |
|---|---|
| Free fatty acids | 5 |
| Triglycerides | 50 |
| Waxes | 20 |
| Squalene | 10 |
| Branched hydrocarbons | 5 |
| Cholesterols | 1 |
| Cholesterol esters | 4 |
| Other cholesterol derivatives | 1 |
| Others | 4 |

## 16.2 TYPES OF EMOLLIENTS

There are various oily materials used as emollients that have high skin occlusion properties and spread smoothly on the skin. For example, hydrocarbons such as Vaseline and squalane, natural oils such as triglyceride, fatty acid esters, lanolin and its derivatives, sterol esters, aliphatic higher alcohol, fatty acids, and ceramides are often used as emollients.[2] Furthermore, emollients that dissolve in both water and polar oils such as diethoxyethyl succinate, triethyl citrate, and polyoxyethylene/polyoxypropylene (PEG/PPG) random copolymer dimethylethers[3] have been developed, and the variety is increasing. These emollients are combined to make the ideal skin care cosmetic with the best emollient effect for different skin types, application touch, season, and many other usage patterns by changing the combination and amount of each ingredient. For example, milky emollient lotions and cream-type emollients are formulated to match the users' needs.

### 16.2.1 Hydrocarbons

Table 16.2 shows a list of INCI hydrocarbons commonly used as emollients in cosmetics.[4]

Squalane is an oil made from squalene, one of the main components of sebum, and is a vital emollient. Squalene, the precursor of squalane, is generated in the human body from acetyl-CoA via the mevalonate pathway and is metabolized into cholesterol. However, not all squalene is metabolized, and some are restored back to the body[5] and are secreted from the sebaceous glands along with other metabolites to create a sebum film. Despite that more squalane can be found in the sebum compared to squalene, squalenes have six double bonds with a lower oxidation stability and are not commonly used in cosmetics except for pentahydrosqualenes, which are partially hydrogenated squalenes. Squalane is a component of the human sebum and its properties such as affinity, permeability, and diffusivity to the skin are superior to other hydrocarbons,[4] and it is an ideal emollient. Most squalanes sold in the market today are extracted from deep-sea shark liver oil. However, due to the decrease of catch in recent years botanical squalane is also used, by refining and hydrogenerating the squalene found in approximately 1% of olive oil and rice bran oil. Highly refined botanical squalane is similar to the squalane from deep-sea shark liver oil in terms of components, but analysis of the small amount of sterols in the squalanes shows that the main sterols in botanical squalanes are phytosterol, and since the main sterols in deep-sea shark liver oil—derived squalanes are cholesterols, it is possible to distinguish the two by analysis.

Liquid paraffin is a colorless and transparent liquid oil that is derived from petroleum. It is made from the middle distillate of the petroleum distillation and refining process to make gasoline and kerosene, and by refining and removing its aromatic compounds present in the impurities with catalyst reduction treatment or by water extraction with sulfuric acid treatment. Since paraffin is cheaper compared to other oils such as ester oil, it is widely used in cosmetics. There are slight differences in components depending on the refinement method, but paraffin is graded by the mixture of hydrocarbons such as naphthene, isoparaffin, and paraffin, and also its viscosity. Mixtures of these grades are also used. Since paraffin is made from mineral oil it may not be well accepted, but in the past it was used as a parting (or releasing) agent for bread (although not in recent years) and has been a common oil component for cosmetics.

**TABLE 16.2** Features of Main Hydrocarbons

| Ingredients | INCI Name | Origin | State at Room Temp. | Use |
|---|---|---|---|---|
| Squalane | SQUALANE | Hydrogenated squalene of shark liver oil or olive oil | Liquid | Paste oil, humectant, emollient, penetrant |
| Pentahydrosqualane | PENTAHYDROSQUALANE | Partially hydrogenated squalene | Liquid | Emollient, skin protection |
| Liquid paraffin | MINERAL OIL | Relatively low boiling point hydrocarbon fractionated and purified from petroleum | Liquid | Emollient, hair conditioning, skin protection |
| Vaseline | PETROLATUM | Purified hydrocarbon having boiling point between liquid paraffin and wax, fractionated and purified from petroleum | Paste | Adhesive, emollient, occlusive agent |
| Polyisobutene | POLYISOBUTENE | Polymer consisting of isobutylene and isoprene units | Paste | Lipophilic thickener |
| Paraffin | PARAFFIN | Petroleum-based wax | Solid | Shape retention agent, feeling improvement agent |
| Microcrystalline wax | MICROCRYSTALLINE WAX | Petroleum-based crystalline wax | Solid | Shape retention agent, feeling improvement agent, Solidification agent for lipstick |

Vaseline is a white semisolid oil paste that is a mixture of isoparaffins that have a melting point slightly higher than liquid paraffin. Vaseline has a high-occlusion effect and has a history as an ointment base in dermatology. Nishiyama et al.[6] have reported that Vaseline has the highest occlusion effect among low-polarity hydrocarbons, indicating that Vaseline is a very effective emollient.

Polyisobutene is a polymer of isobutene, which is derived at oil plants, and is can be produced from isobutylenes and isoprenes. Polyisobutene is graded based on the polymerization of these components. Paraffin wax and microcrystalline wax are derived from the distillation residue of petroleum. The main component of paraffin wax is straight-chain hydrocarbons (normal paraffin), but in microcrystalline the amount of wax branched hydrocarbons (isoparaffin) and cyclic hydrocarbon (cycloparaffin) is higher than that compared to paraffin wax and the crystals are also smaller. Paraffin wax and microcrystalline wax are used as thickeners and solid agents for skin creams, eye shadows, and lipstick.

### 16.2.2 Natural Oils

The main component of a glycerin extracted from plants and animals is triglyceride. Triglycerides consist of three ester bonded fatty acid groups to the hydroxyls of a glycerin molecule. A small amount of diesters and monoesters can also be present. Common vegetable oils used in cosmetics are olive oil, avocado oil, sesame oil, almond oil, rice bran oil, safflower oil, shea butter, camellia oil, castor oil, macadamia nut oil; common animal fats and oils used are beef tallow, horse tallow, and egg yolk oil. The fatty acids in triglyceride depend on the oil; for example, a rare fatty acid residue like the polyester of hydroxyl stearic acid can be found in castor oil. Natural oils have a higher polarity than hydrocarbons and have different properties, and although the moisture containment (water-holding capacity) is weaker than that of hydrocarbons, natural oils have functions to smoothen and soften skin and hair. Natural oils can also dissolve ultraviolet (UV) absorbers and other materials due to their high polarity.

### 16.2.3 Fatty Acid Esters

Fatty acid esters are synthesized by dehydrating fatty acids and alkyl alcohol, and have a conditioning effect of softening the skin to create a smoothing sensation. They are also added to cosmetics to dissolve high-polarity active ingredients and UV absorbers. Esters of straight-chain fatty acids and lower alcohols are effective for dissolving

slightly soluble ingredients for oils with a light touch during application. Dihydraulic acid esters, esters with two ester groups such as tripropylene glycol dineopenntanoate, have a very high polarity and are especially effective for dissolving materials such as UV absorbers. Isostearic acids and other liquid oils with branched fatty acids and unsaturated fatty acids are commonly used as emollients. Higher fatty acid esters and esters of higher alcohols with relatively high melting points are added to skin creams to adjust the application touch. Additionally, the fatty acid ester of polyglycerin is an ester oil with a very high water-holding function.[7]

### 16.2.4 Lanolin, Lanolin Derivatives, and Sterol Esters

Lanolin is found in sheep sebaceous glands and is a semisolid oil with a complex composition of cholesterols and many long-chain α-hydroxy acid esters. Lanolin has a unique tenacity and is used in skin creams and lipsticks, and is an emollient with a high water-holding property. Lanolin derivatives that are hydrolyzed, fractional crystallized, alkoxylated, or quaternized are also commonly used in cosmetics. Furthermore, they are used to synthesize cholesterol fatty acid esters and phytosterol fatty acid esters to imitate the cholesterol esters in the sebum or intercellular lipids. As an example of fatty acids, macadamia nut fatty acids have many palmitoleic acids that are found in sebum and can hold water up to three times their own weight, Macadamia nut fatty acid is used along with other fatty acids.

### 16.2.5 Aliphatic Higher Alcohol and Fatty Acids

Aliphatic higher alcohols and fatty acids are not effective emollients when used alone, but they show emollient effects when used with hydrophilic surfactants to form a self-organization called alpha gel.[8] As shown in Fig. 16.1, alpha gels have a long axis structure of higher alcohols, fatty acids, and surfactants and a structure similar to the structure of lamellar liquid crystals. Alpha gels are made of honeycomb-shaped crystals that show hexagonal crystals when viewed from above.[9] They can store water in their hydrophilic groups,[8,10] and they have high occlusive and moisture-retaining properties.

### 16.2.6 Ceramides

Stratum corneum intercellular lipids are lamellar-structured self-organized lipids that exist in the stratum corneum between corneocytes, and they protect the skin from external stimulants and the evaporation of the moisture in corneocytes. Ceramides are one of the main components of stratum corneum intercellular lipids, and are composed of 15% cholesterol ester, 5% cholesterol, 5% fatty acid, and 5% sugar ceramide. Suzuki et al.[11] have reported that synthesized pseudo-ceramide, cholesterol, and stearic acid create a semistable alpha gel (which chronologically transfers to gamma gels) as shown in Fig. 16.2. By emulsification of the gel with liquid crystal emulsion, the

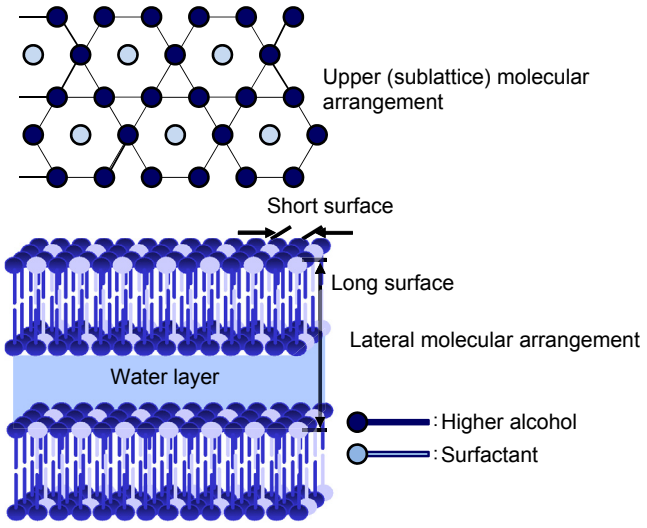



FIGURE 16.1 Molecular structure of alpha gels.

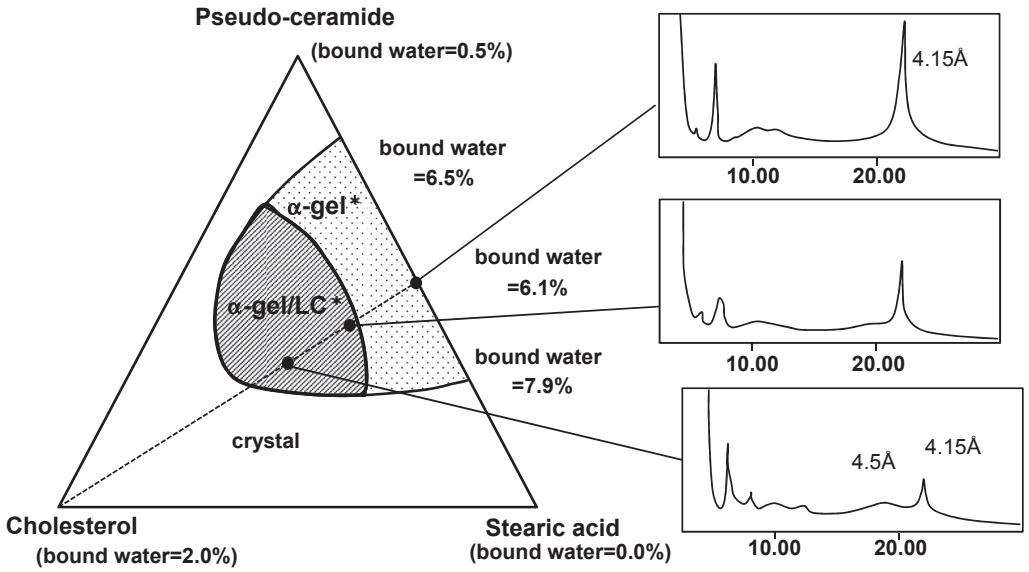



FIGURE 16.2 X-ray diffraction and three-component phase diagram of pseudo-ceramide alpha gels.

emulsion confers a higher conductance value to the skin compared to other emulsions (meaning the moisture in the skin is maintained).

## 16.2.7 Water-Soluble Oils

When designing oil molecules, the engineer should know that oils become mutually soluble to oil and water by increasing the polarity, and commonly known water-soluble oils are shown in Fig. 16.3.

The polarity of the oils shown in Fig. 16.3 is between the polarity of moisturizers and polar oils, and although they are not soluble to hydrocarbons such as liquid paraffin or squalane, they are soluble to high-polarity oils such as triglyceride. These oils do not have a critical micelle concentration when dissolved to water, and they do not create a molecular cluster like surfactants. Among the compounds shown in Fig. 16.3 triethyl citrate, 1,4-cyclohexanedicarboxylic acid bis-ethoxydiglycol succinate, diethoxyethyl succinate, and bis-ethoxydiglycol succinate, only dissolve into water by several percent, PEG/PPG random copolymer dimethylether is mutually soluble to water and ester oils at any desired ratio. It is assumed that when they are dissolved in water, a conformational change occurs and the PEG faces outward, allowing them to be mutually soluble. And when they are dissolved

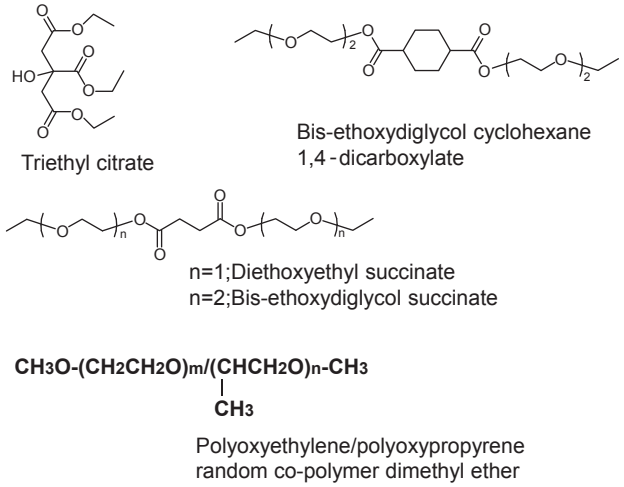



FIGURE 16.3 Water-soluble oils used in cosmetics.

in ester oils, the PPG faces outward. PEG/PPG random copolymer dimethylether can also be used a cosurfactant for surfactants to make an ultrafine emulsion.[12,13] These oils independently have moisture-retaining properties but can also be used to reduce the stickiness of glycerin.

## 16.3 EVALUATION OF EMOLLIENTS

There have been various attempts to evaluate emollients by quantifying the application touch, and to evaluate the moisturizing effect or prevention of dehydration. The oils are also evaluated by testing their water-holding capacity or the occlusion effect to measure how much evaporation is restrained.

### 16.3.1 Spreading Value

Oils with compatibility to the skin with a light touch are preferred as emollients. As a simple method to evaluate the compatibility to the skin with a light touch, the spreading value can be measured by dropping a fixed amount of oil to the skin and measuring its area size after a fixed period.[14,15] If the spreading value is larger, the oil feels lighter. Fig. 16.4 shows the correlation of the spreading value and the oil molecular weight by applying one oil droplet to the skin and measuring the surface area after 5 min.

Normal lipids with carbon-to-carbon bonds show a negative correlation between the spreading value and their molecular weight, and oils with smaller molecular weight show a larger spreading value.

On the contrary for silicon oil, segment rotation occurs with the Si—O bond with even a small amount of energy, resulting in a large spreading value and light application touch though its molecular weight is around 1000. The application touch of cosmetics is adjusted by choosing the best balance of various ingredients from semisolid oils to light oils.

### 16.3.2 Evaluation of Oil Friction and Stickiness

There are largely two methods to measure the skin surface friction using instruments.[16] One is the rotation method and is used to measure the human skin surface friction,[17–19] and the other is the sliding method, where cosmetics and other substances are applied to synthetic leather or pigskin to evaluate the friction using a frictional feel analyzer. Several studies have been reported using the sliding method.[20–22] Masaki et al. have reported that the smoothness of oil and the average friction coefficient (MIU) show a negative correlation with a 0.758 correlation coefficient.[23] The rotating friction test and frictional feel analyzer are used to evaluate the horizontal friction on the skin surface, but an alternative method has been proposed by Kusakari et al. using a rolling method to evaluate the vertical sliding friction.[24] With this method, a roller is attached to the tip of the frictional feel analyzer sensor, and when it is rolled on an oil-applied surface it can measure the vertical stickiness by measuring the oil detached from the surface as it rolls. There are reports that the rolling friction has a correlation with the spreading value (Fig. 16.5).

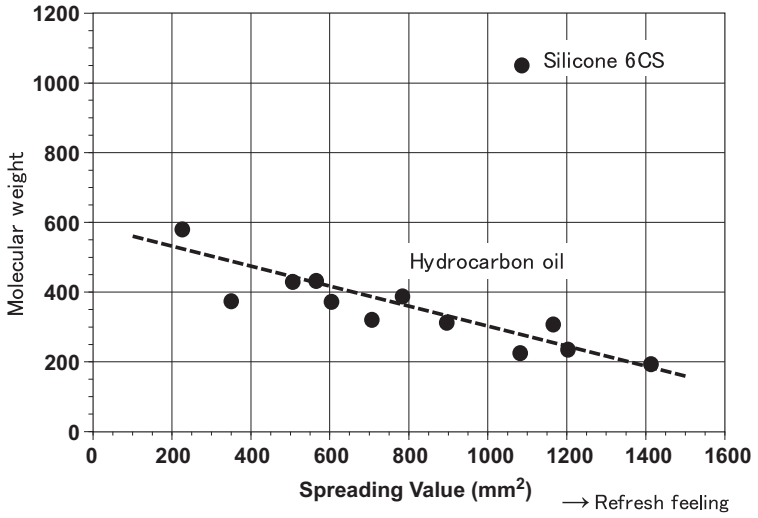



FIGURE 16.4 Correlation of spreading value and molecular weight.

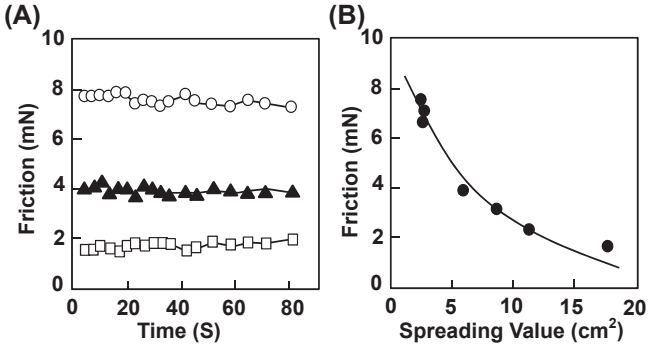



FIGURE 16.5 Correlation of rolling friction and spreading value.

The measured friction for pentaerythrityl tetraoctanoate (○), trioctanoin (▲), and dimethyl polysiloxane (□) is shown in (A). The relation between the friction and spreading value of oils is shown in (B).

### 16.3.3 Occlusion Effect

The occlusion effect is the effect of suppressing moisture evaporation from the skin. Although turnover of the skin accelerates when it becomes coarse, Takahashi et al.[25] have reported that the turnover slows down when the skin is protected with gauze and becomes even slower when covered by a Finn Chamber. This indicates that the occlusion effect of preventing inner moisture from evaporation is a vital function of emollients.

The occlusion effect can be measured by measuring the amount of water vaporized under a fixed temperature and humidity with a container with water, sealed with an acetylcellulose layer or filter paper with evenly applied oil. Nishiyama et al.[6] have used this method to systematically compare the occlusion effect of various oils and moisturizing creams, and reported that the occlusion effect is higher with oils with lower polarity (inorganic organic balance: IOB)[26] as shown in Fig. 16.6, but with silicone oil the occlusion effect is lower than that of organic oils. Additionally, they have reported that glycerin has the lowest occlusion effect as a moisturizer, and each moisturizer tested lowered the occlusion effect dependent on the concentration, suggesting that this is highly related to the moisture-absorbing property of the moisturizers.

### 16.3.4 Skin Flexibility Test

Deraflex and Cutometers are often used to test the firmness and flexibility of the skin when cosmetics are applied. These methods use suction methods by attaching a sensor to the skin and decreasing the pressure in the sensor to

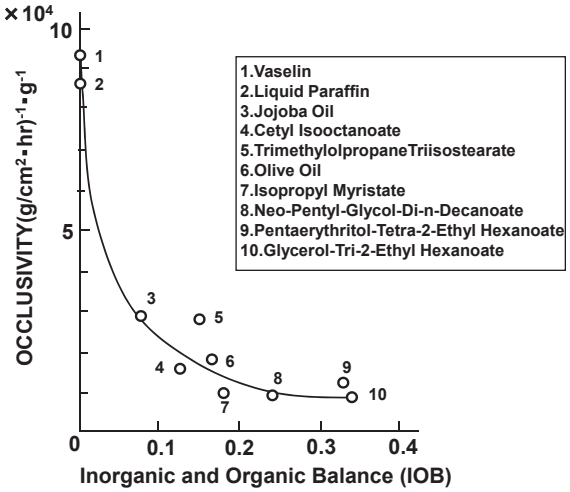



FIGURE 16.6 Correlation of the occlusion effect and polarity (IOB) of oils.

TABLE 16.3 Effect to Skin Viscoelasticity of Skin Softening Lotion

| Subject | Elasticity | Viscosity |
|---|---|---|
| 1 | 0.86* | 0.81* |
| 2 | 0.73* | 0.74* |
| 3 | 0.90* | 1.02 |
| 4 | 0.87* | 0.87 |
| 5 | 1.28* | 0.97 |
| Mean | 0.93 | 0.88 |

evaluate the dynamic properties of the skin from the height of the lifted skin. Table 16.3 shows Umeya et al.'s test results of the change in skin viscoelasticity of the forearm of female test subjects from age 20 to 25, both before softening lotion was applied and 5 min after application.[27] These results show that softening lotion decreases both the viscoelasticity and flexibility of the skin.

However, this method shows the dynamic properties of whole skin including dermis, and is not suitable for measuring the flexibility caused solely by the change of the stratum corneum. To measure such properties, a testing instrument called Venustron is being developed. With this instrument, a rod in its resonance vibration state is placed on the skin, and the vibration of the skin surface is measured by checking the change in the sensor's resonance vibration.[28] Using this method, the moisture content of water-loaded stratum corneum and the resonant frequency was measured in vivo, and results indicated that both were highly correspondent.[29]

## 16.4 THE FUTURE OF EMOLLIENTS

As stated in the beginning of this chapter, emollients are expected to evolve in two trends: one using 100% natural oils such as ecocert and other organically certified oils; and the other using asymmetric synthesis to design functional oil molecules. For organic ingredients, a unified international standard is expected to be established in the near future. For the latter, the use of various multifunctional oils is expected to grow, such as ceramides and biorelated materials that were previously expensive and rare, or oils that are soluble to both water and polar oil.

## References


1. Wheatley VR. *Pro Sc Sect* May 1963;**39**:25–8.
2. Website. *Soc Cosmet Chem Jpn*. http://www.sccj-ifscc.com/terms/detail.php?id=14.
3. Ohmori T, Yamamura Y, Nakahara K, Miyahara R, Hosokawa K, Maruyama K, et al. *J Oleo Sci* 2006;**55**(7):365–75.
4. *J Am Coll Toxicol Spec Issue* 1982;**1**(2):37–56. Second Report of the Cosmetic Ingredient Review Expert Panel.
5. Kaiya A. *Fragrance J* 2007;**20**:65–70.
6. Nishiyama S, Komatsu H, Tanaka M. *J Soc Cosmet Jpn* 1983;**16**(2):136–43.
7. Noguci Y. *Fragrance J* 2007;**20**:113–7.
8. Orita M, Uchiyama M, Hanamoto T, Yamashita O, Takeuchi K, Katayama Y, et al. *J Soc Cosmet Jpn* 2012;**46**(1):25–32.
9. Fukushima S, Yamaguchi M. *Yakugakuzasshi* 1981;**101**:1010–5.
10. Watanabe K, Inoue H, Teshigawara T, Kimura T. *J Oleo Sci* 2012;**61**(1):29–34.
11. Suzuki T, Imokawa G, Kawamata A. *J Chem Soc Jpn* 1993;**10**:1107–17.
12. Miyahara R, Watanabe K, Ohmori T, Nakama Y. *J Oleo Sci* 2006;**55**(8):403–11.
13. Miyahara R, Watanabe K, Ohmori T, Nakama Y. *J Oleo Sci* 2006;**55**(9):473–82.
14. Salka BA. *Cosmet Toilet* 1997;**112**:101–6.
15. Kakoki H. *Fragrance J* 2007;**20**:2–6.
16. Egawa M, Hirao T, Takahashi M. *J Soc Cosmet Chem Jpn* 2003;**37**(3):187–94.
17. Nacht S, Close JA, Yeung D, Gans EH. *J Soc Cosmet Chem* 1981;**32**:55–6.
18. Highley DR, Coomey M, Denbeste M, Wolfram I. *J Invest Dermatol* 1971;**84**:37–43.
19. Comanish S, Bottoms E. *Br J Dermatol* 1977;**69**:303–5.
20. Nakajima K, Narasaka H. *Int J Cosmet Sci* 1993;**15**:135–51.
21. Hironaka S. *Hyoumen* 1999;**37**(6):329–38.
22. Suganuma K, Niwa M. *J Soc Cosmet Chem Jpn* 1991;**24**(3):212–9.
23. Masaki K, Totani N. *J Soc Cosmet Chem Jpn* 1998;**32**(1):59–64.
24. Kusakari K, Yoshida M, Matsuzaki F, Yanaki T, Fukui H, Date M. *J Cosmet Sci* 2003;**54**(4):321–33.

25. Takahashi M, Machida Y, Marks R. *J Soc Cosmet Chem* 1987;**38**:321−31.
26. Kohda Y, Honma Y, Sato S, Yuuki Gainen Z. *Kiso to Ohyou (Organic concept diagram − basics and applications)*: Sankyou-Shuppann Co. Ltd; 2008.
27. Umeya J, Takahashi M, Komatsu H, Machida Y, Fukushima S. *J Soc Cosmet Chem Jpn* 1986;**20**(2):98−102.
28. Omata S. *Hihu no Mekanizumu no Kaimei to Keisoku·Hyoukahou(Explication, measurement and estimation method of a mechanism of skin)*. Gijutsu-jouhoukyoukai Co. Ltd.; 1999. p. 262−78.
29. Takahashi M. *J Soc Cosmet Chem Jpn* 2002;**36**(2):93−101.

CHAPTER

# 17

# Bioactive Ingredients: Benefits of Cosmetics Stimulated Through Biological Aspects

*H. Masaki*

**Tokyo University of Technology, Hachioji, Tokyo, Japan**

## 17.1 INTRODUCTION

In Europe it is allowed to officially claim benefits of cosmetic products based on evidence that can objectively prove their efficacy. On the other hand, beneficial claims of cosmetic products are legally restricted in Japan, because according to pharmaceutical laws cosmetics are defined as products showing weak potency on the skin. However, Japanese consumers strongly demand beneficial effects in cosmetic products and quasi-drugs like pharmaceutical products. Thus, cosmetic scientists always make efforts to develop products that meet these consumer demands. There are substantial differences in benefits between cosmetic products and pharmaceutical products. Although some side effects are allowed in pharmaceutical products, no effects that disrupt skin conditions are allowed in cosmetic products. In other words, cosmetic products should provide benefits and be safe to use on the skin.

The benefits of cosmetic products are roughly divided into physical, visual, biological, and psychological benefits considering their action aspects. Psychological benefits are realized by fragrance and makeup products. For instance, the scent of lavender leads to relaxation for human beings. Makeup sometimes gives confidence and encouragement for women. In addition, the behavior of makeup helps improve the function of elderly women who suffer from dementia. These psychological benefits are expected as new benefits of cosmetic products. The effects of makeup products are also recognized to have physical and visual benefits.

When using cosmetic products, consumers expect to improve skin problems through biological actions on the skin. Recent dermatological studies have clarified the mechanisms involved in a number of skin problems. It is considered that the appearance of skin problems is caused by various alterations in cellular functions. Although the mission of this chapter is to introduce bioactive ingredients that can prevent or improve skin problems, it is a challenge to introduce each ingredient from the aspects of its diversity and the low standardization as a cosmetic bioactive ingredient, since the discovery of each new mechanism creates new approaches to develop bioactive ingredients. Thus, in this chapter, the mechanisms causing skin problems are reviewed focusing on dry skin, pigmented spots, and wrinkling to show current knowledge used to develop new bioactive ingredients.

## 17.2 DEVELOPMENT DIRECTIONS OF BIOACTIVE INGREDIENTS

### 17.2.1 Overview of Bioactive Ingredients for Dry Skin and Rough Skin

The improvement of dry skin and the care of rough skin are fundamental benefits of cosmetic products. Generally, moist skin is a condition when adequate water is retained in the stratum corneum (SC). In contrast, dry skin has a low-water-holding capacity in the SC and has high levels of evaporation of water (transepidermal water loss; TEWL) through the SC. Rough skin is considered to be dry skin with a disruption of the skin surface morphology "KIME" and scaling. Severe dry skin often develops itching, such as in senile xerosis. As one of its causes, it is thought that sensory nerves invade into the epidermis due to the stimulation of dryness to more easily feel sensory irritations.

*Cosmetic Science and Technology: Theoretical Principles and Applications*
http://dx.doi.org/10.1016/B978-0-12-802005-0.00017-3



Copyright © 2017 Elsevier Inc. All rights reserved.

These facts suggest that skin dryness enhances the susceptibility of the skin to environmental stimuli and leads to the development of sensitive skin. Dry skin initiates the decline of the function to retain water in the SC. Water retention in the SC depends upon its water-holding capacity and barrier function. Water is retained in the SC by natural moisturizing factor (NMF), which is composed of free amino acids, hydroxyl acids, urea, and metal ions. The skin barrier function is constructed by two factors: lamellar structures composed of intercellular lipids in interstitial areas of the SC, and tight junctions in the granular layer. Further, it has been reported that aquaporin 3, which is a cellular water channel in keratinocytes, also contributes to water retention in the skin. Considering the prevention or improvement of skin dryness and rough skin, the characteristics required for bioactive ingredients should be to treat factors related to water retention in the SC.

### 17.2.2 Corneocytes and Bioactive Ingredients

Keratinocytes move toward the surface of the epidermis as they terminally differentiate. In that process, keratinocytes lose their intracellular organelles and nuclei, which results in cell death. Thus, the terminal differentiation of keratinocytes is recognized as a type of apoptosis. The terminal differentiation gives marginal bands formed by several proteins instead of the plasma membrane composed of polar lipids. Those marginal bands are called the cornified cell envelope (CE). The CE is constructed of loricrin, involucrin, filaggrin, small proline-rich protein, and so on, which are covalently bonded by transglutaminase-1.[1] Furthermore, the outside of the CE is covered with a lipid envelope to give a hydrophobic property to the corneocytes. The lipid envelope is constructed by covalent bonds between the c-terminals of involucrin in the CE and ω-hydroxy ceramides that are also catalyzed by transglutaminase-1.[2] The lipid envelope serves as a scaffold for construction of the lipid lamellar structure between each corneocyte. On the other hand, the inside of each corneocyte is filled with filaments made of keratin. The structure of the CE is difficult to solubilize, even with a sodium dodecyl sulfate aqueous solution under boiling.[3]

By the way, recent studies have reported the existence of carbonylated proteins in the SC at sun-exposed sites. In addition, carbonylated proteins are found in dry skin at a high frequency. Since increased levels of carbonylated proteins were observed in a study of the surface of an artificially dried reconstructed epidermal equivalent, it is considered that exposure to dry conditions induces protein carbonylation in the SC.[4] Additionally, an epidemiological survey also indicated that carbonylated proteins in the SC are negatively correlated with the surface water content of the SC and are positively correlated with TEWL.[5] In an in vitro study, protein carbonylation in SC treated with acrolein showed a decrease of the bound water content.[6] The sum of these results demonstrate the possibility that carbonylated proteins formed under dry conditions increase skin dryness, and thus suppressing protein carbonylation would be an effective approach to maintain a healthy SC and skin moisture function. Protein carbonylation is proceeded by reactive aldehyde compounds produced during the process of lipid peroxidation.[7] Thus, application of antioxidants such as tocopherols should also be a useful treatment.

### 17.2.3 Intercellular Lipids in the SC and Bioactive Ingredients

Intercellular lipids are stored in lamellar bodies in granular cells and are composed of ceramides (50%), cholesterol (25%), free fatty acids (10–25%), and a small amount of cholesterol sulfate. The lipids form a bilayer structure and the lipid bilayers are piled up in spaces between corneocytes. Ceramides are major intercellular lipids and are amide compounds consisting of sphingosines (long-chain amines) and free fatty acids. Ceramide levels decrease with age and this results in dry skin like senile xerosis.[8] Thus, the stimulation of ceramide synthesis is a general and useful approach to maintain skin moisture. The production of ceramides is started by the synthesis of sphingosines from serine and palmitoyl-CoA catalyzed by serine palmitoyltransferase (SPT),[9] and finally an amide bond between sphingosines and free fatty acids is formed by ceramide synthase. Ceramides are stored in lamellar bodies as forms of glucosylceramides and sphingomyelins, and are converted to ceramides by β-cerebrosidase and sphingomyelinase after secretion into the interstitial areas of the SC.[10,11] Ascorbic acid and niacinamide have been reported as enhancers of ceramide synthesis by keratinocytes.[12,13]

### 17.2.4 Role of Tight Junctions in Barrier Function and Bioactive Ingredients That Induce Tight Junction-Related Components

Tight junctions are located at the vertical cell membrane of granular cells in the second layer of the granular layer as adherens junctions composed of claudin-1, claudin-23, occludin, zonulae occludens-1 (ZO-1), and so on. Tight junctions reversibly adhere to adjacent granular cells like a zipper structure. Although that structure can be easily

disrupted by capric acid, it is promptly restored by removing the acid.[14–16] Tight junctions also contribute to atopic dermatitis, which is caused by a dysfunction of the skin barrier.[17] Since atopic dermatitis patients show downregulated expression of toll-like receptor 2 (TLR2) in keratinocytes, this demonstrates that the dysfunction of tight junctions due to the downregulation of TLR2 is one of the pathogenic factors of atopic dermatitis.[18,19] Regarding its care, it has been reported that Indigo naturalis, which is a Chinese medical plant, induces claudin-1 expression in keratinocytes.[20]

### 17.2.5 Natural Moisturizing Factor and Bioactive Ingredients

NMF consists of free amino acid (40%), pyrrolidone carboxylic acid (12%), lactic acid (12%), urea (7%), and mineral ions. Lactic acid, urea, and mineral ions originate from sweat, and free amino acids are yielded from filaggrin. The importance of filaggrin in skin moisture function was demonstrated by a study in which dysfunction of the filaggrin gene was shown to be a predisposing factor for atopic dermatitis.[21] Filaggrin is processed from the precursor protein profilaggrin, which is a major component of keratohyalin granules in granular cells.[22,23] Profilaggrin is a 500 kDa macromolecule composed of phosphorylated filaggrin molecules coupled by a peptide linker. Profilaggrin becomes filaggrin by cleaving the peptide linker in the final stage of terminal differentiation of keratinocytes. Firstly, profilaggrin is decomposed to filaggrin by furin, profilaggrin endoproteinase I, calpain I, and skin-specific retroviral-like aspartic protease (SASPase) after dephosphorylation by phosphatase 2A.[24,25] The role of filaggrin is to organize the keratin protein to a filamentous structure in intracellular corneocytes.[26] After playing that role, filaggrin is deiminated by peptidyl arginine deimidase (PAD) 1 or PAD 3, and is then decomposed into deiminated filaggrin fragments by calpain I and caspase 14. Finally, filaggrin is broken down into free amino acids by bleomycine hydrolase.[27] Regarding the reinforcement of the skin's water retaining capability by NMF, two major directions, promoting the synthesis of filaggrin and inhibiting its normal degradation have been proposed.

### 17.2.6 Sensitive Skin and Bioactive Ingredients

Sensitive skin is defined as skin susceptible to environmental stimuli, such as ultraviolet (UV) rays, temperature, chemicals, and so on, and to endogenous stimuli, such as psychological stress and the alteration of hormonal balance with the menstrual cycle.[28–31] Sensory irritation results from the activation of the terminals of c-fibers, which are localized in the upper dermis of the skin. The stinging irritation caused by topical application of cosmetics is also one of the sensory irritations due to the activation of c-fibers.[32] Dry skin could be especially susceptible to sensory irritation since a dry skin animal model prepared by acetone treatment showed the elongation of c-fibers into the epidermis associated with an increase of nerve growth factor (NGF) and a decrease of semaphorin 3A (sema3A).[33] The development of c-fibers is regulated by the balance of NGF, an acceleration factor, and sema3A, a suppression factor. Although there is little knowledge about the development mechanisms of sensitive skin at present, adjusting the balance between NGF and sema3A is proposed as a direction to develop bioactive ingredients to restore sensitive skin.

### 17.2.7 Bioactive Ingredients on the Regulation of Epidermal Terminal Differentiation

Lysophosphatidic acid (LPA), a member of the phospholipid family, upregulates the mRNA expression levels of profilaggrin, SPT, occludin, and claudin-1 due to an increased intracellular $Ca^{2+}$ concentration.[34] Topical application of LPA at a concentration of 0.2% for 6 weeks improved the SC associated with an increase of water content in the SC.

## 17.3 OVERVIEW OF PIGMENTED SPOTS

Pigmentation appears on the skin surface due to the continuous synthesis of melanin by melanocytes that can be stimulated by endogenous or exogenous factors. Many studies have demonstrated the contributions of peripheral keratinocytes and fibroblasts to the activation of melanocytes. Melanin is synthesized in melanosomes of melanocytes and is catalyzed by tyrosinase. Melanosomes that have accumulated melanin are transferred to the tips of the dendrites of melanocytes and are incorporated into the peripheral regions of neighboring keratinocytes. The diffusion of melanosomes into the epidermis results in the visible skin pigmentation. Although melanin synthesis is substantially a defense reaction to protect the nuclei of keratinocytes, skin hyperpigmentation is classified as a skin problem, especially for Asian people regarding skin beauty. Thus, cosmetic scientists in Japan are actively attempting to identify the underlying mechanisms of skin pigmentation that are initiated by UV exposure. The

development of bioactive ingredients to prevent skin pigmentation has proceeded along the pigmentation mechanisms introduced in the following sections.

## 17.3.1 Melanin Synthesis and Bioactive Ingredients

Melanin synthesis requires the contribution of melanosome-related proteins, which include enzymes directly involved in melanin synthesis and structural proteins that create an environment for melanin synthesis. Among the enzymes, tyrosinase, which catalyzes the hydroxylation of tyrosine to 3,4-dihydroxyphenylalanine (DOPA) and the oxidation of DOPA to DOPAquinone, is the rate-limiting and key enzyme in melanin synthesis. Furthermore, melanin synthesis is also modified by tyrosinase-related protein-2 (TRP-2: dopachrome tautomerase) and TRP-1 [DHICA (dihydroxyindole carboxylic acid) oxidase].[35] After glycosylation in the endoplasmic reticulum and Golgi, tyrosinase is transported into melanosomes and initiates melanin synthesis. As structural proteins, Pmel-17 (silver locus protein), which produces the filamentous structure in melanosomes to stabilize tyrosinase, and P-protein, which has been reported to act as a proton pump in melanosomes to adjust the melanosomal pH, contribute to melanin synthesis in order to prepare the optimal environment in melanosomes.[36–38] The mRNA expression levels of tyrosinase, TRP-1, and TRP-2 are regulated by microphthalmia-associated transcription factor.[39,40]

### *17.3.1.1 Bioactive Ingredients: Inhibitors of Tyrosinase Activity*

Inhibitors of tyrosinase have been developed and include ascorbic acid derivatives such as sodium or magnesium ascorbic acid phosphate, ascorbic acid glucoside, β-arbutin, kojic acid, 4-butyl resorcinol, ellagic acid, and 4-(4-hydroxyphenyl)-2-butanol (Fig. 17.1). These ingredients inhibit tyrosinase activity. All of those ingredients, except the ascorbic acid derivatives, work as competitive inhibitors of tyrosinase due to their phenolic hydroxyl group. On the other hand, the ascorbic acid derivatives show a reducible inhibition of tyrosinase activity working as proton donors. Furthermore, kojic acid inhibits tyrosinase activity by chelating the $Cu^{2+}$ metal required for its catalytic activity.[41]

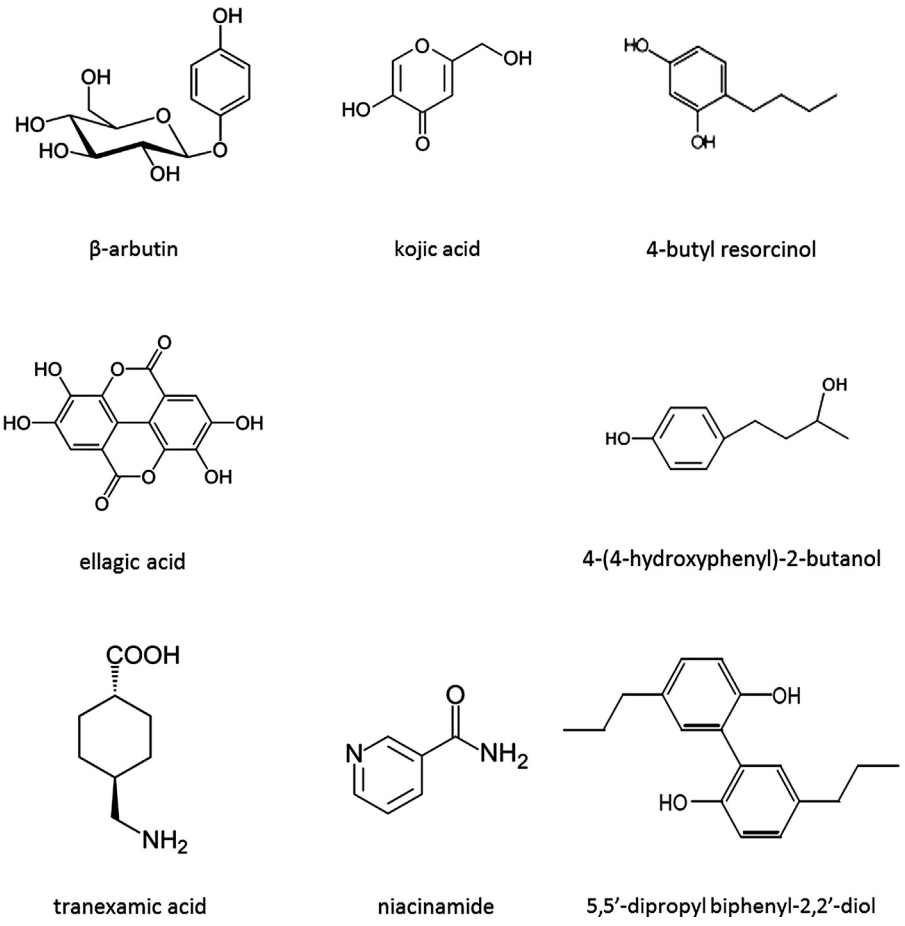



FIGURE 17.1 Chemical structures of whitening bioactive ingredients.

#### *17.3.1.2 Bioactive Ingredients: Inducing Instability of Tyrosinase*

5,5′-Dipropyl biphenyl-2,2′-diol and linoleic acid have been developed as bioactive ingredients that induce tyrosinase decomposition. 5,5′-Dipropyl biphenyl-2,2′-diol suppresses the transport of tyrosinase to melanosomes due to its interference with tyrosinase maturation.[42,43] In general, immature tyrosinase is decomposed after ubiquitination by the ubiquitin-proteasome system.[44] Linoleic acid induces the ubiquitination of tyrosinase and results in the degradation of tyrosinase.[45]

### 17.3.2 Melanocyte Stimulation Factors and Bioactive Ingredients

UV exposure of the skin enhances the secretion of various melanocyte stimulation factors from keratinocytes and even from melanocytes themselves. These melanocyte stimulation factors induce melanin synthesis effects in melanocytes in both paracrine and autocrine fashions. Endothelin-1 (ET-1),[46,47] stem cell factor,[48–50] α-melanocyte stimulating hormone,[51–54] β-fibroblast growth factor,[55,56] hepatocyte growth factor,[57] granulocyte macrophage colony-stimulating factor (GM-CSF),[58] leukotriene C4,[59] and prostaglandin $E_2$ ($PGE_2$)[60] have been identified as melanocyte stimulation factors. In addition, reactive oxygen species, such as $H_2O_2$ and nitric oxide radicals, enhance melanin synthesis by stimulating melanocytes.[61–64]

Among melanocyte stimulation factors, the excess synthesis of $PGE_2$ elicited by UV exposure induces sunburn and results in delayed tanning. Antiinflammatory ingredients such as tranexamic acid, tranexamic acid cetyl ester, and tetra-hexyldecanoic acid ascorbyl suppress the UV-induced skin pigmentation.[65,66] Furthermore, a Chamomilla extract is able to suppress UV-induced skin pigmentation by interfering with ET-1 signaling.[67]

### 17.3.3 Melanosome Transfer Into Keratinocytes and Bioactive Ingredients

Mature melanosomes are incorporated into keratinocytes through the phagocytosis pathway.[68] The melanosome-phagocytotic mechanism of keratinocytes has been shown to involve the activation of protease-activated receptor-2, which is a seven transmembrane domain G-protein receptor, through processing by serine proteinases. Thus, melanosome phagocytosis into keratinocytes is suppressed by inhibitors of serine protease such as soybean trypsin inhibitor.[69] These facts suggest the possibility of serine protease inhibitors as bioactive ingredients inhibiting melanosome transfer. Melanosomes phagocytosed into keratinocytes are serially digested from the lipid membrane of melanosomes, melanin-protein complexes, to small melanin granules. A recent study has proposed that the decomposition is proceeded by the autophagy system through fusion of melanosomes and lysosomes.[70] So far, niacinamide has been developed as an inhibitor of melanosome transfer into keratinocytes.[71] However, bioactive ingredients that act on melanosome degradation have not yet been developed.

## 17.4 OVERVIEW OF ANTIAGING FOCUSING ON WRINKLING

Skin aging is recognized by wrinkling and sagging. Since solar exposure and age are factors that accelerate skin aging, skin aging is defined as photoaging and intrinsic aging, respectively. However, it is difficult to discuss skin aging separately as photoaging and intrinsic aging since both types of aging are caused by alterations of the extracellular matrix in the dermis. Missing collagen fibers and oxytalan fibers are observed in the papillary regions of the dermis. Those alterations induce a decrease in skin elasticity. Considering these phenomena, characteristics sought after for bioactive ingredients with expected antiaging effects include the suppression of dermal matrix decomposition and its reconstruction.

### 17.4.1 Fibroblasts, Major Players in Construction of the Dermal Matrix

Fibroblasts are critical cells in construction of the dermal matrix. Fibroblasts isolated from elderly donors showed a lower synthetic capability for collagen than did those isolated from young donors.[72] Fibroblasts in elderly skin are atrophied compared to those in young skin. The dermal structure in elderly skin reveals extensive fragmentation of the collagen fibers. Obviously, there are structural alterations in the environment where fibroblasts reside. These facts indicate the possibility that differences in the function of collagen synthesis originate from environmental differences that surround fibroblasts.[73] Although fibroblasts generally adhere through integrin α2β1,[74] a single exposure of the skin to UV light by a solar simulator downregulates the mRNA expression levels of integrin α2β1 and endo180, which is a collagen receptor.[75] Endo180 substantially plays a role in the cleanup of collagen fragmented

by matrix metalloprotease-1 (MMP-1) in lysosomes after its internalization, and results in eliciting an environmental regeneration of the dermal matrix. However, the downregulation of endo180 after UV exposure causes the accumulation of collagen fibers fragmented by MMP-1 and results in atrophic figures of fibroblasts associated with decreasing collagen synthetic function. These facts emphasize the importance of creating the dermal structure in normal conditions.

## 17.4.2 Collagen and Bioactive Ingredients

To maintain a healthy dermal structure, our body always progresses with the degradation and production of collagen fibers. In photoaged and intrinsically aged skin, an imbalance between the degradation and production of collagen fibers occurs. The degradation of collagen is started by MMP-1, which is synthesized by keratinocytes and fibroblasts. Oxidative stress induced by reactive oxygen species (ROS) triggers MMP-1 synthesis in both types of cells. UV irradiation increases MMP-1 secretion from cells through an elevation of intracellular ROS level.[76] Differences of MMP-1 synthesis are observed in fibroblasts derived from elderly donors and from young donors. The differences are due to various intracellular ROS levels, because fibroblasts derived from elderly donors showed a lower level of catalase protein than those derived from young donors.[77] ROS upregulates the mRNA expression level of MMP-1 by increasing the expression of the transcription factor, AP-1, which is a heterodimer of c-Jun and c-Fos.[78,79] Further, decorin, which is a proteoglycan, provides tolerance against collagen fragmentation by MMP-1.[80] Elastase produced by neutrophils digests decorin and finally reduces the tolerance against MMP-1. UV irradiation also increases the infiltration of neutrophils into the papillary dermis. Regarding collagen degradation, bioactive ingredients should have properties to suppress MMP-1 synthesis and its activity, and should additionally reduce neutrophil recruiting factors such as IL-8 and should inhibit neutrophil elastase.

On the other hand, collagen synthesis usually regulates TGF-β1 and SMAD signaling[81]. TGF-β regulates SMAD signaling by binding to the TGF-β1 receptor (T-β1R) and TGF-β2 receptor (T-β2R). UV irradiation inactivates SMAD signaling by reducing T-β2R,[82] and finally decreases collagen synthesis. Further, a feedback mechanism of collagen synthesis has been reported by which CYR61/CCN1 (Cysteine-rich angiogenic inducer 61 or CCN family member 1) is upregulated by AP-1 and suppresses collagen synthesis.[83] These facts suggest potential approaches to develop bioactive ingredients as follows: one is to prevent the reduction of T-β2R following UV irradiation, and another is to suppress AP-1 synthesis. Regarding AP-1 synthesis, since ROS triggers AP-1 synthesis, antioxidants are potent candidates.

### *17.4.2.1 Bioactive Ingredients for Treatment With Collagen Depletion: Isoflavone and Triterpenoids*

Daidzein (Fig. 17.2), which is an isoflavone found in soybeans, stimulates collagen synthesis by fibroblasts, and shows a chemically similar structure to estradiol, which is a female hormone. In addition, genistein restores collagen

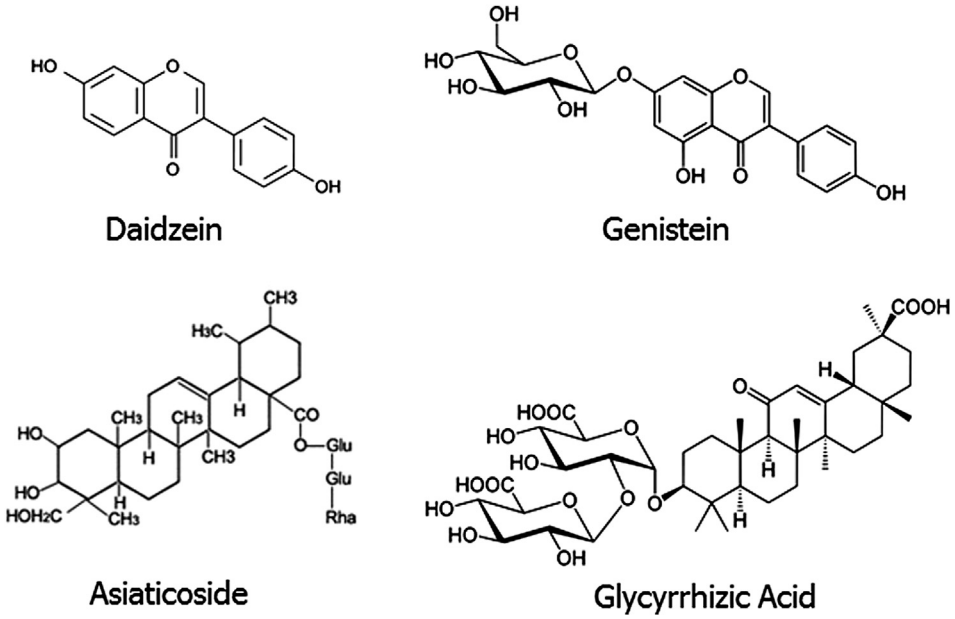



FIGURE 17.2 Chemical structures of isoflavones and triterpenoids.

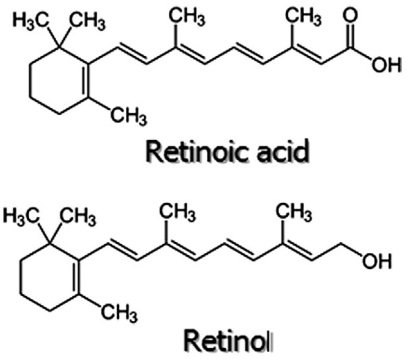



FIGURE 17.3 Chemical structures of retinoids.

synthesis by fibroblasts initiated by oxidative stress through the regulation of ERK1/2 signaling.[84] Ursolic acid and asiaticoside belong to the triterpenoid family. Ursolic acid[85] also increases collagen synthesis. The effect of asiaticoside on collagen synthesis is exhibited through the activation of TβI-R kinase.[86] Furthermore, glycyrrhizic acid, which is a widely used antiinflammatory agent, suppresses MMP-1 synthesis stimulated by UVB irradiation.[87]

#### 17.4.2.2 Bioactive Ingredients for Treatment With Collagen Depletion: Vitamins

Retinoic acid (Fig. 17.3) is a well-known antiaging bioactive ingredient.[88] However, the Japanese ministry prohibits its formulation in cosmetics due to its teratogenic potential. Thus, retinol is widely used as an antiaging bioactive ingredient. Retinol increases collagen synthesis and hyaluronic synthesis, and suppresses CYR61/CCN1 that is increased in photoaged skin.[89]

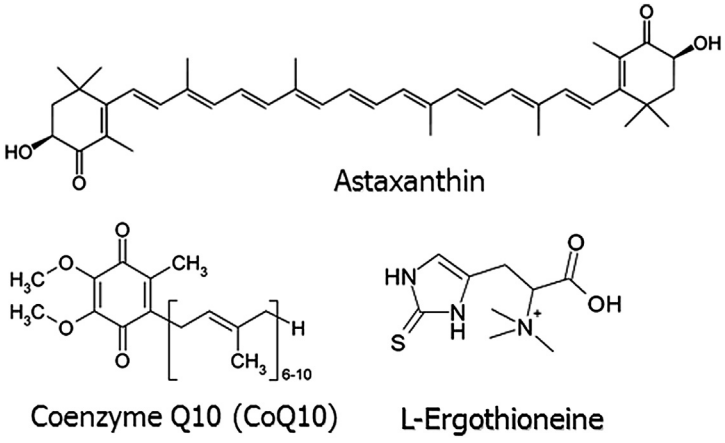
#### 17.4.2.3 Bioactive Ingredients for Treatment With Collagen Depletion: Antioxidants

As described in a previous section, intracellular oxidative stress triggers and accelerates alterations of the dermal matrix. Thus, antioxidants (Fig. 17.4) are considered to be potent antiaging bioactive ingredients. Astaxanthin, which is a carotenoid and a strong quencher against singlet oxygen, reduces MMP-1 and the fibroblast-derived elastase, neprilysin, after UVA irradiation.[90] Coenzyme $Q_{10}$ ($CoQ_{10}$), also known as ubiquinone, shows antiaging effects in vivo and in vitro. $CoQ_{10}$ suppresses MMP-1 synthesis by UVA-exposed fibroblasts, and IL-6 secretion of UVB-exposed keratinocytes. In addition, topical application of 1% $CoQ_{10}$ for 5 months results in a reduction of wrinkles.[91] L-Ergothioneine, which is a sulfur-containing amino acid with an antioxidative property, reduces MMP-1 and TNF-α of UVA-exposed fibroblasts.[92]

#### 17.4.2.4 Bioactive Ingredients for Treatment With Collagen Depletion: Natural Products

Phospholipids show restoration effects on collagen synthesis that is disrupted by UV exposure.[93] Among phospholipids (Fig. 17.5), phosphatidylserine (PS), lysophosphatidylserine (LPS), lysophosphatidic acid (LPA), N-acetyl phytosphingosine (NAPS), and tetra-acetyl phytosphingosine (TAPS) restore the UV-induced decrease in

FIGURE 17.4 Chemical structures of antioxidants.



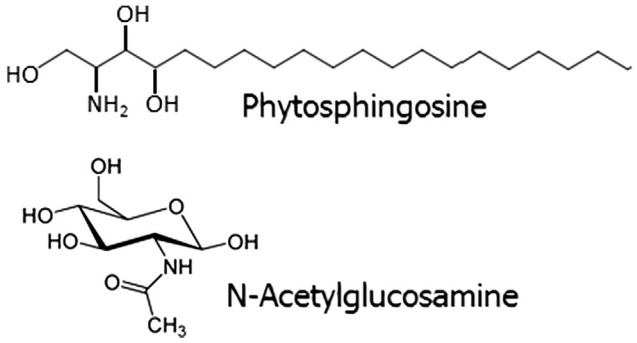



FIGURE 17.5 Chemical structures of natural products.

collagen synthesis, and in addition, PS, LPS, and LPA increase collagen synthesis in physiological conditions. Furthermore, NAPS, TAPS, LPA, PS, lysophosphatidylglycerol, and LPS suppress MMP-1 synthesis that is elevated by UV irradiation. N-Acetylglucosamine, a constituent sugar of glycosaminoglycan, also reduces the increase of MMP-1 induced by UVB irradiation.[94]

### 17.4.3 Elastin Fibers and Bioactive Ingredients

Elastin fibers play an important role in skin elasticity; they are fibrous protein complexes consisting of microfibrils and tropoelastin. Microfibrils, a scaffold fibrous protein, are formed by fibullin-1 being supported by microfibrillar-associated protein 4 (MFAP-4) and latent TGF-β binding protein 4.[95] Tropoelastin, which is absorbed on microfibrils by coacervation supported by several matricellular proteins like fibulin-4 and fibulin-5, is cross-linked by lysyl oxidase.[96] All those components are synthesized by fibroblasts. Although reductions of MFAP-4 and fibulin-5 have been reported in photoaged skin,[97,98] their mechanisms of action are still unclear. In either case, reduction of those matricellular proteins disrupts the assembly of the elastin fibrous structure. In contrast to collagen fibers, elastin fibers are hardly accepted as an antiaging concept. Solar elastosis in which elastin accumulates in the reticular dermis is a typical symptom of photoaged skin. As an antiaging concept regarding elastin fibers, it is thought that the regeneration of oxytalan fibers in the papillary dermis is a crucial approach. However, since we don't have any knowledge about the regeneration of oxytalan fibers, we should expect future studies to develop the underlying mechanism.

On the other hand, it has been known that elastin fibers are digested by elastases derived from neutrophils and fibroblasts.[99] Fibroblast-derived elastase, which is a membrane-bound type, has been identified as neprilysin. Neprilysin synthesis is stimulated by UVA irradiation, and IL-1α, IL-1β, IL-6, IL-8, and GM-CSF contribute to that stimulation. Elastase from neutrophils also digests elastin fibers after cleavage by cathepsin G.[100] To prevent the decomposition of elastin fibers, bioactive ingredients should have a direct inhibition against both elastases and/or modulate soluble factors involved in elastase synthesis of fibroblasts.

## 17.5 CONCLUSIONS

This chapter, entitled "Bioactive ingredients," introduced the onset mechanisms of skin problems at the points of moisture, pigmentation, and aging. Knowing the onset mechanisms is useful to develop bioactive ingredients to treat the corresponding skin problems. The author hopes that the information in this chapter is helpful for your research and development.

## References

1. Eckert RL, Yaffe MB, Crish JF, Murthy S, Rorke EA, Welter JF. Involucrin—structure and role in envelope assembly. *J Invest Dermatol* 1993;**100**:613–7.
2. Stewart ME, Downing DT. The omega-hydroxyceramides of pig epidermis are attached to corneocytes solely through omega-hydroxyl groups. *J Lipid Res* 2001;**42**:1105–10.
3. Sun TT, Green H. Keratin filaments of cultured human epidermal cells. Formation of intermolecular disulfide bonds during terminal differentiation. *J Biol Chem* 1978;**253**:2053–60.

4. Yokota M, Shimizu K, Kyotani D, Yahagi S, Hashimoto S, Masaki H. The possible involvement of skin dryness on alterations of the dermal matrix. *Exp Dermatol* 2014;**23**(Suppl. 1):27–31.
5. Fujita H, Hirao T, Takahashi M. A simple and non-invasive visualization for assessment of carbonylated protein in the stratum corneum. *Skin Res Technol* 2007;**13**:84–90.
6. Iwai I, Hirao T. Protein carbonyls damage the water-holding capacity of the stratum corneum. *Skin Pharmacol Physiol* 2008;**21**:269–73.
7. Vistoli G, De Maddis D, Cipak A, Zarkovic N, Carini M, Aldini G. Advanced glycoxidation and lipoxidation end products (AGEs and ALEs): an overview of their mechanisms of formation. *Free Radic Res* 2013;**47**(Suppl. 1):3–27.
8. Masaki H, Tezuka T. The changes of epidermis with aging. *Jpn J Dermatol* 1986;**96**:189–93.
9. Harris IR, Farrell AM, Grunfeld C, Holleran WM, Elias PM, Feingold KR. Permeability barrier disruption coordinately regulates mRNA levels for key enzymes of cholesterol, fatty acid, and ceramide synthesis in the epidermis. *J Invest Dermatol* 1997;**109**:783–7.
10. Imokawa G. A possible mechanism underlying the ceramide deficiency in atopic dermatitis: expression of a deacylase enzyme that cleaves the N-acyl linkage of sphingomyelin and glucosylceramide. *J Dermatol Sci* 2009;**55**:1–9.
11. Zhang L, Hellgren LI, Xu X. Enzymatic production of ceramide from sphingomyelin. *J Biotechnol* 2006;**123**:93–105.
12. Uchida Y, Behne M, Quiec D, Elias PM, Holleran WN. Vitamin C stimulates sphingolipid production and markers of barrier formation in submerged human keratinocyte cultures. *J Invest Dermatol* 2001;**117**:1307–13.
13. Tanno O, Ota Y, Kitamura N, Katsube T, Inoue S. Nicotinamide increases biosynthesis of ceramides as well as other stratum corneum lipids to improve the epidermal permeability barrier. *Br J Dermatol* 2000;**143**:524–31.
14. Yamamoto T, Kurasawa M, Hattori T, Maeda T, Nakano H, Sasaki H. Relationship between expression of tight junction-related molecules and perturbed epidermal barrier function in UVB-irradiated hairless mice. *Arch Dermatol Res* 2008;**300**:61–8.
15. Furuse M, Hata M, Furuse K, Yoshida Y, Haratake A, Sugitani Y, Noda T, Kubo A, Tsukita S. Claudinbased tight junctions are crucial for the mammalian epidermal barrier: a lesson from claudin-1-deficient mice. *J Cell Biol* 2002;**156**:1099–111.
16. Kurasawa M, Kuroda S, Kida N, Murata M, Oba A, Yamamoto T, et al. Regulation of tight junction permeability by sodium caprate in human keratinocytes and reconstructed epidermis. *Biochem Biophys Res Commun* 2009;**381**:171–5.
17. Kuo IK, Yoshida T, De Benedetto A, Beck LA. The cutaneous innate immune response in patients with atopic dermatitis. *J Allergy Clin Immunol* 2013;**131**:266–78.
18. De Benedetto A, Agnihothri R, McGirt LY, Bankova LG, Beck LA. Atopic dermatitis: a disease caused by innate immune defects? *J Invest Dermatol* 2009;**129**:14–30.
19. Kuo IK, Carpenter-Mendini A, Yoshida T, McGirt LY, Ivanov AI, Barnes KC, Gallo RL, Borkowski AW, Yamasaki K, Leung DY, Georas SN, De Benedetto A, Beck LA. Activation of epidermal toll-like receptor 2 enhances tight junction function: implications for atopic dermatitis and skin barrier repair. *J Invest Dermatol* 2013;**133**:988–98.
20. Lin YK, Chen HW, Leu YL, Yang YL, Fang Y, Su Pang JH, Hwang TL. Indigo naturalis upregulates claudin-1 expression in human keratinocytes and psoriatic lesions. *J Ethnopharmacol* 2013;**30**:614–20.
21. McGrath JA, Uitto J. The filaggrin story: novel insights into skin-barrier function and disease. *Trends Mol Med* 2008;**14**:20–7.
22. Manabe M, O'Guin WM. Keratohyalin, trichohyalin and keratohyalin-trichohyalin hybrid granules: an overview. *J Dermatol* 1992;**19**: 749–55.
23. Dale BA, Gown AM, Fleckman P, Kimball JP, Resing KA. Characterization of two monoclonal antibodies to human epidermal keratohyalin: reactivity with filaggrin and related proteins. *J Invest Dermatol* 1987;**88**:306–13.
24. Sandilands A, Sutherland C, Irvine AD, McLean WH. Filaggrin in the frontline: role in skin barrier function and disease. *J Cell Sci* 2009;**122**: 1285–94.
25. Matsui T, Miyamoto K, Kubo A, Kawasaki H, Ebihara T, Hata K, Tanahashi S, Ichinose S, Imoto I, Inazawa J, Kudoh J, Amagai M. SASPase regulates stratum corneum hydration through profilaggrin-to-filaggrin processing. *EMBO Mol Med* 2011;**13**:320–33.
26. Lynley AM, Dale BA. The characterization of human epidermal filaggrin. A histidine-rich, keratin filament-aggregating protein. *Biochim Biophys Acta* 1983;**744**:28–35.
27. Kamata Y, Taniguchi A, Yamamoto M, Nomura J, Ishihara K, Takahara H, Hibino T, Takeda A. Neutral cysteine protease bleomycin hydrolase is essential for the breakdown of deiminated filaggrin into amino acids. *J Biol Chem* 2009;**284**:12829–36.
28. Pons-Guiraud A. Sensitive skin: a complex and multifactorial syndrome. *J Cosmet Dermatol* 2005;**3**:145–8.
29. Muizzuddin N, Marenus KD, Maes DH. Factors defining sensitive skin and its treatment. *Am J Contact Dermat* 1998;**9**:170–5.
30. Frosch PJ, Kligman AM. A method of apraising the stinging capacity of topically applied substances. *J Soc Cosmet Chem* 1977;**28**:197–209.
31. Berardesca E, Fluhr JW, Maibach HI. What is sensitive skin? In: Berardesca E, Fluhr JW, Maibach IH, editors. *Sensitive skin syndrome*. New York: Taylor & Francis; 2006. p. 1–6.
32. Campero M, Baumann TK, Bostock H, Ochoa JL. Human cutaneous C fibres activated by cooling, heating and menthol. *J Physiol* 2009;**587**: 5633–52.
33. Tominaga M, Ozawa S, Tengara S, Ogawa H, Takamori K. Intraepidermal nerve fibers increase in dry skin of acetone-treated mice. *J Dermatol Sci* 2007;**48**:103–11.
34. Yahagi S, Koike M, Okano Y, Masaki H. Lysophospholipids improve skin moisturization by modulating of calcium-dependent cell differentiation pathway. *Int J Cosmet Sci* 2011;**33**:251–6.
35. Yamaguchi Y, Hearing VJ. Physiological factors that regulate skin pigmentation. *Biofactors* 2009;**35**:193–9.
36. Lee ST, Nicholls RD, Jong MT, Fukai K, Spritz RA. Organization and sequence of the human P gene and identification of a new family of transport proteins. *Genomics* 1995;**26**:354–63.
37. Ancans J, Tobin DJ, Hoogduijn MJ, Smit NP, Wakamatsu K, Thody AJ. Melanosomal pH controls rate of melanogenesis, eumelanin/phaeomelanin ratio and melanosome maturation in melanocytes and melanoma cells. *Exp Cell Res* 2001;**268**:26–35.
38. Solano F, Martínez-Esparza M, Jiménez-Cervantes C, Hill SP, Lozano JA, García-Borrón JC. New insights on the structure of the mouse silver locus and on the function of the silver protein. *Pigment Cell Res* 2000;**13**(Suppl. 8):118–24.
39. Yamaguchi Y, Brenner M, Hearing VJ. The regulation of skin pigmentation. *J Biol Chem* 2007;**282**:27557–61.
40. Wan P, Hu Y, He L. Regulation of melanocyte pivotal transcription factor MITF by some other transcription factors. *Mol Cell Biochem* 2011;**354**: 241–6.

41. Nakamura K, Yoshida M, Uchiwa H, Kawa Y, Mizoguchi M. Down-regulation of melanin synthesis by a biphenyl derivative and its mechanism. *Pigment Cell Res* 2003;**16**:494–500.
42. Halaban R, Cheng E, Zhang Y, Moellmann G, Hanlon D, Michalak M, Setaluri V, Hebert DN. Aberrant retention of tyrosinase in the endoplasmic reticulum mediates accelerated degradation of the enzyme and contributes to the dedifferentiated phenotype of amelanotic melanoma cells. *Proc Natl Acad Sci USA* 1997;**94**:6210–5.
43. Ando H, Kondoh H, Ichihashi M, Hearing VJ. Approaches to identify inhibitors of melanin biosynthesis via the quality control of tyrosinase. *J Invest Dermatol* 2007;**127**:751–61.
44. Ando H, Watabe H, Valencia JC, Yasumoto K, Furumura M, Funasaka Y, Oka M, Ichihashi M, Hearing VJ. Fatty acids regulate pigmentation via proteasomal degradation of tyrosinase: a new aspect of ubiquitin-proteasome function. *J Biol Chem* 2004;**279**:15427–33.
45. Imokawa G, Miyagishi M, Yada Y. Endothelin-1 as a new melanogen: coordinated expression of its gene and the tyrosinase gene in UVB-exposed human epidermis. *J Invest Dermatol* 1995;**105**:32–7.
46. Yada Y, Higuchi K, Imokawa G. Effects of endothelins on signal transduction and proliferation in human melanocytes. *J Biol Chem* 1991;**266**:18352–7.
47. Hachiya A, Kobayashi A, Ohuchi A, Takema Y, Imokawa G. The paracrine role of stem cell factor/c-kit signaling in the activation of human melanocytes in ultraviolet-B-induced pigmentation. *J Invest Dermatol* 2001;**116**:578–86.
48. Bertolotto C, Buscà R, Abbe P, Bille K, Aberdam E, Ortonne JP, Ballotti R. Different cis-acting elements are involved in the regulation of TRP1 and TRP2 promoter activities by cyclic AMP: pivotal role of M boxes (GTCATGTGCT) and of microphthalmia. *Mol Cell Biol* 1998;**18**:694–702.
49. Kawaguchi Y, Mori N, Nakayama A. Kit(+) melanocytes seem to contribute to melanocyte proliferation after UV exposure as precursor cells. *J Invest Dermatol* 2001;**116**:920–5.
50. Giebel LB, Spritz RA. Mutation of the KIT (mast/stem cell growth factor receptor) protooncogene in human piebaldism. *Proc Natl Acad Sci USA* 1991;**88**:8696–9.
51. Bertagna X. Proopiomelanocortin-derived peptides. *Endocrinol Metab Clin North Am* 1994;**23**:467–85.
52. Schauer E, Trautinger F, Köck A, Schwarz A, Bhardwaj R, Simon M, Ansel JC, Schwarz T, Luger TA. Proopiomelanocortin-derived peptides are synthesized and released by human keratinocytes. *J Clin Invest* 1994;**93**:2258–62.
53. Suzuki I, Cone RD, Im S, Nordlund J, Abdel-Malek ZA. Binding of melanotropic hormones to the melanocortin receptor MC1R on human melanocytes stimulates proliferation and melanogenesis. *Endocrinology* 1996;**137**:1627–33.
54. Schwahn DJ, Xu W, Herrin AB, Bales ES, Medrano EE. Tyrosine levels regulate the melanogenic response to alpha-melanocyte-stimulating hormone in human melanocytes: implications for pigmentation and proliferation. *Pigment Cell Res* 2001;**14**:32–9.
55. Halaban R, Langdon R, Birchall N, Cuono C, Baird A, Scott G, Moellmann G, McGuire J. Basic fibroblast growth factor from human keratinocytes is a natural mitogen for melanocytes. *J Cell Biol* 1988;**107**:1611–9.
56. Halaban R, Ghosh S, Baird A. bFGF is the putative natural growth factor for human melanocytes. *In Vitro Cell Dev Biol* 1987;**23**:47–52.
57. Matsumoto K, Tajima H, Nakamura T. Hepatocyte growth factor is a potent stimulator of human melanocyte DNA synthesis and growth. *Biochem Biophys Res Commun* 1991;**176**:45–51.
58. Imokawa G, Yada Y, Kimura M, Morisaki N. Granulocyte/macrophage colony-stimulating factor is an intrinsic keratinocyte-derived growth factor for human melanocytes in UVA-induced melanosis. *Biochem J* 1996;**313**:625–31.
59. Morelli JG, Yohn JJ, Lyons MB, Murphy RC, Norris DA. Leukotrienes C4 and D4 as potent mitogens for cultured human neonatal melanocytes. *J Invest Dermatol* 1989;**93**:719–22.
60. Scott G, Fricke A, Fender A, McClelland L, Jacobs S. Prostaglandin E2 regulates melanocyte dendrite formation through activation of PKCzeta. *Exp Cell Res* 2007;**313**:3840–50.
61. Ochiai Y, Kaburagi S, Okano Y, Masaki H, Ichihashi M, Funasaka Y, Sakurai H. A Zn(II)-glycine complex suppresses UVB-induced melanin production by stimulating metallothionein expression. *Int J Cosmet Sci* 2008;**30**:105–12.
62. Warren JB. Nitric oxide and human skin blood flow responses to acetylcholine and ultraviolet light. *FASEB J* 1994;**8**:247–51.
63. Murad F, Forstermann U, Nakane M, Pollock J, Tracey R, Matsumoto T, Buechler W. The nitric oxide-cyclic GMP signal transduction system for intracellular and intercellular communication. *Adv Second Messenger Phosphoprotein Res* 1993;**28**:101–9.
64. Roméro-Graillet C, Aberdam E, Clément M, Ortonne JP, Ballotti R. Nitric oxide produced by ultraviolet-irradiated keratinocytes stimulates melanogenesis. *J Clin Invest* 1997;**99**:635–42.
65. Maeda K, Naganuma M. Topical trans-4-aminomethylcyclohexanecarboxylic acid prevents ultraviolet radiation-induced pigmentation. *J Photochem Photobiol B* 1998;**47**:136–41.
66. Ochiai Y, Kaburagi S, Obayashi K, Ujiie N, Hashimoto S, Okano Y, Masaki H, Ichihashi M, Sakurai H. A new lipophilic provitamin C, tetraisopalmitoyl ascorbic acid (VC-IP), prevents UV-induced skin pigmentation through its anti-oxidative properties. *J Dermatol Sci* 2006;**44**:37–44.
67. Wasmeier C, Hume AN, Bolasco G, Seabra MC. Melanosomes at a glance. *J Cell Sci* 2008;**121**(Pt 24):3995–9.
68. Ando H, Niki Y, Yoshida M, Ito M, Akiyama K, Kim JH, Yoon TJ, Matsui MS, Yarosh DB, Ichihashi M. Involvement of pigment globules containing multiple melanosomes in the transfer of melanosomes from melanocytes to keratinocytes. *Cell Logist* 2011;**1**:12–20.
69. Seiberg M, Paine C, Sharlow E, Andrade-Gordon P, Costanzo M, Eisinger M, Shapiro SS. The protease-activated receptor 2 regulates pigmentation via keratinocyte-melanocyte interactions. *Exp Cell Res* 2000;**254**:25–32.
70. Murase D, Hachiya A, Takano K, Hicks R, Visscher MO, Kitahara T, Hase T, Takema Y, Yoshimori T. Autophagy has a significant role in determining skin color by regulating melanosome degradation in keratinocytes. *J Invest Dermatol* 2013;**133**:2416–24.
71. Hakozaki T, Minwalla L, Zhuang J, Chhoa M, Matsubara A, Miyamoto K, Greatens A, Hillebrand GG, Bissett DL, Boissy RE. The effect of niacinamide on reducing cutaneous pigmentation and suppression of melanosome transfer. *Br J Dermatol* 2002;**147**:20–31.
72. Varani J, Dame MK, Rittie L, Fligiel SE, Kang S, Fisher GJ, Voorhees JJ. Decreased collagen production in chronologically aged skin: roles of age-dependent alteration in fibroblast function and defective mechanical stimulation. *Am J Pathol* 2006;**168**:1861–8.
73. Varani J, Schuger L, Dame KM, Leonard C, Fligiel SW, Kang S, Fisher GJ, Voorhees JJ. Reduced fibroblast interaction with intact collagen as a mechanism for depressed collagen synthesis in photodamaged skin. *J Invest Dermatol* 2004;**122**:1471–9.
74. Tiger CF, Fougerousse F, Grundström G, Velling T, Gullberg D. Alpha11beta1 integrin is a receptor for interstitial collagens involved in cell migration and collagen reorganization on mesenchymal nonmuscle cells. *Dev Biol* 2001;**237**:116–29.

75. Tang S, Lucius R, Wenck H, Gallinat S, Weise JM. UV-mediated downregulation of the endocytic collagen receptor, Endo180, contributes to accumulation of extracellular collagen fragments in photoaged skin. *J Dermatol Sci* 2013;**70**:42–8.
76. Quan T, Qin Z, Xia W, Shao Y, Voorhees JJ, Fisher GJ. Matrix-degrading metalloproteinases in photoaging. *J Invest Dermatol Symp Proc* 2009;**14**: 20–4.
77. Shin MH, Rhie GE, Kim YK, Park CH, Cho KH, Kim KH, Eun HC, Chung JH. $H_2O_2$ accumulation by catalase reduction changes MAP kinase signaling in aged human skin in vivo. *J Invest Dermatol* 2005;**125**:221–9.
78. Rittié L, Fisher GJ. UV-light-induced signal cascades and skin aging. *Ageing Res Rev* 2002;**1**:705–20.
79. Kida Y, Kobayashi M, Suzuki T, Takeshita A, Okamatsu Y, Hanazawa S, Yasui T, Hasegawa K. Interleukin-1 stimulates cytokines, prostaglandin E2 and matrix metalloproteinase-1 production via activation of MAPK/AP-1 and NF-kappaB in human gingival fibroblasts. *Cytokine* 2005;**29**:159–68.
80. Li Y, Xia W, Liu Y, Remmer HA, Voorhees JJ, Fisher GJ. Solar ultraviolet irradiation induces decorin degradation in human skin likely via neutrophil elastase. *PLoS One* August 30, 2013;**8**(8):e72563.
81. Verrecchia F, Mauviel A, Farge D. Transforming growth factor-beta signaling through the Smad proteins: role in systemic sclerosis. *Autoimmun Rev* 2006;**5**:563–9.
82. Quan T, He T, Kang S, Voorhees JJ, Fisher GJ. Ultraviolet irradiation alters transforming growth factor beta/smad pathway in human skin in vivo. *J Invest Dermatol* 2002;**119**:499–506.
83. Quan T, Qin Z, Xu Y, He T, Kang S, Voorhees JJ, Fisher GJ. Ultraviolet irradiation induces CYR61/CCN1, a mediator of collagen homeostasis, through activation of transcription factor AP-1 in human skin fibroblasts. *J Invest Dermatol* 2010;**130**:1697–706.
84. Sienkiewicz P, Surazyński A, Pałka J, Miltyk W. Nutritional concentration of genistein protects human dermal fibroblasts from oxidative stress-induced collagen biosynthesis inhibition through IGF-I receptor-mediated signaling. *Acta Pol Pharm* 2008;**65**:203–11.
85. Both DM, Goodtzova K, Yarosh DB, Brown DA. Liposome-encapsulated ursolic acid increases ceramides and collagen in human skin cells. *Arch Dermatol Res* 2002;**293**:569–75.
86. Lee J, Jung E, Kim Y, Park J, Park J, Hong S, Kim J, Hyun C, Kim YS, Park D. Asiaticoside induces human collagen I synthesis through TGFbeta receptor I kinase (TbetaRI kinase)-independent Smad signaling. *Planta Med* 2006;**72**:324–8.
87. Afnan Q, Adil MD, Nissar-Ul A, Rafiq AR, Amir HF, Kaiser P, Gupta VK, Vishwakarma R, Tasduq SA. Glycyrrhizic acid (GA), a triterpenoid saponin glycoside alleviates ultraviolet-B irradiation-induced photoaging in human dermal fibroblasts. *Phytomedicine* 2012;**15**:658–64.
88. Fisher GJ, Datta S, Wang Z, Li XY, Quan T, Chung JH, Kang S, Voorhees JJ. c-Jun-dependent inhibition of cutaneous procollagen transcription following ultraviolet irradiation is reversed by all-trans retinoic acid. *J Clin Invest* 2000;**106**:663–70.
89. Quan T, Qin Z, Shao Y, Xu Y, Voorhees JJ, Fisher GJ. Retinoids suppress cysteine-rich protein 61 (CCN1), a negative regulator of collagen homeostasis, in skin equivalent cultures and aged human skin in vivo. *Exp Dermatol* 2011;**20**:572–6.
90. Suganuma K, Nakajima H, Ohtsuki M, Imokawa G. Astaxanthin attenuates the UVA-induced up-regulation of matrix-metalloproteinase-1 and skin fibroblast elastase in human dermal fibroblasts. *J Dermatol Sci* 2010;**58**:136–42.
91. Inui M, Ooe M, Fujii K, Matsunaka H, Yoshida M, Ichihashi M. Mechanisms of inhibitory effects of CoQ10 on UVB-induced wrinkle formation in vitro and in vivo. *Biofactors* 2008;**32**:237–43.
92. Obayashi K, Kurihara K, Okano Y, Masaki H, Yarosh DB. L-Ergothioneine scavenges superoxide and singlet oxygen and suppresses TNF-alpha and MMP-1 expression in UV-irradiated human dermal fibroblasts. *J Cosmet Sci* 2005;**56**:17–27.
93. Cho S, Kim HH, Lee MJ, Lee S, Park CS, Nam SJ, Han JJ, Kim JW, Chung JH. Phosphatidylserine prevents UV-induced decrease of type I procollagen and increase of MMP-1 in dermal fibroblasts and human skin in vivo. *J Lipid Res* 2008;**29**:1235–45.
94. Hwang YP, Kim HG, Han EH, Choi JH, Park BH, Jung KH, Shin YC, Jeong HG. N-Acetylglucosamine suppress collagenases activation in ultraviolet B-irradiated human dermal fibroblasts: Involvement of calcium ions and mitogen-activated protein kinases. *J Dermatol Sci* 2011;**63**:93–103.
95. Kasamatsu S, Hachiya A, Fujimura T, Sriwiriyanont P, Haketa K, Visscher MO, Kitzmiller WJ, Bello A, Kitahara T, Kobinger GP, Takema Y. Essential role of microfibrillar-associated protein 4 in human cutaneous homeostasis and in its photoprotection. *Sci Rep* 2011;**1**:164. http://dx.doi.org/10.1038/srep00164.
96. Noda K, Dabovic B, Takagi K, Inoue T, Horiguchi M, Hirai M, Fujikawa Y, Akama TO, Kusumoto K, Zilberberg L, Sakai LY, Koli K, Naitoh M, von Melchner H, Suzuki S, Rifkin DB, Nakamura T. Latent TGF-β binding protein 4 promotes elastic fiber assembly by interacting with fibulin-5. *Proc Natl Acad Sci USA* 2013;**110**:2852–7.
97. Kadoya K, Sasaki T, Kostka G, Timpl R, Matsuzaki K, Kumagai N, Sakai LY, Nishiyama T, Amano S. Fibulin-5 deposition in human skin: decrease with ageing and ultraviolet B exposure and increase in solar elastosis. *Br J Dermatol* 2005;**153**:607–12.
98. Yano K, Kadoya K, Kajiya K, Hong YK, Detmar M. Ultraviolet B irradiation of human skin induces an angiogenic switch that is mediated by upregulation of vascular endothelial growth factor and by downregulation of thrombospondin-1. *Br J Dermatol* 2005;**152**:115–21.
99. Morisaki N, Moriwaki S, Sugiyama-Nakagiri Y, Haketa K, Takema Y, Imokawa G. Neprilysin is identical to skin fibroblast elastase: its role in skin aging and UV responses. *J Biol Chem* 2010;**285**:39819–27.
100. Schmelzer CE, Jung MC, Wohlrab J, Neubert RH, Heinz A. Does human leukocyte elastase degrade intact skin elastin? *FEBS J* 2012;**279**: 4191–200.

CHAPTER

# 18

# Fragrance

*S. Herman*

**Diffusion LLC, Totowa, NJ, United States**

## 18.1 INTRODUCTION

Fragrance is a critical aesthetic component in most personal care and household products. Consumers shopping for a shampoo will invariably smell it, as this is the only assessment that can be made in a store. Thus fragrance is an essential product attribute at the point of sale and during use. The emotive effects of fragrance are such that it even contributes to the perception of a product's functionality, even if there is no factual basis for such a judgment.

Fragrance can also be viewed as an expensive ingredient that has no true functional value. Fragrance can create stability problems for the formulator, and some consumers have demonized fragrance as an unnecessary cause of irritation and allergic reactions. In fact our products would be much less appealing without an appropriate smell enhancing the product attributes and marketing profile. Formulators must know how to use fragrance as an integral part of their products, and consumers must continue to trust in their safety and beneficial properties.

## 18.2 NATURAL PRODUCTS

Until the end of the 19th century all fragrances were solely composed of natural products. Even now, after 150 years of aroma chemical development, natural products are still a vital component of most fragrances. There are nuances of natural products that have never been perfectly replicated by synthetic means. Even if a natural component can be synthesized, it may be too difficult or expensive a process to be a practical alternative. Many parts of a plant can be used, and many extraction methods applied.

Enfleurage is an historic extraction process rarely used today. It makes wonderful products and can be used successfully on heat-sensitive materials, but it is far too time and labor consuming and expensive. A large framed glass plate called a chassis is spread with animal fat. Flower petals are applied to it by hand, and the essential oil migrates from the petals to the plate. As the petals are depleted, usually in a few days, new ones are applied. Once the fat is totally saturated with the aromatic oils, it is called pomade. When the pomade is dissolved in alcohol, it is possible to separate the aromatic material from the fat. The alcohol is then driven off, leaving behind the absolute. The absolute, which is alcohol soluble, is the finest and most expensive aromatic product.

Expression or cold pressing of fruit oils originated in the citrus industry. Essential oil is contained in small pockets on the fruit's skin. Cold pressing involves puncturing the skins of the whole fruit or the fruit peel and mechanically pressing the oil out. The essential oil is then collected below the container. A small amount of juice is also extracted, which is separated from the oil with a centrifuge. Orange, grapefruit, lemon, lime, tangerine, mandarin, and bergamot can be extracted by this method. Since the fruits commonly used are high-volume flavor materials, it is usually very cost effective to make these oils unless there is a problem with a crop such as bad weather.

Products such as orange oil contain a very high level of limonene, a terpene that may be undesirable. Limonene has minimal olfactive value and easily oxidizes into sensitizing materials. The process of "folding" removes most of the limonene by distillation, leaving a more concentrated product. If 10 drums of orange oil are processed and nine drums of limonene removed, the resultant product is termed orange oil 10-fold or 10X. The folded oil has a much stronger odor value and its use can reduce stability issues in many applications. The limonene that is removed can be used in inexpensive flavors or fragrances or for institutional cleaning.

*Cosmetic Science and Technology: Theoretical Principles and Applications*
http://dx.doi.org/10.1016/B978-0-12-802005-0.00018-5



Copyright © 2017 Elsevier Inc. All rights reserved.

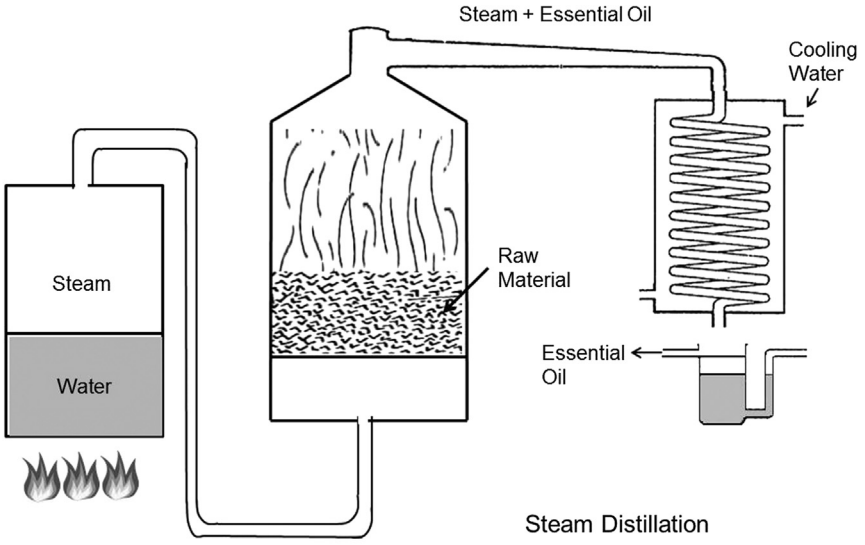



**FIGURE 18.1** Steam distillation.

Steam distillation (Fig. 18 1) is a common extraction process for aroma compounds, working well for most heat-tolerant materials. Adding steam to the native material creates an azeotrope that lowers the boiling points of the compounds being extracted. Steam is injected into the material and vaporizes the essential oils present. A condenser cools the liquid, which will separate into oil and water phases. The oil can then be drawn off. For some materials too sensitive for steam distillation, solvent extraction can be used. The plant matter is placed in a static extractor on perforated trays. A benzene-free nonpolar solvent or solvent mix, 8 to 10 times the weight of the plant matter, is added. The extractor is closed and the solvent is passed through the material from 3 to 15 times. The solvent is transferred to a decanter to remove any water present. The water-free solvent is transferred to a concentrator. Heat is applied to remove the solvent, and the material left behind is referred to as a concrete.

The concrete can be gently heated and blended with ethyl alcohol. A rotative filter is then used to remove approximately 80% of the waxes and terpenes. The resultant solution is chilled and the remaining waxes precipitated. The ethyl alcohol is evaporated under a vacuum and the resulting product is termed the absolute. The absolutes of certain flowers such as jasmine, rose, and tuberose are among the most beautiful, potent, and expensive components of fine fragrances.

An even more delicate process uses $CO_2$ supercritical extraction. $CO_2$ is easily compressed to a supercritical liquid phase at ambient temperatures and has lipophilic solvent properties. The solubility of supercritical liquids changes with temperature and pressure, which allows the fine-tuning of the extraction. A second solvent can also be added to further refine the process. Dissolved waxes can be present in the product, similar to what results from standard solvent extraction. Many unique olfactive products can be achieved by this process.

Natural products are not necessarily safer than synthetics, a common misconception among consumers. They are complex mixtures that can include undesirable components, such as irritants or phototoxins, an example being the bergaptenes in bergamot oil. Low-color materials are also needed for some purposes, Rectification is a process of cleaning oils through fractional distillation. Materials with cleaner odor, low color, and low residue can result.

Individual components known as isolates can be separated from essential oils. For example, eugenol can be extracted from clove leaf oil, and eucalyptol from eucalyptus oil. Orange oil can yield many valuable components such as octanal, decanal, valencene, and sinensal. There can be technical difficulty in obtaining some of these products in high yield, as the boiling points can be too close to allow efficient separation. Nonetheless, constant progress continues to yield new products of technical and aesthetic value.

Many plants, particularly citrus species like orange and lemon, biochemically synthesize a family of chemicals called terpenes (Fig. 18.2). Large quantities of aroma chemicals can be extracted from this basic supply at low cost. Isoprene is the basic building block of terpenes, with head-to-tail unions forming the larger polymer structures.

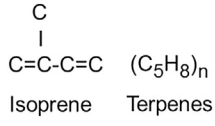



**FIGURE 18.2** Isoprene rule.

Because terpenes have had commercial importance for many years, common historical names have endured:

| *n* | Name | Formula |
|---|---|---|
| 2 | Monoterpene | $C_{10}H_{16}$ |
| 3 | Sesquiterpene | $C_{15}H_{24}$ |
| 4 | Diterpene | $C_{20}H_{32}$ |
| 6 | Triterpene | $C_{30}H_{48}$ |

Terpenes can have open or closed rings, double bonds, and readily accept hydroxy or carboxy groups. Many of the transitions between these forms occur easily, so it is easy to synthesize numerous derivatives with an interesting olfactory range. The structures in Fig. 18.3 illustrate some of the major types of natural terpenes. The flat depiction of terpenes, particularly a puckered bicyclic terpene like pinene, does not do justice to the complexity of its three-dimensional structure, which is illustrated in greater detail in Fig. 18.4.

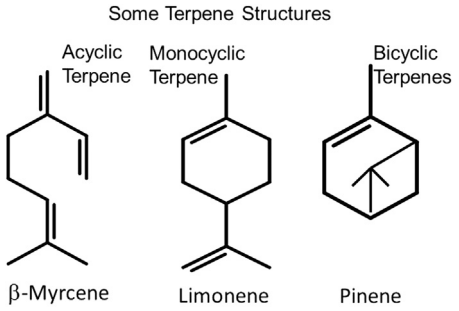



**FIGURE 18.3** Examples of terpene structures.

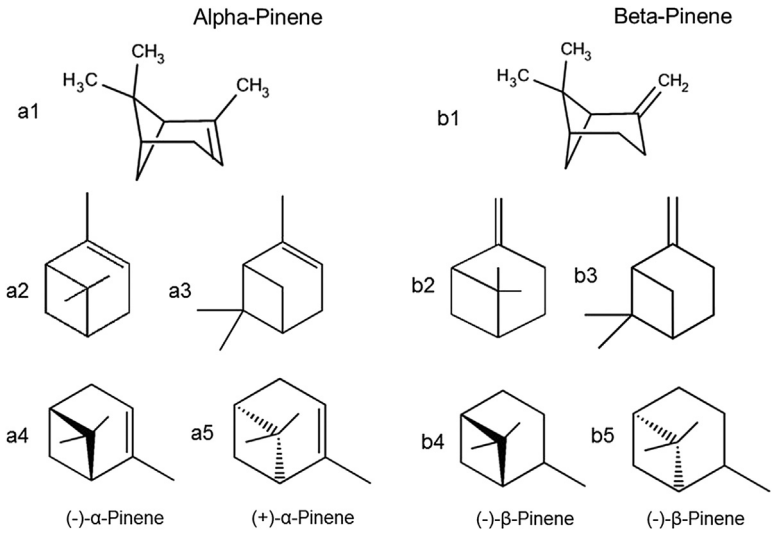



**FIGURE 18.4** Stereochemistry of pinenes.

**TABLE 18.1** Landmarks in the History of Fragrance-Related Science

| | |
|---|---|
| 1834 | Cinnamic aldehyde isolated from cinnamon oil |
| 1837 | Benzaldehyde isolated from bitter almond oil |
| 1844 | Methyl salicylate identified in wintergreen oil |
| 1856 | Cinnamic aldehyde synthesized |
| 1863 | Benzaldehyde synthesized |
| 1868 | Coumarin synthesized |
| 1876 | Vanillin synthesized |
| 1888 | Discovery of nitro musks |
| 1919 | Linalool synthesized |
| 1923 | Amyl cinnamaldehyde discovered |
| 1934 | Muscone synthesized |
| 1939 | Leopold Ruzicka wins Nobel Prize for Chemistry |
| 1971 | Synthesis of α and β damascone |

## 18.3 AROMA CHEMICALS

Starting in the 1850s, advances in organic chemistry made possible an explosive expansion of the perfumer's palette. First, individual odorous materials from natural products were isolated and later synthesized. Next, new chemicals were created that did not exist in nature, making possible a revolution in fragrance design. Table 18.1 shows a few highlights in aroma chemistry history. One scientist, Leopold Ruzicka deserves special mention. He won the 1939 Nobel Prize in Chemistry[1] for work he did for the fragrance industry, especially in synthesizing large ring compounds and exploiting the isoprene rule.

Aroma raw materials are characterized by great chemical diversity. They are all organic compounds, so their chemistry is based on the properties of carbon. The size of aroma molecules ranges from C5 to C17, with Helvetolide, molecular weight 284, the largest current example. Nitrogen and oxygen are common heteroatoms, with sulfur appearing occasionally. These elements are also known as osmophores, a broad term for groups that, when present in a molecule, are responsible for its odor. Aroma molecules have olfactive thresholds from $10^{-6}$ to $10^{-2}$ g/L. Some minimal polarity is necessary to interact with the odor receptors.

Esters are the largest family of aroma chemicals. They can be easily produced by the reaction product of a carboxylic acid with an alcohol in the presence of an acid catalyst. At high pH and elevated temperature, the reverse of the esterification reaction occurs, which is termed hydrolysis, and results in a total change in odor quality. Hydrolysis also occurs, but at a reduced rate, at low pH. Low-molecular-weight esters have a fruity odor, examples being the odors of apples (methyl butyrate) or bananas (3-methylbutyl acetate).

Alcohols contain a hydroxyl (OH) group and can be aliphatic or aromatic. If the hydroxyl group is directly attached to an aromatic ring it is a phenol and has much different properties. Phenols can be very unstable and can create severe color changes. Phenols are very sensitive to oxidation and can undergo autoxidation. An example is vanillin (Fig. 18.5), a major component of vanilla. Other examples of phenolics are methyl salicylate, eugenol, and thymol. Even though there are other functional groups attached to the ring, the phenol group still exerts its influence as an independent reactive factor.

Glycols are similar to alcohols, having two or more hydroxyl groups (Fig. 18.6). They are common diluents in perfumery, especially dipropylene glycol (DPG). Propylene glycol, butylene glycol, and hexylene glycol are other examples. Nonpolar diluents are also useful. The polarity of the diluent affects the polarity and thus the solubility properties of the fragrance oil. Thus, DPG is better in a shampoo, and DEP or benzyl benzoate is better in a candle.

Aldehydes and ketones are closely related. Aldehydes can be aromatic or aliphatic. Aldehydes are easy to oxidize or reduce. Even under the mildest conditions, some aldehydes can be oxidized in air. Benzaldehyde is particularly reactive because the functional group is attached directly to the aromatic ring and there are no other reactive sites on the molecule. Benzaldehyde readily exhibits autoxidation to benzoic acid, an odorless white powder.

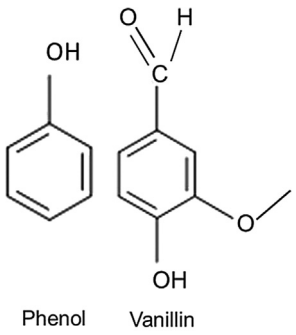



FIGURE 18.5 Phenolic structures.

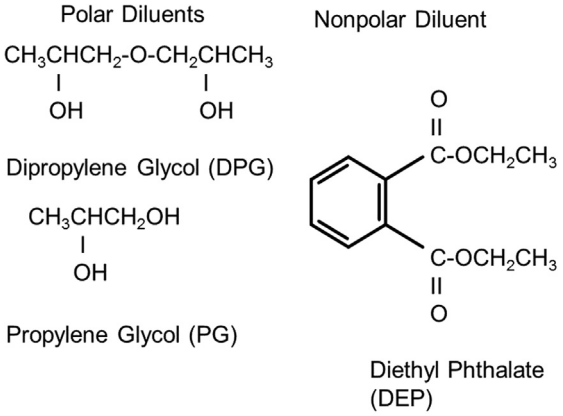



FIGURE 18.6 Fragrance diluents.

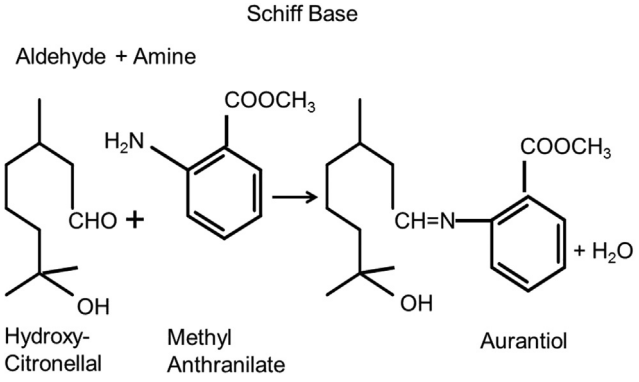



FIGURE 18.7 Schiff base.

Aldehydes can condense with primary amine to form Schiff bases. An important example is hydroxycitronellal and methyl anthranilate, which yields Aurantiol (Fig. 18.7). The reaction can take place slowly if both components are present in a fragrance, contributing to the natural aging of the oil. Alternatively, the Schiff base can be intentionally created by a reflux reaction with the water drawn off and the resultant product used as an ingredient. Ketones are much less reactive than aldehydes but are easily reduced to secondary alcohols.

Heterocyclics are cyclic compounds that contain one or more heteroatoms: oxygen, nitrogen, or sulfur. They are identified by the prefixes Aza- for nitrogen, Oxa- for oxygen, and Thia- for sulfur. They are typically five- or six-member rings, and rings can be fused. Ring sizes are denoted by suffixes: -irane for a 3-membered ring, -etane for 4, -olane for 5, -ane for 6, and -epam for 7. The rings can be aromatic or nonaromatic. Some common heterocyclic structures are shown in Fig. 18.8.

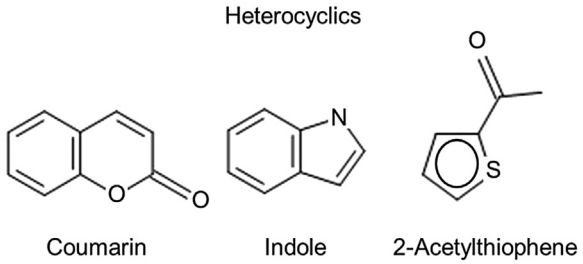



FIGURE 18.8 Heterocyclics.

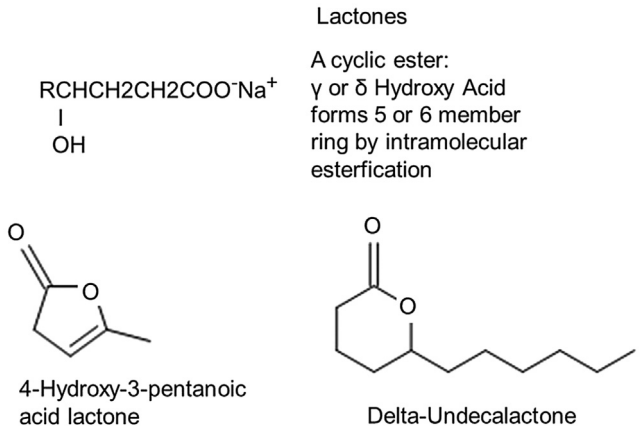



FIGURE 18.9 Lactones.

Nitriles contain triple-bonded nitrogen, −C≡N. Nitriles occur naturally in plant and animal sources. Over 120 naturally occurring nitriles have been isolated from terrestrial and marine sources. Nitriles are commonly encountered in fruit pits, especially almonds, and during the cooking of cabbage, Brussels sprouts, and cauliflower, which release nitriles through hydrolysis. A nitrile sometimes has an odor similar to its corresponding aldehyde. Nitriles are more stable than aldehydes to oxidation and extremes of pH.

Lactones are cyclic esters. Common examples are γ or ô hydroxy acids forming 5- or 6-member rings by intramolecular esterification as shown in Fig. 18.9 with some examples of lactones used in perfumery. Lactones react under the same conditions as noncyclic esters.

There is a specialized nomenclature for sulfur-containing molecules. For example, thioethers, thioesters, and thioacetals are characterized by C−S−C bonds. Thiol groups contain the structure R−SH. Disulfides have an R−S−S−R with a covalent sulfur-to-sulfur bond.

Originally, musk came from the male musk deer. Real, naturally derived musk is rare and expensive, and many synthetic compounds are made to satisfy the demands of perfumery. The first successful synthetics were nitro musks. The nitro musks—musk xylene, musk ketone, and musk ambrette—were historically important but experienced regulatory problems. More recent molecules have been polycyclic musks, macrocyclic musks, and acyclic musks. Examples of each are shown in Fig. 18.10.

Nonionic surfactants may be used as a fragrance ingredient when extra polarity is needed to make a "water-soluble" version. A surfactant such as polysorbate 20 at a 3:1 ratio is a common solution. This does not make fragrances truly water soluble, but creates a microemulsion that is visibly clear. The mechanism is hydrogen bonding, so a clear solution can reversibly become hazy when heated, as the thermal energy becomes greater than the hydrogen bonding.

## 18.4 FRAGRANCE CREATION AND DUPLICATION

Historically, fragrance creation was a slow and haphazard process, working with a limited range of materials and producing a limited spectrum of aromas, mostly floral, citrus, and woody. The introduction of synthetic chemicals at the end of the 19th century vastly increased the size and complexity of the perfumer's palette. Perfumers were able to work primarily by trial and error in the early period, slowly accumulating a library of acceptable blends. The number and diversity of the new materials required a method to give logic to the perfumer's art.

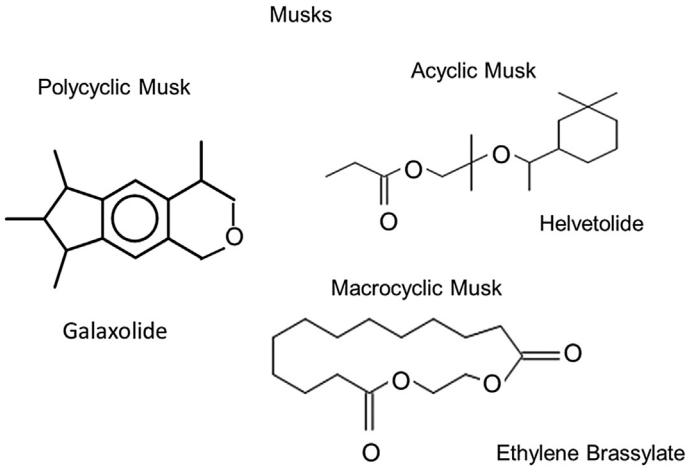



FIGURE 18.10 Musks.

The challenge of systematizing fragrance creation was accepted by a generation of perfumers in the early 20th century led by Jean Carles (1892–1966). Fortunately for posterity, Carles wrote an invaluable series of papers entitled "A Method of Creation in Perfumery."[2] The raw materials Carles used are not always available to the modern perfumer, but the principles used by Carles are of permanent value, and his examples of accords will be discussed.

Jean Carles did not believe that perfumers necessarily have an exceptional sense of smell but rather that they must develop a refined olfactory memory through practice. First, the student learns to identify contrasting odors, then various members within an odor family. Examples of contrasting notes are indole, linalool, menthol, phenylethyl alcohol, and vanillin. An odor family of balsam notes includes cinnamyl acetate, cinnamic alcohol, ethyl cinnamate, and amyl salicylate.

After the olfactory memory is developed, the volatility of various perfume materials is studied. Very volatile materials comprise the "top note" of a finished perfume, those of intermediate volatility and tenacity become the "modifiers" or "middle notes," and the low volatility, tenacious products constitute the "base notes." When smelling a fragrance out of the bottle all these notes are present, but during use the fragrance evolves continuously as materials evaporate in order of volatility.

The characteristic odor of a single material is called a *note*. Mixtures of two or more materials, having a unified olfactory theme, are called *accords*. Jean Carles develops a chypre note based on oakmoss, beginning by evaluating a series of ratios with ambergris:

| | | | | | |
|---|---|---|---|---|---|
| Oakmoss | 9 | 8 | 7 | 6 | 5 |
| Ambergris | 1 | 2 | 3 | 4 | 5 |

The perfumer's choice was the 6:4 ratio, which needed additional musk character, resulting in this chypre accord:

| | |
|---|---|
| Oakmoss | 5 |
| Ambergris | 4 |
| Musk ketone | 1 |

Materials of medium volatility are used to modify the base accord. Middle notes are often florals, and in this example, an animal note is included, resulting in the following blend:

| | |
|---|---|
| Absolute rose | 3 |
| Absolute civet 10% | 1 |
| Oakmoss | 6 |
| Ambergris | 4 |
| Musk ketone | 1 |

Some pleasant, highly volatile notes are added to create the top note, which is the sparkle that creates the immediate impression of the fragrance. The result becomes:

| | |
|---|---|
| Sweet orange oil | 4 |
| Bergamot | 1 |
| Absolute rose | 3 |
| Absolute civet 10% | 1 |
| Oakmoss | 6 |
| Ambergris | 4 |
| Musk ketone | 1 |

The ratio of 25% top notes, 20% modifiers, and 55% base notes is characteristic of a well-balanced blend. This formula demonstrates how notes combine into accords, and how materials of different volatilities combine to make a fragrance that evolves in an acceptable way over its lifetime. Many more materials can be added to round out the fragrance and provide interest and complexity, but the overall composition is maintained.

Another important component of a fragrance is a fixative, a material that reduces the volatility of another fragrance ingredient. These materials extend the life of the fragrance, a very important property for consumer satisfaction. Fixitives typically have lower volatility than the other materials in the formula. Some common fixatives are musks, benzyl benzoate, terpinoid gums like Hercolyn D (methyl hydrogenated rosinate), and olibanum (frankincense).

The Jean Carles example was designed for hydroalcoholic use. Perfumes for functional products are balanced differently, emphasizing either the top notes (for impact) or the base notes (for substantivity). Since cost is a factor, inexpensive odorless solvents such as dipropylene glycol or diethyl phthalate are included to reduce the price. Linear fragrances, which maintain their character through the evaporative cycle, can be used for fine fragrances (e.g., Trésor) or even air fresheners.

Fragrance houses have the capability of duplicating fragrance products with great accuracy. A fragrance is almost always a complex mixture of chemicals. The gas chromatograph (GC) separates these components by passing the mixture through a column packed with a material that interacts with the components in varying degrees. Fig. 18.11 shows an example output. The separate portions can then be placed in a mass spectrometer (MS) for the identification of the chemical structure. The GC−MS chromatogram alone is not sufficient in identifying the composition of a fragrance. A database of values of aroma chemicals is required to convert the raw data into the information needed to reconstruct the target oil.

The vapors over a fragranced object or in the air can be identified by the addition of head space analysis. Solid phase microextraction is a sophisticated version of this technology. A glass globe is placed over the object being analyzed, and a porous material absorbs the aroma chemicals. The quantity extracted can then be analyzed and is proportional to the concentration in the sample, so the odor can be quantitatively replicated. This has been used by fragrance companies to replicate many odors in the environment, from flowers and exotic woods to the canopy of the Amazon rain forest.

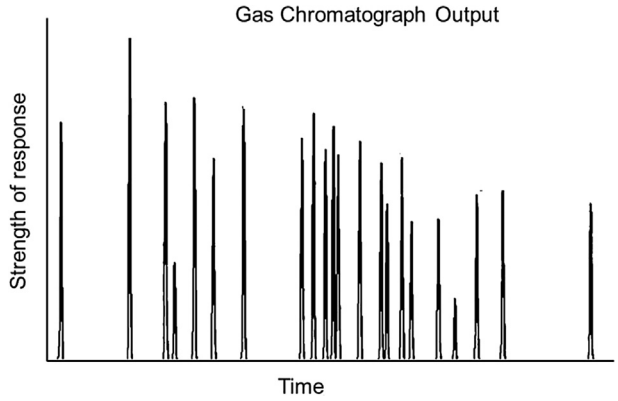



FIGURE 18.11 Gas chromatograph output.

The electronic nose (e-nose) is different from a GC and also does not take the place of the human nose. It is a quality control device capable of responding to chemicals in the air. An e-nose consists of three major parts: (1) a sample delivery system generates headspace and injects sample into detection system; (2) the detection system reacts to the presence of specific molecules, making it undergo a chemical change and produce a useable electronic signal; and (3) a computing system combines the responses of individual sensor elements and generates sample information.

An e-nose can use metal oxides or conducting polymers that change conductivity when bound to airborne molecules. Possible transducer sensors include quartz crystal microbalances, surface acoustic wave sensors (SAWs), and metal oxide semiconductor sensors. The quartz microbalance uses piezoelectric crystals that increase in mass as odorants are absorbed, altering the oscillation frequency. SAW devices consist of two electrodes (source and receptor) over a sandwich of a piezoelectric thin film. Metal oxides employ oxidation/reduction reactions on the surface that is in contact with the gas.

## 18.5 POLARITY

A key property for understanding the behavior of fragrances with products such as emulsions and surfactant systems is the polarity of the individual fragrance components. This is created by slight concentrations of charge in parts of the molecule and is a guide to where in a complex system a specific molecule is most likely to be.

Chemistry is usually concerned with strong forces: covalent or polar bonds. Solubility depends on weak forces. The Van der Waals force is loosely used to describe all weak intermolecular forces, including London dispersion, Keesom, and Debye forces. A common measure of polarity is the solubility parameter (SP). Two versions are common, the Hildebrand solubility parameter from the early 20th century, and more recently the Hansen solubility parameter (HSP).

Hildebrand developed an equation to calculate the SP of a small molecule based on the fact that cohesive energy is overcome when liquids boil. The following equation is used to determine the Hildebrand solubility parameter as the square root of the cohesive energy density: $\sigma = ((\Delta H\text{-}RT)/V)^{1/2}$. The cohesive energy density is the energy required to completely remove a unit volume of molecules from their neighbors to infinite separation. It is equal to the heat of vaporization divided by molar volume. Hildebrand determined that the square root is a good indicator of solvency.

Charles Hansen developed the Hansen solubility parameters in 1967 and has refined the system over the years. This concept took the Hildebrand solubility parameter concept, which was based on a one-dimensional or free-energy parameter, and expanded it to a three-dimensional cohesive energy parameter. HSP utilizes components of the cohesive energies derived respectively from polarity, dispersion, and hydrogen bonding.

Hansen solubility parameter in practice (HSPiP) is a computer program that creates 3D images of solubility regions.[3] It was designed originally to optimize solvents for polymers, which in itself is useful for personal care applications. A green ball in the HSPiP graphical image is the compatible volume in three dimensions. Databases have been added for cosmetic and fragrance materials, further enhancing its value in our industry. The basic formula used to compute the HSP is:

$$\delta^2_{\text{Total}} = 4\delta^2_{\text{P}} + \delta^2_{\text{D}} + \delta^2_{\text{H}}$$

where $\delta_{\text{Total}}$ is the distance from the target HSP, $\delta_{\text{P}}$ is the contribution from dipolar intermolecular forces, $\delta_{\text{D}}$ is the contribution from dispersion forces, and $\delta_{\text{H}}$ comes from hydrogen bonds between molecules.

Clog P is an alternate way to look at polarity. P is the partition coefficient, the ratio of a molecule's partitioning between water and oil. The data is more linear as a logarithm. If it is done by a computer program rather than wet chemistry, it is calculated. Thus Clog P is a computer calculation of the logarithm of the water/oil partition coefficient. Clog P values are available for most fragrance materials.

Both Clog P and HSP are valuable for determining where fragrance ingredients will partition between the different phases of a base, or if a solution will be clear. A change of solvents can often adjust the values to solve clarity or viscosity problems.

The HSPiP program computes several functions that are valuable in fragrance and flavor chemistry. Some of these functions include solvent optimization, skin permeation, diffusion and volatility calculations, and, of course, solubility parameter calculations. The permeation of molecules in skin is looked upon as a hydrophobic—lipophilic interaction due to the hydrophobic nature of human skin. Relative to fragrance, determining the amount of material that can permeate the skin cannot only determine the efficacy of the product but also indicate its likely safety to the consumer.

By their fundamental nature, fragrances are small molecules with low polarity. This makes them likely to be skin irritants, to penetrate the skin, and get into the blood. There is nothing intrinsically unsafe about that, it's just simple chemistry and biology in action. It does not mean that fragrances are not safe as typically used. But it does mean that the guidelines set by the industry must be followed without exception.

## 18.6 FRAGRANCE APPLICATIONS

Hydroalcoholics are a common fragrance application, typically in the form of perfume, cologne, and aftershave. The basic components are fragrance oil, alcohol, and water. Common additives are color, chelating agents like EDTA, antioxidants such as BHT, and ultraviolet (UV) absorbers. In manufacturing, the fragrance oil is added into the alcohol and then the water added. Commercial alcohol contains ethanol, water, and a denaturant. To discourage drinking the alcohol, it is poisoned with a denaturant. The denaturant is selected from materials that cannot readily be distilled out. Denaturing exempts the alcohol from the taxes normally imposed on the ingestible version.

When the perfume oil is placed in solution the aging process begins. The container is important: stainless steel and glass-lined vats are best. Iron should never be in contact with the solution. All hoses, gaskets, and stirrers should be carefully chosen to ensure compatibility. The solution should be aged in a covered container at room temperature for at least a week. Fine fragrances should be aged as long as six months, but this is often impractical. Mass-market fragrances are frequently not aged at all, with chilling and filtering done in a continuous process. Continuous processing is only practical for very large production.

Aftershaves are an economical delivery system for male fragrances. The alcohol content is limited to 60–65% to avoid stinging, since minor cuts and abrasions often occur during shaving. Emollient oils such as glycerin and propylene glycol are frequently added for feel, as are healing agents for cuts.

When a fragrance compound is incorporated into an emulsion system a variety of processes can occur. An emulsion has water, oil, and interfaces where individual fragrance materials can partition based on chemical and physical properties. The aqueous phase also usually contains areas of liquid crystal structures, loosely organized regions of fatty acids. Many fragrance materials can discolor an emulsion system—indole and vanillin are classic examples. High levels of fragrance can break an emulsion. It is important to conduct a full battery of stability tests including elevated temperatures, freeze-thaw, and UV radiation exposure comparing unfragranced to fragranced samples to ensure product integrity. Testing in the final packaging is also necessary.

Another process occurs when the emulsion is applied to the skin. When applying external shear, the emulsion breaks, and the water and other volatiles will evaporate quickly. What is left on the skin after application is the oil phase, most of the fragrance, and the emulsifiers. This will re-emulsify the fragrance, retarding its evaporation and thus muting its character and impact.

The viscosity of a surfactant system can be built by the judicious selection of surface-active materials. Many formulators build viscosity solely with the addition of salt, which is a less-expensive approach. Fragrance is easily solubilized by surfactants, but a low active formula with a high level of salt may become hazy when fragrance is added. In these cases, fragrances mixed with nonionic surfactants such as polysorbates may be needed to achieve clarity.

In addition, many surfactant systems such as bath gels are colored, creating light-stability problems when fragrances are present. Cosmetic colors contain molecules that are chromophores, structures that emit light in the visible spectra thereby becoming visible colors. Examples of chromophores are conjugated double bonds and the azo group. A standard stability test involves exposure to UV light. Some aroma chemicals, such as benzaldehyde, create free radicals when exposed to UV. In the free radical state, they can react with the color-generating structures and cause pronounced discoloration.

## 18.7 PHYSICAL CHEMISTRY OF AROMA CHEMICALS

The evaporation properties of a fragrance can best be understood by applying the laws of the physical chemistry of mixtures. Many characteristics of fragrances are based on their cohesive properties. Evaporation rate, boiling point, vapor pressure, diffusivity, and molar mass are important examples. The thermodynamics of cohesion is well understood for simple systems, but harder to apply to complex mixtures such as fragrances.

A fragrance material must be volatile, have an acceptable odor threshold, and consist primarily of C, H, and O atoms with occasional N and S. Volatility demands a range of C5 to C17. Olfactive thresholds range from $10^{-6}$ to $10^{-2}$ g/L. Raoult's law explains the properties of vapor pressure over a complex solution. The vapor pressure of

component A, $P_A$, is given by its vapor pressure as a pure solution times its mole fraction in the solution, $X_A$. For a simple mixture of A and B, $P_{total} = P_A X_A + P_B X_B$. For complex perfume mixtures, the process is expanded to include each component.

A solution that obeys Raoult's law is called an ideal solution. Nonideal behavior can result in higher or lower pressures, and this is one reason why fragrance mixtures sometimes produce unexpected properties.

Henry's law states that at a constant temperature, the amount of a given gas that dissolves in a liquid is directly proportional to the partial pressure of that gas in equilibrium with that liquid. The activity coefficient is defined by a combination of Henry's and Raoult's laws, and can provide the scientific basis for understanding how fixatives can prolong fragrance life and affect the top note impact.

## 18.8 ENCAPSULATION AND CONTROLLED RELEASE

Encapsulation of fragrance allows novel delivery systems, can release fragrance under specific triggers, and can protect fragrance in a hostile chemical environment. The history of encapsulation started in 1927 when capsules were spray-dried with an oil and gum acacia coating. In 1955 the National Cash Register Company received a patent for encapsulation, using the technology to make carbon paper. The first major fragrance use was the "scratch and sniff" sampling of Giorgio fragrance in 1983.

Controlled release can provide fragrance when and where it is needed. It can also counteract loss of intensity during use. A practical use of encapsulation is to protect a fragrance chemical from a hostile environment. Common triggers of release are water, heat, or pH. Mechanical action can also function as a release mechanism.

Microencapsulation is the process by which individual particles or droplets of solid or liquid material are surrounded or coated with a continuous film of polymeric material to produce capsules in the micrometer to millimeter range. Capsules can have a liquid inside a shell, multiple liquid areas in a shell, or the liquid spread through a matrix (Fig. 18.12).

Common shell materials are gums (gum arabic, sodium alginate, carrageenan), carbohydrates (starch, dextran, sucrose), celluloses (carboxymethylcellulose, methylcellulose), lipids (beeswax, stearic acid, phospholipids), and proteins (gelatin, albumin). Microencapsulation methods include physicochemical processes, such as coacervation and solvent evaporation, and physicomechanical processes, such as spray-drying.

Contemporary formulation may use nanotechnology, where the first generation technologies such as liposomes are being replaced by newer structures such as solid lipid nanoparticles and nanostructured lipid carriers. Nanosized particles that have a shell and an interior space that can be used to load perfume are called nanocapsules. Polymers have been widely used to create nanocapsules, which are then functionalized for various applications. Application of nanoencapsulation in fragrance products enables more efficient, prolonged, and time-controlled release of the scent. Using this approach, materials can be engineered to be stable in aqueous solution, nontoxic, and biodegradable.

## 18.9 ANTIBACTERIAL EFFECTS OF ESSENTIAL OILS

It has long been known that many essential oils possess the ability to inhibit bacterial growth. Martindale in 1910[4] used the phenol coefficient to characterize the effectiveness of essential oils, work that is still the basis of many

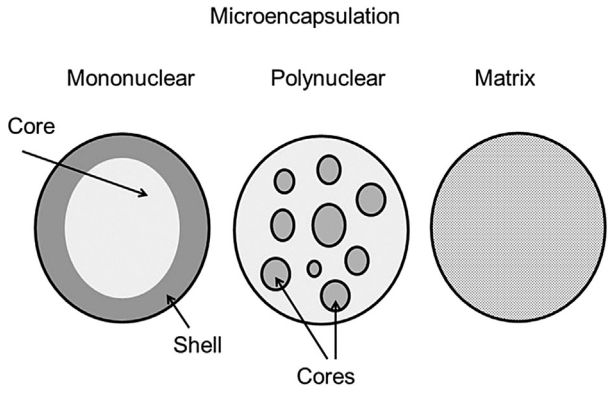



FIGURE 18.12 Microencapsulation.

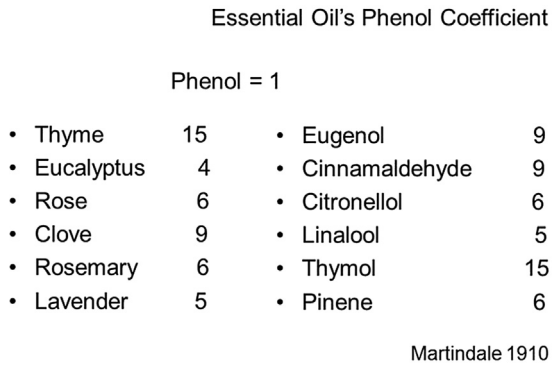



**FIGURE 18.13** Essential oil's phenol coefficient.

claims. The phenol coefficient itself is now only of historical interest. It is the concentration of phenol at which the compound kills the test organism divided by the concentration of the test compound that kills the organism under the same conditions. Materials that are more effective than phenol have a coefficient greater than 1; those that are less effective have a coefficient less than 1. The phenol coefficients of some essential oils are shown in Fig. 18.13.

Because of the demand for novel preservative systems, essential oils are still valuable for their activity. There are limits to their application since they can be irritants, they have strong odors, and their efficacy is not enough to provide preservation without the assistance of more conventional solutions.

## 18.10 MALODOR

The chemistry of malodor molecules is fundamentally different from most fragrance molecules. Malodor molecules frequently contain nitrogen or sulfur. Sulfur imparts the skunk excretion in its distinctive aroma, and nitrogen creates the smell of a rotten egg or cigarette smoke. Because they have unique chemistry, it is possible to destroy a malodor without destroying a fragrance at the same time.

Most compounds are susceptible to oxidation. In many materials, this can lead to a decomposition of the malodor creating substance, removing the odor. Chlorine dioxide is a commercial example. While commercially useful, this approach is not compatible with the use of fragrance as a solution.

Zwaardemaker pairs are conjugates of odorants that neutralize each other's respective odors. Examples are butyric acid and oil of juniper, ethyl mercaptan and eucalyptol, skatole and cedarwood, and tobacco and wintergreen oil. Their usefulness in malodor is increased as an appropriate fragrance can be built around the aromatic component of the pair.

To some extent all fragrances may assist in masking malodor, but some materials are much more effective than others. Aldehydes, orange oil, minty, fruity, and green notes are often useful. Fragrance companies have also designed nonaroma chemicals targeting malodor. A classic example is Veilex 1 (1-cyclohexylethyl butyrate), patented in 1980 by Bush Boake Allen (now part of IFF). Veilix molecules may bind to the same receptors in the nose as malodor molecules, eliminating the perception of the malodor. Other commercial malodor counteracting molecules are Meelium and Metazene.

Two of the most pervasive materials used in malodor products are zinc ricinoleate (Fig. 18.14) and cyclodextrin (Fig. 18.15). They both capture malodor molecules but use very different mechanisms.

Zinc binds very strongly to nitrogen and sulfur, both characteristically found in malodor molecules. When a malodor molecule can bind to the zinc, the chains of zinc ricinoleate can fold to totally encapsulate it. Zinc ricinoleate can also bind to many fragrance molecules, which is one limit on its use. It is also very hard to solubilize in many applications. Since ricinoleic acid comes from castor oil, this material has been positioned as a naturally derived product.

Cyclodextrin comes in three different forms (alpha, beta, gamma) and is shaped like a truncated cone. Cyclodextrin is relatively polar on the outside and nonpolar on the inside, so it can capture aroma chemicals or malodor molecules in its interior and be compatible with water-based delivery systems. This material is used extensively in P&G's Febreze line and is covered by many patents. In addition to cyclodextrin as an active material, this patent also specifies a preferred Clog P of three or less for fragrances. It is unclear which has the most malodor effect in the finished consumer products, the cyclodextrin or the fragrances.

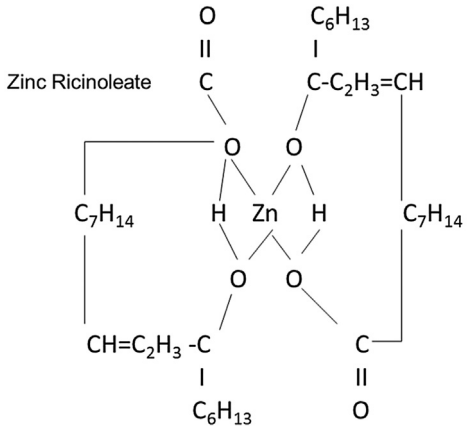
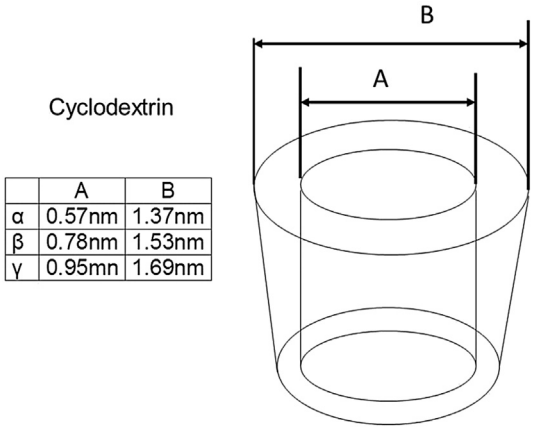



FIGURE 18.14 Zinc ricinoleate.




| | A | B |
|---|---|---|
| α | 0.57nm | 1.37nm |
| β | 0.78nm | 1.53nm |
| γ | 0.95mn | 1.69nm |

FIGURE 18.15 Cyclodextrin.

## 18.11 SAFETY AND REGULATORY CONCERNS

No aspect of fragrance is more important than its safety and regulatory compliance. No fragrance, no matter how beautiful it may smell, can be marketed without complete compliance. Consumers assume the products they use are safe and effective, and that the manufacturers take their responsibilities as a top priority. There are two broad classes of regulation: mandatory requirements from official agencies, and those specifically self-imposed by the fragrance industry with voluntary compliance.

Mandatory requirements apply when fragrances are simply considered a mixture of chemicals, and all the chemical safety rules apply. Safety data sheets, certificates of analysis, the Toxic Substances Control Act, and the European Union's Registration, Evaluation, Authorization, and Restriction of Chemicals registrations are examples. The Volatile Organic Compound regulations of the California Air Resources Board, which can be narrowly viewed as just a state regulation, are equally important. The European regulation requiring labeling of a specific list of alleged allergens, while geographically limited, is also of great importance in the global marketplace.

The fragrance industry established self-regulation when the Research Institute for Fragrance Materials[5] (RIFM) was established in 1966. RIFM is financially supported by the fragrance industry but functions independently. RIFM generates a safety dossier that is reviewed by the RIFM Expert Panel (REXPAN) and the results are published in peer-reviewed journals. RIFM itself does not publish or enforce specific industry guidelines based on its findings.

The International Fragrance Association[6] (IFRA) was created in 1973. The fragrance organizations of individual countries such as IFRA North America, formerly the Fragrance Materials Association, are members. IFRA evaluates the RIFM publications and, based on the best possible scientific appraisal, issues industry guidelines, which are freely available online. All responsible fragrance suppliers follow these guidelines, and global conformance is excellent.

From the inception of RIFM to the mid-1990s, the emphasis of testing focused on the individual use of fragrance on the skin. The reason was simple—the most intimate and prolonged exposure to humans from fragranced products came via personal care products. Fragrance use was divided into two broad categories: "skin contact" and non-skin contact." "Skin contact" was further divided into "leave on" and "rinse off." Rinse-off products were deemed less of a safety issue—until one addressed the fate of chemicals going down the drain!

In the 1990s the use of fragrance changed in ways significant for safety assessment. Personal use moved away from perfumes and colognes to bath and skin products. Environmental fragrance delivery through scented candles and plug-in air fresheners created much more respiratory exposure. Finally, the environmental movement focused attention on the fate of fragrance in water, its consequences for aquatic life, and from there back into the food chain, finally ending in our bodies. Four guidance papers elucidated the scientific basis for all RIFM activities.

Determining environmental safety may be even more complicated than determining dermal or respiratory safety. The RIFM guidance paper uses data and models to estimate the effects of fragrance materials on the aquatic environment. More than 2100 aroma molecules were assessed, with 92.3% having negligible effect on the environment at current volumes of use. The evaluation used KOW, molecular weight and usage volume. The "predicted environmental concentration" (PEC) was compared to the "predicted no effect concentration" (PNEC), ascertained by a quantitative structure-activity relationship. If PEC/PNEC $< 1$, the material passed the initial screen. For questionable materials, "ecological structure-activity relationships" was applied. This approach was a highly conservative risk-based screening without requiring experimental ecotoxicological or fate data.

Quantitative risk assessment (QRA) has the goal of minimizing, or ideally eliminating completely, skin sensitization caused by fragrance. It is a refinement of all the dermal safety data accumulated over many years. The method involves the determination of a benchmark (no expected sensitization induction level, or NESIL), application of sensitization assessment factors (SAF), and the calculation of consumer exposure through product use. It reduces to a simple relationship:

$$\text{Acceptable Exposure Level (AEL)} = \frac{\text{WoE NESIL}}{\text{SAF}}$$

where NESIL = No-Expected-Sensitization Induction Level; WoE = Weight of Evidence; SAF = Sensitization Assessment Factor.

The "weight of evidence" is the conclusion reached by the REXPAN after evaluation all the available literature and data on a material.

After many years of evolving methodology, RIFM updated and combined all its methods in a new guidance document available to the industry at the end of 2015.[7] A basic, extremely simplified, version of the RIFM algorithm (Fig. 18.16) describes the essential steps, with different endpoints for skin safety, respiratory effects, or environmental impact. Innovations introduced by RIFM included increased reliance on computer programs (in silico), and the introduction of the threshold of toxicological concern (TCC). The TCC was created for the food industry with the cooperation of the US Food and Drug Administration (FDA) to deal with the numerous chemicals present at extremely low levels that are extremely unlikely to have any negative effects.

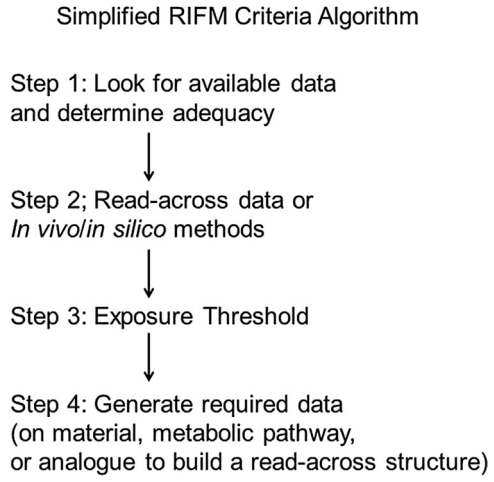



**FIGURE 18.16** Research Institute for Fragrance Materials criteria algorithm.

The goal of the new guidance document and algorithm is to apply the best possible science for the foreseeable future and to have a single flow path for a material entering the evaluation process to be assessed. RIFM is now in the process of putting all known fragrance materials through this screening. Even though safety testing has been done for many years, it is still necessary to reevaluate every material due to the changing requirements for dermal, respiratory, and environmental concerns.

## 18.12 THE REGULATION OF FRAGRANCE

Fragrance formulas are almost always kept confidential by the suppliers who create them. The formulas are considered intellectual property and the name "Fragrance" on the product, plus an allergen report for EU labels, satisfies the legal requirements for disclosure. The fragrance house necessarily provides a large number of supporting documents such as safety data sheets, product data sheets, IFRA conformance certificates, and EU allergen statements. The formulator is usually not privy to the details of the process whereby these documents are generated.

IFRA has several ways of classifying fragrance materials. Most have no restrictions. Some are banned outright and cannot be used under any circumstances. Some have restricted levels in different applications. Some have quality standards limiting trace components of concern. Some are fine themselves but can oxidize to produce sensitizers, and must only be used in conjunction with an antioxidant.

The most necessary fragrance-specific document for every user to have on file is the IFRA Certificate. It usually specifies limits on the use of the fragrance in a number of application categories. For some products there is a separate specification for leave-on products and nonskin contact products. Every two years RIFM publishes an amendment containing updated regulations and it is necessary to review all the regulatory documents on every fragrance to make changes if necessary.

## 18.13 NATURAL, GREEN, ORGANIC, AND SUSTAINABLE FRAGRANCES

The pervasive use of synthetic chemicals in modern perfumery has opened the door for a counter movement, the promotion of natural and organic fragrances. The exact definition of *natural* is hazy, as some type of manipulation is necessary to make almost every product useable in a fragrance composition. Natural compounds can be defined as products derived from plants via extraction, expression, or distillation without intentional chemical reaction or modification. Solvents have traditionally been used in many processes, but some groups limit their use exclusively to heat and water.

An issue arises in the difference between "natural" and "nature identical." Phenyl ethyl alcohol exists in rose oil. It can also be synthesized. It is virtually impossible to distinguish by chemical analysis between the naturally extracted and synthetic molecules, and the synthetic compound can be added to a naturally derived rose oil to "extend it." Recent technology utilizing isotopes identification has made it possible to identify the source of some compounds, but this is not in common use.

Creating fragrances exclusively with natural materials may pose challenges. They tend to be more expensive and despite the common perception linking "natural" with "safe," these may often cause skin irritation and sensitization reactions. In addition, the components of many natural products are prone to oxidation and decomposition and they frequently discolor and change odor. In addition to technical drawbacks, on the creative side being deprived of synthetics severely restricts the perfumer's palette.

To be certified as organic the composition must comply with specific regulatory guidelines and create a precise paper trail. Organic certification is a legal process in the United States created and monitored for food products by the United States Department of Agriculture that was extended to personal care products and fragrances. An organic fragrance is restricted to natural product compositions that are certified, which further reduces the raw material palette, elevates the price, and can create raw material shortages.

The FDA, in an alliance with stakeholders from the industry, created Design for the Environment guidelines for fragrances. This has been revised and rebranded as Safer Choice.[8] The fragrance criteria apply to household products such as laundry detergent and all-purpose cleaners, but not air fresheners or personal care products. It was intended to include the evaluation of very small quantities often excluded in environmental analysis and to move the industry to more environmentally friendly alternatives.

An attempt to make more stringent requirements in a document known as version 2.1 of the Criteria for Fragrances proved impractical to implement and the program reverted to the original Interim Fragrance Criteria. These documents are very long, technical, and detailed, and for those with a strong interest can be easily accessed online.

## 18.14 FRAGRANCE AND THE MIND

The chemical properties of fragrance are important, but there are also emotional and psychological aspects that are a major reason that smells are so important to people. Aspects that the formulator should be familiar with are aromatherapy, aromascience, and pheromones.

Aromatherapy is an ancient discipline involving the therapeutic effects of essential oils. Many fragranced products claim aromatherapy effects, usually based on folkloric information. The fragrance industry prefers to position itself with aromascience, defined as physical and psychological effects of fragrance backed by scientific testing. Much of the fragrance industry's research in aromascience is conducted by the Monell institute in Philadelphia.

The physiological basis of the effects of fragrance on the emotions concerns the basic anatomy of the olfactory system The odor receptors transmit a signal through the olfactory bulb to the limbic system of the brain, the location of human emotions. The sense of smell is ancient, its decoding is direct, and it helps explain the tangible impact scent has on most people.

Many tests have been conducted to identify aromas that are stimulating, relaxing, increase physical or mental performance, or effect emotions. Combining a relaxing smell with a relaxing delivery system such a candle or bubble bath in a serene environment can have an effective total effect.

Claims have been made for certain chemicals having pheromonal effects on humans, particularly androstenone, androstenal, and copulans (short-chain fatty acids). The most widely cited proof of pheromonal behavior is McClintock's 1971 paper on menstrual synchrony and suppression.[9] A recent book by Doty[10] has assigned human pheromones to the realm of myth. In fact, hard science on human pheromonal behavior is hard if not impossible to find, especially by Doty's standards, and the fragrance scientist should deal with pheromones with extreme skepticism.

## 18.15 THE FRAGRANCE BRIEF

Fragrance marketers like Coty and Estee Lauder do not make their own fragrances, nor do celebrities like Britney Spears labor in a lab. It is much more efficient to leave the creation of fragrances to companies deep in the appropriate expertise. Fragrance suppliers with names unfamiliar to the public make the scented juice, and the process is directed by a fragrance brief.

Fragrance briefs set all the key parameters for a new fragrance or a set of line extensions like bath gels or candles. Sometimes the initial request is highly imaginative, wanted to match a series of romantic pictures or the sensation of walking through a rain forest after a thunderstorm. Others can be very precise—a complex floral with a strong rose/jasmine core and haunting amber dry down.

The required information starts with the product type, including chemical or physical characteristics. The intended market, packaging, and price are key inputs. There must be a time frame for development and testing. Fragrance suppliers are well staffed with specialists in all phases of the commercial development process: perfumers, evaluators, expert panels, marketing departments, and analytical and application chemists who all play important roles in creating a successful submission.

The closer the customer works with the fragrance house, the greater the chance of success. Exact knowledge of the finished applications, packaging, pricing, target audience, and competitive products are all critical. A project that begins "just give us something that smells nice and don't worry what it costs" is doomed from the beginning.

## 18.16 CONCLUSIONS

Fragrance is an important aspect of our lives and a key component of many product types from designer perfumes to all-purpose cleaners. The creativity of the perfumers, the chemical expertise of the applications lab, regulatory diligence, and intelligent use of marketing are some necessary ingredients for success. Many pieces must fit together to make the ideal fragrance for each application, but the result will be a superior product and a satisfied consumer.

## 18.17 A BASIC FRAGRANCE LIBRARY

**Classics:**

Guenther, Ernest. *The essential oils*, six volumes, Van Nostrand Co. 1948–52 (republished Jepson Press 2007).

Arctander, Steffen. *Perfume and flavor materials of natural origin*, published by the author 1960 (republished by Allured Publishing 2003).

Arctander, Steffen. *Perfume and flavor chemicals*, two volumes, published by the author 1969 (republished by Allured Publishing 2000).

**General works:**

Muller PM, Lamparsky D, editors. *Perfumes: Art science & technology*: Elsevier Science; 1991.

Sell CS, Pybus DH, editors. *The chemistry of fragrances*: RSC; 1999.

Herman S. *Fragrance applications: A survival guide*: Allured Publishing; 2001.

Rowe D, editor. *Chemistry and technology of flavors and fragrances*: Blackwell; 2005.

Sell C. *Understanding fragrance chemistry*: Allured Publishing; 2008.

## References


1. www.nobelprize.org/nobel_prizes/chemistry/laureates/1939/ruzicka-facts.html.
2. Carles J. *A method of creation in perfumery* [Researches #December 11, 1961, #December 12, 1962, #December 13, 1963].
3. http://hansen-solubility.com.
4. Martindale W. *Perf Essent Oil Rec* 1910;**1**(11):266.
5. www.rifm.org.
6. www.ifraorg.org.
7. Api AM, et al. Criteria for the Research Institute for Fragrance Materials, Inc. (RIFM) safety evaluation process for fragrance ingredients. *Food Chem Toxicol* August 2015;**82**(Suppl. S1–S19). http://dx.doi.org/10.1016/j.fct.2014.11.014.
8. www.epa.gov/saferchoice/standard.
9. McClintock MK. Menstrual synchrony and suppression. *Nature* January 21, 1971;**229**:244–5.
10. Doty R. *The great pheromone myth*. Johns Hopkins University Press; 2010.

CHAPTER

# 19

# Amino Acids, Peptides, and Proteins

*E. Oshimura*[1], *K. Sakamoto*[2]

[1]Ajinomoto Co., Inc., Tokyo, Japan; [2]Tokyo University of Science, Chiba, Japan

## 19.1 INTRODUCTION

Cosmetic science is a fusional discipline of various scientific and technical fields such as biology, chemistry, chemical engineering, psychology, and more, but all should be built on the base of understanding on skin and hair biology, as these are primary targets of cosmetic or personal care products. Comprising 60–70% of the body weight, water is the largest component of human body, next is proteins with about 20%, which not only serve as the structural backbone for cells and organs but also participate in various biochemical processes within cells to keep the body alive. Maintaining water in the body is an essential function of skin, the largest organ of the human body, and the stratum corneum (SC), the outmost layer of only about 15–20 μm thickness, plays the key role of the barrier function.

Studies on functions of endogenous amino acids/proteins in the skin and effects of topically applied ones to the skin have a long history. Statistically, the numbers of patents filed suggest that the number of studies conducted in recent years is increasing. Fig. 19.1 shows the number of patent applications filed and journals during the past 20 years. The sharp increase in patent applications that started around 2001 is still ongoing.

In spite of the growing interest among cosmetic scientists, for most consumers, the terms *amino acid* or *peptide* in personal care applications are still not as familiar as some other biochemical compounds such as vitamin or even various vegetable oils; many would recognize the term *protein* as valuable, but only as a nutrient. However, in fact amino acids have been used in cosmetics for a long time and the number of products with amino acids or peptides is increasing as a corollary of the herein mentioned animated research activities.

## 19.2 CHEMISTRY OF AMINO ACIDS, PEPTIDES, AND PROTEINS

### 19.2.1 Chemistry of Amino Acids

According to a rigid chemical definition, an amino acid is an organic acid that possesses at least one amino group.[1] Almost a limitless number of molecules would fall under this definition, as an acid could be carboxylic, sulfonic, or phosphoric, and there are numerous ways in which these chemical functional groups attach to a backbone structure.

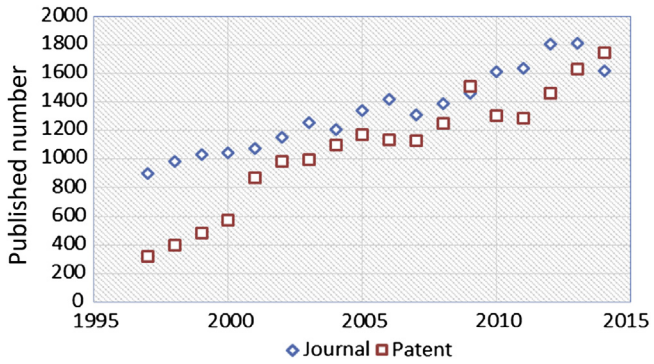



FIGURE 19.1 Number of journals and patents submitted in the last 20 years.

*Cosmetic Science and Technology: Theoretical Principles and Applications*
http://dx.doi.org/10.1016/B978-0-12-802005-0.00019-7



Copyright © 2017 Elsevier Inc. All rights reserved.

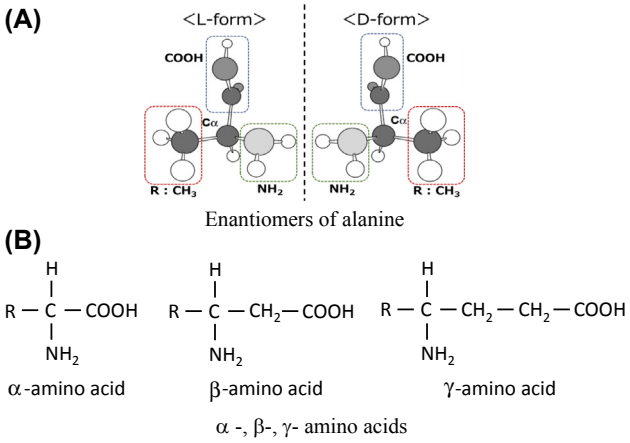



FIGURE 19.2 **Structures of amino acids. (A) Enantiomers of alanine (B) α-, β-, γ- amino acids.**

In general, the term is limited to the group of natural L-α-amino acids that build proteins, and some other naturally occurring compounds.

All amino acids as constituents of proteins are α-amino acids, which refers to the molecular structure within which the amino group is attached to the same carbon atom as the carboxyl group. This carbon of α-amino acids is asymmetric except for the one in glycine, and all amino acids as constituents of proteins are L-amino acids (Fig. 19.2A).

Amino acids with a β-, γ-structure, or with a sulfonate acid group instead of a carboxyl group are found in living organisms in the form of small peptides or as "free" amino acids (Fig. 19.2B). The term *free* is used to describe the amino acids that are not embedded in proteins. Additionally, recent improvements of analytical technology permitted the quantitative determination of the very small amount of D-amino acids that exist in the human body, and their functions are coming to light.[2–5]

Since amino acids incorporate both acidic and basic functional groups, as the pH is lowered in an aqueous solution, a proton is transferred from the acidic carboxy functional group to the amino functional group to form a structure called a zwitterion. The predominant molecular species present in the solution depends on the pH of the solution, and at a characteristic pH, the zwitterion predominates and the negatively and positively charged molecular species are present in equal concentration. This pH, which is characteristic to each amino acid and called the isoelectric point (pI). This has to be taken into account in applications, as the solubility of the amino acid drops at pI. Amino acids that possess one amino functional group and one carboxy functional group are called neutral amino acids and they have pI between 5 and 7, the pH range used in most cosmetic applications. (Review Articles 2)

### 19.2.2 Amino Acids as Building Blocks of the Living Body

Only about 20 kinds of L-amino acids occur in nature, and these amino acids constitute the 'monomers' in the molecular structures of proteins (Table 19.1). These amino acids encoded from codons are called proteogenic amino acids. Some additional amino acids are also found in special proteins, for example, hydroxyproline and hydroxylysine occur in collagen; they are produced by hydroxylation of the amino acids proline and lysine following protein synthesis.[6]

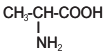
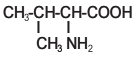
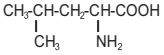
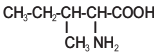
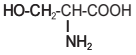
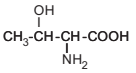
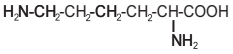
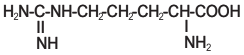
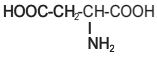
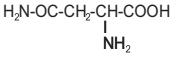
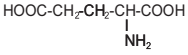
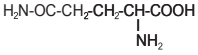
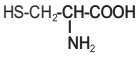
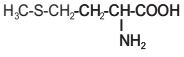
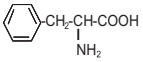
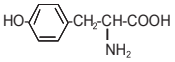
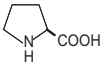
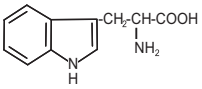
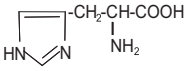
Peptides are polymers of amino acids, consisting of approximately 50 or fewer amino acids, of molecular weight up to 10,000. Peptides of larger size are often referred to as polypeptides, when there is no need to imply their functions as biopolymers. Proteins consist of one or more polypeptides or other ligands such as metal cations, coenzymes, etc., and they have to be assembled properly in order to exhibit biochemical functions. Functional groups of the side chain of amino acid residues have a critical role to form and maintain the structure; for example, an abundance in glycine is frequently observed in fibril proteins that form helical structures such as keratin (intermediate filament[7]) or fibroin (silk protein)[8] as a glycine polymer forms the most favorable angle of each amino acid residue along with the long axis.[9]

## 19.3 PROTEINS AND AMINO ACIDS AS BIOCHEMICAL COMPOUNDS

### 19.3.1 Proteins in Skin and Hair

Although various types of proteins exist in skin such as enzymes, antibodies, receptors, and so on, structural proteins in the epidermis and dermis are of special concern to cosmetic chemists.[10,11]

**TABLE 19.1** Proteinogenic Amino Acids Found in Human Proteins

| Group | Amino Acid | Abbreviations | | Structure |
|---|---|---|---|---|
| I Aliphatic amino acids (A) Neutral amino acids | Glycine | Gly | G |  |
| | Alanine | Ala | A |  |
| | Valine | Val | V |  |
| | Leucine | Leu | L |  |
| | Isoleucine | Ile | I |  |
| | Serine | Ser | S |  |
| | Threonine | Thr | T |  |
| (B) Basic amino acids | Lysine | Lys | K |  |
| | Arginine | Arg | R |  |
| (C) Acidic amino acids and their amides | Aspartic acid | Asp | D |  |
| | Asparagin | Asn | N |  |
| | Glutamic acid | Glu | E |  |
| | Glutamin | Gln | Q |  |
| (D) Sulfur-containing amino acids | Cysteine | Cys | C |  |
| | Methionine | Met | M |  |
| II Aromatic amino acids | Phenylalanine | Phe | F |  |
| | Tyrosine | Tyr | Y |  |
| III Heterocyclic amino acids | Proline | Pro | P |  |
| | Tryptophan | Trp | W |  |
| | Histidine | His | H |  |

### *19.3.1.1 Keratin*

Keratin is a group of fibril structural proteins forming the SC cells (called "keratinocyte"), hair, and nails. The term *keratin* is derived from a Greek word meaning horn and originally denoted the mixture of insoluble proteins in the SC or "horny layer." The recent understanding is that keratins are members of a family of proteins called intermediate filament (IF) proteins.[12,13] A common secondary structure of all IF proteins is that IF proteins consist of

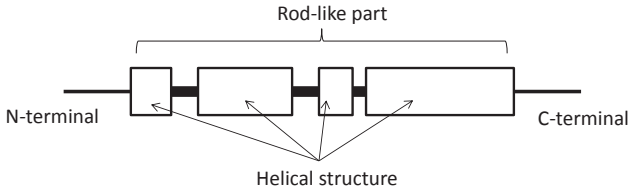



FIGURE 19.3 **Schematic structure of intermediate filament.** Many types of intermediate filaments are known, and all have four helical blocks connected with short linkages. Although keratin is known as a cysteine-rich protein, most of them are found in N- and C-terminal parts. *Reconfigured from Marshall RC, Orwin DFG, Gillespie JM. Structure and biochemistry of mammalian hard keratin.* Electron Microsc Rev *1991;**4**:47–83.*

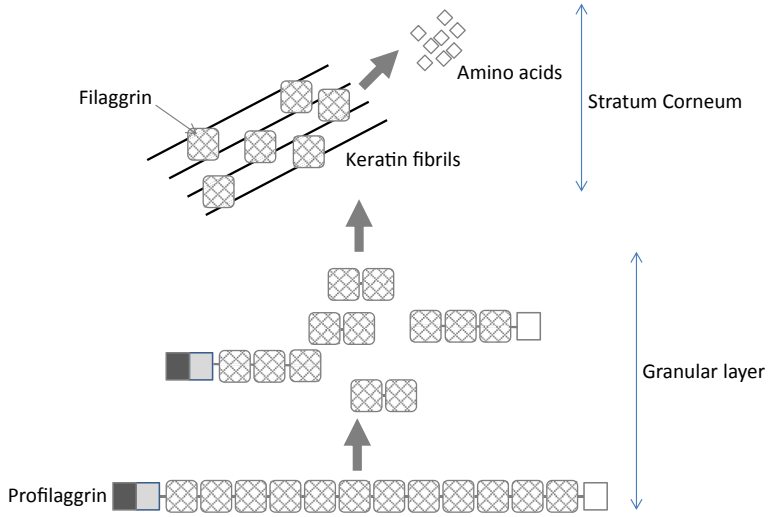



FIGURE 19.4 **Amino acid formation from profilaggrin.**[17] Profilaggrin is stored in an inactive form within keratohyalin granules. It is degraded into free filaggrin monomers in multiple steps. In the SC, the filaggrin monomers bind to keratin filaments to help keratinocyte differentiation and apoptosis. Filaggrin undergoes further degradation into free amino acids and derivatives.

α-helical domains separated into four blocks via three shorter linkages and nonhelical N- and C-terminals (Fig. 19.3). Although keratin is well known as a cysteine-rich protein, the cysteine residue content varies from around 3% of SC keratin to over 7% of human hair keratin.[14] The major force that keeps the helical structure is considered to be hydrophobic interaction and as a consequence, keratin is basically a hydrophobic protein. When IFs are assembled into higher level of molecular structures, disulfide bonds play a major part in stabilizing the complex structure.

Unlike the high interest there has been in researching collagen, studies on the involvement of keratin in aging were neglected for a long time; however, it has been revealed recently that keratin also undergoes glycation and carbonylation, resulting in alteration of SC's optical properties.[15,16]

#### *19.3.1.2 Filaggrin*

Filaggrin[17] (derived from filament-aggregating protein) binds to IFs[18] in epithelial cells during the epidermal terminal differentiation process to help them form an insoluble keratin matrix. Filaggrin is synthesized as a histidine-rich large precursor protein, profilaggrin, which is the main constituent of the keratohyalin granules within the granular layer of the epidermis. The precursor protein is activated by cleavage into 10–12 filaggrin monomers, and after finalization of the epidermal differentiation, filaggrin undergoes subsequent degradation in the SC to release free amino acids (Fig. 19.4), a major component of natural moisturizing factor (NMF) (Table 19.2).

#### *19.3.1.3 Collagen*

Collagen[20–22] is probably the protein that consumers know best, not only in cosmetic applications but also in medical uses and in the food industry (gelatin); in truth, collagen is the most abundant protein in mammals as it serves a vital role as a scaffold within the extracellular matrix. In skin, collagen is the main constituent of the dermis, representing about 75% of the dry weight. The collagen fibers form tough networks providing the dermis with strength, tension, and elasticity.

**TABLE 19.2** Composition of Natural Moisturizing Factor[19]

| | wt% |
|---|---|
| Amino acids | 42.2 |
| Pyrrolidone carboxylic acid (PCA) | 12.2 |
| Lactate | 11.3 |
| Urea | 6.7 |
| Others | 27.6 |

Almost 30 types of collagen have been identified so far; most of them form long fibrils that are triple helices. This triple-helical structure of collagen arises from a repeating of gly- X-Y sequence, where X and Y can be any amino acid; often proline (28%) and hydroxyproline (38%), respectively.

The structure of collagen fibers denature by ultraviolet (UV) light and this is one of the major causes of skin aging. UV exposure causes changes of the fiber network structure and loss of skin elasticity, and finally induces wrinkling.[23,24] Glycation of skin collagen is proposed to be responsible for the loss of fairness in skin, another signal of aging.[25,26]

#### *19.3.1.4 Elastin*

Elastin[22,27] is an insoluble extracellular matrix protein in connective tissue, serving a major role in organs where its elastic recoil and resilience are required, such as the large arterial blood walls, lung parenchyma, and the dermis. In the dermis, elastin plays a major role to provide a scaffold along with collagen. It is reported that once elastin is synthesized and laid in the extracellular matrix, it does not undergo turnover.[28] Damages or changes of elastin should account for changes in elasticity observed in matured skin. Cross-linking of collagen and elastin results in wrinkle formation. More drastic changes in elastin fibers are also observed in photoaged skin, characterized by an accumulation of amorphous elastin protein and disorder in the structural layout.[29,30]

### 19.3.2 Amino Acids in Skin

#### *19.3.2.1 Natural Moisturizing Factor (NMF)*

Originally NMF was defined as a complex mixture of free amino acids and other low-molecular-weight, water-soluble compounds found in corneocytes.[19c,31] NMF is known to contribute to the maintenance of water balance in the SC. The main components of NMF are amino acids, pyrrolidone carboxylic acid (PCA), and lactic acid, which comprise 40%, 12%, and 12% by total weight of NMF, respectively (Table 19.2). The amino acids and PCA are produced within the SC by degradation of filaggrin,[32,33] and this process is suggested to be triggered by decrease in humidity.[17] In contrast to the amino acids, insensible perspiration is probably responsible for the supply of lactic acid and other minerals.

Fig. 19.5 shows composition of the free amino acids in NMF. This composition does not agree with that of filaggrin, for example, citrulline and alanine are abundant whereas glutamic acid and arginine tend to show lower proportions in NMF than in filaggrin, due to further metabolism inside the SC. PCA is produced from glutamic acid,[19b,34–36] citrulline and ornithine are metabolites of arginine, and alanine is a metabolite of aspartic acid.

It has been found that the amino acid amount found in the SC correlates with the skin moisture[37] (Fig. 19.7), and in nonhealthy skin both amino acids and PCA are decreased.[38] Loss of profilaggrin or filaggrin by genetic mutations leads to a poorly formed SC, which is also prone to dehydration. Koyama et al. reported that experimental induction of keratosis by treatment with a surfactant resulted in a marked reduction of amino acid metabolites PCA, urocanic acid, citrulline, and aniline.[38]

#### *19.3.2.2 Urocanic Acid*

*Trans*-urocanic acid (*trans*-UCA, Fig. 19.6B) is produced as a metabolite from histidine in the SC and is converted to the *cis* isomer by UV-B (280–310 nm).[39,40] In an aqueous solution, the conversion reaches equilibrium when the *trans-cis* ratio reaches about 1:1.[41] *Trans*-urocanic acid has been proposed to provide weak endogenic UV protection, and *cis*-UCA in turn is known to be involved in immunosuppression induced by UV irradiation.[42] Although the mechanism in detail is not still clear and there is a controversial discussion about consequences of *cis*-UCA behaviors, the fact that only SC and liver produce UCA is suggestive in view of skin as the front line of the fight against extraneous influences.[43]

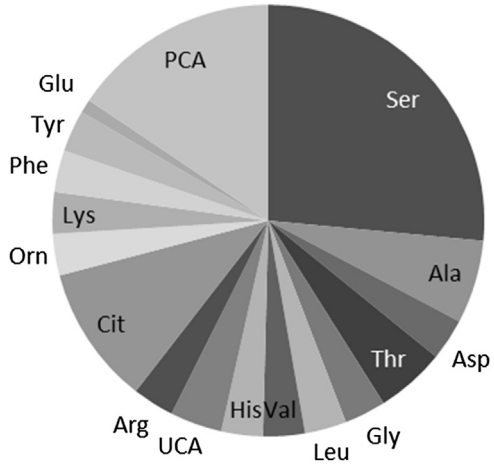



FIGURE 19.5 **Amino acids composition of NMF.** Urocanic acid (UCA) and PCA are included as they are produced from histidine and glutamic acid, respectively. Citrulline and ornithine are amino acids not coded by codons. NMF was recovered from tape-stripped SC layers and analyzed by amino acid analyzer. The low concentration of glycine in comparison to the amino acid composition of filaggrin is probably explained by the low recovery rate of this small molecule. *(Data by AJINOMOTO Co., Inc., not published).*

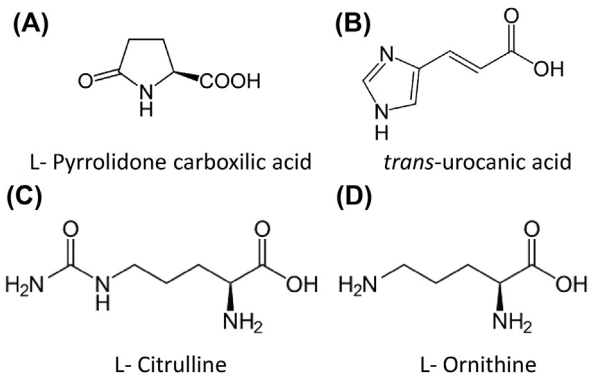



FIGURE 19.6 **Nonproteogenic amino acids and amino acid derivatives found in NMF. (A) L-Pyrrolidone carboxilic acid (B) *trans*-urocanic acid (C) L-citrulline (D) L-ornithine.**

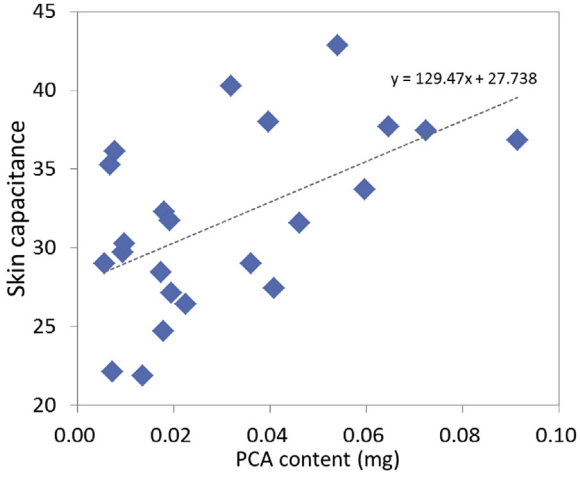



FIGURE 19.7 **Correlation between PCA content in the staratum corneum and skin capacitance.** *(Data by AJINOMOTO Co., Inc., not published.)*

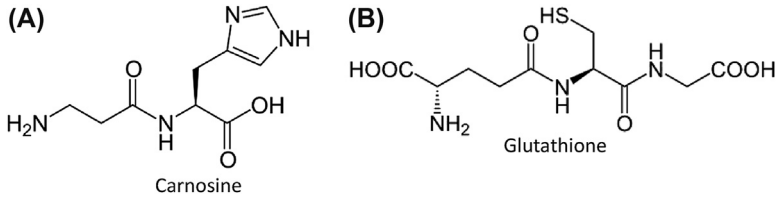



FIGURE 19.8 **Antioxidant peptides occurring in the human body.**

### 19.3.3 Peptides Occurring in the Body

Our bodies produce many peptides. Most of the peptides have relatively high molecular weight, and are sometimes described as small proteins; they act as signaling molecules or hormones. There are smaller peptides such as di- or tripeptides, and they seem to have more direct involvement in biochemical processing. These peptides often have slightly different chemical structure from proteins made up of encoded amino acids, fleeing attacks from proteases. Two peptides with antioxidant activities occurring in the body are described next.

#### *19.3.3.1 Carnosine (β-Alanylhistidine)*[44–46]

Carnosine (Fig. 19.8A) is a dipeptide of β-alanine and histidine found in muscles and brain tissues. Carnosine has been proven to show antioxidant activities, which is contributed by its histidine residue; for example, it acts as a scavenger for reactive oxygen species (ROS) and unsaturated aldehydes formed by peroxidation of cell membrane fatty acids. Carnosine acts as an antiglycating agent as well and is speculated to be involved in enhanced aging process caused by diabetes.

#### *19.3.3.2 Glutathione*

Glutathione[47,48] is a tripeptide of glutamic acid, cysteine, and glycine with a peptide linkage between the γ-carboxyl group of the glutamate side-chain and the amine group of cysteine (Fig. 19.8B). Glutathione exists not only in mammals but also in plants and fungi, proving this compound has particularly important roles in living creatures. In fact, glutathione is a powerful antioxidant whose efficacy is based on the thiol group of cysteine. It detoxifies hydrogen peroxide into water and reduces disulfide bonds formed within proteins by oxidative stress into cysteine.

## 19.4 AMINO ACIDS IN COSMETICS

### 19.4.1 Production of Amino Acids

Amino acids are produced commercially either by hydrolysis of proteins, chemical synthesis, or biochemical processes. Hydrolysis is suitable for amino acids for which inexpensive proteins rich in content of specific amino acids are available; for example, cysteine is extracted from keratins from feathers. Theoretically, all amino acids can be produced by biochemical processes, however, in reality, chemical processes are advantageous for simple amino acid such as glycine and DL-alanine. For amino acids with relatively large overall demand, the fermentation process is suitable; examples include glutamic acid, lysine, threonine, methionine, arginine, and so on. For some amino acids, chemoenzymatic processes are employed.

In many cases purification could be the key. Chirality control is often troublesome when a chemical process is used. Biochemical processes have the advantage of chirality control, but proteins and metals should be carefully removed by purification, as these materials have the potential to cause skin sensitization.

### 19.4.2 Humectants

Amino acids are widely used as humectants,[49] a range of ingredients that provide hydration effects as a result of their hygroscopicity. Among various amino acids, proline and PCA have particularly high hygroscopicity and also show a synergistic effect when mixed.[19c]

Although the SC produces amino acids by itself to keep it hydrated, these amino acids are easily lost during bathing or washing[50] (Fig. 19.9). They will recover to the original level eventually,[51] however, within the recovery period the skin faces risk of dehydration. Oota reported that sodium PCA incorporated in cleansing preparations efficiently prevents decrease of the skin PCA and decrease of the skin moisture.[52]

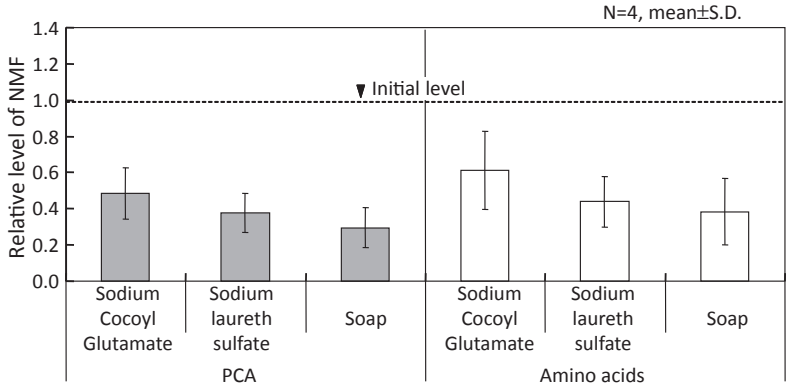



FIGURE 19.9 **Decreases of pyrrolidone carboxylic acid and amino acids in the stratum corneum caused by cleansing by a surfactant.**[53]

## 19.4.3 Neutralizer/pH Adjuster

Amino acids that possess additional carboxylic groups on their carbon backbone—glutamic acid and aspartic acid—are called acidic amino acids, and those with additional basic groups—lysine, arginine, and histidine—are called basic amino acids. In cosmetic applications these are recognized as organic acids or amines and are used as neutralizers or pH adjusters.

Controlling pH of cosmetic applications during long storage is important to provide functions on-target and to maintain quality of the products. Many products are equipped with a pH buffering system in order to stabilize their pH against possible degradation, oxidization, or lot variance of some raw materials. Being dibasic acids, glutamic acid and aspartic acid have the potential to provide buffering effects. These acidic amino acids are also used to react with a fatty amide tertiary amine to turn it into a quaternary amine, a conditioning agent for hair care.

As a basic amino acid, arginine is used in various applications as a neutralizer or a pH adjuster; lysine on the contrary has less popularity due to its characteristic odor that is not preferable for cosmetics. Acrylate polymers, one of the most popular polymers for rheology control, have to be neutralized in order to function as a thickeners. Arginine-neutralized acrylate polymers show improved potency as hair fixative polymers to the ones neutralized with triethanol amine. Arginine is also employed as an alkalizer in oxidative coloring agents and bleaching agents to reduce the irritative odor of ammonia and to develop milder products for the hair and the scalp. Arginine prevents a decrease of tensile strength and hair surface hydrophobicity, which are caused by oxidative coloring; arginine also seems to prevent undesirable effects of hydrogen peroxide on hair proteins and hair surface lipids.[54]

## 19.4.4 Antioxidant Activity

Several researchers have reported antioxidant activity of amino acids; most of the reports appear in the fields of food chemistry and of medicine.[55–58] Nawar[57] summarized these reports to the point—amino acids have been reported to act as antioxidants, pro-oxidants and/or to have no effects on oxidation. These seem to contradict each other. As Celermajer concluded,[55] the reality is probably that most amino acids have only weak and nonspecific antioxidant properties that are attributed mainly to their α-amino groups, and their activity is largely affected by condition of use because of this weakness. Still, in some conditions, specific amino acids exhibit stronger antioxidant activities.

UV rays from the sun contribute to the generation of free radicals and ROS that stimulate inflammatory processes in the skin; the process known as photoaging. In photoaged skin, accumulation of disorganized elastin and its microfibrillar component in the deep dermis and a severe loss of interstitial collagens are observed. Some amino acids are known to react with ROS. For example, the imidazole group of histidine has a high affinity toward singlet oxygen, one ROS.[59] Proline is reported to decrease oxidization of lipids induced by UV radiation.[60]

## 19.4.5 Cysteine

Cysteine is a sulfur-containing amino acid. It is unstable in the air. In proteins it usually exists as a cystine by forming a disulfide bond between two cysteine residues, carefully protected inside of the protein in order to function as a stabilizer for high-order structure of the protein, or an active center for its bioactivity.

Cysteine itself is a powerful antioxidant and has the potential to trap ROS, and is promising as an antiaging active. Due to the fact that cysteine tends to be absorbed into cells where it cannot exhibit its antioxidant property, N-acetyl cysteine (NAC) is often used instead for this purpose.[61] In addition, cysteine has a skin-whitening property as well. During the biosynthesis process of melanin, cysteine accelerates the pathway directed to formation of pheomelanin, which produces yellowish or reddish colors and blocks formation of eumelanin that produces dark colors.[62] However, due to its low stability and characteristic odor, it is difficult to incorporate cysteine itself into skin care products.

An application where cysteine is used at a relatively high concentration is in waving lotions.[63] In fact, its characteristic odor is not so bad in comparison to the typical reducing agent thioglycolic acid. Both cysteine and NAC are used as reducing agents for permanent wave treatment in Japan and some other Asian countries where one source of cysteine—human hair—is abundant.[64] Hair dressers claim that thioglycolic acid forms sharp "ridges," whereas cysteine and NAC tend to form softer waves with subtle nuance.

### 19.4.6 Amino Acids for Hair Care

In contrast to the case of skin, the existence of naturally occurring amino acids within hair fibers is not known. Amino acids that are often detected in hair are most likely to be consequences of protein degradation. However, even these amino acids or topically applied ones have proven to provide various benefits for hair such as moisturization, improvement in combability, imparting luster, color retention, and fiber structure reconstruction.[65]

Among various amino acids, arginine is typically preferred in hair care preparations. Arginine is a basic amino acid with a $pK_2 = 9.04$, so it bears a cationic charge at a pH below 9. Therefore, arginine has strong affinity for hair in a pH range of 4–9. Above all, the guanidinium group of arginine is known to have quite high affinity for hair protein,[66] and it seems that arginine enhances uptake of other amino acids with lower affinity for hair. Fig. 19.10 shows the amount of PCA and amino acids taken up by hair from the mixture solutions.

### 19.4.7 Amino Acid Derivatives

Since allthe amino acids incorporate at least one acidic functional group and at least one basic functional group, and all amino acids except for glycine possess at least one chiral carbon, amino acids provide excellent foundations as starting materials for derivatives. Fig. 19.11 shows chemical processes that could be employed for modifications of amino acids. Using these processes, a wide range of cosmetic ingredients have been developed and introduced into

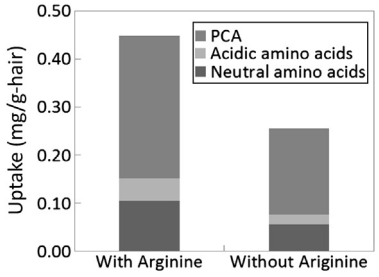



FIGURE 19.10 **Uptake of amino acids by hair.** Hair tresses were immersed in the test material solution for 30 min and rinsed in running tap water and dried. PCA and amino acids were extracted from the hair by a phosphate buffer solution (10 mM, pH 3.5) and subjected to quantitative determination by LC-MS. *(Data by AJINOMOTO Co., Inc., not published.)*

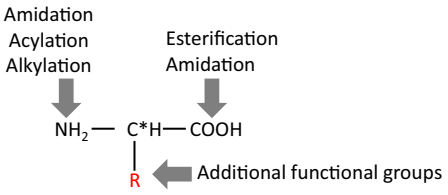



FIGURE 19.11 **Amino acids as starting materials for chemical modification.**

the market. In the following section some examples that show the uniqueness and potential of amino acid derivatives are described.

### 19.4.7.1 Amino Acid Surfactants

Amino acid surfactants have been the subject of many studies for a long time.[67] Surfactants derived from glutamic acid, aspartic acid, glycine, alanine, threonine, arginine, and proline have been produced commercially, and the interest in them has grown recently due to mounting concern on mildness of cosmetic ingredients and sustainability. Although chemical processes have been predominant due to their relatively low cost, bioprocesses such as enzymatic or chemoenzymatic ones could be the focus of new approaches in the near future to meet demands and concerns in the personal care market for "green chemistry."

More than a century ago, Bondi synthesized N-lauroyl glycine and alanine and found that they were biodegraded into amino acids and fatty acids,[68] and in the following 50 years it was made clear that acyl amino acids occur in nature.[69–71] Takehara et al. conducted extensive studies on their physicochemical properties and applications for personal care,[72–76] and also established commercially applicable production process.[77] Acylglutamate first appeared in the personal care market in Japan in 1972, and in 1973 a mild syndet bar made of acylglutamate was launched as a solution for people with skin troubles. It was not alkaline.[78,79]

The compatibility of acylglutamate with skin and hair is outstanding even compared to various mild surfactants,[80,81] and it leaves a velvety soft touch to the skin. However, its foamability is only comparable to other mild surfactants, that is, not quite satisfactory in comparison to conventional anionic surfactants. To meet the demands of "mainstream" consumers who are interested in mildness but not ready to sacrifice rich foam for mildness, acyl derivatives of neutral amino acids were introduced next.[82–84] These products have soap-like foaming and sensorial properties, but in contrast to soap they maintain surface activity around neutral pH or below. For example, potassium lauroyl glycine maintains foamability at pH 6–7, whereas potassium laurate does not produce foam in this pH range (Fig. 19.12). This provides apparent benefits to skin. Most proteins including keratin swell at alkaline pH. This means skin becomes more susceptible to loss of NMFs or lipids.[85] Moreover, the solubility of amino acids increases at alkaline pH, so neutral to weakly acidic conditions are favorable in order to prevent loss of NMFs and to maintain skin condition.[86,87]

### 19.4.7.2 Powdery Material

The acyl amino acids described before have an acylated α-amine, but due to the low reactivity of α-amine, a fatty acid has to be activated by chlorination beforehand in order to introduce an acyl chain. Lysine has another amino group on the side chain and acylation of this ε-amino group is easier.[89] ε-lauroyl lysine was first prepared aiming at a new group of amphoteric surfactants, but the product turned out to be hardly soluble either in water or in any kind of cosmetic solvents.[90] Finally, it was introduced into the market as a powdery ingredient[91] and is widely used mainly in color cosmetics with its excellent lubricity (Figs. 19.13 and 19.14) and properties to prevent a drying effect caused by inorganic powders.

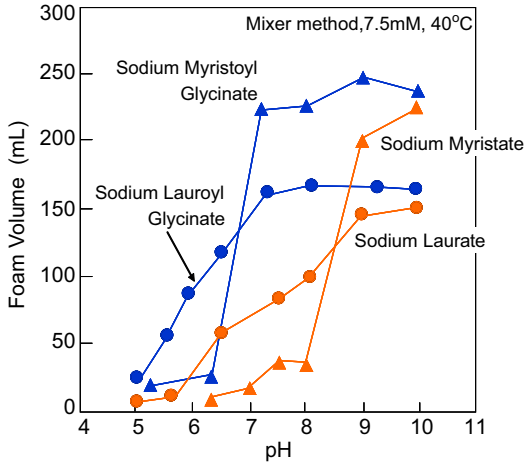



FIGURE 19.12 **pH dependence of foamability of sodium acyl glycinates and sodium fatty acids.**[88]

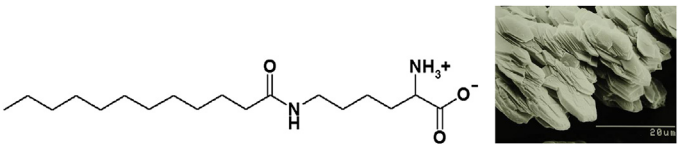



FIGURE 19.13 **Chemical structure of $N^{\varepsilon}$-lauroyl lysine and SEM photograph of the powder.**

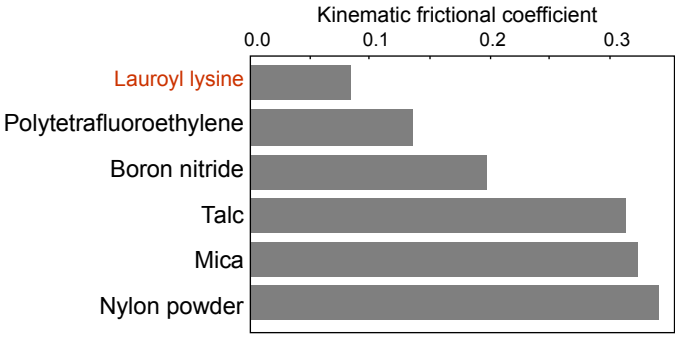



FIGURE 19.14 **Kinetic frictional coefficient of various powder materials.**[92]

### *19.4.7.3 Oil Gelatinization Agents*

Sometime in 1972, while trying to purify a crude N-lauroyl-L-glutamic acid (L-LGA) as a promising new surfactant mild to skin and gentle to the environment, researchers happened to make oil gels with iridescent colors.[93] Subsequent findings of the formation of chiral micelles for the series of optical active acylamino acid salts including L-LGA salts in aqueous solution[94–96] drove their attention to significance of molecular chirality for these phenomenon; eventually L-LGA gel was found to be an early example of lyotropic cholesteric liquid crystal as a self-assembly of the chiral surfactant L-LGA.[97,98] The gels formed by L-LGA have a hierarchical chiral structure induced by LGA's molecular chirality. On the other hand, racemic LGA (DL-LGA) did not form a gel.

It was a time when AJINOMOTO Co., Inc., a leading manufacturer of amino acids in the world, was conducting projects to develop functional materials from amino acids for industrial applications, and coincidently another researcher in a different team found a similar but even stronger gel formation property for a derivative of L-LGA, dibutyl lauroyl glutamide (LGDB) (Fig. 19.15A).[99,100]

From these findings a general hypothesis of three elemental requirements to construct hierarchical chiral self-assemblies was developed. First, the molecule as a unit of chiral self-assembly must be optically active, or in other

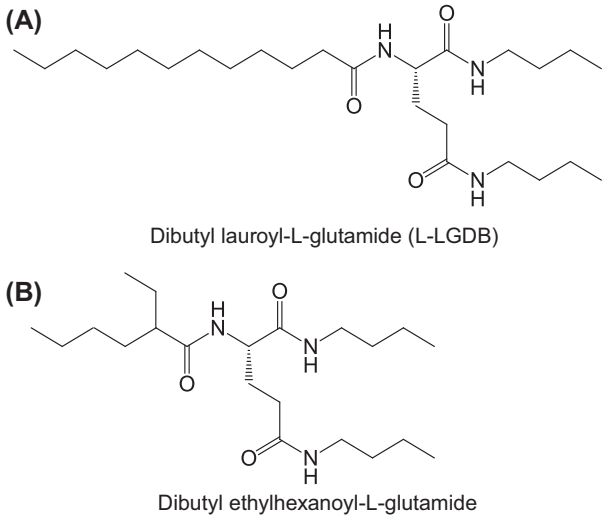



FIGURE 19.15 **Low-molecular-mass oil gelators derived from glutamic acid. (A) Dibutyl lauroyl-L-glutamide (B) dibutyl ethylhexanoyl-L-glutamide.**

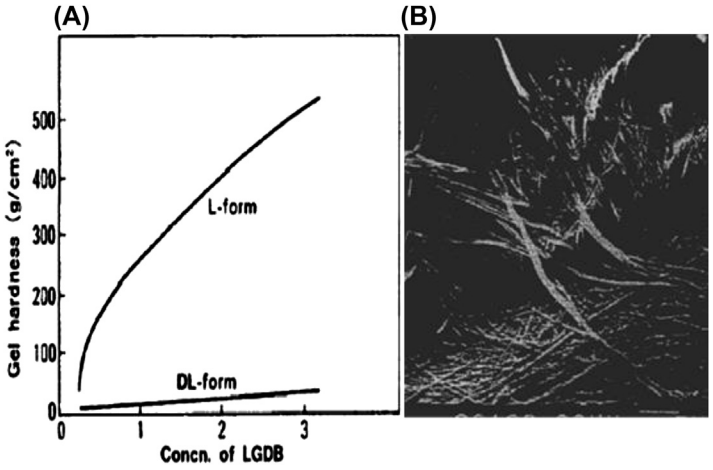



FIGURE 19.16 **Gel formation by LGDB (A) gel hardness of L- or DL-LGBD in tridecane (B) SEM photograph of fibril structures for the L-LGBD gel.**

words, must have an asymmetric structure. Second, the molecule must bear donors and acceptors to form intermolecular hydrogen bonds through the optically active center so that the resulting hydrogen bonding expands the asymmetric geometry to the assembled molecules. The third requirement is that the molecule should be amphiphilic so that the molecule has the affinity to accommodate the organic molecule to be gelatinized.

Since then there have been many reports that lipoamino acids form fibril structures to turn oil into gel. Extensive research reported by Hanabusa et al. shows a wide variety of potential molecules in this regard.[101–104] The nature of the fibers is a chiral self-assembly of amphiphilic molecules. The fibers, in sizes sometimes only visible by a transmission electron microscope, form a three-dimensional network within the media to turn it into a gel. Materials that show such properties are called low molecular-mass oil gelators (LMOGs) and have recently gained a lot of attention both from academics and from industries.[105]

In the 1970s the development of a gelling agent for the remediation of spilled oils based on LGDB was conducted and the product was endorsed by the Japanese Marine Conservation Agent as one of the systems equipped to ships. In reality, there were not many actual applications reported afterwards, possibly because the cost of the agent was not competitive to other methods for the cleaning up of spilled oil.[100] As a final application to cosmetics, not only LGBD but another type of LMOG derived from glutamic acid was introduced as a cosmetic ingredient.[106] Its chemical structure is shown in Fig. 19.15B. The amide groups on the molecules are involved in first-order fiber formation via hydrogen bonding, and chirality of the glutamate structure is critical to performance as gelators as shown in Fig. 19.16. The fiber aggregates can form very hard gels suitable for stick-type of applications such as lipsticks or antiperspirant sticks in which traditionally waxes have been used as a structurant. Thanks to the size of the structures that these gelators form, appearance and sensorial properties of the final products are quite different from the ones with waxes; the stick can be crystal clear and provide a melting touch on the skin.

## 19.5 PEPTIDES IN COSMETICS

When more than two amino acids are covalently bound and not considered to be proteins, they are called peptides. In cosmetics, the term "peptide" often implies that it is synthetically prepared from amino acids or other small molecule materials that are physiologically active. In other words, they are expected to act as cosmeceutical ingredients. Due to increasing demand for cosmetics with convincing skin care effects and advances in peptide synthesis technology, the number of new peptides for personal care use has been dramatically increasing in the last decade.[107–111] Many of them claim antiaging effects; they often target dermal matrix protein collagen or elastin via various physiological pathways. Gorouhi and Maibach in 2008 did comprehensive research as seen through studies and reports on peptides in topical use for antiaging[112] and classified them into four categories: signal peptides, enzyme inhibitor peptides, neurotransmitter inhibitor peptides, and carrier peptides. Popular claims for peptides that act in the epidermis are antioxidant,[113] UV protection, and cellular regulation, and there are some more peptides that aim at specific areas such as hair restoration or antimicrobial properties.[114] Typical functional peptides are summarized by Takeoka[107] as shown in Table 19.3.

**TABLE 19.3** Functional Peptides as Cosmetic Ingredients, Classes and Applications[107]

| INCI Name | Number of Amino Acids | Sequence | Target Organ | Function |
|---|---|---|---|---|
| Hexanoyl dipeptide-3 Norleucine acetate | 2 | RA | Stratum corneum (SC) | Moisturization |
| Glycyl Glycine | 2 | GG | Stratum corneum | Moisturization |
| Alanyl Glutamine | 2 | AQ | Stratum corneum | Moisturization |
| Poly(Tripeptide-6) | – | (PHypG)n | Epidermis (ED) | Antiaging |
| Hexacarboxymethyl Dipeptide-12 | 2 | KK | SC & ED | Moisturization/Metabolic stimulation |
| Glycyl Tyrosine | 2 | GY | Epidermis | Antiaging/UV protection |
| Acetyl Dipeptide-3 Aminohexanoate | 2 | RAhxA | Epidermis | Antimicrobial |
| Carnosine | 2 | AH | Epidermis | Antioxidation |
| Dimer Tripeptide-43 | 3 | DCR | Epidermis | Antioxidation/Antiaging |
| Tripeptide-3 | 3 | RGS | Epidermis | Cytotonic |
| Acetyl Tetrapeptide-11 | 4 | PPYL | Epidermis | Antiaging |
| Acetyl Tetrapeptide-15 | 4 | YPFF | Epidermis | Antiirritation |
| Acetyl Tetrapeptide-2 | 4 | KDVY | Epidermis | Antiinflamation/Antiaging |
| Acetyl Tetrapeptide-22 | 4 | HLLR | Epidermis | Moisturization |
| Tetrapeptide-26 | 4 | SPLQ | Epidermis | UV protection/Metabolic stimulation |
| Pentapeptide-31 | 5 | REMN | Epidermis | Stem cell |
| Acetyl Hexapeptide-1 | 6 | LAHFRW | Epidermis | Antiinflamation/UV protection |
| Acetyl Hexapeptide-37 | 6 | SPAGGP | Epidermis | Moisturization |
| Acetyl Hexapeptide-49 | 6 | FFFHV | Epidermis | Antiinflamation/UV protection |
| Hexapeptide-42 | 6 | IQACRG | Epidermis | Moisturization/UV protection |
| Hexapepitde-2 | 6 | HWAWFK | Epidermis | Moisturization |
| Acetyl sh-Heptapeptide-1 | 7 | DEETGEF | Epidermis | Antioxidation/UV protection |
| Nonapepitde-1 | 9 | HWAWFK | Epidermis | Antimelanogenesis |
| Decapepitde-4 | 10 | CDLRRLEMYC | Epidermis | Stemcell |
| Oligopeptide-20 | 12 | RRLEMYCAPLKP | Epidermis | Metabolic stimulation |
| Oligopeptide-34 | 12 | ISLDTQYGGRGD | Epidermis | Antimelanogenesis/ Antiinflammation |
| Oligopeptide-24 | 13 | CMYIEGGGGRGDG | Epidermis | Metabolic stimullation/ Antiaging |
| Oligopeptide-6 | 15 | RDFTKATNIRLRFLR | Epidermis | Antiaging |
| Diaminopropionoyl Tripeptide-33 | 3 | APH | ED & dermis | Antioxydation/UV protection |
| Hexapeptide-33 | 6 | SFKLRY | ED & dermis | Antiaging/Regeneration |
| Hexapeptide-10 | 6 | SIKVAV | Basement membrane | Antiaging |
| Palmitoyl Dipeptide-5 Diaminobutyroyl Hydroxythreonine | 2 | KVDabT KVDab | Basement membrane | Antiaging |
| Caprooyl tetrapeptide-3 | 4 | KGHK | BM & dermis | Antiaging/Regeneration |
| Decarboxy Carnosine HCL | 2 | AH | Dermis | Antiaging/Antiglycation |

*Continued*

**TABLE 19.3** Functional Peptides as Cosmetic Ingredients, Classes and Applications[107]—cont'd

| INCI Name | Number of Amino Acids | Sequence | Target Organ | Function |
|---|---|---|---|---|
| Tripeptide-29 | 3 | GPHyp | Dermis | Antiaging |
| Dipepitded-8 | 2 | AHyp | Dermis | Antiaging |
| Dipeptide-4 | 2 | CG | Dermis | Antioxidation/UV protection |
| Acetyl dipeptide-1 Cetylester | 2 | YR | Dermis | Antiiritation/Antiaging |
| Acetyl Tripeptide-30Citrulline | 3 | RHH | Dermis | Antiaging |
| Trifluoroacetyl Tripeptide-2 | 3 | VYV | Dermis | Antiaging |
| Tetradecyl Aminobutyroylvalylaminobutyric Urea Trifluoroacetate | 3 | DabVDab | Dermis | Antiaging |
| Tripeptide-1 | 3 | GHK | Dermis | Antiaging |
| Tripeptide-1 | 3 | GHK | Dermis | Antiaging |
| Tripeptide-10 citrulline | 3 | KDI | Dermis | Antiaging |
| Palmitoyl tripeptide-1 | 3 | GHK | Dermis | Antiaging |
| Palmitoyl Tripeptide-38 | 3 | KMO2K | Dermis | Antiaging |
| Palmitoyl Tripeptide-5 | 3 | RFK | Dermis | Antiaging |
| Acetylarginyltryptophyl Diphenylglycine | 4 | RPhgWPhg | Dermis | Antiaging |
| Tetrapeptide-1 | 4 | LPTV | Dermis | Antiaging |
| Acetyl Tetrapeptide-9 | 4 | QDVH | Dermis | Antiaging |
| Tetrapeptide-5 | 4 | LEHA | Dermis | Antiaging |
| Palmitoyl Tetrapeptide-7 | 4 | GQPR | Dermis | Antiinlfamation/Antiaging |
| Palmitoyl pentapeptide-4 | 5 | KTTKS | Dermis | Antiaging |
| Palmitoyl Hexapeptide-12 | 6 | VGVAPG | Dermis | Antiaging |
| Hexapeptide-11 | 6 | FVAPFP | Dermis | Antiaging |
| Hexapepitde-3 | 6 | KLDAPT | Dermis | Antiaging |
| Hexapeptide-9 | 6 | GPQGPQ | Dermis | Antiaging |
| Acetyl decapeptide-3 | 10 | YRSRKYYSWY | Dermis | Antiaging |
| Dipeptide Diaminobutyroyl Benzylamide Diacetate | 2 | APDab | Subcutis/Hypodermis | Muscle relaxant |
| Pentapeptide-18 | 5 | YAGFL | Subcutis/Hypodermis | Muscle relaxant |
| Acetyl hexapeptide-8 | 6 | EEMQRR | Subcutis/Hypodermis | Muscle relaxant |
| Acetyl Glutamyl Heptapeptide-1 | 7 | EEMQRRAD | Subcutis/Hypodermis | Muscle relaxant |
| Acetyl Hexapeptide-38 | 6 | SVVVRT | Subcutaneous fat | Lipolysis |
| Decapeptide-2 | 10 | PLDTAKVRLQ | Subcutaneous fat | Lipolysis |
| Dipeptide-2 | 2 | VW | Blood vessels | Antivasoconstrictor |
| Acetyl Tetrapeptide-5 | 4 | AHSH | Blood vessels | Antivasoconstrictor |
| Biotinoyl Tripeptide-1 | 3 | GHK | Hair follicle | Hair growth |
| Acetyl tetrapeptide-3 | 4 | KGHK | Hair follicle | Hair growth Gray hair |
| Octapeptide-2 | 8 | KLKKTETQ | Hair follicle | Hair growth |
| Oligopeptide-74 | 11 | LSSKMYHTKGQ | Hair follicle | Hair growth Gray hair |
| Oligopeptide-41 | 13 | ASAKWTHNGGEMF | Hair follicle | Hair growth |

### 19.5.1 Production of Peptides

Peptides can be prepared either by degradation of proteins or by synthesis from amino acids, and for both ways chemical process and biochemical process are applicable. When peptides are produced by degradation of proteins, they are called "hydrolyzed proteins" and not peptides.

Protein hydrolysis achieved by boiling in acid or base leads to random breakdown into peptides or amino acids, whereas the enzymatic approach breaks specific amide bonds. Fluctuation in quality of the original protein and high risk of microorganism contamination are always troublesome when dealing with natural materials.

Preparing target peptides chemically by connecting amino acids in the proper sequence is a time-consuming, complicated process. Solid-phase synthesis became the standard for preparation of relatively small size peptides in the lab, but this is not quite suitable for commercial production. Most of the peptides that are introduced into market are produced by biochemical process using bioengineering.

Peptides in some cases further undergo chemical modification in order to improve transdermal absorption or distribution to the target area within the skin. An approach is the use of fatty acid derivatives to increase the lipophilic property of the peptide. For example, the palmitoyl derivative of the polypeptide interferon penetrates across human skin five- to sixfold greater than the simple peptide.[115] The caprooyl derivative of tetrapeptide-3 shows good skin permeability[116] whereas the acetyl derivative of the same peptide was proven to accumulate within follicles.[117]

## 19.6 PROTEINS IN COSMETICS

Proteins themselves are barely used in cosmetic applications due to their cost and handling; most native proteins have relatively low solubility in water and there is a fear of skin sensitization potential. Hydrolyzed proteins are used instead; despite this confusing nomenclature they are usually broken down to peptides having a few amino acid residues, and often contain free amino acids to some extent. They no longer retain their original functions as biopolymers, but they still provide some benefits based on the characteristic amino acid residues. In addition, skin sensitization potential is diminished if they are properly cleaved. Hydrolyzed collagen and hydrolyzed keratin used to be the most popular, but these were "banned from market" after an outbreak of BSE in the 1990s. Since then various hydrolyzed proteins of vegetable origin, silk protein, and collagen from maritime creatures have been introduced instead.

Amino acid homopolymers, both of natural origin or chemically synthesized, are also known. γ-Polyglutamic acid (γ-PGA) is a natural polymer, a component of the mucilage of the fermented soy bean food "Natto."[118] Some species of *Bacillus* including *Bacillus natto* secrete γ-PGA as a by-product during fermentation. This polymer is classified as a film-forming agent; it forms a smooth and soft film on the skin and provides hydration and protection of the skin. Polyaspartic acid on the other hand is prepared synthetically as a mixture of α- and γ-condensate.[119,120] Polymerization degree of the grade available as a cosmetic ingredient now falls within the range of a peptide. As a cosmetic ingredient, sodium polyaspartate provides excellent moisturizing and conditioning effects for skin and hair, and additionally it shows a pigment-dispersing property in an aqueous media, which could be useful as the variety of dispersants applicable for aqueous applications is limited. ε-Polylysine is produced by fermentation and was used as a preservative in food[121,122] in Japan for almost 30 years, but in the database of the Personal Care Product Council in the United States it is listed as a film former and a conditioning agent.

## 19.7 CONCLUSIONS

This chapter has attempted to provide an overview of amino acids, peptides, and proteins in cosmetics with emphasis on their roles in skin and uses in personal care applications. One of the major considerations in the personal care field is biocompatibility and environmental compatibility of ingredients. On the other hand there is a great demand from aging populations for products with real efficacies. Amino acids and peptides will likely be a focus of extensive studies from both points of view, with their positions as biomaterials and potential as still-underexplored fields. In the future we could expect certain development of green chemicals based on amino acids, peptides, and proteins that fulfill the functions mentioned herein, with accompanying economic feasibility while addressing increasing concerns of environmental friendliness and sustainability.

## References


1. Greenstein JP, Winitz M. In: *Chemistry of the amino acids*, vol. 1. New York: John Wiley & Sons, Inc.; 1961 [Chapter 1].
2. Ollivaux C, Soyez D, Toullec J. Biogenesis of D-amino acid containing peptides/proteins: where, when and how? *J Peptide Sci* 2014;**20**: 595–612.
3. Ritz-Timme S, Laumeier I, Collins MJ. Aspartic acid racemization: evidence for marked longevity of elastin in human skin. *Br J Dermatol* 2003; **149**:951–9.
4. Hamase K, Konno R, Morikawa A, Zaitsu K. Sensitive determination of D-amino acids in mammals and the effect of D-amino-acid oxidase activity on their amounts. *Biol Pharm Bull* 2005;**28**:1578–84.
5. Ashida Y, Tojo Y, Shimada S, Okamura C, Mita M, Hamase K. Presence of free of D-amino acids in the skin and their physiological functions. *Bio Industry* 2011;**28**:40–4 [in Japanese].
6. Yamauchi M, Sricholpech M. Lysine post-translational modifications of collagen. *Essays Biochem* 2012;**52**:113–33.
7. Steinert PM, et al. Amino acid sequences of mouse and human epidermal Type II keratins of M, 67,000 provide a systematic basis for the structural and functional diversity of the end domains of keratin intermediate filament subunits. *J Biol Chem* 1985;**260**:7142–9.
8. Asakura T, Ito T, Okudaira M, Kameda T. Structure of alanine and glycine residues of *Samia cynthia* ricini silk fibers studied with solid-state $^{15}N$ and $^{13}C$ NMR. *Macromolecules* 1999;**32**:4940–6.
9. Mieda1 S, Aida M. Dipole moments of amino acid residues, gly and ala, in α-helix: quantum chemical building blocks for macrodipole moment of α-helical polypeptide. *Chem Lett* 2012;**41**:1579–80.
10. Ferraro V, Antona M, Santé-Lhoutellier V. The "sisters" α-helices of collagen, elastin and keratin recovered from animal by-products: functionality, bioactivity and trends of application. *Trends Food Sci Tech* 2016;**51**:65–75. and references therein.
11. Morita A. Skin aging and environmental factors. *Nippon Koshohin Gakkaishi* 2013;**37**:6–10 [in Japanese].
12. Steinert PM, Steven AC, Roop DR. The molecular biology of intermediate filaments. *Cell* 1985;**42**:411–9.
13. Marshall RC, Orwin DFG, Gillespie JM. Structure and biochemistry of mammalian hard keratin. *Electron Microsc Rev* 1991;**4**:47–83.
14. Yu J, Yu D, Checkla DM, Freedberg IM, Bertolino AP. Human hair keratins. *J Invest Dermatol* 1993;**101**:56S–9S.
15. Iwai I, Ikuta K, Murayama K, Hirao T. Change in optical properties of stratum corneum induced by protein carbonylation in vitro. *Int J Cosmet Sci* 2008;**30**:41–6.
16. Kawabata K. The glycation of cytokeratin in the epidermis. *Amino Acid Res* 2014;**8**:109–16 [in Japanese].
17. Sandilands A, Sutherland C, Irvine AD, McLean WHI. Filaggrin in the frontline: role in skin barrier function and disease. *J Cell Sci* 2009;**122**: 1285–94.
18. Steinert PM, Cantieri JS, Teller DC, Londale-Eccles JD, Dale BA. Characterization of a class of cationic proteins that specifically interact with intermediate filaments. *Proc Nat Acad Sci USA* 1981;**78**:4097–101.
19. a. Jacobi OK. About the mechanism of moisture regulation in the horny layer of the skin. *Proc Sci Sect Toilet Goods Assoc* 1959;**31**:22–4;
    b. Laden K, Spitzer R. Identification of a natural moisturizing agent in skin. *J Soc Cosmet Chem* 1967;**18**:351–60;
    c. Sakamoto K. The development of two new moisturizing ingredients. *Cosmet Toilet* 1984;**99**:109–17.
20. Wu G, et al. Proline and hydroxyproline metabolism: implications for animal and human nutrition. *Amino Acids* 2011;**40**:1053–63.
21. Ottania V, Martinia D, Franchia M, Ruggeria A, Raspantib M. Hierarchical structures in fibrillar collagens. *Micron* 2002;**33**:587–96.
22. Igarashi T, Nishino K, Nayar SK. *The appearance of human skin*. Department of Computer Science, Columbia University; 2005. Technical Report: CUCS-024–05.
23. Fisher GJ, et al. Molecular basis of sun-induced premature skin ageing and retinoid antagonism. *Nature* 1996;**379**:335–9.
24. Chung JH, et al. Modulation of skin collagen metabolism in aged and photoaged human skin *in vivo*. *J Invest Dermatol* 2001;**117**:1218–24.
25. Dyer DG, et al. Accumulation of maillard reaction products in skin collagen in diabetes and aging. *J Clin Invest* 1993;**91**:2463–9.
26. Jeanmarie C, Danoux L, Pauly G. Glycation during human dermal intrinsic and actinic ageing: an in vivo and in vitro model study. *Br J Dermatology* 2001;**145**:10–8.
27. Mithieux SM, Weiss AS. Elastin. *Adv Protein Chem* 2005;**70**:437–61.
28. Campbell E, Pierce J, Endicott S, Shapiro S. Evaluation of extracellular matrix turnover. Methods and results for normal human lung parenchymal elastin. *Chest* 1991;**99**:49S.
29. Sherratt MJ. Tissue elasticity and the ageing elastic fibre. *Age* 2009;**31**:305–25. and references therein.
30. Tzaphlidou M. The role of collagen and elastin in aged skin: an image processing approach. *Micron* 2004;**35**:173–7.
31. a. Spier HW, Pascher G. The water-soluble components of the peripheral horny layer of the skin (skin surface); quantitative analyses. II. Nitrogen-free acids and bases; water-soluble total sulfur. *Arch Klin Exp Dermatol* 1955;**201**:181–92 [in German];
    b. Spier HW, Pascher G. Zur analytischen und funktionellen Physiologie der Hautoberflache [For analytical and functional physiology of the skin surface]. *Hautarzt* 1956;**7**:55–60.
32. Scott IR, Harding CR, Barrett JG. Histidine-rich protein of the keratohyalin granules. Source of the free amino acids, urocanic acid and pyrrolidone carboxylic acid in the stratum corneum. *Biochem Biophys Acta* 1982;**719**:110–7.
33. Horii I, et al. Histidine-rich protein as a possible origin of free amino acids of stratum corneum. *J Dermatol* 1983;**10**:25–33.
34. Wolfersberger MG, Tabachnick J. Enzymatic formation of L-pyrrolidone carboxylic acid in mammalian epidermis and other tissues. *J Invest Dermatol* 1974;**62**:587–90.
35. Barrett JG, Scott IR. Pyrrolidone carboxylic acid synthesis in guineapig epidermis. *J Invest Dermatol* 1983;**81**:122–4.
36. Koyama J, Morikawa Y, Matsumoto I. Studies on free amino acids in human stratum corneum of epidermis. *J Soc Cosmet Chem Jpn* 1981;**15**: 45–53 [in Japanese].
37. Horii I, et al. *J Soc Cosmet Chem Jpn* 1980;**14**:172 [in Japanese].
38. Koyama J, Horii I, Kawasaki K, Nakayama Y, Morikawa Y, Mitsui T. Free amino acids of stratum corneum as a biochemical marker to evaluate dry skin. *J Soc Cosmet Chem* 1984;**35**:183–95 [in Japanese].
39. Baden HP, Pathak MA. The metabolism and function of urocanic acid in skin. *J Invest Dermatol* 1967;**48**:11–7.
40. Scott IR. Factors cotrolling the expressed activity of histidine ammonia-lyase in the epidermis and the resulting accumulation of urocanic acid. *Biochem J* 1981;**194**:829–38.

41. Horikoshi S, Sato T, Sakamoto K, Abe M, Serpone N. Microwave discharge electrodeless lamps (MDEL). Part VII. Photo-isomerization of trans-urocanic acid in aqueous media driven by UV light from a novel Hg-free Dewar-like microwave discharge thermally-insulated electrodeless lamp (MDTIEL). Performance evaluation. *Photochem Photobiol Sci* 2011;**10**:1239–48.
42. Norval M, Simpson TJ, Ross JA. Urocanic acid and immunosuppression. *Photochem Photobiol* 1989;**50**:267–75.
43. Yamashita Y, Sakamoto K. Role of urocanic acid in the stratum corneum. In: Sakamoto K, editor. *Amino acid and peptide in the forefront of cosmetic ingredients*. Tokyo, Japan: CMC Research K.K.; 2015. p. 260–72 [Chapter 25].
44. Aruoma OI, Laughton MJ, Halliwell B. Carnosine, homocarnosine and anserine: could they act as antioxidants in vivo? *Biochem J* 1989;**264**: 863–9.
45. Klebanov GI, et al. Effect of carnosine and its components on free-radical reactions. *Membrane Cell Biol* 1998;**12**:89–99.
46. Babizhayev MA, et al. L-carnosine (β-alanyl-L-histidine) and carcinine (β -alanylhistamine) act as natural antioxidants with hydroxyl-radical-scavenging and lipid-peroxidase activities. *Biochem J* 1994;**304**:509–16.
47. Meister A. Glutathione-ascorbic acid antioxidant system in animals. *J Biol Chem* 1994;**269**:9397–400.
48. Pompella A, Visvikis A, Paolicchi A, Tata V, Casini AF. The changing faces of glutathione, a cellular protagonist. *Biochem Pharmacol* 2003;**66**: 1499–503.
49. Takehara M. Recent applications of amino acids for cosmetics: interactions and synergistic effects of amino acids. *Cosmet Toiletries* 1983;**98**: 51–6.
50. Robinson M, Visscher M, Laruffa A, Wickett R. Natural moisturizing factors (NMF) in the stratum corneum (SC). I. Effects of lipid extraction and soaking. *J Cosmet Sci* 2010;**61**:13–22.
51. Robinson M, Visscher M, Laruffa A, Wickett R. Natural moisturizing factors (NMF) in the stratum corneum (SC). II. Regeneration of NMF over time after soaking. *J Cosmet Sci* 2010;**61**:23–9.
52. Oota R, Oshimura E. Changes in contents of PCA and moisture in the *Stratum corenum* induced by cleansing: effects of moisturizer incorporated in cleansing preparations. In: *Poster presentation at 9th Asian society of cosmetic society conference Yokohama*; 2009.
53. Oshimura E. Approach for optimized mild cleansing - development and applications of natural mild cleansing surfactants -. *J Soc Cosmet Chem Jpn* 2012;**46**:183–7 [in Japanese].
54. Oshimura E, Ino M. Effects of arginine on hair damage via oxidative coloring process. *J Cosmet Sci* 2004;**55**:S155–70.
55. Adams MR, Vien Phu C, Stocker R, Celermajer DS. Lack if antioxidant activity of the antiathrogenic compound L-arginine. *Atherosclerosis* 1999;**146**:329–55.
56. Farag RS, Osman SA, Hallabo S, Girgis AN, Nasr AA. Linoleic acid oxidation catalyzed by various amin S. A. o acids and cupric ions in freeze-dried model systems. *J Am Oil Chem Soc* 1978;**55**:708–10.
57. Chen ZY, Nawar WW. The role of amino acids in the autoxidation of milk fat,. *J Am Oil Chem Soc* 1991;**68**:47–50.
58. Martinez-Tome M, Garcia-Carmona F, Antonia Muricia M. Comparison of the antioxidant and pro-oxidant activities of broccoli amino acids with those of common food additives. *J Sci Food Agric* 2001;**81**:1019–26.
59. Ishitsuka Y. Protection of UV-irradiated human skin. *Finechemical* 2002;**31**:45–53 [in Japanese].
60. Alia P, Saradhi P, Mohanty P. Involvement of proline in protecting thylakoid membranes against free radical-induced photodamage. *J Photochem Photobiol B* 1997;**38**:253–7.
61. Kitazawa M, Iwasaki K. Functional cosmetic ingredients derived from amino acid. In: Sakamoto K, editor. *Amino acid and peptide in the forefront of cosmetic ingredients*. Tokyo, Japan: CMC Research K.K.; 2015. p. 286–96 [Chapter 7].
62. Solano F. Melanins: skin pigments and much more—types, structural models, biological functions, and formation routes. *New J Sci* 2014:1–28, 498276.
63. Iwasaki A. Cysteine waving lotions, past improvements and future prospects in the Japanese market. *Cosmet Toiletries* 1985;**109**:69–78.
64. Edman WW, Klemm EJ. Permanet wave review. *Cosmet Toiletries* 1985;**100**:23–9.
65. Oshimura E, Abe H, Oota R. Hair and amino acids: the interactions and the effects. *J Cosmet Sci* 2007;**58**:347–57.
66. Arai M, Suzuki T, Kaneko Y, Miyake M, Nishikawa N. Properties of aggregates of amide guanidine type cationic surfactant with 1-hexadecanol adsorbed on hair. *Proc Int Conf Colloid Surface Sci* 2001:1005–8.
67. Xia J, Nnanna IA, Sakamoto K. Amino acid surfactants: chemistry, synthesis, and properties. In: Xia J, editor. *Protein-based surfactants: synthesis: physicochemical properties, and applications, surfactant science series*. 1st ed., vol. 101. New York (USA): Marcel Dekker Inc.; 2001. p. 75–122 [Chapter 4].
68. Bondi S. Lipoproteins and the significance of cellular fatty degeneration. II. Lipopeptides: lauryl glycine and lauryl alanine. *Z Biochem* 1909; **17**:543–52.
69. Nagai S. Enzymatic hydrolysis of N-palmitoyl-amino acids by *Mycobacterium avium*. *J Biochem* 1961;**50**:428–33.
70. Wheatley VR, Flesch P, Jackson E, Elizabeth C, Coon WM, Mandol L. Chemical composition of the horny layer lipids. *J Invest Dermatol* 1964; **43**:395–406.
71. Ham P, Wheatley VR. Horny-layer lipids. III. Hydrolysis studies, before and after chromatography, of the polar (hexane-insoluble) lipids from stratum corneum. *J Invest Dermatol* 1967;**49**:206–13.
72. Takehara M, Yoshimura I, Takizawa K, Yoshida R. Surface-active N-acylglutamate. I. Preparation of long-chain N-acylglutamic acid. *J Amer Oil Chem Soc* 1972;**49**:157–61.
73. Takehara M, Moriyuki H, Yoshimura I, Yoshida R. Surface-active N-acylglutamate. II. Physicochemical properties of long-chain N-acylglutamic acids and their sodium salts. *J Amer Oil Chem Soc* 1972;**49**:143–50.
74. Takehara M, Moriyuki H, Arakawa A, Yoshimura I, Yoshida R. Surface-active N-acylglutamate. III. Physicochemical properties of sodium long chain N-acylglutamates. *J Amer Oil Chem Soc* 1973;**50**:227–9.
75. Takehara M, Yoshimura I, Yoshida R. Surface-active N-acylglutamate. IV. Physicochemical properties of triethanoleamine long chain N-acylglutamates. *J Amer Oil Chem Soc* 1974;**50**:227–9.
76. Takehara M, Yoshida R. Acylglutamate- a new surfactant for cosmetics and toiletries. *Cosmet Toiletries* 1979;**94**:31–9.
77. Yoshida R, Takehara M, Shibue A, Usuba Y. The development of new surfactant N-acylglutamate. *Yukagaku* 1977;**26**:1–7.
78. Nakayama H, Ooshiro A, Yoshimura I, Harada R, Miyashiro M. The safety evaluation tests and the clinical evaluation of acylglutamate. *Fragrance J* 1977;**5**:15–26.

79. Saito T. Low irritation soaps in Japan. *Cosmet Toiletries* 1983;**98**:111–3.
80. Kanari M, Kawasaki Y, Sakamoto K. Acylglutaate as an anti-irritant for mild detergent system. *J Soc Cosmet Chem Jpn* 1993;**27**:498–505.
81. Thau P. Surfactant for skin cleansers. In: Rieger M, Rhein LD, editors. *Surfactants in cosmetics, surfactant science series*. 2nd ed., vol. 68. New York (USA): Marcel Dekker Inc.; 1997. p. 285–306.
82. Shiojiri E, et al. Properties and applications of acylglycinate; a newly developed amino acid based surfactant. *J Soc Cosmet Chem Jpn* 1996;**30**: 410–9.
83. Mikami N, Oota R. An amino acid based surfactant targeting shampoo based on a natural concept. *SÖFW-J* 2008;**134**:27–32.
84. Gesslein BW, Oshimura E, Popova K. An all natural moisturizing surfactant with high foaming power. *SÖFW J* 2013;**139**(6). 20, 22–25.
85. Okuda M, Yoshiike T. Correlation between epidermal barrier function and skin cleansing methods. *Nippon Hifuka Gakkai Zasshi* 2000;**110**: 2115–22 [in Japanese].
86. Bechor R, Zlotogorski A, Dikstein S. Effects of soaps and detergents on the pH and casual lipid levels of the skin surface. *J Appl Cosmetol* 1988; **6**:123–8.
87. Korting HC, Kober M, Mueller M, Braun-Falco O. Influence of repeated washings with soap and synthetic detergents on pH and resident flora of the skin of forehead and forearm. *Acta Derm Venereol (Stockholm)* 1987;**67**:41–7.
88. Kaneko D. Properties and applications of amino acid surfactants. In: *Oral presentation at Yukagaku (oil chemistry) autumn seminar*; 1999.
89. Japan Patent No. 854326 *Method of producing $N^{\omega}$-acyl basic amino acids*. 1977.
90. Yokota H, Sagawa K, Eguchi C, Takehara M. New amphoteric surfactants derived from lysine. I. Preparation and properties of Ne-acyllysine derivatives. *J Amer Oil Chem Soc* 1985;**62**:1716–9.
91. Sagawa K, Takehara M, Yokota H. New functional powder derived from amino acid – properties of Amihope® LL and its applications. *Fragrance J* 1986;**14**:71–4.
92. Sagawa K, Takehara M. New cosmetic powder derived from amino acid – properties of Amihope LL and its cosmetic uses -. *Funntai-to-Kogyo* 1987;**19**:1–7 [in Japanese].
93. Sakamoto K, Yoshida R, Hatano M. Liquid crystals composed of N-acylamino acid. Circular dichroism in liquid crystals composed of N-lauroyl-L-glutamic acid and aromatic solvents. *Chem Letters* 1976:1401–4.
94. Yoshida R, Takehara M, Sakamoto K. Surfactants derived from amino acids I. Critical micelle concentrations of the salts of optically active and racemic N-acylamino acids. *J Oil Chem Jpn (Yukagaku)* 1975;**24**(8):538–41 [in Japanese].
95. Sakamoto K, Hatano M. Formation of chiral aggregation of acylamino acids in solutions. *Bull Chem Soc Jpn* 1976;**53**:3399–4343.
96. Sakamoto K. Self organization of amino acid based chiral surfactants: evaluation of organized structures and interaction with biological system. *J Oleo Sci* 2005;**5**(12):573–87.
97. Sakamoto K, Yoshida R, Hatano M, Tachibana T. Liquid crystals composed of N-acylamino acid. I. Circular dichroism and selective light transmission in cholesteric liquid crystals composed of N-acylamino acids and organic solvents. *J Soc* 1978;**100**(22):6898–902.
98. Sakamoto K. Liquid crystals composed of N-acylamino acid. II. Influence of crystalline structure of N-acyl-L-glutamic acid on the formation of liquid crystals. *Mol Cryst Cryst* 1980;**59**:59–72.
99. Saito T, Matsuzawa Y, Ninagawa S, Honna M, Takesada M, Takehara M. *Gels of nonpolar liquids with N-acyl amino acids and their derivatives as gelling agents*. Japan Patent No.934597. 1978.
100. Sakamoto K. Development of gelling agent for spilled oils. In: Somasunraran P, et al., editors. *Oil spill remediation: colloid chemistry-based principles and solutions: Wiley series on surface and interfacial chemistry*. NY: Wiley; 2014. p. 231–45. ISBN:1118206703.
101. Hanabusa K, Tange J, Taguchi Y, Koyama T, Shirai H. Small molecular gelling agents to harden organic liquids. *J Chem Soc Chem Commun* 1993;**15**:390–2.
102. Hanabusa K, Hiratsuka K, Shirai H. Easy preparation and useful character of organogel electrolytes based on low molecular weight gelator. *Chem Mater* 1999;**11**:649–55.
103. Okabe S, Hanabusa K, Shibayama M. Gelation mechanism and microstructure of organogels formed with various types of gelators. *Polym Sci Part B: Polm Phys* 2005;**43**:3567–74.
104. Suzuki M, Sato T, Shirai H, Hanabusa K. Powerful low-molecular-weight gelators based on L-valine and L-isoleucine with various terminal groups. *New J Chem* 2006;**8**:1184–91.
105. Hanabusa K, Suzuki M. Development of low-molecular-weight gelators and polymer-based gelators. *Polymer J* 2014;**46**:776–82.
106. Saito K, Sugimoto T, Yamato N. Characteristics of novel oil gelling agents derived from amino acid and their applications to cosmetics. *Fragrance J* 2009;**35**:60–5 [in Japanese].
107. Takeoka A. Peptides as cosmetic ingredients, classes and applications. In: Sakamoto K, editor. *Amino acid and peptide in the forefront of cosmetic ingredients*. Tokyo (Japan): CMC Research K.K.; 2015. p. 16–33 [Chapter 2].
108. Blanes-Mira C, Clemente J, Jodas G, Gil A, Fernandez-Ballester G, Ponsati B, et al. A synthetic hexapeptide (argireline) with antiwrinkle activity. *Int J Cosmet Sci* 2002;**24**:303–10.
109. Pauly G, et al. Small proteoglycans in the skin: new targets in the fight against aging. *IFSCC Magazine* 2008;**11**:21–9.
110. Puig A, Anton JMG, Mangues M. A newdecorin-like tetrapeptide for optimal organization of collagen fibres. *Int J Cosmet Sci* 2008;**30**:97–104.
111. Watson RE, Long SP, Bowden JJ, Bastrilles JY, Barton SP, Griffiths CE. Repair of photoaged dermal matrix by topical application of a cosmetic'antiageing' product. *Br J Dermatol* 2008;**158**:472–7.
112. Gorouhi F, Maibach HI. Role of topical peptides in preventing or treating aged skin. *Int J Cosmet Chem* 2009;**31**:327–45.
113. Kobayashi K, et al. Direct assessments of the antioxidant effects of the novel collagen peptide on reactive oxygen species using electron spin resonance spectroscopy. *J Pharm Sci* 2011;**116**:97–106.
114. Rahnamaeian M, Vilcinskas A. Short antimicrobial peptides as cosmetic ingredients to deter dermatological pathogens. *Appl Microbiol Biotechnology* 2015;**99**:8847–55.
115. Foldvari M, et al. Palmitoyl derivatives of interferon alpha: potential for cutaneous delivery. *J Pharm Sci* 1998;**87**:1203–8.
116. Lucas Meyer Cosmetics. *ChroNOlineTM A biometric lipopeptide that boots the production of key components at the DEJ for maximal fine lines and wrinkles reduction. Claim substantiation sheet*. 2012.
117. Lucas Meyer Cosmetics. CAPIXYL™ anti-aging hair care complex, biomimetic peptide combined with a red clover extract - for stronger and thicker hair and lashes active ingredients technical file.

118. Ben-Zur N, Goldman DM. γ-Poly glutamic acid: a novel peptide for skin care. *Cosmet Toiletries* 2007;**122**:65–74.
119. Wolk SK, et al. One- and two-dimensional nuclear magnetic resonance characterization of poly(aspartic acid) prepared by thermal polymerization of L-aspartic acid. *Macromolecules* 1994;**27**:7613–20.
120. Abe H, Sakamoto K. Development of salt of poly (aspartic acid). *Fragrance J* 1996;**24**:47–52.
121. Nishihara T, et al. Antimicrobial activity of positive colloids against food-poisoning bacteria. *Bokin Bobai* 1992;**20**:241–5.
122. Fukushi H. Antimicrobial mechanism of polylysine and development of various polylysine preparations as food additives. *Shokuhin Kogyo* 2002;**45**:27–34.

## Review Articles Relating to the Chapter

1. Takehara M. Recent development of amino acids for cosmetics: interactions and synergestic effects of amino acids. *Cosmet Toiletries* 1983;**98**(7): 51–6.
2. Sakamoto K. Amino acids and derivatives cosmeceuticals and active cosmetics [Chapter 15]. In: Howard I, Maibach HI, et al., editors. *Cosmeceuticals and active cosmetics*. 3rd ed. CRC Press; 2015. p. 165–78. ISBN-10:1482214164, ISBN-13:978-1482214161.
3. Sakamoto K. Lessons from nature for development of amino acids and related functional materials for cosmetic applications. *IFSCC Magazine* 2013;**2**:79–85.
4. Takehara M. Properties and applications of amino acid based surfactants. *Colloids Surf* 1989;**38**:149–67.
5. Sakamoto K. Current market development and trend in amino acid and protein based surfactants. In: Xia J, editor. *Protein-based surfactants: synthesis: physicochemical properties, and applications, surfactant science series*. 1st ed., vol. 101. New York (USA): Marcel Dekker Inc.; 2001. p. 75–122 [Chapter 4].

CHAPTER

# 20

# Botanical Ingredients

*O. Ifuku*

**Maruzen Pharmaceuticals Co., Ltd., Fukuyama, Hiroshima, Japan**

## 20.1 INTRODUCTION

A wide variety of botanical ingredients are used in cosmetics, and their application is increasing year over year. Botanical substances have different characteristics like the following when compared to synthetic ingredients or other natural ingredients such as animal-derived ingredients and mineral ingredients: (1) The image of the products is positive since they are natural ingredients; (2) In general, there is a public perception that botanical ingredients are safe and are environmentally friendly due to their biodegradability and renewability; (3) Their effect is usually mild and sustained; and (4) When the ingredients are not used as single components, the subcomponents often help slightly soluble components to become easily soluble.

Botanical substances are used for various purposes in cosmetics, but they are mainly used for their effectiveness and have expanded remarkably in recent years. However, botanical ingredients are also frequently used as base materials to meet trends such as nonadditive cosmetics. When botanical ingredients are used as base materials, they are usually used as a substitute for synthetic materials with similar effects. For example, botanical oils such as olive oil and jojoba oil are frequently used as a substitute for mineral oils, and dyes of safflower, lithospermum root, or gardenia are often used to substitute for tar-based dyes. Additionally, soy isoflavone, botanical glycerin, and hyaluronate are used as moisturizers to avoid use of petrochemical surfactants and synthetic polymers. Furthermore, rosemary extract and hinokitiol are used as alternatives to synthetic preservatives, and essential oils are used as aromatic substances instead of petroleum-based synthetic aromatic substances.

Plant-derived ingredients do not necessarily mean that they are safe, as they can cause specific plant allergies or rashes. Since the effect is mild, their preservative efficacy may be weaker than synthetic preservatives, and since natural ingredients are not limited to plants, safe ingredients are often found with other natural ingredients like those derived from animals or natural mineral dyes. In this chapter, we will learn the current trends and challenges of botanical ingredient development in cosmetics by understanding characterisrutics of plant-derived substances.

## 20.2 BOTANICAL SUBSTANCES

### 20.2.1 The Diversity of Botanical Substances

Botanical substances are classified into primary metabolites and secondary metabolites. Primary metabolites are substances that are vital to preserve the organism, such as amino acids, sugars, and nucleic acids, and are chemical substances common in each organism in a taxonomic group. On the other hand, secondary metabolites are low-molecular compounds derived from primary metabolites and are not necessarily essential to an organism. The fundamental difference between primary metabolites and secondary metabolites are that secondary metabolites are unique to each organism. Unlike animals, plants do not have the ability to move by themselves, and thus have evolved to produce a plethora of secondary metabolites in order to adapt to their surrounding environment, mainly to provide vital defense functions against organic and inorganic stress. Humans consume primary metabolites of plants as nutrients, but the botanical substances that have been used for medicinal purposes are all secondary metabolites. It is believed that there are a quarter million species of higher plants in the world,[1] and the variety of secondary metabolites is

*Cosmetic Science and Technology: Theoretical Principles and Applications*
http://dx.doi.org/10.1016/B978-0-12-802005-0.00020-3



Copyright © 2017 Elsevier Inc. All rights reserved.

abundant, as well as their chemical structure. There is even a theory that estimates over a million plant-derived secondary metabolites exist in the entire plant kingdom.[2] In other words, the botanical substances that have been used by humans are only a small fraction of these extremely diverse chemicals, and countless possibilities for use still remain.

### 20.2.2 The Characteristics of Botanical Substances as Ingredients

Unless they are purified to isolate a specific substance, botanical ingredients are mostly used as plant extracts or as dried ingredients. In this case, the main characteristic is that the ingredient is a multicomponent system. It is important to specifically define the plant, the part of the plant, and the treatment to assure stable supply of botanical ingredients. Caution is required when using botanical ingredients, since plants sold in the market can differ by region even though they have the same name, and the scientific name sometimes changes as studies in the region progress. Additionally, the individual chemical composition may change depending on the region, season, and/or climate, and the quality may differ even if the originating plants are well managed and the parts are specified. If possible, cultivated plants should be preferred over wild plants in order to control the ingredients under fixed conditions. Moreover, it is important to consider refinement and other treatment methods to remove components that can have a negative effect on the ingredients' safety and stability. Setting quality standards for each material and controlling the quality is a key point in botanical ingredients. Botanical ingredients show a variety of effects due to their unique multicomponent systems. The reason for the botanical ingredient's effect to work mildly and sustained is thought to be from the activity balance between the active component's effect and subcomponent's effect working subcutaneously. In other words, stability of standardized substances, like the active components and subcomponents, is essential. Standardization and unification of the compositions in botanical ingredients remains a vital task in botanical ingredients.

## 20.3 REGULATIONS REGARDING BOTANICAL SUBSTANCES

There are international regulations and documentation such as the Washington Convention and the Red List that are stipulated for protecting rare organisms, and these must be checked when acquiring ingredients. The Convention on Biological Diversity, on the other hand, acknowledges the economic value of organisms. This perspective is an important topic in the cosmetics industry, and in this section we will provide an overview of this convention along with a narrative history.

### 20.3.1 The Convention on Biological Diversity[3]

The Convention on Biological Diversity (CBD) was adopted in 1992 and was one of the international environmental agreements that was signed and opened at the United Nations Conference on Environment and Development (UNCED) held on May 22, 1992 in Rio de Janeiro.[4] This convention came into effect in 1993, and as of 2015, 195 parties excluding the United States have joined as participating countries. The international conference of this convention is called the Conference of Parties (COP) and is held every two years. (COP − CBD). The last conference was the COP12 held in Pyeong Chang (South Korea) in 2014, and the next COP13 is scheduled to be held in Mexico.

The objectives of this convention are: (1) to preserve the diversity of organisms and their habitats on Earth; (2) to use biological resources with sustainability; and (3) to share the profits and benefits of the resources equally and fairly. The third item, access and benefit sharing (ABS), is especially for acknowledging the sovereign rights of the origin countries of natural resources including genetic resources, rather than preserving the common international benefit, and this item is strongly influenced by the hosting country.

To ensure ABS, a voluntary guideline (the Bonn Guideline) was set in the CBD held in 2002 (COP6) as a reference for establishing domestic legislation or documenting contracts.[5] This guideline was set to clarify the standards of "prior informed consent" and "mutually agreed terms." However, the Bonn Guideline was a voluntary guideline and was not obligatory, and has been criticized that it is too weak for properly distributing the benefits and profits gained from genetic resources back to the country of origin. With this criticism, discussion began at the Johannesburg Summit (the World Summit on Sustainable Development) held that year to establish a binding "international regime"). There have been many negotiations since this summit, but there has also been strong conflict between the countries of origin and countries utilizing the genetic resources, or between developing countries and developed countries, and the negotiations have been slow. However, in 2010 this conflict was dramatically resolved politically at the COP10 held in Nagoya, and the Nagoya protocol on Access to Genetic Resources and the Fair and Equitable Sharing of Benefits Arising from their Utilization to the Convention on Biological Diversity was established, which came into effect in

2014.[6] Developed countries must be cautious about the domestic legislations of the genetic resource—providing countries. Currently, it is assumed that the signing countries are setting the rules regarding supply of genetic resources.

Developing countries claimed these five items to be included in the Nagoya protocol: (1) All products derived from the genetic resources should be subject to benefit sharing; (2) Traditional knowledge should be clearly stated as subject to benefit sharing; (3) The ABS rules should have retroactive provision and should be applicable to resources accessed prior to the protocol; (4) Fair and equal access and use of genetic resources should be monitored by the resource utilizing countries; and (5) Protest against the developed countries' request to exclude pathogenic organisms from ABS.

These claims were reflected to the Nagoya protocol as follows: (1) "Derivatives" was not explicitly stated in the items, but the term "utilization of genetic resources" was used and the scope of the protocol was stipulated as the "utilization of genetic resources." (2) A standard for defining "traditional knowledge" was not stipulated, but the handling of traditional knowledge was acknowledged as the same level of genetic resources, including benefit sharing in accordance with domestic legislation. (3) For retroactive provision, the protocol did not acknowledge benefit sharing for resources accessed prior to the protocol. (4) The protocol added an item that at least one checkpoint must be set for the monitoring of utilization of genetic resources, but the checkpoints were not defined. (5) The protocol did not define its scope with pathogenic organisms. In the Nagoya protocol, additional important topics were set, such as efforts in balancing the compliance of the country of origin and country of utilization, and establishing a clearing house regarding access and benefit sharing.

### 20.3.2 Actual Industrial Use and Issues of Genetic Resources

Since the economic situation differs with each industrial field, the utilization of genetic resources and benefit sharing also differs drastically. The cosmetics industry and health food industry are unique in how they require a stable supply of genetic resources in large volumes. Also, unlike the medical drug industry, the value of traditional knowledge tends to have more value. In general, the utilizing company would feel that the benefit sharing is complete if the ingredients are directly bought from the genetic resource's country of origin. However, the distribution channel of genetic resources follows a complex and diverse route from the country of origin and follows many stages, often going through many countries. In this case, an entity to oversee the entire distribution of these various routes is required in order to properly distribute the benefits and access. Furthermore, a stable supply of genetic resources cannot be obtained only from Mother Nature, and cultivation systems must be developed. Development of cultivation systems will create employment in the countries of origin and can be viewed as nonmonetary benefit sharing. Regardless of how the resources are distributed, regulations with countries of origin are expected to become stronger even in the cosmetics industry, so consulting experts on distribution including ethical aspects should be effective for businesses.[7–9]

## 20.4 ORGANIC COSMETICS

### 20.4.1 The "Natural Cosmetics" Trend

"Natural" became a global trend in cosmetics in the 1970s, starting in the United States, where cosmetics with plant-derived ingredients were differentiated and marketed as phytocosmetics or herbal cosmetics, and naturally derived ingredients were largely admired.[10] As an example, some cosmetics during this period used ginseng extract as one of their ingredients.[11] In Japan, luffa cylindrica and hamamelis (witch hazel) were used traditionally and were used as ingredients for skin toners, but in the 1970s, as the first "natural cosmetics" fad began, extracts of herbal ingredients such as aloe, camomile, and glycyrrhiza were added in cosmetics.

### 20.4.2 What is Organic?

After 25 years of studying agriculture in India, Albert Howard was the first person to propose organic agriculture, in his text *An Agricultural Testament* in 1940.[12] Organic agriculture is often confused with "pesticide-free" or "chemical-free," but is a concept of agriculture to preserve biodiversity by nurturing the circulation of resources and by maintaining the balance of the habitat. The US Department of Agriculture's National Organic Program is a reference for organic certification.[13]

### 20.4.3 Green Chemistry

The demand for organic cosmetics and natural cosmetics from consumers has become stronger, and so has the concern for global environmental protection. Sustainability, reducing environmental impact, and effective use of

energy resources has become more and more important, and the value of botanical ingredients that are environmentally and human friendly are expected to increase. The COSMOS-standard[14] recommends the use of natural or naturally derived ingredients, especially organic agriculture-derived ingredients, and strongly suggests that the concept of environmentally friendly "green chemistry" is also adopted. There are many activities that are being promoted globally to accomplish a sustainable society. The following are the 12 Principles of Green Chemistry proposed by Dr. Anastas of the United States.[15]

1. It is better to prevent waste than to treat or clean up waste after it has been created.
2. Synthetic methods should be designed to maximize the incorporation of all materials used in the process into the final product.
3. Wherever practicable, synthetic methods should be designed to use and generate substances that possess little or no toxicity to human health and the environment.
4. Chemical products should be designed to affect their desired function while minimizing their toxicity.
5. The use of auxiliary substances (e.g., solvents, separation agents, etc.) should be made unnecessary wherever possible and innocuous when used.
6. Energy requirements of chemical processes should be recognized for their environmental and economic impacts and should be minimized. If possible, synthetic methods should be conducted at ambient temperature and pressure.
7. A raw material or feedstock should be renewable rather than depleting whenever technically and economically practicable.
8. Unnecessary derivatization (use of blocking groups, protection/deprotection, temporary modification of physical/chemical processes) should be minimized or avoided if possible, because such steps require additional reagents and can generate waste.
9. Catalytic reagents (as selective as possible) are superior to stoichiometric reagents.
10. Chemical products should be designed so that at the end of their function they break down into innocuous degradation products and do not persist in the environment.
11. Analytical methodologies need to be further developed to allow for real-time, in-process monitoring, and control prior to the formation of hazardous substances.
12. Substances and the form of a substance used in a chemical process should be chosen to minimize the potential for chemical accidents, including releases, explosions, and fires.

Unlike previous activities that promote waste recycling, green sustainable chemistry is a concept that promotes reducing resource and energy from the beginning, and to design products and manufacturing processes to minimize or eliminate derivatization of waste and toxic materials. Along with these concepts, there are many certifications that relate to botanical ingredients such as on the effective use of organisms, preservation and cultivation, and economic return to resource-possessing countries, which are also important to the cosmetic industry.

### 20.4.4 The International Trend of Organic Cosmetics and Natural Cosmetics

Consumers have become more conscious about the safety of cosmetics, leading to a stronger demand for cosmetics using botanical ingredients, and many organic cosmetics and natural cosmetics are now being manufactured and are spreading globally. However, even though there are many certification authorities around the world, a trusted unified standard to certify organic cosmetics and natural cosmetics is yet to be established and is still in a changing phase. A global standard has been established for organic foods, and the foundation of this standard was proposed by an international nongovernmental organization, the International Federation of Organic Agriculture Movements. However, these standards are not applied to cosmetics, and various certification authorities certify cosmetics based on their own standards. Historically speaking, the first natural cosmetics standard was set by Germany-based BDIH, founded by a task force of 19 German natural cosmetics manufacturers in 2001. Following the establishment of BDIH, many certification authorities started their own certification, and in 2010 a certification authority named COSMOS was founded in the European Union (EU) and the COSMOS-Standard was established.[16] This was the world's first international standard that defined organic cosmetics and natural cosmetics. The participating certification authorities are BDIH,[17] Cosmebio,[18] Ecocert Greenfile,[19] ICEA,[20] and Soil Association.[21] The arrangement between the participating authorities required some time, and the standard was aimed to be effective by 2015, but has been postponed. Additionally, use of some petroleum-based synthetic substances such as synthetic preservatives and synthetic surfactants is approved under the COSMOS-Standard, and has been under question from a consumer standpoint.

# 20.5 THE EFFECTIVENESS OF BOTANICAL SUBSTANCES

## 20.5.1 The Effectiveness of Botanical Materials

One of the main reasons to use botanical ingredients in cosmetics is for their physiological effects. Skin care cosmetics are used primarily for moisturization, but many dermatological effects are added to differentiate the products. Expectations are strong with botanical materials to meet these additional effects. Such effects may be their antiinflammatory action, tightening of the skin, ultraviolet (UV) absorption, antioxidative effects, cell growth stimulation, melanin inhibition to prevent senile pigment freckles, metabolism stimulation, circulation improvement and revitalization of the skin, and prevention of small wrinkles. However, only limited effects can be promoted unless the evaluation methods are unified. This is why botanical materials are being developed to add effective physiological effects as dermatological research evolves and new physiological systems of the skin are revealed. Extracting stable substances from botanical ingredients can be challenging. The components of botanical extracts are complex and can be largely affected by the season, agricultural environment, geographical condition, manufacturing method, and storing conditions. Thus, it is vital to determine the active components of botanical extract and control the component quality standards for a stable supply with reliable functions and effects.

We will use the widely researched glycyrrhiza (licorice root) as an example of how botanical materials are researched and developed. Glycyrrhiza has a long history in both Eastern and Western cultures as an effective plant, and has also been used as a botanical ingredient in modern drugs ever since the structure of its active component, glycyrrhizic acid, was determined in 1937.

### *20.5.1.1 Glycyrrhiza*

Licorice is the root or stolon of plants in the *Glycyrrhiza* genus in the perennial herbaceous plant legume family, distributed from northeast China to mid-Asia and southern Europe, with saponin glycoside as its main substance. It is believed that they were used for tonics and beauty agents since they were first found in the Mesopotamian valley 4000 years ago. The dried roots and stolon (Fig. 20.1) themselves are also referred to as licorice, and the rough extract or rough purified products using water or alcohol, or their main active substance, a triterpene glycoside called glycyrrhizic acid (Fig. 20.2), is used in a considerable 70% of Chinese herbal medicine prescriptions. They are widely used in medicine and cosmetics for their antiinflammatory and antihepatitis action. Glycyrrhizic acid is known to be 200 times sweeter than sucrose (sugar), and there is a strong demand in the food industry for glycyrrhiza as a natural sweetener.[22] In Japan, they are commonly added to soy sauce, miso, and pickles since the sweetener has an effect of reducing saltiness. They are also commonly used globally as a fragrant for cigarettes.[23]

Among the *Glycyrrhiza* genus, the most commonly used species are *Glycyrrhiza glabra*, *Glycyrrhiza inflata*, and *Glycyrrhiza uralensis*. The species of glycyrrhiza and the habitats are shown in Table 20.1. The effects of glycyrrhizic acid are not limited to antiinflammatory action, and show antiallergy, detoxification, and antiulcer action. They also



FIGURE 20.1 The root and stolon of the *Glycyrrhiza glabra*.

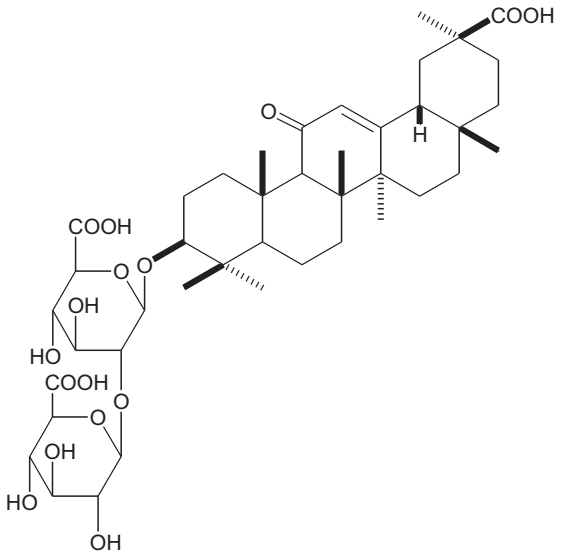



**FIGURE 20.2** Structure of glycyrrhizin.

**TABLE 20.1** Principal Component and the Licorice of Origin

| Locality | Glycyrrhiza Species | Water-Soluble Component | Major Species-Specific Flavonoid Component |
|---|---|---|---|
| China Northeast<br>~ Inner Mongolia<br>~ Northwest | *G. uralensis* | Glycyrrhizic acid, liquiritigenin, isoliquiritigenin, and their glycosides | Licocoumarone, glycycoumarin, licoricidin |
| Shinkyo | *G. inflata* | Glycyrrhizic acid, liquiritigenin, isoliquiritigenin, and their glycosides | Licochalcone A, licochalcone B |
| Mongolia | *G. uralensis* | Glycyrrhizic acid, liquiritigenin, isoliquiritigenin, and their glycosides | Licocoumarone, glycycoumarin, licoricidin |
| Central Asia, such as Afghanistan and Uzbekistan | *G. glabra* | Glycyrrhizic acid, liquiritigenin, isoliquiritigenin, and their glycosides | Glabridin, glabrene |
| Europe, such as Italy | *G. glabra* | Glycyrrhizic acid, liquiritigenin, isoliquiritigenin, and their glycosides | Glabridin, glabrene |

have been reported to remove reactive oxygen species and have oxidative stress defense,[24] and are studied for antiviral actions against HIV[25] and hepatitis C virus.[26] There also reports on the effectiveness against burn wound opportunistic infection.[27] Glycyrrhiza is widely used in cosmetics mainly for medicinal effects such as antiinflammatory action and antiallergy action.

Glycyrrhetic acid, an aglycone of glycyrrhizic acid, has been reported to show not only antiinflammatory and antiallergy actions, but also antibacterial action.[28] Along with glycyrrhizic acid analogues, flavonoid glycosides such as liquiritin or isoliquiritin, and specimen-specific flavonoids such as glabridin, glycycoumarin, and licochalcone A are found in licorice (Table 20.1). Approximately 150 substances of lipophilic flavonoid alone have been isolated and/or identified.[29]

The structures are diverse as well as their effects. As an example in cosmetics, glabridin (Fig. 20.3) is used for effects such as antioxidative effects,[30] estrogen-like activities,[31] and has been reported to have a, inhibition effect for melanogenesis.[32] Additionally, liquiritin (Fig. 20.4) shows whitening effects,[33] liquiritigenin shows antifungal action,[34] isoliquiritigenin shows effects such as antioxidative effects[35] and histamine H2 blocking,[36] and licochalcone (Fig. 20.5) A shows antiinflammatory action.[37] These flavonoid glycosides have been identified as flavone glycoside, chalcone glycoside, or isoflavone glycoside, and have been reported to show many pharmacologic actions such as antioxidative, antiinflammatory, antitumor, or anticancer actions.[38–42]

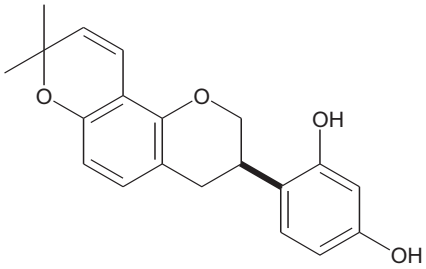
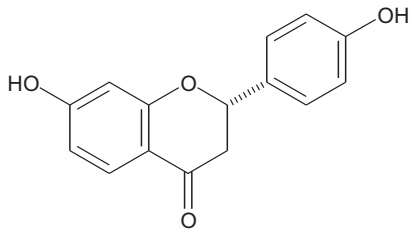
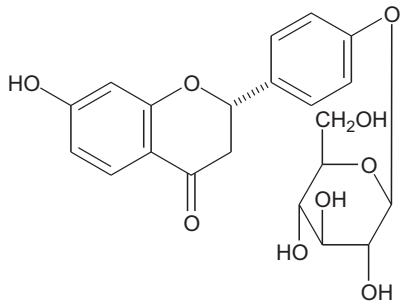



**FIGURE 20.3** Structure of glabridin.




Liquiritigenin




Liquiritin

**FIGURE 20.4** Structure of liquiritin and liquiritigenin.

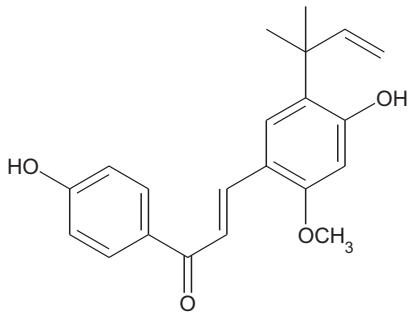



**FIGURE 20.5** Structure of licochalcone A.

Overall, the flavonoid components of licorice show many effects and indicate that glycyrrhizic acid, the main component of licorice, is not the only effective component and suggests the wide applications of licorice (Table 20.2).

Many other botanical extracts are used or researched in cosmetics, and here we will see some examples of extracts where the active substance has been identified. Note that not all of these examples are applied in actual products and are examples of research in botanical extracts.

#### *20.5.1.2 Amla* (Emblica officinalis)

Amla is a woody plant in the euphorbiaceae family found in India. In Indian traditional medicine, known as Ayurveda, amla is listed as of the most important herbs and is known to have effects such as tonic and rejuvenation.

TABLE 20.2 Use of Licorice

| Industry Type | Effect | Use |
|---|---|---|
| Medicine | Anti-inflammatory effect, anti-allergic effect, fibroblast proliferation effect, granuloma formation action, antibody forming inhibitory action, stress reaction inhibitory action, anti-ulcer effect, detoxification | Gastritis, gastric ulcer, duodenal ulcer, stomachodynia, gastric hyperacidity, hangover, autointoxication, dermatitis, urticaria, eczema, drug intoxication, hepatitis, jaundice, various pain, moist cough, conjunctivitis |
| Cosmetics | | Cream, lotion, hair tonic, soap, bath agent, toothpaste |
| Food | Salt familiar, umami, flavoring, sweetness, flavor enhancement | Soy sauce, miso, pickled vegetables, food boiled down in soy sauce, soup, sauce, dainty, fish paste products, drink, frozen dessert, confectionery, candy, cocoa, dairy products |

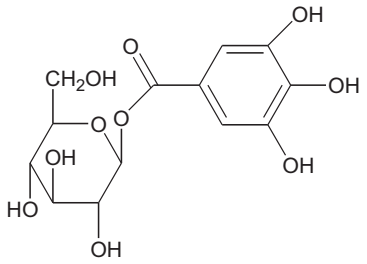



FIGURE 20.6 Structure of β-glucogallin.

The oil of amla is one of the world's oldest hair conditioners, but in recent research it has been reported to have fibroblast proliferation stimulation and procollagen biosynthesis stimulation action.[43] Furthermore, recent studies revealed that it also has whitening action, strong antioxidative effects, and MMP-1 blocking action, and its strong antioxidative effect was found to be from β-glucogallin (Fig. 20.6).[44]

#### 20.5.1.3 *Ashwagandha* (Withania somnifera)

Ashwagandha is one of the most commonly used herbal medicines in the Ayurveda, and has been used for purposes such as antiinflammatory action, antistress, revitalization, and memory enhancement.[45] It is also said to moisturize the skin, and is used as an external agent for preventing freckles and wrinkles. Recent research reports that the concentration of intracellular reduced glutathione is maintained with induced expression of glucose-6-phosphate dehydrogenase, showing reactive oxygen species removal activity, thus ashwagandha is a botanical material that is expected to prevent cell death and aging caused by UV.[46] The active components of ashwagandha have been identified as steroid lactones, namely withaferin-A (Fig. 20.7), withanolide-A, withanoside, and withanone.[47–50]

#### 20.5.1.4 Duabanga grandiflora

*Duabanga grandiflora* is a tree in the lythraceae family, found in the Malay Peninsula, the Yunnan Prefecture in China, and other subtropical rain forests and highlands, and its seed decoct has been used in folk medicine for food poisoning, stomachache, peptic ulcer, and other purposes. Recent studies show possibilities with cosmetic application with its effect of promoting production of type-III collagen that decreases with age,[51] and the effective component has been identified as a hydrolytic tannin, eugeniin (Fig. 20.8).[52]

#### 20.5.1.5 *Acerola* (Malpighia emarginata)

Acerola is an evergreen shrub with edible bright red fruit found in the West Indies and from Northern South America to Central America. The extract of acerola contains large amounts of polyphenols, and among these polyphenols, quercitrin (Fig. 20.9) is a characteristic flavonol glycoside that is reported to have advanced glycation endproduct inhibiting action[53] and antiinflammatory action.[54]

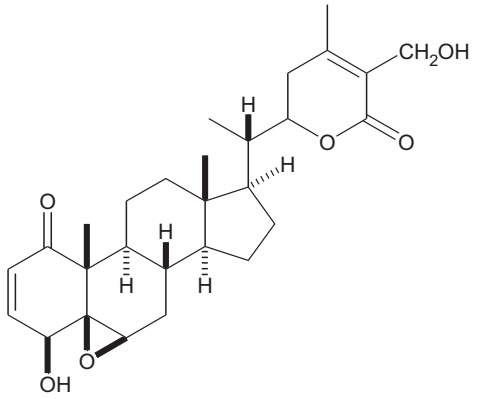



**FIGURE 20.7** Structure of withaferin A.

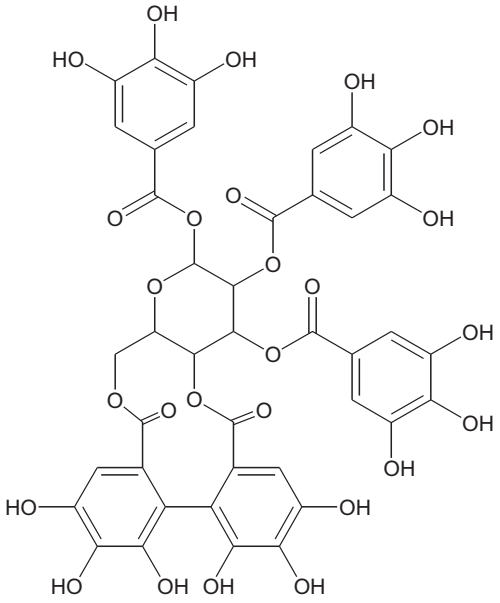



**FIGURE 20.8** Structure of eugeniin.

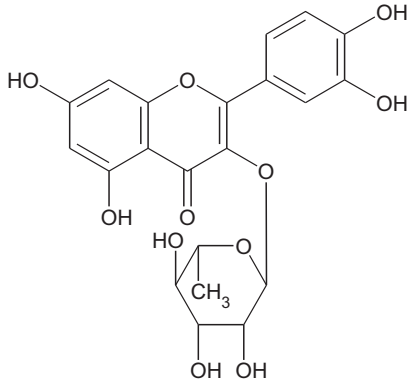



**FIGURE 20.9** Structure of quercitrin.

#### 20.5.1.6 Anastatica hierochuntica

*Anastatica hierochuntica* is an annual plant in the Brassicaceae family, found in the Sahara Desert and that grows by spreading on the ground. It has been an amulet for women in Ancient Egypt, and is believed to be effective against female disorder, and many active substances have been identified.[55,56] In cosmetics, many active substances have been identified from this plant that inhibit melanogenesis, and the active systems has been reported as tyrosinase inhibiting activity, or TRP-2 mRNA expression inhibition.[57]

#### 20.5.1.7 *Ginkgo* (Ginkgo biloba)

Ginkgo leaf extract is known to accelerate thioredoxin reductas-1-gene expression, and the active substance kaempferol has been found to inhibit epidermal intracellular oxidation and it has been reported that it has potential for antiaging action of the skin.[58]

#### 20.5.1.8 *Green Perilla* (Perilla frutescens *Var.* crispa *f.* viridis)

Chalcone is an aromatic enone in the flavonoid family and is a precursor of flavone. Many chalcones have been found from plants,[59] and have been reported to show antiinflammatory action and/or antioxidative effects.[60] DDC (Fig. 20.10) is a chemical compound that has chalcone as its main structure and is found in Green perilla. The DDC activates in the organism's antioxidative system through Nrf2-ARE pathway and induces the expression of antioxidative enzymes, and is reported to show cellular defense action against in vivo oxidative stress.[61]

#### 20.5.1.9 Veratrum album *Subsp.* oxypetalum

In 1939, a polyphenol *trans*-resveratrol (Fig. 20.11) was found from *Veratrum album*, a plant in the liliaceae family. In 1988, this substance was reported to be in grape skin, and in 1992 the French Paradox was reported, where the rate of ischemic heart disease patients was lower with subjects who reported higher wine consumption.[62] In cosmetics, they are reported to have antiinflammatory action by inhibiting NF-κB functions that cause inflammation.[63] Furthermore, they are reported to inhibit the expression of MSH receptors, melanocortin 1 receptors, and block the downstream signals that synthesize them.[64]

#### 20.5.1.10 Citrus unshiu

β-cryptoxanthin (β-CPX) was identified as the active component of *Citrus unshiu*. β-CPX is a carotenoid that has been reported to improve osteoporosis and obesity. It is reported to inhibit the expression of ET-1 receptors endothelin A and endothelin B receptors (EDNRA, EDNRB) under UVB stimulation.[65]

#### 20.5.1.11 *Artemisia* (Artemisia indica *Var.* maximowiczii)

Artemisia is a perennial herb in the Artemisia genus of the Asteraceae family, and is found in hills and fields around the world. The chemical substances of Artemisia consist of essential oil, flavonoids, and polyphenols (Fig. 20.12),[66–70] and are reported to show many antioxidative effects.[71–73]

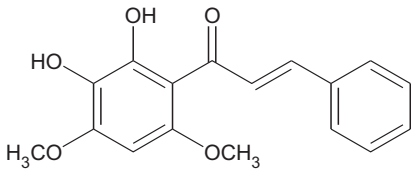



FIGURE 20.10 Structure of DDC (2′,3′-dihydroxy-4′,6′-dimethoxychalcone).

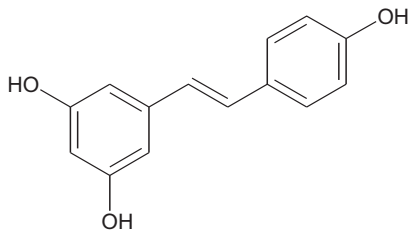
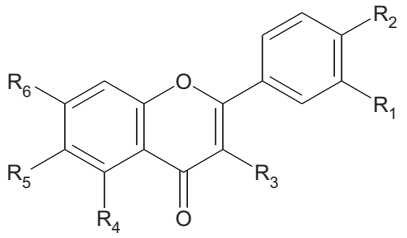



FIGURE 20.11 Structure of *trans*-resveratrol.




| $R_1$ | $R_2$ | $R_3$ | $R_4$ | $R_5$ | $R_6$ | Name |
|---|---|---|---|---|---|---|
| -H | -OH | $-OCH_3$ | -OH | -H | $-OCH_3$ | kaempferol; 3,7-dimethyl ether |
| -OH | -OH | -OH | -OH | -H | -OH | quercetin |
| $-OCH_3$ | -OH | $-OCH_3$ | -OH | -H | -OH | quercetin 3,3'-dimethyl ether |
| -OH | -OH | $-OCH_3$ | -OH | -H | $-OCH_3$ | quercetin 3,7-dimethyl ether |
| $-OCH_3$ | -OH | $-OCH_3$ | -OH | -H | $-OCH_3$ | quercetin 3,7,3'-dimethyl ether |
| $-OCH_3$ | -OH | $-OCH_3$ | -OH | $-OCH_3$ | $-OCH_3$ | quercetagenin 3,6,7,3'-tetramethyl ether |
| $-OCH_3$ | $-OCH_3$ | $-OCH_3$ | -OH | $-OCH_3$ | $-OCH_3$ | quercetagenin 3,6,7,3',4'-pentamethyl ether |

FIGURE 20.12 Structure of the flavonoid aglycones found in *Artemisia vulgaris*.

#### *20.5.1.12* Xylocarpus granatum

*Xylocarpus granatum* is a plant in the mahogany family originating in Bangladesh, and its secondary metabolite has been reported to have a unique chemical structure and interesting biological effects.[74] For example, the active component of methanol extract of the leaf has been identified as a new chemical compound through isolation and analysis using Wnt signal blocking as an indicator.[75] On the other hand, the Wnt signal has been reported to control pigment stem cells' differentiation to skin melanocyte,[76] and has been a subject of interest in whitening.

### 20.5.2 Effectiveness of Botanical Aroma Compounds

Plants are a reservoir of aroma compounds. The biosynthesized aroma compounds often have structures similar to neurotransmitters or hormones, and show various medicinal effects. Here we will focus on the medicinal effects of the aroma compounds that work directly on cells or biomolecules instead of the effects caused by their smell or flavor. Tea tree oil (*Melaleuca alternifolia*) and terpinen-4-ol have been found effective to inhibit human M14 melanoma cell growth,[77] and peppermint oil has been reported to show antivirus action.[78] Furthermore, some mixed essential oils have shown synergistic effects,[79,80] and some have been reported to enhance skin permeability.[81,82] Other effects are also known, such as the free radical scavenging action of citrus essential oils,[83] or inhibition action of reactive oxygen species increase and cell death caused by UV and nitrogen dioxide with rosemary oil and its main component, 1,8-cineol.[84] Rosemary and other essential oils have been reported to have antibacterial action against bacteria such as *Propionibacterium acnes*,[85,86] and many essential oils have been reported to show antiinflammatory action with arachidonic acid cascade—related enzyme blocking.[87,88] It is also known that TRP receptors that react to temperature stimulation and pain are activated with essential oil components, and menthol has the effect of creating a cool feeling by raising the threshold temperature of cold receptor TRPM8.[89,90] Furthermore, camphor activates heat receptor TRPV3.[91] Grapefruit oil has been shown to inhibit neutral fat accumulation by inhibiting expression of genes that relate to neutral fat synthesis with glycerol-3-phosphate dehydrogenase.[92] Even when focusing on the medicinal effect of aroma compounds, you will understand how they have potential for many effects.

## 20.6 THE FUTURE AND CHALLENGES IN BOTANICAL SUBSTANCE DEVELOPMENT

### 20.6.1 Safety of Botanical Substances

Allergic contact dermatitis is caused when allergen substances penetrate into the skin and cause a delayed cellular immunity. Once a foreign substance that causes dermatitis is recognized as a skin sensitization allergen (sensitization), it causes a memory effect in the immune system and the allergen causes allergic response for the rest of one's life. As such, it is vital to confirm if the ingredients can cause skin sensitization. Safety should be the first and foremost priority in cosmetics, and cosmetics distributors owe the responsibility for their products and the responsibility to guarantee safety for their consumers.

However, banning animal testing in cosmetics started in the EU from 2004 and became effective in 2013,[93] and this trend is spreading globally. Although the trend against animal testing is spreading, in vitro testing methods for tests such as toxicokinetics, repeated dose toxicity, carcinogenicity, skin sensitization, or genotoxicity are yet to be established.[94] Furthermore, databases of in silico testing and structure-activity relationship are generally utilized as one of the few alternatives to animal testing, but the data is usually on high-purity single substances and is difficult to apply to multicomponent systems such as plant extracts. With food, experience from consumption is a strong basis to avoid allergy, but an incident occurred recently in Japan with hydrolyzed wheat protein (Glupal-19S) in soap, causing acute wheat allergy response, and this became a strong public incident. This is a notorious case that proved food allergy could be caused transdermally and not only by consumption.[95–98] Though this is a very rare case, it shows that such reactions can occur and they must be considered in development, and indicates that materials that have been proven safe from a long history as herbal medicines as well as for consumption still have advantage in development. Furthermore, there are expectations for plants that have been thoroughly studied in ethnobotanic research and the results have reported not only on the effects and activity but also on safety.[99] No matter how they are chosen, it is important to limit the target ingredients to those with abundant information on their safety, for example, plants with histories as herbal medicines. An alternative direction of botanical substance research that is actively being studied is using ingredients that have been proven safe for dermatological use, and studying their mechanisms to reveal new function systems.

### 20.6.2 Development by Fermentation of Botanical Substance

New methods are being studied to produce active components of plants without relying on extraction. Let's take glycyrrhiza as an example.

China is a main supplier of glycyrrhiza, but the habitat of glycyrrhiza is being destroyed and environmental damage is increasing due to the growing demand in China and overgathering of wild glycyrrhiza. With this change, gathering and export restriction of rare plants such as glycyrrhiza is being considered like that of rare earths, and there is a growing concern on price raise or stable supply. Decrease of the supply of high-grade glycyrrhiza with high glycyrrhizic acid content has also become a problem, and factory harvesting examinations and other methods of breeding high glycyrrhizic acid content glycyrrhiza breeds are being actively studied.[100] In the future, molecular breeding of high glycyrrhizic acid content will become more important, but there are also new endeavors using fermentation engineering with microbes to produce glycyrrhizic acids. To achieve this method, it is vital to identify the biosynthesis mechanism and synthesis enzymes of glycyrrhizic acids. We will take a look at the current progress of this fermentation method.

The carbon structure of glycyrrhizic acid is β-amyrin, a triterpene commonly found in many plants. β-amyrin synthase closes the rings of 2,3-oxidosqualene.[101] cDNA encoding β-amyrin synthase has been isolated from many species including *G. glabra*. Glycyrrhizic acid is biosynthesized with the oxidation of the C-11 and C-30 carbon and the glycosylation reaction of the third hydroxyl group of β-amyrin. These steps were predicted to be caused by two oxidation enzymes and two glycosylation enzymes. In 2008, Muranaka et al. identified the enzyme (CYP88D6) that changes 11-oxo-β-amyrin, a biosynthesized intermediate of glycyrrhizic acid by using a two-step hydroxylation reaction at the 11th position of β-amyrin as a catalytic reaction.[102] Furthermore, their approach successfully identified a second enzyme (CYP72A154), which is responsible for C-30 oxidation in the glycyrrhizin pathway. The CYP72A154 catalyzes three sequential oxidation steps at C-30 of 11-oxo-β-amyrin, and changes 11-oxo-β-amyrin to glycyrrhizic acid, which corresponds to the aglycon of glycyrrhetic acid[103] (Fig. 20.13). These biosynthesis genes expressed in an engineered yeast strain and glycyrrhetic acid was successfully synthesized. However, the yield of glycyrrhetic acid using transgenic yeast is still low and still needs further improvement to get enough yield for actual application. Methods for higher productivity must be studied, such as molecular breeding to optimize triterpenoid production by improving the mevalonate pathway or controlling the sterol pathway after 2,3-oxidosqualene. Some glycosylation enzymes of glycyrrhizic acid have also been identified, and industrial fermentation methods for glycyrrhizic acid production from glycyrrhetic acid is steadily advancing.[104]

## 20.7 CLOSING REMARKS

The history of the relationship between humans and plants is extremely long, and humans have used plants in every aspect of life, not only in cosmetics but for food and medicine as well. We have always relied on plants, when developing botanical materials for cosmetics it is needless to say that botanical substances are natural

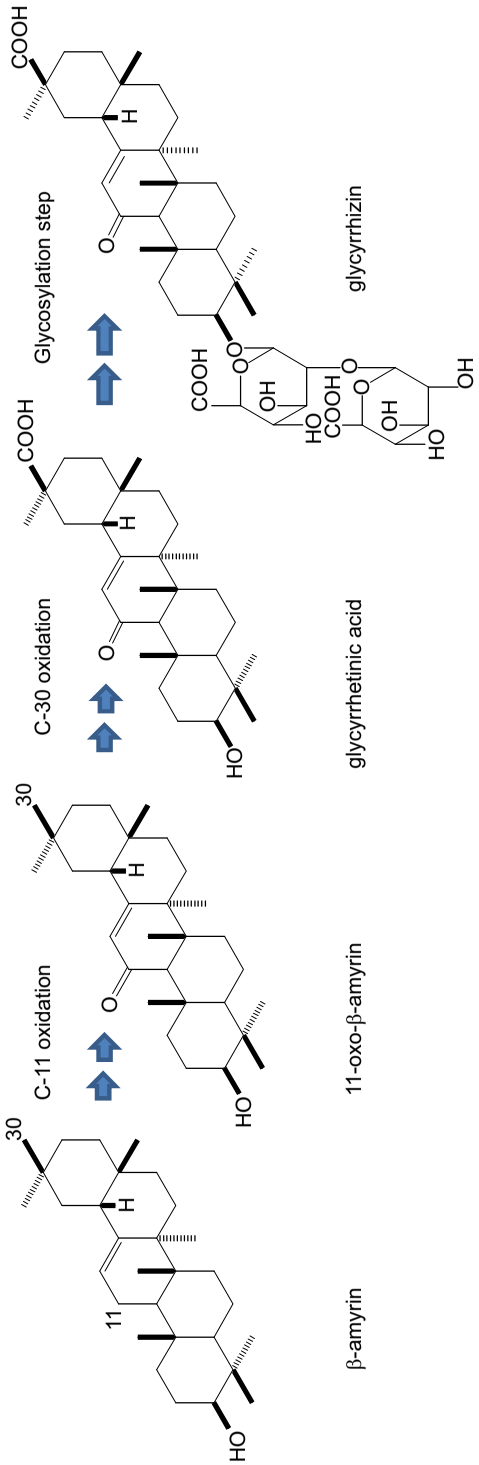



FIGURE 20.13 Proposed pathway for biosynthesis of Glycyrrhizin.

substances that must be treated differently from other chemicals. Safety assurance must be the foundation, but many specific areas must also be pursued, such as securing resources, being compliant with the Convention on Biological Diversity, standardization of materials, and unification of compositions. As fundamental research advances and the mechanisms of the skin and body are revealed, development of botanical substances will also advance to make more effective cosmetic ingredients and medicinal substances. Strong evidence will become required in cosmetics as well as a scientific basis of the effectiveness, and the demand for evidenced-based cosmetics is stronger. When looking at the future of cosmetics, the hopes for botanical materials with infinite potential seem even more promising.

## References


1. Judd, et al. *Plant systematics: A phylogenetic approach*. 2nd ed. Massachusetts (USA): Synauer; 2002.
2. Afnedi FM, Okada T, Yamazaki M, Hirai-Morita A, Nakamura Y, Nakamura K, et al. KNApSAcK family databases: Integrated metabolite-plant species databases for multifaceted plant research. *Plant Cell Physiol* 2012;**53**(2):1−12.
3. www.cbd.int/convention/text/.
4. Koester V. The biodiversity convention negotiation process and some comments on the outcome. *Environ Policy Law* 1997;**27**(3):175−92.
5. www.cbd.int/doc/publications/cbd-bonn-gdls-en.pdf.
6. www.mabs.jp/archives/nagoya/index.html.
7. Watanabe KN, Teh GH. Wanted: bioprospecting consultants. *Nat Biotechnol* 2011;**29**(10):873−5.
8. Okada Y, Watanabe KN. Social responsibility for the use of genes, genomes and biotechnology in biotechnology companies: A commentary from the bioethical viewpoint. *J Comm Biotechnol* 2008;**14**(2):149−67.
9. Okada Y, Watanabe KN. Rationalization of the genes as a corporate stakeholder based on international laws. *J Int Biotechnol Laws* 2008;**5**: 103−12.
10. Lundmark LD. Plant-derived ingredients and phytocosmetic emulsions. *Drug Cosmet Ind* October, 1978;**58**−**68**:152−3.
11. Chang JC. Ginseng and cosmetics. *Cosmet Toilet* 1977;**92**(5):50−7.
12. Howard A. *An agricultural testament*. New York and London: Oxford University Press; 1940.
13. www.ams.usda.gov/nop.
14. www.cosmos-stadard.org.
15. Anastas PT, Warner JC. *Green chemistry: theory and practice*. New York: University Press; 1998.
16. www.cosmos-standard.org.
17. www.ionc.info.
18. www.cosmebio.org.
19. www.ecocert.com/en/natural-and-organic-cosmetics.
20. www.icea.info.
21. www.soilassociation.org.
22. Hayashi H, Sudo H. Economic importance of licorice. *Plant Biotechnol* 2009;**26**:101−4.
23. Gibson MR. Glycyrrhiza in old and new perspectives. *J Nat Prod* 1978;**41**(4):348−54.
24. Hidaka I, Hino K, Korenaga M, Gonda T, Nishina S, Ando M, et al. Stronger neo-minophagen C$^{TM}$, a glycyrrhizin-containing preparation, protects liver against carbon tetrachloride-induced oxidative stress in transgenic mice expressing the hepatitis C virus polyprotein. *Liver Int* 2007;**27**:845−53.
25. Hattori T, Ikematsu S, Koito A, Matsushita S, Maeda Y, Hada M, et al. Preliminary evidence for inhibitory effect of glycyrrhizin HIV replication in patients with AIDS. *Antiviral Res* 1989;**11**:255−62.
26. Ashfaq UA, Masoud MS, Nawaz Z, Riazuddin S. Glycyrrhizin as antiviral agent against hepatitis C virus. *J Transl Med* 2011;**9**:112−8.
27. Yoshida T, Yoshida S, Kobayashi M, Herndon DN, Suzuki F. Glycyrrhizin restores the impaired production of β-defensins in tissues surrounding the burn area and improves the resistance of burn mice to *Pseudomonas aeruginosa* wound infection. *J Leukoc Biol* 2010;**87**:35−41.
28. Kim HK, Park Y, Kim HN, Choi BH, Jeong HG, Lee DG, et al. Antimicrobial mechanism of β-glycyrrhetinic acid isolated from licorice, *Glycyrrhiza glabra*. *Biotechnol Lett* 2002;**24**:1899−902.
29. Nomura T, Fukai T. *Phenolic constituents of licorice (Glycyrrhiza species)*. New York: Springer, Wien; 1998. p. 1−140.
30. Yu XQ, Xue CC, Zhou ZW, Li CG, Du YM, Liang J, et al. In vitro and in vivo neuroprotective effect and mechanisms of glabridin, a major active isoflavan from *Glycyrrhiza glabra* (licorice). *Life Sci* 2008;**82**:68−78.
31. Tamir S, Eizenberg M, Somjen D, Stern N, Shelach R, Kaye A, et al. Estrogenic and antiproliferative properties glabridin from licorice in human breast cancer cells. *Cancer Res* 2000;**60**:5704−9.
32. Yokota T, Nishio H, Kubota Y, Mizoguchi M. The inhibitory effect of glabridin from licorice extracts on melanogenesis and inflammation,. *Pigm Cell Res* 1998;**11**:355−61.
33. Amer M, Metwalli M. Topical liquiritin improves melasma. *Int J Dermatol* 2000;**39**:299−301.
34. Lee JY, Lee JH, Park JH, Kim SY, Choi JY, Lee SH, et al. Liquiritigenin, a licorice flavonoid, helps mice resist disseminated candidiasis due to *Candida albicans* by Th1 immune response, whereas liquiritin, its glycoside from, does not. *Int Immunopharmacol* 2009;**9**:632−8.
35. Vaya J, Belinky PA, Aviram M. Antioxidant constituents from licorice roots: isolation, structure elucidation and antioxidative capacity toward LDL oxidation. *Free Radic Biol Med* 1997;**23**(2):302−13.
36. Kim DC, Choi SY, Kim SH, Yun BS, Yoo ID, Reddy NRP, et al. Isoliquiritigenin selectively inhibits $H_2$ histamine receptor signaling. *Mol Pharmacol* 2006;**70**:493−500.
37. Kolbe L, Immeyer J, Batzer J, Wensorra U, Dieck KT, Mundt C, et al. Anti-inflammatory efficacy of licochalcone A: correlation of clinical potency and in vitro effects. *Arch Dermatol Res* 2006;**298**:23−30.
38. Chin YW, Jung HA, Liu Y, Su BN, Castoro JA, Keller WJ, et al. Anti-oxidant constituents of the roots and stolons of licorice (*Glycyrrhiza glabra*). *J Agric Food Chem* 2007;**55**:4691−7.

39. Kwon GT, Cho HJ, Chung WY, Park KK, Moon A, Park JHY. Isoliquiritigenin inhibits migration and invasion of prostate cancer cells: possible mediation by decreased JNK/AP-1 signaling. *J Nutr Biochem* 2009;**20**:663–76.
40. Jayaprakasam B, Doddaga S, Wang R, Holmes D, Goldfarb J, Li XM. Licorice flavonoids inhibit eotaxin-1 secretion by human fetal lung fibroblasts in vitro. *J Agric Food Chem* 2009;**57**:820–5.
41. Ma J, Fu NY, Pang DB, Wu WY, Xu AL. Apoptosis induced by isoliquiritigenin in human gastric cancer MGC-803 cells. *Planta Med* 2001;**67**: 754–7.
42. Kumar S, Sharma A, Madan B, Singhal V, Ghosh B. Isoliquiritigenin inhibits IκB kinase activity and ROS generation to block TNF-α induced expression of cell adhesion molecules on human endothelial cells. *Biochem Pharmacol* 2007;**73**:1602–12.
43. Fuji T, Wakaizumi M, Ikami T, Saito M. Amla (*Emblica officinalis* Gaertn.) extract promotes procollagen production and inhibits matrix metalloproteinase-1 in human skin fibroblasts. *J. Ethnopharmacol* 2008;**119**:53–7.
44. Majeed M, Bhat B, Jadhav AN, Srivastava JS, Nagabhushanam K. Ascorbic acid and tannins from *Emblica officinalis* Gaertn. fruits-A revisit. *J Agric Food Chem* 2009;**57**(1):220–5.
45. Mishara LC, Singh BB, Dagenais S. Scientific basis for the therapeutic use of *Withania somnifera* (Ashwagandha): a review. *Altern Med Rev.* 2000;**5**(4):334–46.
46. Widodo N, Shah N, Priyandoko D, Ishii T, Kaul SC, Wadhwa R. Deceleration of senescence in normal human fibroblasts by withanone extracted from ashwagandha leaves. *J Gerontol A Biol Sci Med Sci* 2009;**64**(10):1031–8.
47. Widodo N, Kaur K, Shrestha BG, Takagi Y, Ishii T, Wadhwa R, et al. Selective killing of cancer cells by leaf extract of ashwagandha: identification of a tumor-inhibitory factor and the first molecular insights to its effect. *Clin Cancer Res* 2007;**13**(7):2298–306.
48. Matsuda H, Murakami T, Kishi A, Yoshikawa M. Structures of withanosides I, II, III, IV, V, VI, and VII, new withanolide glycosides, from the roots of Indian *Withania somnifera* DUNAL. and inhibitory activity for tachyphylaxis to clonidine in isolated guinea-pig ileum. *Bioorg Med Chem* 2001;**9**:1499–507.
49. Zhao J, Nakamura N, Hattori M, Kuboyama T, Tohda C, Komatsu K. Withanolide derivatives from the roots of *Withania somnifera* and their Neurite outgrowth activities. *Chem Pharm Bull* 2002;**50**(6):760–5.
50. Kuboyama T, Tohda C, Zhao J, Nakamura N, Hattori M, Komatsu K. Axon- or dendrite-predominant outgrowth induced by constituents from ashwagandha. *Neuroreport* 2002;**13**(14):1715–20.
51. Keene DR, Sakai LY, Bachinger HP, Burgeson RE. Type III collagen can be present on banded collagen fibrils regardless of fibril diameter. *J Cell Biol* 1987;**105**:2393–402.
52. Tsukiyama M, Sugita T, Kikuchi H, Yasuda Y, Arashima M, Okumura H. Effect of *Duabanga grandiflora* for human skin cells. *Am J Chin Med* 2010;**38**(2):387–99.
53. Hanamura T, Hagiwara T, Kawagishi H. Structural and functional characterization of polyphenols isolated from acerola (*Malpighia emarginata* DC.) fruit. *Biosci Biotechnol Biochem* 2005;**69**(2):280–6.
54. Medina FS, Vera B, Galvez J, Zarzuelo A. Effect of quercitrin on the early stages of hapten induced colonic inflammation in the rat. *Life Sci* 2002;**70**:3097–108.
55. Yoshikawa M, Xu F, Morikawa T, Ninomiya K, Matsuda H. Anastatins A and B, new skeletal flavonoids with hepatoprotective activities from the desert plant *Anastatica hierochuntica*. *Bioorg Med Chem Lett* 2003;**13**:1045–9.
56. Yoshikawa M, Morikawa T, Xu F, Ando S, Matsuda H. (7R,8S) and (7S,8R) 8-5′ linked neolignans from Egyptian herbal medicine *Anastatica hierochuntica* and inhibitory activities of lignans on nitric oxide production. *Heterocycles* 2003;**60**(8):1787–92.
57. Nakashima S, Matsuda H, Oda Y, Nakamura S, Xu F, Yoshikawa M. Melanogenesis inhibitors from the desert plant *Anastatica hierochuntica* in B16 melanoma cells. *Bioorg Med Chem* 2010;**18**:2337–45.
58. Sugahara M, Nakanishi J, Katsuta Y. Kaempferol enhanced the intracellular thioredoxin system in normal cultured human keratinocytes. *Biosci Biotechnol Biochem* 2010;**74**(8):1701–3.
59. Izumi Y, Sawada H, Sakka N, Yamamoto N, Kume T, Katsuki H, et al. p-Quinone mediates 6-hydroxydopamine-induced dopaminergic neuronal death and ferrous iron accelerates the conversion of p-quinone into melanin extracellularly. *J Neurosci Res* 2005;**79**:849–60.
60. Yamamoto N, Izumi Y, Matsuo T, Wakita S, Kume T, Takada-Takatori Y, et al. Elevation of heme oxygenase-1 by proteasome inhibition affords dopaminergic neuroprotection. *J Neurosci Res* 2010;**88**:1934–42.
61. Izumi Y, Matsumura A, Wakita S, Akagi KI, Fukuda H, Kume T, et al. Isolation, identification, and biological evaluation of Nrf2-ARE activator from the leaves of green perilla (*Perilla frutescens* var. *crispa* f. *viridis*). *Free Radic Biol Med* 2012;**53**:669–79.
62. Renaud S, de Lorgeril M. Wine, alcohol, platelets, and the French paradox for coronary heart disease. *Lancet* 1992;**339**:1523–6.
63. Horio Y, Hayashi T, Kuno A, Kunimoto R. Cellular and molecular effects of sirtuins in health and disease. *Clin Sci* 2011;**121**(5):191–203.
64. Chen YJ, Chen YY, Lin YF, Hu HY, Liao HF. Resveratrol inhibits alpha-melanocyte-stimulating hormone signaling, viability, and invasiveness in melanoma cells. *Evid Based Complement Alternat Med* 2013:1–8. 20, Article ID 632121.
65. Shimoda H, Shan SJ, Tanaka J, Maoka T. β-Cryptoxanthin suppresses UVB-induced melanogenesis in mouse; involvement of the inhibition of prostaglandin E2 and melanocyte-stimulating hormone pathways. *J Pharm Pharmacol* 2012;**64**:1165–76.
66. Mohamed AEHH, EI-Sayed MA, Hegazy ME, Helaly SE, Esmail AM, Mohamed NS. Chemical constituents and biological activities of *Artemisia herba-alba*. *Rec Nat Prod* 2010;**4**(1):1–25.
67. Nisra LN, Singh SP. α-Thujone, the major component of the essential oil from *Artemisia vulgaris* growing wild in nilgiri hills. *J Nat Prod* 1986; **49**:941.
68. Nikolova M. Infraspecific variability in the flavonoid composition of *Artemisia vulgaris* L. *Acta Bot Croat* 2006;**65**(1):13–8.
69. Toda S. Inhibitory effects of polyphenols in leaves of *Artemisia princeps* PAMP on protein fragmentation by Cu(II)-$H_2O_2$ in vitro. *J Med Food* 2004;**7**(1):52–4.
70. Toda S. Polyphenol content and antioxidant effects in herb teas. *Chinese Med* 2011;**2**:29–31.
71. Toda S. Antioxidative effects of polyphenols from leaves of *Artemisia princeps* PAMP on lipid peroxidation. *J Food Biochem* 2005;**29**:305–12.
72. Nugroho A, Lee KR, Alam MB, Choi JS, Park HJ. Isolation and quantitative analysis of peroxynitrite scavengers from *Artemisia princeps* var. *orientalis*. *Arch Pharm Res* 2010;**33**(5):703–8.
73. Kim MJ, Han JM, Baek NI, Bang MH, Chaung HG, Choi MS, et al. In vitro antioxidant and anti-inflammatory activities of Jaceosidin from *Artemisia princeps* Pampanini cv. Sajabal. *Arch Pharm Res* 2008;**31**(4):429–37.

74. Ueda M. Chemical biology of natural products on the basis of identification of target proteins. *Chem Lett* 2012;**41**:658–66.
75. Toume K, Kamiya K, Arai MA, Mori N, Sadhu SK, Ahmed F, et al. Xylogranin B: A potent Wnt signal inhibitory limonoid from *Xylocarpus granatum*. *Org Lett* 2013;**15**(23):6106–9.
76. Yamada T, Hasegawa S, Inoue Y, Date Y, Yamamoto N, Mizutani H, et al. Wnt/β-catenin and kit signaling sequentially regulate melanocyte stem cell differentiation in UVB-induced epidermal pigmentation. *J Invest Dermatol* 2013;**133**:2753–62.
77. Calcabrini A, Stringaro A, Toccacieli L, Meschini S, Marra M, Colone M, et al. Terpinen-4-ol, the main component of *Melaleuca alterifolia* (tea tree) oil inhibits the in vitro growth of human melanoma cells. *J Invest Dermatol* 2004;**122**:349–60.
78. Schuhmacher A, Reichling J, Schnitzler P. Virucidal effect of peppermint oil on the enveloped viruses herpes simplex virus type 1 and type 2 in vitro. *Phytomedicine* 2003;**10**:504–10.
79. Miyazawa M, Watanabe H, Umemoto K, Kameoka H. Inhibition of acetylcholinesterase activity by essential oils of mentha species. *J Agric Food Chem* 1998;**46**:3431–4.
80. Savelev S, Okello E, Perry NSL, Wilkins RM, Perry EK. Synergistic and antagonistic interactions of anticholinesterase terpenoids in *Salvia lavandulaefolia* essential oil. *Pharmacol Biochem Behav* 2003;**75**:661–8.
81. Fang JY, Lee YL, Hwang TL, Cheng HC, Hung CF. Development of sesquiterpenes from *Alpinia oxyphylla* as novel skin permeation enhancers. *Eur J Pharm Sci* 2003;**19**:253–62.
82. Monti D, Chetoni P, Burgalassi S, Najarro M, Saettone MF, Boldrini E. Effect of different terpene-containing essential oils on permeation of estradiol through hairless mouse skin. *Int J Pharm* 2002;**237**:209–14.
83. Choi HS, Song HS, Ukeda H, Sawamura M. Radical-scavenging activities of citrus essential oils and their components: detection using 1,1-Diphenl-2-picrylhydrazyl. *J Agric Food Chem* 2000;**48**:4156–61.
84. Saito Y, Shiga A, Yoshida Y, Furuhashi T, Fuzita Y, Niki E. Effects of a novel gaseous antioxidative system containing a rosemary extract on the oxidation induced by nitrogen dioxide and ultraviolet radiation. *Biosci Biotechnol Biochem* 2004;**68**(4):781–6.
85. Fu Y, Zu Y, Chen L, Efferth T, Liang H, Liu Z, et al. Investigation of antibacterial activity of rosemary essential oil against *Propionibacterium acnes* with atomic force microscopy. *Planta Med* 2007;**73**:1275–80.
86. Tsai ML, Lin CC, Lin WC, Yang CH. Antimicrobial, antioxidant, and anti-inflammatory activities of essential oils from five selected herbs. *Biosci Biotechnol Biochem* 2011;**75**(10):1977–83.
87. Miguel MG. Antioxidant and anti-inflammatory activities of essential oils: a short review,. *Molecules* 2010;**15**:9252–87.
88. de Cassia da Silveira e Sa R, Andrade LN, de Sousa DP. A review on anti-inflammatory activity of monoterpenes,. *Molecules* 2013;**18**:1227–54.
89. McKemy DD, Neuhausser WM, Julius D. Identification of a cold receptor reveals general role for TRP channels in thermosensation. *Nature* 2002;**416**:52–8.
90. Masamoto Y, Kawabata F, Fushiki T. Intragastric administration of TRPV1, TRPV3, TRPM8, and TRPA1 agonists modulates autonomic thermoregulation in different manners in mice. *Biosci Biotechnol Biochem* 2009;**73**(5):1021–7.
91. Moqrich A, Hwang SW, Earley TJ, Petrus MJ, Murray AN, Spencer KSR, et al. Impaired thermosesstation in mice lacking TRPV3, a heat and camphor sensor in the skin. *Science* 2005;**307**:1468–72.
92. Haze S, Sakai K, Gozu Y, Moriyama M. Grapefruit oil attenuates adipogenesis in cultured subcutaneous adipocytes. *Planta Med* 2010;**76**: 950–5.
93. Commission Staff Working Document. *Timetables for the phasing-out of animal testing in the framework of the 7th Amendment to the Cosmetics Directive (Council Directive 76/768/EEC)*. 2004. p. 1210. EN, SEC82004.
94. Adler S, et al. Alternative (non-animal) methods for cosmetics testing: current status and future prospects-2010. *Arch Toxicol* 2011;**85**:367–485.
95. Fukutomi Y, Itagaki Y, Taniguchi M, Saito A, Yasueda H, Nakazawa T, et al. Rhinoconjunctival sensitization to hydrolyzed wheat protein in facial soap can induce wheat-dependent exercise- induced anaphylaxis. *J Allergy Clin Immunol* 2011;**127**(2):531–3.
96. Chinuki Y, Morita E. Wheat-dependent exercise-induced anaphylaxis sensitized with hydrolyzed wheat protein in soap. *Allergol Int* 2012;**61**: 529–37.
97. Hiragun M, Ishii K, Hiragun T, Shindo H, Mihara S, Matsuo H, et al. The sensitivity and clinical course of patients with wheat-dependent exercise- induced anaphylaxis sensitized to hydrolyzed wheat protein in facial soap-secondary Publication. *Allergol Int* 2013;**62**:351–8.
98. Nakamura M, Yagami A, Hara K, Sano A, Kobayashi T, Aihara M, et al. A new reliable method for detecting specific IgE antibodies in the patients with immediate type wheat allergy due to hydrolyzed wheat protein: correlation of its titer and clinical severity. *Allergol Int* 2014;**63**: 243–9.
99. Sampson J. Ethnobotanical enquiry into plants: searching out new agents for inflammation and dermatological diseases. *Cosmet Toilet* 1998; **113**(11):75–82.
100. Kojoma M, Hayashi S, Shibata T, Yamamoto Y, Sekizaki H. Variation of glycyrrhizin and liquiritin contents within a population of 5-year-old licorice (*Glycyrrhiza uralensis*) plants cultivated under the same conditions. *Biol Pharm Bull* 2011;**34**(8):1334–7.
101. Hayashi H, Huang P, Kirakosyan A, Inoue K, Hiraoka N, Ikeshiro Y, et al. Cloning and characterization of a cDNA encoding β-amyrin synthase involved in glycyrrhizin and soyasaponin biosyntheses in licorice. *Biol Pharm Bull* 2001;**24**(8):912–6.
102. Seki H, Ohyama K, Sawai S, Mizutani M, Ohnishi T, Sudo H, et al. Licorice β-amyrin 11-oxidase, a cytochrome P450 with a key role in the biosynthesis of the triterpene sweetener glycyrrhizin. *Proc Natl Acad Sci USA* 2008;**105**(37):14204–9.
103. Seki H, Sawai S, Ohyama K, Mizutani M, Ohnishi T, Sudo H, et al. Triterpene functional genomics in licorice for identification of CYP72A154 involved in the biosynthesis of glycyrrhizin. *Plant Cell* 2011;**23**:4112–23.
104. Seki H, Tamura K, Muranaka T. P450s and UGTs: Key players in the structural diversity of triterpenoid saponins. *Plant Cell Physiol* 2015;**56**(8): 1463–71.

CHAPTER

# 21

# Functional Materials for Hair

C.M. *Rocafort*

**BASF Corporation, Florham Park, NJ, United States**

## 21.1 INTRODUCTION

Hair care has always been inspired by global fashion trends and images of celebrities and models in lifestyle magazines, television and movies, or a licensed cosmetologist's recommendation. With this new age of connectivity, global market trends are seen virtually at the moment instead of weeks or months later. Manufacturers are adapting to a society that relies on technology for every capacity of life. Consumers are shopping with their smart phones and assessing social media (i.e., YouTube videos, Facebook posts, Twitter, etc.) via beauty blogs and other multimedia to research products, reviews, and ingredients before they purchase. This poses challenges to the consumer who desires a particular style that may not be achievable depending on their specific hair type, color, texture, damage magnitude, and environmental factors. In contrast to the situation several decades ago, when hair care products such as shampoos and conditioners were generally segmented according to hair type (normal, oily/greasy, and dry) and provided basic claims such as cleansing, conditioning, detangling, and removing impurities, most global hair care brands today such as Pantene Pro-V (P&G), Sunsilk (Unilever), and Garnier (L'Oréal), are now segmented by the desired look (curly, smooth, natural), demographic group (men, women, children), hair texture (natural curly, fine, thick, multitextured), and treatment benefit (antidandruff, antipollution, antifrizz, antibreakage, repair, color revival, color care, volume enhancement, moisture renewal, scalp care, smoothing and sleeking, strengthening, etc.). Consumers want "customized" solutions for their specific hair type, to enhance the style and condition of their hair, as well as products that give hair a healthy sensorial feel and provide a feeling of increased well-being. They want healthy and shiny hair that transcends age, gender, and nationality. Consumers choose their hair care products based on their specific hair unmet needs, sensorial aspects of the product itself or the sensorial experience before, during, and after using the product, and the specific benefits they are searching for.[1] Functional materials are included in hair care formulations to provide noticeable benefits to consumers. Other advantages include formulation stability and aesthetics, and/or improving the feel of the product on the hair when it is applied, rinsed from the hair, or dried.

This chapter will review functional materials used in hair shampoos and conditioners from a "back to basics" perspective. I'll start with the key functional ingredients that make up a shampoo and conditioner chassis and their specific function in the formulations, review the leading global hair care market trends and key consumer needs and drivers, and then map these trends and needs to "customized" industry solutions by defining some of the latest functional ingredients and technologies that are providing the desired benefits to the hair.

## 21.2 FUNCTIONAL MATERIALS FOR HAIR SHAMPOOS

The primary function of a shampoo is to clean both the hair and scalp of oils, dirt, skin particles, dandruff, environmental pollutants, and other contaminant particles that gradually build up on hair. The goal is to remove the unwanted buildup without stripping out so much as to make hair unmanageable. The main benefits of a shampoo are cleansing and conditioning. This is achieved by depositing conditioning ingredients onto the hair surfaces. These ingredients decrease fiber friction, through charge interaction between the negatively charged hair and the positively charged conditioning agent, making the hair feel smooth and slick and easier to comb.

*Cosmetic Science and Technology: Theoretical Principles and Applications*
http://dx.doi.org/10.1016/B978-0-12-802005-0.00021-5



Copyright © 2017 Elsevier Inc. All rights reserved.

There are three chapters in this book dedicated to the topics of surfactants, polymer surfactant interactions, and phase diagrams of surfactants, so I will not address these topics here. My intent is to present a "back to basics" approach where I will review the key functional ingredients that make up a shampoo and conditioner chassis and their specific function in the formulation, and then to discuss what new functional ingredients have been introduced to address the leading global market trends and key consumer needs.

Table 21.1 lists the shampoo ingredients, the weight percent range for that ingredient, some specific raw material examples, and their function(s) in the chassis.[2]

The key consumer benefits of a shampoo are:

- Excellent combability
- Superior volume control
- Soft and natural smooth hair feel
- Help repair damaged hair
- Thermal protection
- Color protection

Further benefits include:

- Silicone-like sleek wet feel of hair
- Avoids buildup
- Natural appearance and shine
- Ease of styling

## 21.3 CO-WASHING/CONDITIONING WASHING/CLEANSING CONDITIONERS[3]

The "wash and go" or "co-wash" trend has been around for several years, and it has become popular again because more and more consumers are looking for products that are gentler on their hair as well as on their hair color. These products gently cleanse hair with no suds or sulfates, leaving hair soft and frizz-free. Co-wash and cleansing conditioners provide a gentle way to clean hair and scalps without stripping natural oils. The gentle cleansing action of these products allow the scalp's oil production to regain balance, resulting in a decrease in overproduction. Typically consumers who use this regimen will shampoo weekly or biweekly in addition to regular co-washing. Based on the wave pattern/curliness of the hair, it is recommended that unless you have natural, curly hair or very dry tightly curly hair, you should think about co-washing as a supplement, not a replacement product. If one suffers from a scalp condition like dermatitis, co-washing occasionally is okay. But a strict no shampoo ("no-poo") regimen could make this condition worse. Also, depending on hair type, you may not see the benefit of co-washing. If you have oily hair, a typical cleansing shampoo is needed to remove excess oil; if you use a co-wash product, this could add extra oil to the hair.

There are certain properties that shampoos or cleansers have that are absent from some co-washing conditioners. For example, many shampoos are formulated with a low pH. The acidity of a shampoo makes it easier to remove dirt and product buildup from the hair.[2] Shampoos have detergents that clean the hair and scalp. Some co-washing conditioners exhibit some of these properties, but not all, so consumers need to check labels for what they want. With less surfactants, cleansing conditioners and co-washing formulas are best left in the hair for a few minutes for optimum cleansing.

## 21.4 MILD SHAMPOOS

Mild surfactants and effective conditioning agents are sought by consumers. Proteins are also incorporated into these systems due to their substantive and film-forming properties to help condition the hair. Excessively curly hair does not become coated with sebum secretions as readily as naturally straight hair, therefore the hair is usually washed on a weekly or every other week basis.

**TABLE 21.1** Shampoo Ingredients and Their Functions

| Ingredient Type | Weight % | Specific Examples | Function |
|---|---|---|---|
| Primary surfactants | 10 to 15 | Ammonium lauryl sulfate | Cleansing agent |
| | | Sodium lauryl sulfate | Used in combination or alone in cleansing sebaceous soil; and excellent lathering properties |
| | | TEA lauryl sulfate | |
| | | Ammonium laureth-2 sulfate | |
| | | Sodium laureth-2 sulfate | |
| | | Ammonium laureth-3 sulfate | |
| | | Sodium laureth-3 sulfate | |
| Sulfate-free surfactants | 0–50% | Sodium C14-16 olefin sulfonate | Mildness, good foamer; soft caring after feel |
| | | Cocamidopropyl hydroxysultaine | |
| | | Sodium cocoyl isethionate | |
| | | Sodium lauryl sulfoacetate | |
| | | Sodium lauroyl sarcosinate | |
| | | Decyl glucoside | |
| | | Lauryl glucoside | |
| | | Coco glucoside | |
| | | Caprylyl/capryl glucoside | |
| Secondary or Co-surfactants | 3 to 5 | Cocodiethanolamide | Foam modifiers; added cleansing; viscosity enhancement |
| | | Lauric diethanolamide | |
| | | Cocomonoethanolamide | |
| | | Cocoamidopropylbetaine | |
| | | Cocamide MEA | |
| | | Cocamine oxide | |
| | | Disodium cocoamphodiproprionate | |
| | | Capric/Lauric/Myristic/Oleic amidopropyl betaine | |
| | | PEG-80 sorbitan laurate | For baby shampoo to improve mildness of the anionics, improve cleansing and lather performance |
| | | Cocoamphocarboxyglycinate | |
| | | Cocoamphopropylsulfonate | |
| | | Decyl glucoside (and) polyglyceryl-10 caprylate/caprate (and) coco-glucoside (and) glyceryl oleate | To improve mildness, moisturizing effect; provide naturally derived |
| Conditioning agents | 0.05 to 1 | Soaps or salts of carboxylic acids; | Improve combability; provide smooth feel |
| | | Cationics including cationic polymers | |
| | | Polyquaternium-6 | |
| | | Polyquaternium-7 | |
| | | Polyquaternium-10 | |
| | | Polyquaternium-16 | |
| | | Polyquaternium-44 | |
| | | Polyquaternium-67 | |
| | | Polyquaternium-86 | |

*Continued*

**TABLE 21.1** Shampoo Ingredients and Their Functions—cont'd

| Ingredient Type | Weight % | Specific Examples | Function |
|---|---|---|---|
| | | Polyquaternium-87 | |
| | | Guar hydroxypropyltrimonium chloride | |
| Silicone Oil(s) | 0 to 2 | Dimethicone | Improved hair feel; wet and dry combability; provides soft, smooth feel; reduced flyaway; shine |
| | | Dimethiconol | |
| | | Amodimethicone | |
| | | Cyclomethicone | |
| | | PEG/PPG dimethicone | |
| Emollients, oils | 0 to 10 | Hydrophobic oils | Super fatting agents |
| | | Dicaprylyl ether (and) lauryl alcohol | |
| | | *Argania spinosa* (Argan) kernel oil | |
| | | Methyl gluceth-10 | |
| | | Glycereth-26 | |
| | | Rosemary leaf oil | |
| | | Moroccan oil | |
| Thickening agents | 0 to 10 | Hydroxyethylcellulose | Improves long-term product stability; aesthetics |
| | | Methylcellulose | |
| | | Xanthan gum | |
| | | Carbomer | |
| | | Acrylates copolymer | |
| | | Sodium chloride | Thickening up to 2%; forms lamellar, liquid crystalline structures |
| Active ingredients | 0.1 to 3 | Antidandruff ingredients (and) boosters | Combats dandruff and protects the hair; strengthens hair; provides moisturization |
| | | Panthenol | |
| | | Vitamins | |
| | | Antipollution actives | |
| | | Scalp actives | |
| Solvents | 0 to 1.5 | Propylene glycol | Clarifies the product or lowers the clear cloud point; lowers viscosity |
| | | Glycerine | |
| Opacifiers and pearlizers | 1 to 2 | Glyceryl stearates and derivatives, pigments, glycol stearate; glycol distearate | Provides opacity, pearlized effects |
| Proteins | 0.01 to 0.5 | Hydrolyzed wheat, soy, rice proteins; hydrolyzed keratin | Provides volume, smoothing, strengthening, and protection of the hair cuticle. |
| Fragrance | Q.S. (typically 0.5–1.5) | Fragrance | Sensory acceptance |
| Colorants | Q.S. | FD&C or D&C colors (USA) | For visual effects |
| Preservatives | Q.S. | Various options—see chapter on preservatives | Protects from microbial contamination; microbiological stability |
| | | Paraben-free; formaldehyde-free | |
| pH regulators | | Citric acid | To adjust pH |
| | | Phosphate buffer | |
| Water | Q.S. to 100 | | Solvent |

## 21.5 ALTERNATIVES FOR SULFATES

Sulfate-containing surfactant systems are widely used and accepted in the market for hair rinse-off products. New formulation concepts without sulfates are a rising trend with consumers desiring mildness. Based on studies conducted by Mintel Global New Products Database,[4] the sulfate-free trend has been growing in the marketplace since 2009. Most consumer products with a sulfate-free claim do not contain sodium lauryl ether sulfate (SLES)/sodium lauryl sulfate (SLS), and the word *sulfate* would not appear on the packaging ingredient label. Most sulfate-free products worldwide have been launched in the United States, United Kingdom, France, and Germany mainly for hair care, specifically shampoos.[6] L'Oréal has launched the most sulfate-free products worldwide, under their EverPure, EverCreme, EverCurl, EverSleek, and EverStrong sulfate-free brands.[5] The main ingredients used in sulfate-free body wash and hair shampoo products in Europe are: betaines, taurates, alkyl polyglucosides, sarcosinates, and succinates.

The claim "sulfate-free" can be interpreted in different ways in the market:

- No SLES/SLS (The word *sulfate* does not appear in the INCI list of ingredients on the package) and this is the most observed interpretation.
- No sulfate residual traces.
- No sulfur-derived ingredients

A summary of sulfate-free alternative functional ingredients is listed in Table 21.2.[7]

## 21.6 PRE-DAMAGE/PRE-SHAMPOOS

Pre-damage claims seek to prepare and protect hair before the damage occurs. In this case, the functional ingredients provide a shield of defense and/or strengthen hair. The treatment is applied prior to shampooing, usually in the form of an oil or a conditioner. Pre-shampoos can be applied the night prior, or immediately before shampooing. Pre-shampoos usually involve a heat source. They help to maintain moisture. The functional ingredients in these types of products are natural oils, vitamins, and conditioning agents.

**TABLE 21.2** Functional Materials to Address Trends: Examples of Sulfate-Free Alternatives

| Functional Material (INCI Name) | Formulation Benefits |
|---|---|
| Sodium cocoyl isethionate | Dense creamy foam; soft caring after feel |
| Disodium lauryl sulfosuccinate | Imparts slip and lubricity |
| | Easy to disperse in water |
| Sodium lauryl glucose carboxylate (and) lauryl glucoside | Excellent foam properties. |
| | Alkyl polyglucosides derivative, Natural Products Association (NPA) approved |
| Lauryl glucoside, coco glucoside | Proven mildness, good foam booster. NPA approved |
| Sodium cocoyl glutamate | Mild amino acid—based surfactant, NPA approved |
| Sodium lauroamphoacetate | Mild, good foamer. Substantive to the hair |
| Sodium cocamphoacetate, glycerin, lauryl glucoside, sodium cocoyl glutamate, sodium lauryl glucose carboxylate | Easy to use sulfate-free blend, NPA approved |
| Decyl glucoside, polyglyceryl-10 caprylate, caprate, coco-glucoside, and glyceryl oleate | Tear-free blend, NPA approved |
| Laureth-7 citrate | Extremely mild surfactant |

## 21.7 CONDITIONERS[8,9]

Conditioning is based on the concept of "substantivity," which characterizes the ability of cosmetic raw materials to modify the hair surface and affect the hair texture. The physical process involved is the adsorption of active materials onto the hair surface, which can change its properties such as:

- Surface potential
- Surface energy
- Friction

Hair is built of protein (keratin) with the composition and sequence of amino acids playing an important role in the process of hair interaction with cosmetic materials.

Other structural elements such as lipids can also contribute to the mechanism of ad(b)sorption of colloidal structures on hair. In general, the sorption of an ingredient on hair is governed by its attraction or binding interaction with the keratin protein.

The partition between the treatment solution and hair and the rate of penetration into the hair are determined by:

- The electrostatic character of the active
- The hydrophilicity of the material
- Its hydrophobic balance
  - If an ingredient is "more hydrophobic," this would mean that a greater amount is deposited onto the hair
- It's diffusion coefficient

For cationic surfactants and polymers, molecular characteristics influence their interactions with hair. These characteristics include molecular weight, charge density, and hydrophobicity.

Some polymers are linear, whereas others are branched and contain hydrophilic side groups. All of these attributes of the polymer can affect the final feel of the formulation on the hair during application, rinse off, or after rinsing, during styling, and after the hairstyle is complete. Body and antifrizz are only two of the many dry attributes that can be affected by the inclusion of Polyquaternium ingredients in a simple or complex formulation.

## 21.8 INTERACTIONS WITH HAIR[8–10]

Properties of hair that play an important role in determining the extent of surfactant or polymer deposition onto hair are the degree of its chemical modification, the presence of absorbed layers on the surface, the isoelectric point, damage magnitude, and hair shape/wave pattern. The function of conditioning polymers on hair is to detangle the hair during application, smooth the hair surface, reduce combing friction, improve wet and dry hair feel, reduce static, and protect the hair fiber. In the product, they act as a co-emulsifier, a complexing agent, and enhance deposition of actives onto hair. Buildup can occur. Some cationic polymers that are very substantive can bind to the hair surface at multiple sites by primarily electrostatic interaction in both adsorption and absorption leading to strong bonding with keratin. This problem can be eliminated with proper choice of cationic polymer and properly formulated products.

Some examples of conditioning polymers are the following:

- PVP (Poly-*N*-Vinyl-2- Pyrrolidone) and its copolymers
- Polyquaternium-11, -28, -16, Copolymers 845, 937, 958
- Acrylates (Polyquaternium-5, -6, -7, -18, -22)
- Quaternized polyvinyl polymers
- Polyquaternium-19, -20
- Quaternized lonenes (Polyquaternium-2, -17, -18, -27)
- Cellulose cationic polymers (Polyquaternium-4, -10, -24)
- Polysaccharides (Guar Hydroxypropyl Trimonium Chloride)
- Natural polymers that have been quaternized (proteins)
- Aminosilicones

Hair is not uniform from the root to the tip due to weathering, age, chemical treatments, etc., so the condition of the hair varies from the scalp to the ends.

Combinations of alkyl quats and polymeric quats are suggested in order to provide the wide diversity of needs for the hair. Just the "right" combination can provide smoothness, luster, strength, and protection.

The conditioner formulation usually contains the basic elements of an emulsion:[9]

- Water
- Primary conditioning agents (quats, cationic polymers, silicones)
- Refatting agents (fatty alcohols, waxes, butters)
- Secondary conditioning agents (natural oils, silicones)
- Emulsifiers (typically nonionic surfactants)
- Specialty additives (proteins, resins, dyes, antioxidants, botanicals)
- Thickeners (viscosity adjusting agents)
- pH Adjusting Agents
- Fragrances
- Preservatives, etc.

The ingredients used in a conditioner or hair treatment product and their function in the formulation chassis are listed in Table 21.3.[8–10]

## 21.9 HAIR DAMAGE AND ITS CAUSES

Hair damage results from both mechanical and chemical trauma that alters the physical structural components of the hair, to either weaken it or make it more susceptible to additional breakage from shampooing and everyday grooming. Sunlight, pool water, and products such as perms, bleaches, straighteners, and permanent hair dyes chemically alter the hair and increase its propensity to further breakage, resulting in cuticle abrasion, or erosion, or even split ends.[11–22] Many of these factors may act in concert to damage the hair, i.e., mechanical effects are often a common overlying factor.

- Sunlight exposure[16–22]
- Mechanical effects, i.e., brushing, combing, handling, toweling, back-combing (teasing)[16]
- Multiple exposure to water and surfactants
- Heating, i.e., blow-drying, heated curlers, tongs[12,13]
- Swimming pool water, i.e., chlorine water
- Harsh chemical processes, i.e., bleaching, permanent waving, dyeing, relaxing
- Combing out styling products, i.e., hairsprays, mousses, and gels
- Pollution[23]

Conditioning agents cannot enhance repair, since repair does not occur, but can temporarily increase the cosmetic value and functioning of the hair shaft until removal of the conditioning agent with cleansing. The cuticle is the main hair structure affected by conditioning agents. An intact cuticle is responsible for the strength, shine, smoothness, softness, and manageability of healthy hair. A layer of sebum coating the cuticle also adds to hair shine and manageability. Conditioning the hair can mitigate this hair damage by improving sheen, decreasing brittleness, decreasing porosity, and increasing strength.

## 21.10 CONDITIONING POLYMERS: SILICONE OILS AND DERIVATIVES[8,24]

Silicones are recognized as multifunctional ingredients in a variety of hair care products. With their unique set of chemical and physical properties, these highly versatile materials not only condition hair but can be used to add shine, make combing easier, provide color protection, help guard against damage from heat styling, enhance hair strength, help repair damaged hair, give a perception of moisturization, aid curl retention, control frizz, add volume, as well reduce volume. There are five silicone product types that are most widely utilized in the formulation of hair care compositions worldwide:

- Amino functionalized silicones
- Unmodified silicones
- Silicone glycol copolymers
- Phenyl-modified silicones
- Silicone resins

**TABLE 21.3** Conditioner Ingredients and Their Function

| Ingredient Type | Weight % | Specific Examples | Function |
|---|---|---|---|
| Primary conditioning agents | 0.5–3% | Alkyl quats, ester quats, cationic/acrylamide copolymers, SAPDMA | Primary conditioning agent; provides easy combing, smooth hair feel, antistatic properties; detangling |
| Secondary conditioning agents | 0.2–1.0% | Polyquaterniums, cationic guar | Easy combing; smooth hair feel, antistatic properties |
| Silicones | 0–2% | Cyclomethicone; dimethicone; dimethiconol; amodimethicone; phenyltrimethicone; | Provides wet and dry comb; smooth wet and dry feel; softness; gloss |
| Oils | 0.5–15% | Natural oils; almond oil; coconut oil; argan oil; Moroccan oil; tea tree oil; grapefruit oil; jojoba oil; safflower oil | Provide moisturization; soft and pliable hair; antifrizz; smooths hair; seals and coats the cuticle; hydrates the scalp; provides shine |
| Polyols | 1–5% | Glycerin; sorbitol; sodium PCA | |
| Emulsifiers | 0–2% | Nonionic, anionic, and cationic emulsifiers, including polymeric emulsifiers | To stabilize the emulsion |
| Fatty alcohols consistency waxes | 0–5% | Fatty alcohols, glyceryl stearate, pentaerythrityl distearate, cetyl Palmitate; bees wax; shea butter; lecithin; phospholipids | For product aesthetics and overall thickness of finished product; provide lubrication; easier combing; smooth hair feel |
| Care ingredients Actives (Reconstructors) | 0.1–5% | Panthenol, proteins, hydrolyzed proteins, keratin, amino acids | For claims benefits; also to provide strengthening, moisturization; film forming; hair feel |
| Vitamins anti-oxidants | 0–2% | Vitamin B, A, E, and F<br>Vitamin E, C, green tea; goji berry; acai; baobabs | Stimulate keratinization; purify and scavenge free radicals, UV protectant; antipollution effect; hydrates the scalp |
| Thickeners/rheology modifiers | 0–2% | HASE thickeners, liquid dispersion polymers, Polyquarternium-86 | To thicken formulation; thinning behavior; to adjust viscosity |
| Emollients | 2–5% | Ethers, esters, shea butter, silicones, hydrogenated polyisobutene | Superfatting agents |
| Chelating agents/ stabilizers | 0–1% | EDTA, pentaerythrityl tetra-di-t-butyl hydroxyhydrocinnamate | To stabilize formulation long term; tie up metals in manufacturing tanks; better formulation in hard water |
| Fragrance | 0–2% | Fragrance | Sensory/aesthetics |
| Dyes | QS | FD&C and D&C colorants | Visual aesthetics |
| Preservatives | 0–1% | Various options paraben-free; formaldehyde-free | Protect from microbial contamination; microbiological stability |
| pH regulators | QS | Citric acid; lactic acid | To adjust pH |
| Water | QS to 100% | Water | Solvent |

It should be noted that the INCI designation may refer to a number of different polymers, and that the descriptions provided are generalizations, pertaining to the average materials in each category. Within one INCI designation, the performance characteristics may be dramatically different. Silicones are described by their percent nitrogen content, molecular weight, molecular weight distribution, and $x$ and $y$ values. Please refer to the book by A. O'Lenick

**TABLE 21.4** Types of Silicones Used in Shampoos and Their Function

| Silicone Type | Function |
|---|---|
| Dimethicone fluids and gums | Improved hair feel, wet/dry comb, softness, shine |
| Siloxysilicates | Volume, body, set retention |
| Amine functional | Wet/dry comb; heavier conditioning; softness, reduced flyaway, shine, opacifier-durability |

The typical use level in a shampoo is in the range of 0–2% weight percent.

**TABLE 21.5** Types of Silicones Used in Conditioners and their Function

| Silicone Type | Function |
|---|---|
| Volatile | Wet comb, transient gloss |
| Dimethicone fluids & gums | Improved hair feel, wet/dry comb, softness, shine |
| Amine functional | Wet/dry comb; heavier conditioning; softness, reduced flyaway, shine, opacifier-durability |
| Phenyl fluids | Shine |
| Organomodified | Conditioning, volume, shine |
| Siloxysilicates | Volume, body, set retention |

The typical use level in a conditioner chassis is in the range of 0.5–2% weight percent.

Jr. *Silicones for Personal Care*[24] for more specific details about each product type. Tables 21.4 and 21.5 list the types of silicones used in shampoos and conditioners and their specific functions in the chassis.[8]

Some examples of silicones currently used in hair care shampoos and conditioners include: dimethicone, cyclomethicone, phenyltrimethicone, amodimethicone, PEG/PPG dimethicone, dimethiconol, and dimethicone copolyol.

## 21.11 SILICONE-FREE ALTERNATIVES

Consumers are the driving force for the push toward silicone-free products. Some limiting factors on the use of silicones in shampoos and conditioners are listed here:

- Tend to be heavy on the hair, causing curl droop;
- Some classes of silicones can cause buildup;
- They reduce the foam of many formulations, limiting their utility;
- Silicone fluids lack solubility in water and in many organics and therefore are very difficult to use in formulations;
- Silicone fluids are greasy so they can make the hair look and feel dirty;
- Silicone fluids need to be emulsified to be used in water-based systems;
- They can interfere with chemical treatment processes—hair color won't absorb, etc.

These limiting factors plus a polluted urban environment have spurred a "silicone-free" alternative trend and new product launches. The alternatives for silicone high-molecular-weight liquid grades and derivatives for hair care are mainly used for conditioning properties, hair protection, repair effect, and gloss enhancement.

See Table 21.6 for a list of silicone-free functional material ingredient options.[25]

TABLE 21.6 Functional Materials to Address Trends: Examples of Silicone-Free Alternatives

| Functional Material (INCI Name) | Formulation Benefit |
|---|---|
| Dicaprylyl ether (and) decyl glucoside (and) glyceryl oleate | Natural-based microemulsion |
| PEG-40 hydrogenated castor oil (and) PEG-7 glyceryl cocoate (and) PEG/PPG-120/10 trimethylolpropane trioleate (and) glycerin | Cost-effective silicone-free alternative |
| PEG-4 distearyl ether (and) sodium laureth sulfate (and) distearyl ether (and) dicaprylyl ether | High-performance multifunctional micronized wax dispersion |
| Coco-caprylate (and) lauryl glucoside (and) glycerin (and) polyglyceryl-2 dipolyhydroxystearate (and) polyglyceryl-3 diisostearate | Microemulsion for mild applications |
| Coco glucoside (and) glyceryl oleate | Lipid layer enhancer |
| Dicocoyl pentaerythrityl distearyl citrate | Aids in deposition of silicone; improves hair shine and hydro-balance |

## 21.12 LEADING GLOBAL HAIR CARE MARKET TRENDS

A summary of the leading global hair care market trends is listed in Table 21.7.

Information was extracted from recent online articles, blogs, market reports, Internet searches, and new product launch reviews to compile this summary. The sources used for this analysis included: Datamonitor, Mintel Global New Products Database, Kline & Company, Euromonitor International; Think with Google; Motley Fool, Industry trade magazines (i.e., Modern Salon, Cosmetics & Toiletries, Global Cosmetic Industry, Household and Personal Products Industry (happi), Cosmetics Design—Asia, and Cosmetics Design—Europe); Computer World, Global Personal Care Industry conferences and trade shows; and manufacturers' websites.

## 21.13 NEW AGE OF CONNECTIVITY

As shown in Table 21.7, with this new age of connectivity, manufacturers are adapting to a global society that relies on technology for every capacity of life. In 2015 there were 8 billion people using smartphones.[26] Consumers are shopping with their smartphones and assessing social media (i.e., YouTube videos, Facebook posts, Twitter, etc.) via beauty blogs and other multimedia to research products, reviews, and ingredients before they purchase; and they are tuning into YouTube videos and hairstyle applications (apps) to test out new hairstyles, hair colors, and hair care regimens. They are looking for products that will deliver on their promise, to help bring out the best in their hair, while using the best possible ingredients to do so. Hair care regimens coupled with choice of products is highly individualized and consumers can be heavily influenced by salon professionals, online blogs, and recommendations.

## 21.14 PRODUCTS HAVING "FREE-FROM" CLAIMS

From a global perspective, "Free-from" alternative claims continue to grow, with paraben-free being the top claim. New commercial launches for sulfate-free, silicone-free, mineral/petroleum-free, and gluten-free are increasing year on year in all regions.

**TABLE 21.7** Summary of Leading Global Hair Care Market Trends

| Leading Global Hair Care Market Trend | Region of the World | Description of the Current Trend |
|---|---|---|
| Age of connectivity | Global | Eight billion people are using smartphones since 2015. Manufacturers are adapting to a society that relies on technology for every capacity of life. |
| Free-from | Global | Paraben-free, sulfate-free, silicone-free, mineral oil/petroleum-free; salt-free, gluten-free |
| Botanical/Herbal ingredients | Global | Herbal ingredients lend naturalness to formulations. Natural and organic ingredients are important in maintaining healthy, nourished hair. |
| Sun care inspired solutions: UV protection | Brazil | Preventive, after-sun treatments, and/or providing multifunctional solutions |
| Skin care–inspired solutions: Antipollution | Asia–Pacific | Pollution is the third highest concern of Chinese women aged 20–49; a growing consumer awareness of pollution effects in urbanized regions |
| Color statements/protection/renewal | Global | Observing bold, temporary statements with color inspiration moving toward smart solutions |
| Antiaging | Asia-Pacific, EU, NA | The human population is getting older; world's population is graying dramatically. Longer working lives lead to new purchasing power and product needs. |
| Frizz prevention/control | Global | All hair textures, all curls, all ethnicities; and the best way to treat texture individually |
| Scalp protecting | Asia-Pacific | Looking beyond antidandruff and offering multifunctional benefits (i.e., moisturization, antipollution, mild formulations |
| Healthy-looking hair | Global | Healthy sensorial feel, shine |
| Sensorial experience-fragrance | EU, Asia-Pacific | Long-lasting fragrance; odor absorbing; multifunctional benefits |
| Sustainable solutions | Global | Use of natural/renewable ingredients. Less packaging, water, transportation |

A minimum of 20% of all hair care products launched in Europe in 2014 claimed to be silicone-free or sulfate-free; and Japan is leading the launches for silicone-free hair products.[4]

## 21.15 BOTANICAL/HERBAL INGREDIENTS

The use of botanicals and herbal extracts continues to be the top global claim for shampoos and conditioners. These ingredients are especially the most important trends in Asia-Pacific where some domestic manufacturers are taking

advantage of the local botanical ingredients to formulate products due to the strong heritage of traditional, plant-based medicines. Sixty-three percent of all hair care launches in Asia in 2014 contained botanicals/herbal extracts.[4] Herbal ingredients lend naturalness to formulations and are sought out by consumers. For example, in Argentina, hair care is a key element of appearance, for both men and women. A large number of Argentinian women are known to wear their hair long, higher than the world average for women. Furthermore, they believe that their hair requires consistent care and looking after, encouraging higher sales of natural and beneficial hair products. This behavior has been spurring the sales of organic products without ingredients like parabens, SLES, SLS, silicones, and more—awareness about which is proactively acquired by urbanized Argentinians accessing social media via beauty blogs and other media.

## 21.16 SUN CARE–INSPIRED SOLUTIONS: ULTRAVIOLET PROTECTION

Today's hair care products do more than simply clean, condition, treat, and style hair as concepts cross over from other market categories with an increasing number of benefits. There are growing concerns of sun damage to hair. Based on Datamonitor, 29% of consumers globally said they are extremely/or very concerned about hair sun damage.[27] Hair care manufacturers are addressing this need by offering products formulated with ultraviolet (UV) absorbers to reduce sun-related fading and discoloration. UV protection is achieved with inclusion of UV absorbers such as benzophenone-4, ethylhexyl methoxycinnamate; dimethylpabapropyl laurdimonium tosylate (and) propylene glycol distearate, and ethylhexyl methoxycinnamate (and) diethylamino hydroxybenzoyl hexyl benzoate. Commercial products are achieving UV protection by launching "preventive" products such as Ouidad Sun Shield Leave-In Spray, "reactive" products with after sun treatment ingredients such as Aveda After Sun Hair Mask, and/or providing "multifunctional solutions" with Kérastase Soleiol CC Crème.

## 21.17 SKIN CARE–INSPIRED SOLUTIONS: ANTIPOLLUTION/RECONSTRUCTION

Skin care–inspired commercial hair care products are also being introduced. We are observing antipollution claims expanding from skin care into hair care, with many new shampoo and conditioner product launches claiming to protect hair from external pollutants. Pollution is the third highest concern of Chinese women aged 20–49;[28] and there is a growing consumer awareness of pollution effects in other global urbanized regions. Manufacturers are turning to a range of ingredients to provide preventative treatments to fight pollution's negative effects. Antioxidants are the most utilized solution for the free radicals generated by pollution and the other irritants of everyday life. Vitamin E, vitamin C (with the most common forms being ascorbic acid and ascorbyl palmitate), and green tea are the most popular. They are frequently used in combination in formulations. Plant extracts are especially popular. Some examples are moringa, white and green tea, acai berry, and *Litchi chinensis* pericarp extract; all of which claim to offer different functional benefits. The botanical peptides extracted from the seeds of the moringa tree were developed to prevent damage from pollution buildup and to keep hair clean by inhibiting the adhesion of particulate pollution to the hair shaft.[23]

External and internal forces affect the quality of the hair. As stated earlier in this chapter, everything from excessive wind, salt air, chlorine, sun, high humidity, to pollution can have a negative impact on the health of hair. Avoiding exposure to harsh weather conditions and unhealthy foods, and an occasional break away from certain chemical hair treatments, as well as the use of properly formulated hair care products will help to protect it. Hair treatment masks have been introduced to address these needs and provide deep-conditioning benefits to hair. In Argentina, Unilever introduced Dove Heat Activated Reconstructor Treatment for hair. The regenerative treatment mask and heat activated serum together generate a gentle heat for a deep hair treatment. The product claims to help restore hair at the deepest layers and leave the hair strong and shiny. In the United States, Pureology introduced Strength Cure Restorative Masque for color-treated hair containing protein, amino acid, and lipid complexes to help strengthen and deeply condition hair that has been microscarred and color damaged. Proteins are very useful for conditioning and moisturizing the hair. The proven substantivity of cosmetic proteins to the hair is well correlated to the degree of damage of the hair. Proteins may act as a humectant and a "moisture reservoir" for dry hair, increasing the rate of moisture uptake from the air and decreasing the rate of moisture loss in arid conditions.[29] Proteins have been shown to aid in repairing hair damage such as split ends and to provide protection from damage such as that which occurs during permanent waving. The effects of protein treatment are not merely surface phenomena, as the cosmetic proteins are shown to penetrate into the hair cortex.

## 21.18 COLOR STATEMENTS/PROTECTION/RENEWAL

Hair color manufacturers are making bold, temporary statements with color inspiration moving toward smart solutions with products such as Garnier Color Styler Intense Wash Out Color where the consumer can style their hair with a temporary color that washes out after two to three shampoos, allowing them the flexibility to change their look anytime they desire. High relative humidity (RH) was shown by S. Ruetsch et al.[18] to be the primary contributing factor to accelerated loss in hair color. The combination of both high RH conditions and unfiltered solar light proved to be the most damaging effect on hair color. Color refresher products such as John Freida's Radiant Red Shampoo and Radiant Red Color Protecting Conditioner contain antifading technology (i.e., color depositing pigments such as Basic Red 51[30]) to revive and maintain the color after hair dyeing. These types of products are also referred to as "color maintenance" products. They add highlights to natural color and help refresh and prolong hair color.

## 21.19 ANTIAGING

Prolonging aging encourages mature hair care consumers to maintain a healthy look longer. As older consumers work longer, they will want to look their best. Western Europe, Asia, and North America's populations are aging; individuals aged 55–64 and 65–74 are the fastest growing demographics.[28] Hair thinning, loss of volume, and dryness due to less sebum production are typically associated with the aging process. Yet, the overall objective for older consumers remains the same—while more people may be using colorants to hide gray hair, they still seek shine, excellent sensory effects, added volume, and other characteristics to achieve healthy-looking hair and well-being. The White Hot hair care brand suitable for gray/white hair is positioned as a multifunctional solution to address many of these hair needs.[4] The brand is formulated with Keravis (to smooth and strengthen hair), blue lupin to remove dull yellow tones, shea butter and white truffle for moisturization, and baobab oil for moisturization. Argan oil provides gloss and shine along with antifrizz properties. Argan oil and jojoba oil provide antiaging properties.

## 21.20 SCALP PROTECTING

Consumers are looking beyond antidandruff scalp protection products and offered multifunctional benefits (i.e., moisturization, antipollution, mild formulations).

## 21.21 SENSORIAL EXPERIENCE: LONG-LASTING FRAGRANCE

Hair care innovations also aim to evoke sensorial experiences through the sense of smell. Fragrance transforms from the shower into a long-lasting experience offering further benefits such as cleansing, UV protection, moisturizing, and taming flyaway hair. Chanel launched Chance Eau Tendre Hair Mist highlighting that the product perfumes hair without drying it out with the added benefits of shine and moisturizing. Shiseido launched MA CHERIE Hair Fragrance. This product provides a long-lasting odor block from food, cigarettes, and other strong smells while also providing deep penetration into damaged cuticles and hair repair from the inside out. It also enhances gloss and shine, and leaves the hair silky smooth to the touch.[4]

## 21.22 SUSTAINABLE SOLUTIONS: USE OF NATURAL/RENEWABLE INGREDIENTS/ NEW PRODUCT FORMS

It has been reported that by 2025, 1.8 billion people will experience absolute water scarcity, and two-thirds of the world will be living under water-stressed conditions.[28] Sustainable solutions will be needed to address and solve this water issue. Two new dry shampoo products recently launched are addressing this issue; namely, Moroccan Oil Dry Shampoo (Israel) which contains an ultrafine rice starch that absorbs oil, buildup, and odor, and Monoi Conditioning Dry Shampoo (Carols Daughter, NY) which absorbs oily buildup for on-the-go styling. The product contains natural starch that helps hair maintain its natural luster and shine and willow bark extract to extend the style of the hair.

Rising consumer interest and purchases are driving the growth in natural product launches and claims. Sixty percent of women worldwide expressed that natural claims highly influenced their choice of beauty products. Four out of 10 new product launches featured natural claims.[4] Use of natural/renewable ingredients is a necessary component to meet those claims. Vitamins are claimed to stimulate the keratinization and to provide essential fatty acids (i.e., Vitamins B, A, E, and F). Antioxidants are positioned for protection and defense. The main ones used in hair care are Vitamins E and C and green tea. Various extracts are made and used, for example, extracts of wheat germ. Marine microelements "Dead Sea minerals," menthol, eucalyptus, and pine are said to be antistress and energizing in leave-in treatments. Plant and medicinal extracts such as rosemary and sage are said to purify and fight free radicals. Ginseng is said to strengthen roots and stimulate natural growth. Super fruits are seen in many new product offerings, such as goji berry, acai, and baobab. See Table 21.8 for an up-to-date list of botanicals, herbal extracts, natural oils, and butters that are currently being sought.

Time-saving claims promote the ideas of fast drying, fast acting, and fast styling within the hair care regimen. Speed and convenience remain important to all consumers, but it is especially important for those consumers who have coarse, thick, porous hair.

**TABLE 21.8** Functional Materials to Address Trends: Some Examples of Botanicals/Herbal Extracts; Natural Oils/Butters

| Functional Material | Formulation Benefit |
|---|---|
| Sunflower | Repairs and protects against breakage |
| Senna | Hair surface smoothing |
| Bush mango wax | Shine, illumination, brilliance |
| Miracle tree | Pollution and environmental protection |
| Lychee | Free radical scavenging |
| Argan oil | Moisturizing |
| Hibiscus | Conditions and detangles |
| Sweet almond oil | Antistatic for damaged hair |
| Linseed oil, sweet almond oil | Visibly restores healthy hair |
| Cashmere wool | Conditions and strengthens |
| Moringa oil | Natural oil |

**TABLE 21.9** Key Consumer Needs and Drivers

| Key Consumer Needs | Consumer Drivers |
|---|---|
| Gloss | Shiny hair, illumination, radiance, brightening |
| Repair | Restore/refill damage, seal split ends, provide smoothness |
| UV protection | Protection against UV light for scalp and hair |
| Heat protection | Prevent the damage from high temperatures that comes with blow drying and curling or straightening with irons |
| Moisturization | Healthy-looking hair; increased suppleness, softness, and sheen of hair |
| Color protection | Prevent color fading, lock color in |
| Volume control | Straight and controlled hair, sealed against climate influences |
| Volume creation and thickening | Push-up effect/lift-up for fine and fragile hair; volume/strength from the inside and outside |
| Convenience | Fast acting, quick drying, in-between refresh |
| Frizz control | Smooth hair; help repair split ends, and seal hair cuticles |

## 21.23 CONSUMER NEEDS AND DRIVERS

A summary of the key consumer needs and drivers for shampoos and conditioners is listed in Table 21.9.

These consumer needs are universal and will drive the functional ingredients and technologies that are required to provide the desired benefits to the hair.

## 21.24 CONCLUSIONS

Based on consumer demand, natural and sulfate-free products continue to be of interest. As a result, formulators are increasingly incorporating natural ingredients in their products while reducing the proportion of synthetic products. Demand for antiaging and natural ingredient–based hair care products is growing. Consumers are also looking for multifunctional hair care products. For example, they want conditioner products that can offer additional benefits such as scalp protection, color protection, sun protection, and frizz protection. As a result, cosmetic manufacturers are developing multifunctional hair care products that offer additional benefits such as antiaging, antifrizz, volumizing, and color protection to hair.

## Acknowledgments

I wish to acknowledge my colleagues Andrew Miller, Guadalupe Pellon, and Katherine Spetrino for helping to provide specific market and consumer needs information; and Joel Basilan and Manasi Chavan for providing specific technical information for this chapter.

I would also like to acknowledge Dr. Robert Lochhead for useful discussions on the preparation of the chapter.

## References

1. http://www.gcimagazine.com/marketstrends/segments/hair/Translating-Trends-for-Hair-Care-Product-Development-190739661.html#sthash.UAvlIDb3.dpuf.
2. Bozza J. In: *Session 1: Shampoos: Formulating Shampoo Products, Society of Cosmetic Chemists- Continuing Education Program, Hair Care Technical Symposium Program*; 2005.
3. http://www.realsimple.com/beauty-fashion/hair/hair-care/co-wash-natural-hair.
4. *Mintel Global New Products Database (GNPD)*. 2015.
5. www.lorealparisusa.com.
6. BASF Corporation. *Alternatives for sulfates*. 2016.
7. Rocafort C. In: *Back to Basics: Hair Conditioners: Formulating and Testing Hair Conditioner Products, Society of Cosmetic Chemists — Continuing Education Program, Hair Care Technical Symposium Program*; 2012.
8. Schueller R, Romanowski P. *Conditioning agents for hair and skin, cosmetic science and technology Series*, **21**. New York: Marcel Decker; 1999.
9. De Polo KF. *A short textbook of cosmetology*. 1st ed. Augsburg (Germany): Verlag fur Chemische Industrie; 1998.
10. Jachowicz J. Hair damage and attempts to its repair. *J Soc Cosmet Chem* July/August 1987;**38**:263–86.
11. Gamez-Garcia. The cracking of human hair cuticles by cyclic thermal stresses. *J Cosmet Sci* May/June 1998;**49**:141–53.
12. McMullen R, Jachowicz J. Thermal degradation of hair II, effect of selected polymers and surfactants. *J Cosmet Sci* July/August 1998;**49**:245–56.
13. Ruetsch SB, Kamath YK, Weigmann HD. Cuticle reinforcement by cationic hair conditioners. *J Cosmet Sci* 1997. Preprints of Annual Scientific Meeting.
14. Susan K, Robinson VNE. The effect of grooming on the hair cuticle. *J Soc Cosmet Chem* July 1982;**33**:203–15.
15. Gao T, Bedell A. Ultraviolet damage on natural gray hair and its photoprotection. *J Cosmet Sci* March/April 2001;**52**:103–18.
16. Hoting E, Zimmermann M. Sunlight induced modifications in bleached, permed, or dyed hair. *JSCC* 1997;**48**:79–91.
17. Ratnapandian S, Warner SB, Kamath Y. Photodegradation of human hair. *JSCC* 1998;**49**:309–20.
18. Ruetsch SB, Kamath Y, Weigmann H-D. Photo degradation of human hair: an SEM study. *JSCC* 2000;**51**:103–25.
19. Santos Noguiera AC, Nakano AK, Joekes I. Impairment of hair mechanical properties by sun exposure and bleaching treatments. *JSCC* 2004;**55**:533–7.
20. Takahashi T, Nakamura K. A study of the photolightening mechanism of red hair with visible and ultraviolet light: comparison to red hair. *JSCC* 2005;**56**:47–56.
21. Takahashi T, Nakamura K. A study of the photolightening mechanism of blond hair with visible and ultraviolet light. *JSCC* 2004;**55**:291–305.
22. BASF Beauty Creations. *Puricare™ brochure*. September 2012.
23. O'Lenick A. *Silicones for personal care*. IL: Allured Publishing Corporation; 2003.
24. BASF. *Silicone alternatives for personal care*. 2016.
25. *Computer world*. 2014.
26. *Datamonitor*. 2015.
27. *Trends 2025 beauty & personal care*. Mintel Group Ltd.; 2016.
28. Breuer MM. "The binding of small molecules to hair", I. The hydration of hair and the effects of water on the mechanical properties of hair. *JSCC* 1972;**23**:447–70.
29. BASF Corporation. *Vibracolor® Cationic hair dyes brochure*. September 2012.
30. *Mintel natural BPC products — skincare, soap & bath and hair care*. February 2015.

CHAPTER

# 22

# Nanotechnology in Cosmetics

*S. Nafisi*[1,2], *H.I. Maibach*[2]

[1]Central Tehran Branch, IAU, Tehran, Iran; [2]University of California, San Francisco, CA, United States

## 22.1 INTRODUCTION

Nanotechnology, a young science, is described as the investigation of material on an atomic or molecular scale. A nanometer (nm) is one-billionth of a meter, and typical atoms are approximately one-third of a nanometer. In general, nanotechnology speaks about dimensions in conjunction with form in a nanometric level.[1–4]

Nanobiotechnology is a branch of nanotechnology that addresses the biological and biochemical application of nanoparticles. It has made room for therapeutic and cosmetic disciplines and health care products for the past four decades. It improves drug efficiency and topical delivery by overcoming drug insolubility problems, protecting them against physical or chemical decomposition and improving penetration by increasing the period of skin permanence, controlling active substance release, and penetrating to skin appendages. Solid evidence for topical therapy has provided higher efficiency by novel nanoformulations over classical agents.[5,6] Outstanding features and behavior of nanomaterials have greatly influenced the cosmeceutical industry. Accelerated employment of nanomaterials in makeup products is indicative of nanotechnology potential in the cosmetics industry. Some nanomaterials containing nanoemulsions, nanogels, and nanoparticles (NPs), such as zinc oxide (ZnO), titanium dioxide ($TiO_2$), silicon dioxide ($SiO_2$), alumina, calcium fluoride, silver, copper, fullerene, etc. are being used in cosmetics.[7–10] Nanoemulsions, for instance, are transparent emulsions with special rheological qualities, enabling them to escalate the amount of salubrious oils while maintaining transparency and the formula's lightness. Mineral NPs, like $TiO_2$ and ZnO-effective ultraviolet (UV) filters reflect and diffuse the visible zone of solar radiation when absorbing UV light and thus are widely utilized in sunscreens. Additional examples of marketed nanocosmetic products are body-firming compounds, bronzers, exfoliant scrubs, eyeliners, and styling gels.[11]

## 22.2 SKIN STRUCTURE AND FUNCTION

### 22.2.1 Skin Structure

Skin, a large organ in weight (16% of body weight) and surface area (1.8 $m^2$), consists of three major structural layers: epidermis, dermis, and hypodermis (subcutis) (Fig. 22.1).

Nails, hair, sebaceous, apocrine, and eccrine sweat glands are skin accessory structures. Anatomical site, sex, and age are effective factors in skin thickness. In comparison with the ventral and flexors, extensor and dorsal are thicker. Palms and soles have the thickest skin (around 4 mm thick), and the thinnest skin is on the eyelids and postauricular region (around 0.05 mm thick). Skin gradually thickens until the fourth or fifth decade and then begins to thin. Thinning is primarily a dermal change, with loss of elastic fibers, epithelial appendages, and ground substance. In comparison with male skin, females have characteristically thinner skin in different anatomic locations. Skin is a dynamic organ that changes constantly throughout life, as cells of the outer layers are continuously replaced by cells of the inner layers[12,13] (Fig. 22.1).

#### *22.2.1.1 Epidermis*

Epidermis, a superficial layer of stratified epithelium develops from ectoderm and acts as the chemical and physical barrier for the body, protecting it from the exterior environment, and is stratified squamous epithelium without blood

*Cosmetic Science and Technology: Theoretical Principles and Applications*
http://dx.doi.org/10.1016/B978-0-12-802005-0.00022-7



Copyright © 2017 Elsevier Inc. All rights reserved.

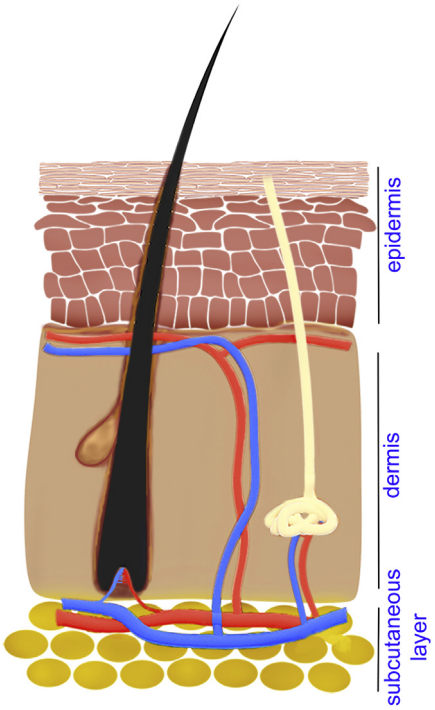



FIGURE 22.1 Human skin layers.

vessels. There is no blood vessel in the epidermis, therefore blood capillaries present in the upper layers of dermis feed cells in the deepest layers by diffusion. The waste disposal will be diffused to skin surface and dermoepidermal junctions. Epidermis is mainly composed of keratinocytes, which are in a constant transition from deeper layers to the superficial. Protein keratins supplied by keratinocytes serve as a bridge and connect the keratinocytes. Layers of epidermis are constructed by the differing phase of keratin maturation, shifting from the lower layers upward to the surface. *Stratum basale* (SB) (basal or germinativum cell layer), s*tratum spinosum* (SS) (spinous or prickle cell layer), s*tratum granulosum* (SG) (granular cell layer), and s*tratum corneum* (SC) (horny layer) are the epidermal layers.

A thin layer of translucent cells in thick epidermis called the *stratum lucidum* represents a transition from the SG and SC, which is not generally seen in thin epidermis. The SS and SG are also known as the Malpighian layer.

The SB is the innermost layer of epidermis next to the dermis and is composed of largely dividing and nondividing keratinocytes adhered to the basement membrane via protein keratin of hemidesmosomes. As keratinocytes divide and differentiate, they shift from SB to the surface.

SS is an epidermal layer between the BS and SG. By reproducing and maturing, basal cells migrate toward the surface and initially form the SS. The cells are adhered by intercellular bridges named desmosomes. Langerhans cells, immunologically active cells that stem from the bone marrow, are found on all epidermis layers, but usually in the middle of this layer. They also exist in the papillary dermis, especially nearby blood vessels. The Langerhans cells act as antigen-producing cells and play a key role in immune reactions of skin[14] (Fig. 22.2).

The SG or granular layer is a thin epidermal layer. They lose their nuclei and cytoplasm by continuing the transition of the keratinocytes from the underlying SS to the surface and appear as granular at this level. These cells have keratohyalin granules containing histidine- and cystine-rich proteins and are capable of binding the keratin filaments together.[15,16]

The SC (also known as corneocytes), the outermost epidermal layer and the final product of keratinocyte maturation, is formed of flattened dead cells with no cell organelles. Lipidic bilayers surround their extracellular space. There are $10 \pm 30$ layers of heaped corneocytes in most areas, with soles and palms having the most. Each corneocyte is confined by a protein envelope and includes water-retaining keratin proteins. The cellular shapes of the keratin proteins and their orientation give strength to the SC. SC is generally made up of three lipid components—cholesterol, ceramides, and fatty acids—and serves as a water reservoir and natural physiological environment for skin.

#### 22.2.1.2 Dermis

Dermis, a layer between subcutaneous tissue and epidermis, consists of connective tissue and cushions the body from strain and stress. It is divided into two layers, the superficial area contiguous to epidermis, known as the

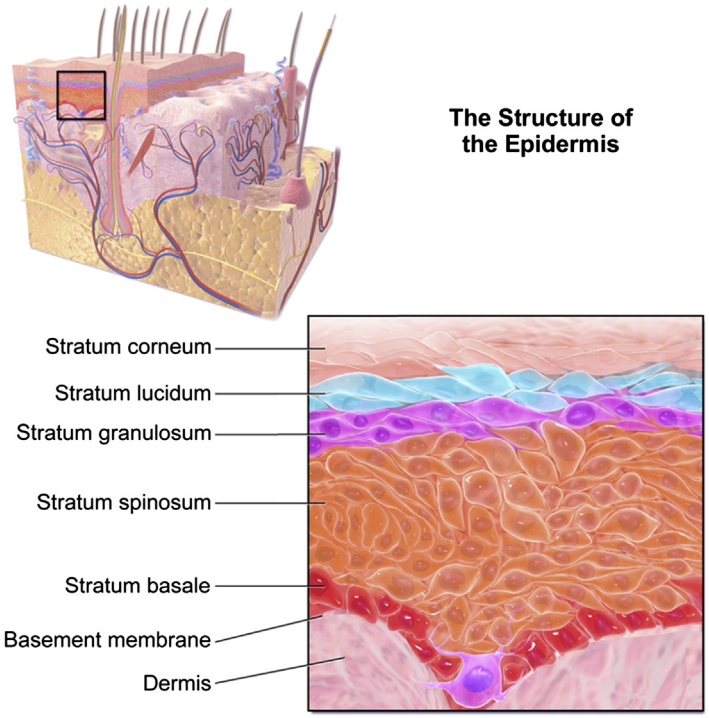



FIGURE 22.2 The structure of the epidermis. *Reproduced with permission from Blausen gallery, 2014.*

papillary region, and a deep, thicker area called reticular dermis.[17,18] Dermal fibroblasts make collagen fibers, structural proteoglycan, and elastin, which embed macrophages and immune-competent mast cells. Seventy percent of the dermis is composed of collagen protein, which provides skin strengthen and toughness. Proteoglycan is in charge of hydration and viscosity to the dermis while elastin supplies normal elasticity and flexibility. Other skin components such as hair, sweat glands, lymphatics, and blood vessels are placed within these cells and fibrous tissue. Dermis thickness changes from 0.6 mm on the eyelids to 3 mm on the back, soles, and palms.[17,18]

#### *22.2.1.3 Hyperdermis (Subcutis)*

Subcutis consists of loose connective tissue and fat that can reach to 3 cm in abdominal parts. Dermis has special corpuscular receptors that transit touch by Meissner's corpuscles and vibration sensations by Pacinian corpuscles. In dermis, all cutaneous nerves have a cell body that provides free sensory nerve detecting temperature and itch on the skin surface. The autonomic nervous system in the dermal layer affects apocrine glands, blood vessels, and hair follicle muscles by adrenergic fibers, whereas eccrine sweat glands are innervated by cholinergic fibers. Sebaceous glands are regulated via the endocrine system and are not innervated by autonomic fibers. A superficial artery plexus is fabricated at the papillary and reticular dermal boundary through the branches of the subcutis. Capillary loops in the papillae of the dermis are created by branches from the plexus. Each contains a single loop of capillary vessels, one arterial and one venous. Dilatation and constriction of these capillary loops control skin temperature. Papillary layer also contains lymphatic meshes that drain the lymph and feed the regional lymph nodes.[18]

#### *22.2.1.4 Derivative Structure of the Skin*

Apart from basic layers and cells, skin has distinct derivative structures such as hair, nails, and sebaceous and sweat glands that can protect the body.[13]

##### 22.2.1.4.1 Hair

Hair grows to the surface at a variable rate. Some parts such as face and scalp have more hair follicles, while the soles, palms, and glans penis are hairless. Hair follicles stem from epidermis and dermis and are derived by germinative cells that make melanin and keratin. The hair shaft has an internal medulla covered by a cortex of keratinocytes and outer cuticle. Hair bulb is also surrounded by a two-layered root sheath. "Goose bumps" of the skin occur

under environmental and emotional stimulation (e.g., cold, fear) via erector pili muscle associated with the hair shaft.[13,15]

#### 22.2.1.4.2 Nails

Fingers are protected by the tips via compact plates of hardened keratin with 0.3–5 mm thickness called nails. Nail matrix, nail bed, and nail plate are their three parts. Nail matrix, the formative layer of cells at the base of the toenail or fingernail, consists of dividing keratinocytes that mature and keratinize to fabricate the nail plate. The visible part of the matrix is represented as white lunula at the base of the nail plate.[13,15]

#### 22.2.1.4.3 Sebaceous Glands

Sebaceous glands are microscopic exocrine glands that secrete an oily or waxy substance (sebum) to lubricate skin and hair. Sebaceous glands originate from epidermal cells and can be found with the follicles of the hair. Sebum, created by holocrine secretion, is released from the fatty cytoplasm by degradation of the cells. Although the full function of these glands remains unknown, they are important in hormonal signaling of the skin and permeability of the epidermal barrier. Antioxidants transport through these glands to skin, protecting skin surface from UV rays. They are inactive in childhood and activate by puberty, being androgen sensitive.[19]

#### 22.2.1.4.4 Sweat Glands

There are approximately 2.5 million sweat glands in the dermis. They are split into two main types: apocrine glands and eccrine glands. Apocrine glands are found in the axillae (armpits), areolas and nipples, eyelids, ear canals, wings of the nostril, perianal region, and some parts of the external genitalia.

Their odorless content that secretes into the hair follicles produces a particular odor following interaction with skin bacteria. These glands are controlled by sympathetic nerve fibers and become active after puberty. The rest of the body surface is covered by eccrine sweat glands, which are the most frequent sweat glands found all over the skin. The highest density of eccrine sweat glands is in palms and soles, and much less on the extremities and the trunk. These glands are innervated by sympathetic nerve fibers and secrete a liquid substance including lactic acid, fatty acid, mucopolysaccharides, and glycoproteins.[20,21]

### 22.2.2 Skin Functions

Skin is of vital function for keeping the biochemical and physiological circumstances of the body in optimum condition. Major functions are:

- Prevents loss of vital body fluids and penetration of toxic substances.
- Regulates body temperature.
- Expels toxic substances with sweat.
- Safekeeping of the body from harmful effects of the sun and radiation.
- Mechanical support.
- Sensory organ for touch, cold, heat, sociosexual, and emotional sensations.
- Immunological function mediated using Langerhans cells.
- Vitamin D synthesis from its forerunners under the effect of sunlight and introversion of steroids.

Skin acts as a two-way barrier, being able to prevent outward or inward passage of water and electrolytes. The epidermis mainly assumes a role as skin barrier. If the epidermis is removed, the remaining dermis becomes permeable.

### 22.2.3 Mechanism of Skin Penetration

SC is a lipophilic medium made up of 5–20% water, 60–80% proteins, 10% lipids, and 5–8% other compounds and is able to absorb lipophilic molecules. Depending on the physicochemical properties, NPs can be absorbed by skin via different pathways. Both hydrophilic and lipophilic molecules can permeate from various routes. SC hinders absorption of NPs. However, the existence of different penetration routes enables the transport and entry to the systemic circulation. Epidermis has a porous scaly appearance with sebaceous and sweat glands, and also hair follicles. There are four pathways for penetrating across skin depending on the physicochemical properties of compounds—two transepidermal routes containing intercellular, transcellular, and two transappendageal

routes—through sweat glands and hair follicles. Generally, all substances pass through skin by a combination of all routes, the relative influence of the routes relying on the molecules' physicochemical characteristics.[22,23]

Note that the word *penetration* is used to demonstrate that an active ingredient is entering the skin to a certain extent. In contrast, the term permeation is used to point to the passing of active ingredient up to the dermis and to the circulatory system. Absorption has a general meaning and indicates either permeation, penetration, or both.

#### 22.2.3.1 Transappendageal Route

The transappendageal route (the shunt route) contains permeation through the sweat glands and across the hair follicles with their associated sebaceous glands. Sebaceous glands, sweat glands, hair follicles, and pores create different openings to the outer surface via their ducts. Ducts have continuous channels throughout the SC for transferring drugs, and many factors such as secretion from glands, the amount and content of secretion control the conveyance of compounds through this route. The transappendageal route is the shortest pathway that a compound takes to reach the systemic circulation. Hair follicles are fed via blood stream and lymph is a potential target for NP penetration and systemic access as well. They provide direct access to the dermal microcirculation. However, they occupy only 0.1% of the entire skin surface and therefore minimally contribute to drug transport.[24–26] Minor drug amounts can actually cross the skin through the follicular route, however; the results of caffeine permeation through human chest skin confirmed that nearly one-third of the compound was absorbed by follicular pathway.[27] Likewise, minoxidil deposition were found in appendageous, SC, and the receptor fluid of full-thickness human abdominal skin. Minoxidil transfer through the appendageal route was described as a key factor in hair growth promotion.[28]

#### 22.2.3.2 Transepidermal Route

In the transcellular route, penetrants pass through the matrix (cytoplasm) of keratinocytes and phospholipid membranes. Thus, penetrants diffuse by the corneocytes of SC, which contain highly hydrated keratin encompassed by lipids attaching the cells. Hydrophilic molecules transfer through this route as an aqueous hydrophilic pathway. This pathway is the shortest, however, penetrants meet great resistance to permeation because the molecules must pass via the lipophilic membrane of each cell. Then the hydrophilic cellular contains keratin and phospholipid bilayer of the cell. These steps are repeated frequently for the molecules to cross full thickness of the SC. Consequently, several partitioning and diffusion steps are required to pass the penetrant through the cell matrix.[29,30] Some drugs cross the skin through this route. Because of minor drug permeability through the corneocytes and several partitionings in the SC, the transcellular pathway is not considered as a dominant route of dermal absorption. Transcellular route is important when a penetration enhancer such as urea is used to increase the corneocytes' permeability by changing the keratin structure.[29–31]

In the intercellular pathway, penetrants pass through the continuous lipid matrix and travel the small spaces between the cells. The tortuous path formed by corneocytes affects the barrier features of this route. Therefore, penetrants need to cross the sequential lipids and aqueous domains using partitioning into the lipid bilayer and diffusing to the inner side. Small molecules can traverse to the intercellular spaces with diffusion rates controlled generally by their lipophilicity, and other physicochemical features such as molecular weight, solubility, and hydrogen bond ability. In contrast, large molecules are physically confined within the lipids. Although SC thickness is only about 20 μm, the actual diffusional path of the most molecules passing through the skin is on the order of 400 μm. Penetration rate was significantly reduced by 20-fold increase in the actual path of permeating molecules. Intercellular pathway has been described as the suitable penetration route for most penetrants and is generally appropriate for uncharged lipophilic molecules.[32–35]

#### 22.2.3.3 Translocation

Dermis includes dendritic cells, a rich supply of blood and macrophages, lymph vessels, and nerve endings. Therefore the particles that traverse the SC and dermis are potentially accessible for recognition by the immune system. Soil particles observed in lymph nodes of patients with podoconiosis demonstrate NP translocation through skin into the lymphatic system.[36,37]

## 22.3 MAJOR NANOCOSMECEUTICAL APPLICATIONS

The cosmetics field deals with a plethora of manufactured articles: shower gels, body lotions, hand creams, aftershave balsams, shampoos and conditioners, shaving foams, antiperspirants, foot gels, moisturizing creams, eye care

creams, lip balms, and similar things. There is also a wide range of makeup products: skin foundations and concealers, eye shadows, micellar lotions, mineral powders, lipsticks and gels, brow pencils, nail lacquers, nail conditioners, cuticle softeners, etc. From the Egyptian era onward, nanomaterials have been utilized in the formulation of cosmetics and skin care products. Makeup industry has seen a great influence of nanotechnology within recent decades. In 1985, the cosmetics trade established nanotechnology-based compounds in which the self-assembling characteristics of phospholipids were used to regulate the biocompatibility of active ingredients. This was the beginning of liposomes application in cosmetics industry, which are widely being used in topical delivery of active ingredients.

Topical treatments of cosmeceutical ingredients as a noninvasive antiaging method have exponentially grown from largely studied retinoids, antioxidants, botanicals, hydroxy acids, hyaluronic acid, and ceramides to recently developed compounds such as peptides and growth factors. New cosmetic creams or gels with retinoids (retinoic acid and its analogues) have been formulated to penetrate the epidermis, the outer layers of skin, and work to repair the lower layers where collagen and elastin reside. They influence skin cells and cause a more youthful state. Olay vitamin creams composed of vitamins A, C, D, E, lycopene, selenium, pycnogenol plus zinc and copper are a widely known skin care line.[38] The world's facial skin care and antiaging market has moved to natural formulations as trusted and easily recognizable ingredients reducing issues about chemicals and unfamiliar active ingredients. Kuno and Matsumoto patented an external agent for skin consisting of an extract formulated from olive plants just as a skin-beautifying feature, especially, as an antiaging factor for skin and/or a whitening factor.[39] Dry emollient compound including monounsaturated jojoba esters was applied for cosmeceutical use.[40] Martin and Belcour-Castro used the plant extract of genus *Chrysanthemum* in a cosmetic compound for stimulating skin and/or hair pigmentation.[41]

## 22.3.1 Antiagings

**A**ntiagings' topical delivery is being used as an important medication alternative to cosmetic surgeries for skin rejuvenation. These formulations may also be used as a preventive antiaging medication that younger women are seeking out. Few pharmaceuticals are sold for the therapy and avoidance of skin aging, conversely, numerous beauty products and herbal medicines are touted in the lay press. In fact, antiaging cosmeceuticals now represent the fastest growing portion of the skin care market. More than ever, patients are questing for an exceptional medicine that is uncomplicated to use, effective, and low priced.[42]

### *22.3.1.1 Hydroxy Acids*

Alpha hydroxy acids (AHAs), a group of organic carboxylic compounds with natural or synthetic sources, are widely used in the cosmetics industry. They can be extracted from food products including glycolic acid (from sugar cane), lactic acid (from sour milk), malic acid (from apples), citric acid (from citrus fruits), and tartaric acid (from grape wine) and have been applied as chemical peels to reduce wrinkles and promote the overall look and feel of skin. For any topical compound to be effective, including AHA, it must penetrate into skin where it can act on living cells. Increasing the bioavailability of AHAs by the nanoformulations is of great interest and attraction.[43,44]

Nanohydroxy acid, a blend of encapsulated actives in lipid NPs (Vetores ativos Multifuncionas), with an average particle diameter of 200−300 nm were synthesized to increase the efficiency of hydroxy acids. Active ingredients in this product were glycolic acid, lactic acid, citric acid, liquid extract, and oat oil. Topical application of nanohydroxy acid decreased the thickness of the SC, promoting the reduction of corneocyte cohesion.[43,45]

Gupta developed hydroxy acids delivery systems for skin resurfacing and antiaging purposes.[46] They succeeded to formulate in situ compounds of the subsidiary products of several hydroxy acids (HA) such as α-hydroxy acids (AHA), β-hydroxy acids (BHA), and polyhydroxy acids (PHA) with certain skin advantages in resurfacing (exfoliation), regulation of topical infections, skin aging, acne, wrinkles, age spots, rosacea, canker sores, striae distensae, skin redness, pimples, and dry skin surroundings of cracking, flaking, and scaling. Most HA subsidiary products didn't cause skin irritation and redness, which are usually created upon skin AHA and BHA application. These compounds are able to form conventional water and oil emulsions, and can be used in formulation of masks, serums, sprays, lotions, gels, creams, cleansers, and anhydrous systems, thus offering a broad range of alternative formulations to address their consumer appeal and acceptance requirements.[46]

### *22.3.1.2 Antioxidants*

Various internal and environmental factors have been shown to increase the presence of oxygen free radicals (ROSs) associated with destructive oxidation. Skin exposure to sunlight UV radiation, particularly UV-B component,

can lead to oxidative destruction of the skin, resulting in erythema, edema, hyperplasia, hyperpigmentation, sunburned cells, immunosuppression, and initiating free radical reactions as promoters of the collagen-destroying processes causing wrinkling, skin aging, and incidence of skin cancer. Antioxidants, the protective compounds against DNA damage, are able to absorb ROS and prevent oxidative DNA damage, primarily 8-oxo-guanine (8oGua). Natural skin antioxidants are lipophilic antioxidants such as vitamins E and $CoQ_{10}$ and hydrophilic antioxidants such as vitamin C, glutathione, and enzymes catalase and superoxide dismutase. An exciting new finding is that the powerful antioxidant ergothioneine and its receptor (OCNT-1) are found in the suprabasal layer of the epidermis, as well as in dermis. This implicates ergothioneine as a new natural component of human skin antioxidant system.[42]

Antioxidants cooperate to regenerate each other after reacting with ROS. For example, oxidation of vitamin C leads to its fast degradation, but vitamin E can generate oxidized vitamin C. In the same way, vitamin C can regenerate ergothioneine. Complete antioxidant protection requires many types of antioxidants, since ROS can be in the form of singlet oxygen, superoxides, or peroxides, as well as others. They can also be sequestered in the water or lipid compartment of cells. Therefore, examination of a skin antioxidant protection system requires consideration of all the antioxidants as a network.[42]

A wide range of botanicals such as soy, white, black and green tea, pomegranates, coffee berries, grape seeds, olives, and mushrooms possess high antioxidant activity. Phytoantioxidants with their high potential have been widely used by cosmeceutical companies in the formulation of sunscreens, moisturizers, antiagings, and skin-based therapies.[47] Because of their high molecular weight, they exhibit low penetration and high instability for sustained and enhanced delivery to skin. Nanosizing of phytoantioxidants by nanosized delivery systems enhances sustained delivery and increases skin-protecting activities. Solid lipid nanoparticles, transferosomes, ethosomes, nanostructured lipid carriers, etc. have been used for increasing delivery of phytoantioxidants in skin care. Curcumin, resveratrol, quercetin, morin, rutin, genistein, vitamins C and E, and green tea catechins have been successfully nanosized using various delivery technologies and incorporated in various gels, lotions, and creams for skin, lip, and hair care for their sustained effects.[48]

#### *22.3.1.3 Botanicals*

Botanicals are valuable sources for natural and organic cosmetic industry. Botanical ingredients, originating from plants (herbs, roots, flowers, fruits, leaves, or seeds), are widely used as components of cosmetics or personal care products. The use of herbal plants in cosmetics goes back six centuries to when these plants were employed for maintaining and enhancing human beauty. They were used as natural colorants, fragrances, for soothing and protecting skin, moisturizing, covering up blemishes, and even treating minor skin conditions; sandalwood and turmeric were used for skin care; henna was used to color the hair; natural oils were used to perfume bodies.[49] Discussion about the most popular ingredients that are being used in skin care products and cosmetics industry follows.

Soy extract, composed of phospholipids, such as phosphatidylcholine and essential fatty acids and other active compounds, such as isoflavones, saponins, essential amino acids, phytosterols, calcium, potassium, iron, and proteases soybean trypsin inhibitor and Bowman- Birk inhibitor, exhibits antioxidant, antiproliferative, and anticarcinogenic activities. Topical application of soy extract lowers hyperpigmentation, enhances skin elasticity, controls oil production, moisturizes the skin, delays hair regrowth, decreases photoaging of the skin, and prevents skin cancers through the estrogen-type and antioxidant effects of its metabolites.[47]

Green tea extracts containing polyphenolic compounds induce antiinflammatory and antioxidant effects and protect skin by modulating biochemical pathways important in cell proliferation, inflammatory responses, and responses of tumor promoters. These extracts have an antiaging effect by decreasing inflammation and scavenging free radicals. Green tea has a photoprotective property owed to reducing the number of sunburned cells, protecting epidermal Langerhans cells from UV damage, and reducing the DNA damage caused by UV radiation. White tea exhibits higher antioxidant activity than green tea. Black tea has a much lower content of catechins and a higher content of other flavonoids, such as quercetin, thioflavine, and kaempferol, than green tea. Application of black tea extracts before and after UV light reduces the signs of cutaneous photodamage, carcinogenesis, and inflammation in human and mouse skin.[47] Topical application of caffeine, the chemical stimulant in tea and coffee, has a sunscreen effect that enhances UVB-induced apoptosis and inhibits the formation of sunlight-induced skin cancer.

German chamomile, or *Matricaria recutita*, with active constituents of terpenoids (bisoprolol, matricine, levomenol, chamazulene), flavonoids (apigenin, luteolin, rutin, quercetin), hydroxycoumarins, mono- and oligosaccharides, and mucilages, has been used as an antimicrobial, antiallergic, antiinflammatory, antioxidant, and analgesic for inflammatory mucocutaneous diseases and wound and burn therapy.

Coffee berries, harvested from the fruit of the coffee plant *Coffea arabica*, contain a high amount of polyphenols including chlorogenic acid, ferulic acid, quinic acid, and condensed proanthocyanidins. This is one of the richest sources of antioxidants and is well known for removing fine wrinkles and skin rejuvenation.[47]

Due to high molecular weight of herbal plants, increasing percutaneous penetration and their efficiency is a current focus of novel research. Recently nanotechnology strategies have been employed to ensure the deepest penetration of vegetal oils, plant botanicals, vitamins, and antioxidants to create lasting results and more radiant skin, instantly. Natural compounds are incorporated into nanoparticles for the improvement of their pharmacodynamic and pharmacokinetic profile. Development of herbal NP formulations has become a frontier investigation in the cosmetics arena.[50,51]

Natural polyphenols present in different herbs do not have long-term stability and are very sensitive to light and heat. They present a poor biodisponibility mainly due to low water solubility. Many of them have a very astringent and bitter taste, which limit their use in topical or in oral medications. To overcome these drawbacks, encapsulation delivery systems have been developed.[51] Encapsulation of essential oils has led to numerous new formulations, which ensures the protection of the fragile oil and enables controlled release.[50] Polymeric particles, liposomes, and solid lipid nanoparticles are considered for encapsulation of natural herb extracts.[50] In order to modify whitening effect, Nanbu developed a whitening-NP cosmetic compound. A high concentration of arbutin (as a hydroquinone glucoside) was used as a melanin synthesis inhibitor.[52] Arbutin has low aqueous solubility, and as a consequence, it is complicated to incorporate it into cosmetic by-products at high concentrations; consequently, a compound of emulsified NPs was developed. A specific quantity of arbutin (α-arbutin or β-arbutin or a compound of both) was incorporated into lecithin, followed by a treatment to prepare arbutin-NPs. The emulsified NPs containing whitening bioactive material in every particle improved the concentration of arbutin in the cosmetic compound. The prepared aqueous arbutin dispersion possessed a particle size between 10 and 150 nm and could alleviate skin diseases such as dullness, age spots, and pigmentation.[52]

#### *22.3.1.4 Retinoids*

Retinoids, a class of vitamin A derivatives, are being used to reduce skin wrinkles[53] and in the treatment of several dermatological diseases such as inflammatory skin disorders,[54] skin cancers,[55] disorders of increased cell turnover (e.g., psoriasis),[56] and photoaging.[57]

Since the last 15 years, there has been significant attention to the strategies for improving retinoids' skin delivery.[56] The delivery system can enhance the steadiness of retinoids like retinoic acid and retinol, abolish/minimize the unsympathetic consequences of topical retinoids, and improve the antiaging effect of retinoids through modifying their dermal distribution or transport. In light of these things, it seems that NPs can be employed as an effective delivery strategy to improve the topical retinoid medications.

Jenning and colleagues studied the ability of solid lipid NPs (SLNs) for delivery of retinol. Interestingly, SLNs yielded a meaningful advance in the steadiness of retinol as compared to the traditional emulsions. Furthermore, highly localized and controlled release of retinol was noticed with SLNs.[58,59] Shah and colleagues explored the ability of SLNs in the course of counteracting the irritant outcomes and in intensifying the physical steadiness of the most utilized retinoid, i.e., tretinoin.[60] Actually, SLN-based tretinoin gels demonstrated dramatic development in the course of the tolerability of tretinoin as compared to the marketed product. Moreover, photostability of tretinoin was significantly enhanced in SLNs as compared to methanolic compound. Again as supposed, the tretinoin-SLNs demonstrated a high level of localization in skin when analyzed through in vitro skin permeation studies. All these consequences were ascribed to the tretinoin encapsulation in nanoparticulate structures.[60] Yamaguchi et al. developed a new drug delivery system for external treatments of photodamaged skin[61] by all-trans retinoic acid (atRA) nanoparticulates. Inorganic-coated atRA nanoparticles could significantly reduce irritation and inflammation over common formulations. Moreover, nanoparticulate of tretinoin exhibited great advancement in photostability in comparison to traditional formulations, which was sustained even after 46 days storage. The greatest outcomes were found in the course of ex vivo studies. Histological assessment in mouse epidermis following daily use of nanoparticulate tretinoin cream for 4 days demonstrated more than double increase in epidermal thickness over common tretinoin-Vaseline product in market. Moreover, nanoparticulate tretinoin medication led to a considerable rise in mRNA amounts of heparin-binding epidermal growth feature. The result was in proficient correlation with increased epidermal thickening, which resulted from nanoparticulate tretinoin application. Interestingly, 4 days' medical care of elderly skin of hairless mice by nanoparticulate tretinoin demonstrated meaningful advancement in fine and rough wrinkling and texture in the neck region. Experiments demonstrated that using NPs can be an ideal choice in topical retinoid treatment while reducing side effects.[61]

With the exception of NPs, numerous nanoformulations such as liposomes, microemulsions, microsponges, and inclusion complexes accompanied by cyclodextrins can also be utilized for enhancing retinoid topical delivery. Their effectiveness in intensifying the endurability, steadiness, and in acne treatment is well established. However, none of them have been assessed for retinoids' effectiveness in aging medication. Accurate study of novel delivery systems including liposomes, niosomes, aspasomes, microsponges, hydrogels, microemulsions, and solid lipid nanoparticles for delivery of antiacne agents such as tretinoin and benzoyl peroxide for treatment of acne has been reported by Date's team.[62]

#### 22.3.1.5 Hyaluronic Acid

HA, a nonsulphated glycosaminoglycan (GAG), is made of replicating polymeric disaccharides of D-glucuronic acid and *N*-acetyl-D-glucosamine attached using a glucuronidic β (1 → 3) bond.[63,64] HA makes specific stable tertiary shapes inside watery compounds.[65] In spite of the simplicity in its structure, without alterations in its sugar compound or without branching points, HA polymer has a variation of physicochemical features. It occurs in a wide range of formats and shapes, contingent on their dimensions, salt concentration, pH, and related cations.[66] In contrast to other GAGs, HA is not covalently linked to a protein core, however, it may create collections with proteoglycans.[67] HA covers a sizable volume of water making high viscosity solutions, unexpectedly at low concentrations.[68]

The greatest impressive histochemical variation discovered in aged skin is remarkable loss of epidermal HA, when HA is still present inside dermis.[69] Causes for this variation in HA homeostasis with aging is unexplored. Synthesis of epidermal HA is affected through the underlying dermis and is under separate influences from the synthesis of dermal HA.[70] Continuing decrease of HA polymers' size also happens by aging of skin.[71] Consequently, the epidermis no longer has the essential molecules for uniting and conserving water molecules—this leads to the reduction of skin wetness. In dermis, the greatest age-related variation is related to increased reactivity of HA with surrounding tissues, which leads to more decreased HA density in dermis. All of the mentioned age-related changes lead to obvious dryness, degradation, and reduction of elasticity that characterize aged skin.[70–75]

To remove age-related changes in skin quality and appearance, soft-tissue dermal fillers composed of hyaluronic acid nanoparticle have been developed. By injection, they are able to fill lines and wrinkles temporarily (or permanently). Dermal fillers of HA nanoparticles are not stable and their half-life is short—their intermolecular chemical cross-links will extend their duration and half-life. HA nanoparticles do not make any collagen and are not involved in tissue generation, but they can simply increase the volume. HA dermal fillers do not have allergenic effects and exhibit minimal side effects and have a reasonable price. Hyaluronic acid nanoparticles have been approved by the US Food and Drug Administration (FDA) as dermal fillers.[72]

Topical delivery of HA is under development owing to easy absorption of nanosized hyaluronic acid into the skin. Recently, the efficacy of new topical products (cream, serum, and lotion) containing nanohyaluronic acid was studied for treating wrinkles, improving hydration and elasticity of human skin. The effect of novel formulation was evaluated by measuring wrinkles, hydration, elasticity, erythema, skin color, uniformity, and pigmentation in the skin of 33 women for eight weeks. Results indicated a significant moisturizing effect after 2, 4, and 8 weeks of treatment. A significantly finer skin structure was observed after 2 weeks of treatment, and skin elasticity showed a remarkable improvement after 2 and 8 weeks of treatment. Wrinkles' depth decreased up to 40%, and skin hydration increased up to 96%, and skin firmness and elasticity were significantly enhanced (up to 55%) at the end of 8 weeks.[73]

For transdermal delivery of lipophilic active ingredients, alcohol-free oil/water hyaluronic acid nanoemulsions were developed. Tocopherol was used as a model ingredient to assess skin permeability and bioavailability. Hyaluronic nanoemulsion performed desirable skin permeable capacity and penetrated through SC and diffused deeper into dermis via follicular and intercellular pathway compared with the control group (ethanol solution). No irritation was found in dermis and skin surface.[74]

In a novel approach, hydrogel nanoparticles were synthesized via a cross-linking reaction between HA and polyethylene glycol in an oil composition as effective carriers in transdermal delivery systems. Results demonstrated the importance of dispersion medium in percutaneous penetration of drugs and topical/transdermal delivery systems.[75]

#### 22.3.1.6 Ceramides

Ceramides are the greatest lipid component of lamellar sheets present in the intercellular spaces of SC. The lamellar sheets provide the epidermal barrier property. The intercellular lipid domain is composed of equimolar concentrations of ceramides, free fatty acids, and cholesterol. Ceramides are a structurally complicated and heterogeneous group of sphingolipids including subsidiary products of sphingosine bases in amide linkage with a variety

of fatty acids. Ceramide differences in chain size, type and size of hydroxylation, saturation, etc. create diversity of the epidermal sphingolipids. Along with the other SC lipids, they form ordered structures. SC intercellular lipid lamellae, the aliphatic chains in the ceramides, and the fatty acids are mainly straight long-chain saturated mixtures with a high melting point and a small polar head group.[76]

Ceramides play a key function in structuring and preserving the skin water permeability barrier. Ceramide along with cholesterol and saturated fatty acids creates a water-impermeable barrier that prevents excessive water loss due to evaporation and entrance of microorganisms.[77] It is demonstrated that the levels of all major lipid species including cholesterol, in particular ceramides, significantly decreases with increasing age.[78]

Ceramides are currently used in cosmetics (0.2%) especially for dry skin conditions and are prescribed as dietary supplements. Companies claim that applying ceramides to the skin, or taking ceramides by mouth, can reduce dryness, lines and wrinkles, and repair and firm aging skin. There are not enough clinical studies to approve the claims and none of the companies have presented robust proof of these claims.[79]

Due to high molecular weight, percutaneous absorption of ceramides is also a controversial debate. Ceramides are very hard to pass through the layers of the skin; it is suggested that they can traverse through the hair follicles and pores to reach the growing levels of skin. For the purpose of improving ceramide permeation, a human-type nanoceramide dispersion called Astalift Jelly Aquarysta was developed, which exhibited permeability up to nine times greater than that of earlier examples.[80]

#### 22.3.1.7 *Depigmenting Agents*

Depigmenting agents function to restrict melanogenesis (the pigmentation pathway by which cells generate melanin) and help the affected site to heal hyperpigmentation. With regard to factors such as popularity, safety, and productiveness for cosmetic purposes, the most popular skin whitening agents are: hydroquinone, kojic acid, monobenzyl ether of hydroquinone, gentisic acid, azelaic acid, licorice, arbutin, retinoids, niacinamide, mequinol, soy, vitamin C, corticosteroids, hydroxystilbene, glutathione, alosein, glycolic acid, *n*-acetyl glucosamine, botanical extracts, and melatonin.[81] Cosmetic depigmenting vehicles are classified based on their mechanisms in Table 22.1. The most successful topical treatment is a triple-combination vehicle composed of hydroquinone (HQ), tretinoin, and fluocinolone acetonide. Numerous mechanisms are targeted for the treatment of hyperpigmentation, particularly, regulation of melanogenesis with the help of inhibiting tyrosinase activity, a crucial enzyme in melanin synthesis. One more course of action is regulation of melanosomes through manipulation of their formation or transfer. Moreover, depigmenting agents function by means of antioxidant or antiinflammatory activities.[82]

Attempting to solve the problem of skin pigmentation without having any side effects, bionanotechnology seems to be the best way to block the chain reactions in different cellular points of the melanogenesis pathway. To improve the whitening efficiency, various depigmenting agents have been loaded to nanoparticles. Different chitin nanofibril-hyaluronan (CN-HA) block copolymeric nanoparticles, entrapping known whitening agents such as methoxydibenzoyl methane, titanium dioxide, silica, alumina as UV filters; ascorbyl phosphate, *Phyllanthus emblica*, undecylenoyl phenylalanine and arbutin; and diacetyl boldine were examined to verify in vitro activity on the melanogenesis

**TABLE 22.1** Classification of Cosmetic Depigmenting Agents Based on Their Mechanisms

| Controlling Tyrosinase | Inhibition of Melanosome Transfer | Antioxidant |
|---|---|---|
| *Inhibition of tyrosinase activity* | Centaureidine | Ascorbic acid |
| Arbutin | Niacinamide (vitamin $B_3$) | α-Tocopherol |
| Azelaic acid | Lectins | 6-Hydroxy-3,4-dihydrocoumarins |
| Kojic acid | Neoglycoproteins | Thioctic acid (α-lipoic acid) |
| 4-*n*-Butylresorcinol | | Resveratrol |
| *Reduction of tyrosinase production* | | |
| Sphingosine-1-phosphate | | |
| Lysophosphatidic acid | | |
| Ceramide | | |
| Sphingosylphosphorylcholine | | |
| *Increase of tyrosinase degradation* | | |
| Linolenic acid | | |
| Linoleic acid | | |
| Oleic acid | | |
| Phospholipase D2 | | |

*Reprinted from Shin JW, Park KC. Current clinical use of depigmenting agents.* Dermatol Sinica *2014;***32***:205–10, Copyright (2016), with permission from Elsevier.*

process. Results demonstrated that the combined activity of different whitening agents entrapped into natural nanoparticles for a period of 6 months on the skin of 40 voluntary subjects, female and male, resulted in an interesting depigmenting effectiveness in different skin areas without any side effects.[83] Depigmenting efficacy potential of a heartwood of *Artocarpus incisus* extract formulated into nanoemulsions was examined in vivo. The nanoemulsion extract exhibited melanogenesis inhibition higher than kojic acid. A strong visible decrease in hyperpigmentation was observed after 6 weeks of treatment with the nanoemulsion formulation.[84,85]

#### 22.3.1.8 Exfoliants

Exfoliants promote skin through removing dead keratinized cells on the SC. Exfoliation is gained via either chemical or mechanical means. Chemical exfoliants such as glycolic acid, salicylic acid, lactic acid, fruit enzymes, malic acid, or citric acid can be found in high concentrations *as* a medication, or in lower concentrations in over-the-counter products. Chemical exfoliants such as α-hydroxy acids, β-hydroxy acids, or enzymes are able to loosen the glue-like substance that maintains the cells with each other, enabling them to exfoliate. This kind of exfoliation is suggested for individuals treating acne.[85–88]

http://www.google.ie/patents/WO2006077156A2?cl=en A kit comprised of different types of peeling gels including a nanocompound, a defatting gel, and a neutralizing gel was provided for chemical skin peeling and the treatment of various cosmetic conditions and dermatological disorders, including dry skin, acne, keratoses, age spots, wrinkles, and disturbed keratinization. The peeling gels were prepared based on conventional peeling compounds, such as glycolic acid, trichloroacetic acid, pyruvic acid, salicylic acid, and Jessner solution, but the presence of nanostructured thixotropic-based inorganic gel strongly increased the peeling effect, allowed the use of lower concentrations of peeling compound, with only minimal skin irritation for the user.[89]

#### 22.3.1.9 Topical Peptides

Cosmeceuticals have recently used peptides as an effective antiaging factor in their creams. The stable, and easily prepared, peptides have opened new fields of modulating molecules applicable to dermatology and skin care industries. They are good candidates for application to areas such as inflammation, pigmentation, cell proliferation, and migration. Peptides are composed of amino acids that accelerate the production of an antiwrinkle protein known as collagen.[90–92]

The greatest concern in employing peptides topically is their low penetration ability. The penetration potential depends on various factors: physicochemical qualities of material (acid dissociation constant [pKa], molecular dimension, steadiness, solubility, binding affinity, and partition coefficient); the timescale of penetration; integrity, thickness, and various parts of the skin, cutaneous metabolism; area, and timescale of application; features of the transdermal instrument; and the production of a local depot at the site of application.[93,94] It is ideal to provide a topical drug with the molecular weight less than 500 Da, considerable aqueous solubility (>1 mg/mL), melting point less than 200°C, moderate log of partition coefficient octanol/water between 1 and 3, and low or few polar centers.[95,96] Diffusivity of the molecules in SC relies on the number of hydrogen-bonding groups on a molecule, being greatest for small nonhydrogen-bonding molecules and reaching a low minimum in addition to near four hydrogen-bonding groups.[97] Because peptides consist of a wide range of amide bonds, they have low diffusivity in skin. Moreover, they are frequently charged at physiological pH and are basically hydrophilic. Consequently, the lipophilic SC is an important hindrance to permeation.[98]

Vehicles are able to improve peptide penetration and enhance delivery. Fatty acid subsidiary products can act as vehicles and increase the lipophilic property of the peptide. For instance, the palmitoyl by-product of the polypeptide interferon penetrates across human skin five- to sixfold greater than the elementary peptide[99,100] and, additionally, facial skin enhancement has been described after topical pal-KTTKS (palmitoyl pentapeptide-4) treatment.[101]

Three main groups of cosmeceutical peptides are used for cosmetics purposes: signal peptides, neurotransmitter-affecting peptides, and carrier peptides. GHK-Cu is the most broadly applied for skin repair and antiaging purposes. Abdulghani and coworkers reported increased antiaging effects in female volunteers' skin by applying the facial cream containing GHK-Cu.[102] Palmitoyl KTTKS is an additional regularly applied peptide that was verified to cause considerable increased penetration than placebo and considered as an effective comparator.[101,103] Acetyl hexapeptide-3 (Argireline1) had promising outcomes. Depth of wrinkles was decreased more than 30% for Argireline1 versus 10% for placebo after 30 days.[104] All the aforementioned samples of peptides suggest that these vehicles may become successful.

### 22.3.2 Moisturizers

Moisturizers are formulations developed to sustain the water content of the skin.[105] Creams and lotions are moisturizers composed of oil and water-soluble components. Humectants and emollients are two agents that play a main role in moisturizers and hydration of the skin. Humectants are components that attract wetness into the SC, bringing about increased hydration of the skin. Examples of humectant factors in makeup are glycerin, propylene glycol, and urea. Emollients are lipid-based components that generate a barrier on the surface of skin to entrap moisture in the skin to control its evaporation. Examples of emollients in cosmetics are oleyl oleate, octyldodecanol, and isopropyl myristate.[106] Moisturizers mimic the role of epidermal lipids in the skin barrier.[105] The intercellular lipid in the SC is composed of ceramides, cholesterol, and fatty acids. Barrier characteristics of the SC are corresponded with the organizational construction of these lipids into lamellar granules in the intercellular space.[107] This compound of lipids additionally has natural moisturizing components containing amino acids, lactic acid, pyrrolidone carboxylic acids, and urea. Because of the hydroscopic attributes of this compound, wetness is able to be preserved in the SC under surprisingly strong circumstances.[108] Moisture content in skin is also important in normal desquamation and barrier integrity.[108] Normal skin plasticity is contingent on moisture amount. Diminished amount of water in skin inhibits enzyme undertaking of the proteinases, glycosidase, and lipases necessary for shedding of the corneocytes. Skin aging happens from the sum of its two components: intrinsic or chronological aging along with photoaging.[106,108] Inherent skin aging happens from the ordinary physiological alters in the body as humans age. Photoaging is attributable to UV irradiation on sun-exposed areas. Photoaging consequently leads to premature skin aging. Dry skin is the result of a reduced potential of aged skin to preserve moisture in the SC. Diminished water quantity in skin generates abnormal desquamation through hindering the protease enzymatic activity, which is in charge of corneodesmosomal degredation.[108] Corneodesmosomes are the major cohesive linkage in the middle of corneocytes that form SC.

Lee and coworkers developed a hydrogel-based ultramoisturizing compound formulation for skin hydration and improving dermal drug delivery. They prepared hydrogel-based ultramoisturizing compound (HUMC) with carbopol 934P, urea, Tinocare GL, grape seed oil, and additional excipients. HUMC2 was suggested as an efficacious carrier for skin hydration, which was able to increase dermal delivery of lipophilic and hydrophilic medicines.[109] A nanosome of urea nanospheres is an example of moisturizer in the market.[110]

Some examples of available antiaging nanocosmeceuticals in the market follow: fullerenes firming antioxidant serum, fullerenes aging skin resuscitating serum, micronized gluconolactate antiaging finishing powder, micronized ingredients vitamin A and C serum, micronized liposomes serum, micronized zinc oxide, micronized titanium dioxide, nanoencapsulated ingredients retinol nanocapsules, nanoencapsulated ingredients retinol nanocapsules vitamin, nanosomes of sodium lactate, nanosomes of calendula, nanosomes of witch hazel, nanosomes of ginseng, nanosomes of urea, nanosomes of vitamins A and E, nanosomes of provitamin B5, nanosomes of alpha-bisabolol and germal II, and nanosomes of vitamin A. Examples of nanocosmeceuticals used for around-eye cream are fullerenes, lyphazome nanospheres, microsomes eye gel, and micronized liposomes.[111,112]

### 22.3.3 Sunscreens

Sunscreens are another frontline protection to prevent DNA damage by means of reflecting or absorbing UV at the skin surface. The absorbed energy is discharged from the sunscreen molecules mainly as fluorescence or heat. Sunscreens are either chemical or physical—the chemical sunscreens principally absorb light and physical sunscreens largely reflect light. Some sunscreens are more photostable than others and no longer have their absorption ability during UV contact. Some of the energy absorbed through sunscreen molecules causes the discharge of ROS, and this is true for both chemical and physical sunscreens. Latest developments in sunscreen improvement have been designed to decrease or remove these concerns. However, there is no proof that the ROS produced through sunscreens in skin leads to crucial amounts of DNA damage.[113,114]

The greatest regularly utilized physical UV filters are the inorganic micropigments, zinc oxide or titanium dioxide in the size range of 10−100 nm. Combination of ZnO and $TiO_2$ creates a broadband UV protection, since ZnO is effective in the UVA range and $TiO_2$ acts in UVB region. The greatest disadvantage of micropigments is that they equally reflect visible light and cause a whitening effect on skin—their agglomeration also reduces their effectiveness.[113,114] However, ZnO NPs and $TiO_2$ NPs are transparent and enhance their cosmetic appeal. ZnO NPs demonstrate the broadest UV protection of all the sensitive components currently available in commercial sunscreens, and it is essential to bear this in mind when exploring the possible risks connected with their implementation. ZnO incorporation

in sunscreens yields broad protection with respect to the known carcinogenic, immunosuppressant, and photoaging results of UVA and UVB.[115] Nevertheless, there are issues about the specific risks of ZnO in sunscreens to human health and the environment. Recently, the Environmental Working Group reported in favor of utilizing sunscreens including ZnO and $TiO_2$ NPs on the basis of current confirmation, although it was noted that the effect of these nanoparticles on damaged skin had not been fully addressed through existing investigations and that there were "considerable unaddressed safety concerns for workers handling these nanomaterials." The report also described inadequate environmental assessments and lack of regulations related to widespread use of these nanoparticles.[112,116–118]

### 22.3.4 Hair Care

Hair has high impact on personal appearance and can be an indicator of individual health.

A variety of conditions including hirsutism, alopecia, and loss of hair color can influence the quality of a patient's life. Nanomaterials have been used as a vehicle for delivery of bioactive agents to the hair follicle and shaft. They permit prolonged contact at the site of action and sustained release of drugs. Presence of hair follicles significantly contributes to the penetration and permeation of topically applied nanosized particles. Follicular distribution is body-region dependent, with some body regions with significantly increased number of follicular orifices such as forehead.[119]

The shampoos composed of nanomaterials are able to improve the residence exposure time on the scalp and hair follicle, enabling effective agents to prepare a preservative layer to keep water in the cuticles. Normally, in the course of washing, the cuticle membrane is opened by hot water, exposing the hydrolipid emulsion layer, whose behavior is to make possible external moisture absorption and prohibit internal moisture reduction. In conventional shampoos, silicone collects on the scalp rather than permeates. Nevertheless, when silicone oil is incorporated into nanomaterials, it swiftly diffuses in hair fibers given its minuscule dimension. The outcomes are enhanced hair moisture, gloss, and lubrication. Their merit is that they do not demolish the hair fiber cuticle, however, the nanosize allows for permeation in the hydrolipid emulsion membrane.[120]

Cationic nanoemulsions can notably recover dry hair, unexpectedly after continued shampooing.[121] Zinc and chitin nanofibril complexes were efficient in decreasing hair flakes and sebum both in culture dish and in living organism. Incorporation of nanomaterial in the formulation improved ingredient deposition in hair and immediately influenced amino acid combination and keratin construction to repair the injured cuticle and cortex.[122]

Silica NPs penetrate minimally or do not penetrate at all. Sampaio et al. developed a new approach for dyeing human hair fibers by means of colored silica NPs of 206 nm. The colored silica NPs easily diffused in bleached hair fibers and were found mainly in the outer areas of the hair structure.[123]

### 22.3.5 Skin Cleanser

Skin is coated by a hydrolipid layer that includes secretions from sebaceous glands and from apocrine and eccrine sweat glands. Decomposition products from cornification and corneocytes in the process of being shed are also present. This layer produces a natural preservation against pathogenic organisms and prevents skin absorption of contaminants and dirt from the environment. Sometimes microorganisms remain on the skin surface and make unpleasant subsidiary products, in particular those generating from the metabolism of mixtures found in apocrine sweat that produce body odor.[124] Consequently, periodic cleansing to erase debris, pollutants, and odors is required to preserve skin healthiness. Cleansing is mandatory to remove soil from the skin surface that is acquired through incidental touching or by intentional implementation.[125]

Silver NPs are employed as skin disinfectant and decontamination. Nano Cyclic Inc. produces a nanocleanser pink soap that is a well-adjusted combination of nanosilver and natural components. It is claimed that it eliminates toxic bacteria and fungi, fights acne, and decreases age spots and sun-injured skin.[126,127] To control spread of epidemic infections, the exposure time of drugs on skin is a key parameter. Nanosilver in concentration of 15 mg/L in handwash is extremely effective against microbes.[126] Silver NPs are able to kill yeasts that cause diseases in the mouth, and consequently can be added in dentifrices. Because of this property, silver NPs have vast applications in veterinary drugs and biological products. Nanosilver skin gel, containing 30 times less silver than silver sulfadiazine, may be a better choice to inhibit infections in burnt skin.[126,128]

### 22.3.6 Lip Care

Lip care is an additional favorable kind of beauty product. Several NPs can be incorporated into lipstick and lip gloss, which soften or soothe the lips through restricting transepidermal water reduction. Korea Research Institute of Bioscience and Biotechnology claims a patent that it is viable to develop pigments exhibiting a broad range of colors by gold or silver NPs through blending in several compositional ratios and whose color could be retained for a long period of time.[129]

Silica NPs employed in lipsticks enhance the homogenous diffusion of pigments. Once utilized, they restrict the pigments from bleeding or migrating into the fine lines of lips.[130] Micronized topaz powder, micronized rose quartz powder, and micronized titanium dioxide are commercial nanomaterials that are being used in the formulations of lip glosses, lip liners, and lipsticks.[111,112]

### 22.3.7 Nail Care

Nanotechnology-based nail beauty products have numerous benefits in comparison with traditional products. An investigation reflected that nail coats having nanosized particles enhance nail firmness and resistance.[131] Nano Labs Corp. as a nanotechnology examination and development company prepared a novel flexible nanonail lacquer having benefits of fast drying to an extremely difficult state, strong against shock, cracking, chipping, and scratching. A unique product that may have outstanding capacity in these beauty products is the incorporation of antifungal NPs in nail polish to cure fungal toenail diseases.[129,132]

Currently, the most important applications of nanotechnology for nail care are related to manicure products claiming to make use of nanoliposome delivery systems that are "generally regarded as safe" (GRAS) elements. Liposomes can vary in dimensions from 15 nm to many microns, however, nanostructures are normally 50–100 nm. Liposomes are mainly brittle, consequently a novel type called a transferosome has been used, which is believed to be more flexible and have enhanced efficiency.[133] Transferosomes are self-assembled lipid droplets with elastic bilayers and optimized permeation in the SC that may be more qualified to get over the barrier function of the nail plate. They can be used to deliver biomolecules, antioxidants like lycopene or tocopherol, or caffeine.[133] Niosomes are nonionic surfactant carriers that are comparable with phospholipid-type liposomes. As a consequence of minimal nail permeability, they are beneficial for delivering effective ingredients such as moisturizers, antioxidants, and others to the natural nail.[134,135] Solid lipid NPs are fragments in a lipid matrix that are generally solid at body temperature. They are used when the components need protection from degradation throughout prolonged periods, e.g., UV absorbers.[136,137] Nanostructured lipid vehicles (NLCs) are similar to SLNs except for their matrix structure, which is twisted. They possess gaps to carry guest components, giving them an extreme loading ability and thus they may be a better alternative for nail-related applications.[133]

To increase drug efficacy, it is essential to keep the required concentrations of the active ingredient at the target site for a specific time span, while minimizing undesirable side issues. Lotions and creams seem to be ineffective due to the extremely resistant natural barrier features of nail plate. To enhance the permeation of active vehicles, different forms of nanocarriers such as nanoemulsions, nanoliposomes, and quantum dots have been suggested. Quantum dots (QDs) are very minuscule NPs, normally 10 nm or less, and they offer abundant novel benefits. QDs are able to be magnetized and controlled to determined places in the body through applying an appropriate electromagnetic field. They can transport two distinct drugs and discharge at different times by being controlled by a remotely engendered electromagnetic tool. The use of nanotechnology in delivery of efficient antifungals is in its infancy. QD technology is also beneficial for other targeted natural nail treatments and therapies. They may possibly be used in future years to design a nail oil that can reversibly change through a range of colors and/or patterns.[133,138,139]

## 22.4 NANOPARTICLES USED IN COSMETICS

Nanotechnology is one avenue—a scientifically diverse discipline—that exploits the complex and remarkably unique properties of matter at nanoscale. Nanomaterials have been extensively researched and used as a vehicle for delivery of bioactive agents within the cosmetic arena.[140,141] Nanomaterials can also be designed to deliver established or developing drug formulations in a sustained, controlled, and targeted manner to avoid adverse systemic side effects. This liberation system not only allows for the enhanced delivery of active substances to the epidermis but also permits prolonged contact at the action site—properties that bring a variety of benefits to cosmetic products. Furthermore, due to their small size, their optical transparency enhances their cosmetic appeal. Therefore, because of

their unique and intrinsic properties, nanomaterials are being increasingly exploited in the development of advanced skin care products, specifically targeting the hair follicle and shaft.[119]

## 22.4.1 Organic Nanoparticles

Organic NPs are usually described as solid tiny pieces made up of organic compounds ranging in size from 10 nm to 1 μm.[1,2] Over the past decades, this class of NPs has encountered a remarkable expansion and intensive inquiries because of their great potential in many industrial lines, especially in dermatology.[142]

### *22.4.1.1 Lipid Nanoparticles (SLNs and NLCs)*

Lipid NPs (LNPs) have attracted remarkable interest throughout the past few decades. SLNs and NLCs are two main kinds of lipid-based NPs. SLNs were designed to decrease the defects of other colloidal vehicles, e.g., emulsions, liposomes, and polymeric NPs, since they have advantages such as good discharge profile and targeted drug delivery with ideal physical steadiness. NLCs are the next generation of SLNs that enhance the stability and potential loading of drugs.[143]

They possess qualities that make them proficient vehicles for makeup implementations like preservation of active compositions against chemical degradation and improvement of the skin water content.[144] Utilization of LNPs as vehicles for sunscreens, antiaging products, and antiacne actives has been examined. Because of the great controlled release behavior of LNPs on skin permeation of active substances, they exhibit good UV-blocking and skin hydration properties. These formulations are similar to lipids' skin structure, there are no skin toxic effects while using them topically.[145]

### *22.4.1.2 Liposomes*

Liposomes are concentric bilayered carriers in which the aqueous core is completely surrounded by a lipid bilayer made up of natural or man-made phospholipids, which are GRAS products. The lipid bilayer of liposomes is able to conjugate with other bilayers like cell membrane, which encourages discharge of its contents, making them effective for cosmetic delivery uses. Their advantages of easy preparation method, improved solubility of active components by skin, and providing the drugs for the cells throughout a sustained period of time make them an appropriate vehicle for cosmetic applications.[10] Vesicles such as monosomes, transferosomes, niosomes, and ethosomes can improve the permeation of substances across skin.[146–149]

### *22.4.1.3 Nanosomes*

Nanosomes are composed of a row of $H_2O$ heads and a row of fatty tails. They are smaller than liposomes and are able to permeate deeply to skin. Once having penetrated, they can integrate themselves in larger molecules. They must only be employed in the products that do not include chemical preservatives, chemical sunscreens, animal by-products, fragrances, and colorants, as these undesirable components will also be moved into deeper skin layers via Nanosomes.[150,151]

### *22.4.1.4 Niosomes*

Niosomes, nonionic surfactant vesicles, can be obtained by the hydration of nonionic surfactants, with or without incorporation of cholesterol or their lipids. They are vesicular systems the same as liposomes and are employed as vehicles of amphiphilic and lipophilic drugs. Niosomes are biodegradable, biocompatible, and nonimmunogenic carriers for drug delivery. These elastic carriers have been broadly assessed for controlled release and targeted delivery for treatment of cancers, viral diseases, and other microbial diseases.[152,153]

### *22.4.1.5 Ethosomes*

Ethosomes are mainly applied for delivery of drugs through a transdermal route. Lipophilic, hydrophilic, or amphiphilic drugs can be encapsulated by ethosomes. Ethosomes are soft, malleable vesicles utilized for delivery of drugs to reach the deep skin layers and/or the systemic circulation. Dimensional range of ethosomes may differ from tens of nanometers to microns. Ethosomes, the altered structure of liposomes,[154] are made up of phospholipids, high concentration of alcohol, and $H_2O$. Considerable concentration of ethanol increases the vesicles' ability to permeate the SC.[155–158]

#### 22.4.1.6 Transferosomes

Transferosomes, infrastructures including hydrophobic and hydrophilic moieties concomitantly, are able to accommodate drug molecules with several solubilities. Transferosomes can deform and pass throughout skin layers without measurable depletion. They overcome the skin permeation difficulties with the help of squeezing themselves along the intracellular lipids of the SC.[159,160] The concept of transferosomes as a vehicle for transdermal delivery was first initiated by Cevc et al. in 1992.[161] Thereafter, numerous experiments have been performed on transferosomes and their viable applications as drug vehicles. Transferosomes with potential transdermal application are composed of lipids and biocompatible membrane softeners. They are more elastic than the usual liposomes and are consequently employed as new vehicles for successful transdermal drug delivery. By applying transferosomes lipid suspension on the skin surface, the produced "osmotic gradient" following water evaporation increases penetration to skin.[162] Transferosomes enter the SC through either intracellular route or transcellular route. With the ideal diffusion qualities of transferosomes, they have been broadly employed as a vehicle for proteins, anticancer drugs, analgesics, antifungal drugs, anesthetics, sex hormones, corticosteroids, insulin, albumin, and similar compounds.[163] Transferosomes are biocompatible and biodegradable nanomaterials as they are built from natural phospholipids. They have great entrapment efficiency, which is about 90% in the case of lipophilic drugs. They protect the encapsulated drug from metabolic degradation. They function as depot, discharging their contents slowly, and are utilized for systemic and topical delivery of drugs. Consequently, transferosomes are able to augment the transdermal flux, continue the release, and enhance the site specificity of bioactive molecules.[164]

#### 22.4.1.7 Cubosomes

Cubosomes, composed of honeycombed structures, consist of two internal watery channels and a large interfacial area. Cubosomes are self-assembled liquid crystalline nanoparticles of definite surfactants accompanied with suitable amount of water that creates unique properties of practical interest. The bicontinuous cubic liquid crystalline phase is optically clear and extremely viscous with particular structure at nanometer range. The term "bicontinuous" indicates separation of two continuous but nonintersecting watery areas by lipid bilayer that is twisted to space-filling structure.[165,166] Cubosomes possess different internal cubic structures and compositions with different drug-loading capabilities. They have great internal surface area, simple preparation method, biodegradable lipids and the potential of encapsulating hydrophobic, hydrophilic, and amphiphilic compounds, targeting and controlled release of bioactive agents. Cubosomes have a vast number of applications in several areas in pharmaceutical industry.[167]

#### 22.4.1.8 Microemulsions

Microemulsions are stable transparent dispersions of water and oil (mixture of various hydrocarbons and olefins) and surfactant. They are prepared by simple mixing of the components and do not require specific preparation conditions. There are three kinds of microemulsions: oil dispersed in water (o/w), water dispersed in oil (w/o), and bicontinuous. The presence of o/w droplets is likely to be a characteristic of microemulsions where the amount of oil is low. In contrast, the existence of w/o droplets is a characteristic of microemulsions where the water fraction is low. Droplet diameter varies in the range of 10–140 nm. Bicontinuous microemulsions may result where the amounts of water and oil are equal. Microemulsion concept was introduced in the early 1940s by Hoar and Schulman who developed a clear single-phase compound using titration of a milky emulsion with a medium-chain alcohol. Schulman and coworkers subsequently coined the term "microemulsion." Microemulsions have been utilized in several disciplines like fuels, detergents, agrochemicals, food, cosmetics, and pharmaceutics.[168–170]

Microemulsions have been approved to increase the absorbance of cosmetic ingredients such as whitening agents, moisturizers, and antioxidant agents, which have low absorption ability due to the barrier behavior of SC.[169]

#### 22.4.1.9 Nanoemulsions

Nanoemulsions have become increasingly significant as possible carriers for delivery of cosmetics active agents. Nanoemulsions can move lipophilic molecules more than liposomes due to their lipophilic interior. Their small-sized droplets with high surface area enable efficient actives movement to the skin.[171,172] Nanoemulsions can satisfactorily be applied in cosmetics, since there is no intrinsic creaming, flocculation, sedimentation, or coalescence such as is observed in macroemulsions. Oil-in-water nanoemulsions play a key role in cosmetics—they are essential in the formulation of products such as body lotions, skin lotions, and sunscreens.

Nanoemulsions have recently been used in NanoGel systems and emulsion-based wet wipes. These new applications are rapidly growing for baby care and as makeup cleansers.[121,173]

#### 22.4.1.10 Multiple Emulsions

Multiple emulsions are complicated vehicle systems in which o/w and w/o emulsions exist in a single system. Lipophilic and hydrophilic surfactants are utilized for stabilizing multiple emulsions. Water-in-oil emulsions can be stabilized by lipophilic (oil-soluble, low HLB) surfactants, while o/w systems are stabilized by hydrophilic (water-soluble, high HLB) surfactants. Multiple emulsions are "emulsions of emulsions," in which the drops of the dispersed phase themselves contain smaller dispersed droplets of a miscible liquid.[174,175] Every dispersed globule in the double emulsion makes a vesicular structure with single or multiple watery compartments divided from the aqueous phase via an oil phase layer. In multiple emulsion system, solute has to transverse from inner miscible phase to outer miscible phase by the middle immiscible organic phase; it is also known as liquid membrane system.[176]

There are two important types of multiple emulsions: w/o/w and o/w/o double emulsions.[177] Multiemulsions are mainly used in cosmetics, pharmaceuticals, and foods. Due to their fine texture, they exhibit a smooth touch upon application. In cosmetics, they can protect an active ingredient from degradation and release it at a controlled rate. They can act as an internal depot and entrap compounds from the outer diluted continuous phase into the inner space.

They improve the solubility of actives and protect the compounds such as vitamin C and E from oxidation. They exhibit slow and sustained release from an internal reservoir into the continuous phase (mostly water). Nonionic skin surfactants are being used for the preparation of multiple emulsions in cosmetics. Multiple emulsions including milk immunoglobulin can protect drugs against acid (pH 2.0), alkali (pH 12.0), and protease enzymes. Multiemulsions are used in formulation of sunscreens, hand creams, makeup cleansers, shaving creams, and antiperspirants for their moisturizing, nutritive, and protective effects,[178–180] More research is being carried out on the stability and preparations methods of multiple emulsions; more applications are expected to appear in the near future.

#### 22.4.1.11 Ultrasomes

Ultrasomes are multilamellar liposomes encapsulating an endonuclease enzyme developed from *Micrococcus luteus*; the enzyme identifies the sun UV damage to the skin and initiates removal of injured DNA.[85] Ultrasomes also protect the immune system through restoring UV-DNA damage and diminish the expression of TNF, IL-1, IL-6, and IL-8. In the tanning response following UV exposure, it is demonstrated that ultrasomes can stimulate the production of melanin by melanocytes in a dose-dependent manner in vitro.[85,181]

The Night Recovery antiaging cream containing a patented ultrasome is claimed to promote the repair of damaged cells, fight wrinkles, sagging skin, and loss of tone and elasticity and boost skin's natural collagen production.[181,182]

#### 22.4.1.12 Photosomes

Photosomes, consisting of the enzyme photolyase enfolded in a liposome structure, are added in sun-care products to protect the sun-exposed skin by discharging a photoreactivating enzyme derived from a marine plant, *Anacystis nidulans*. The enzyme is activated via light and is able to function over the day to enhance skin DNA repair. Combined with ultrasomes, they form an "intelligent" DNA restorative system.[85,183]

Lancaster's 365 Cellular Elixir serum is claimed to protect the DNA skin by 30% and accelerate skin's DNA repair performance by up to 60%, restoring DNA damage caused by pollution, UV radiation, and stress and retarding the aging process in cells. It is stated that the DNA action compound is made by ultrasomes and Photosomes.[183]

#### 22.4.1.13 Aquasomes

Aquasomes, three-layered self-assembled structures, are made up of a solid nanocrystalline core with oligomeric outer layer to which biochemically active molecules are adsorbed. Aquasomes are called "bodies of water" because of their water-like properties. Their hydrophilic part can protect fragile biological molecules and maintain the conformational integrity. Their high surface area provides high surface exposure in targeting the bioactive molecules such as peptides and hormones, antigens and genes to specific sites.

Genesphere cream, containing Aquasomes, is claimed to remove wrinkles, smooth lines, and eliminate crow's feet.[85]

## 22.4.2 Inorganic Nanoparticles

Metals, metal oxides, and nonmetals are being used in various types of cosmetics as color cosmetics, face and body care products, hair cosmetics, herbal cosmetics, delivery systems, etc. The main inorganic nanoparticles that are being used in cosmetic industry follow.[184]

### *22.4.2.1 Nanosilver*

Silver nanoparticles (AgNPs) possesses a broad spectrum of antimicrobial activity.[126] They provide a safer alternative to conventional antimicrobial agents in the form of a topical antimicrobial formulation. Antimicrobial activity depends on the surface area and size of silver nanoparticles. AgNPs with larger surface area—to—volume ratios exhibit greater antibacterial efficiency. Nanosilver has shown antiinflammatory and healing properties and can repair skin tissue.

Tiny gold and silver nanoparticles are used in certain day and night creams to give the skin a fresher appearance. Nanosilver is used in toothpastes, soaps, deodorants, wet wipes, lip products, as well as face and body foams. Skin cleanser soap containing nanosilver exhibit antibacterial and antifungal properties and was found effective in treating acne and sun-damaged skin. AgNPs can also be used to kill yeasts such as *Candida glabrata* and *Candida albicans*, which cause infections in the mouth. Therefore, silver nanoparticles are being used in veterinary, pharmaceutical, and biological products. The nanosilver skin gel, which contains 30 times less silver than silver sulfadiazine, is a better choice for the skin of burn patients to treat infections.[126,185,186]

### *22.4.2.2 Nanogold*

Gold nanoparticles (GNPs) are different from gold particles; the larger size is a yellow inert solid whereas GNPs are a wine red compound with antioxidant properties. GNPs exhibit different sizes ranging from 1 nm to 8 μm, and they also simultaneously present distinct forms like suboctahedral, spherical, octahedral, icosahedral multiple twined, decahedral, multiple twined, tetrahedral, irregular shape, nanotriangles, hexagonal platelets, nanorods, and nanoprisms.[187,188]

GNPs are able to interact with the skin barrier, enhancing delivery and improving the skin permeability of high-molecular-weight active agents. GNPs are considered as promising candidates for skin immunization and optimizing transdermal delivery systems. Toxicity of GNPs for transdermal delivery systems requires further research.[189]

### *22.4.2.3 Zinc Oxide and Titanium Oxide*

ZnO and $TiO_2$ minerals are generally utilized in sunscreens as inorganic physical sun blockers. Owing to the fact that ZnO is effective in the UVA range and $TiO_2$ is effective in UVB, the mixture of the mentioned particles assures broadband UV protection. To resolve the whitening effect or ghost effect of sunscreens due to the presence of micro-sized $TiO_2$ and ZnO, nanosized particles (100 nm) have been increasingly substituted. With the application of $TiO_2$ and ZnO NPs, the unwanted skin whitening disappears, but the necessary balance between UVB and UVA protection will change. Application of micro- and nanosized ZnO dispersions and nanosized $TiO_2$ particles may eliminate the problem.[190]

### *22.4.2.4 Silica Nanoparticles*

Silicones have been widely introduced in cosmetic and personal care products due to their pleasing properties and feel and low toxicity. They can deliver lipophilic, hydrophilic, and silicophilic ingredients to their site of action via encapsulation. They are able to stabilize, protect, and transport actives such as lipophilic vitamins A and E and hydrophilic vitamin C. Volatile silicones can release the transported actives after they evaporate, therefore they can be used for antiperspirants or fragrances. Also, silicones improve the spreading of sunscreen ingredients in skin, raising the sun protection factor (SPF) level of the products.[8,9,181]

## 22.4.3 Polymeric Nanoparticles

Polymeric NPs designed for cutaneous delivery are developed with biocompatible polymers (200—300 nm). Permeation of polymeric nanoparticles in skin is related to the factors that prompt drug discharge process such as NP size and viscosity of formulations. Some reports have evaluated formulations in a qualitative method, however, in vivo influence of the rheological qualities on skin penetration is not fully understood. Polymeric NPs can affect the drugs' activity through their effect on physicochemical properties of formulations. They can regulate

drug discharge and increase drug adherence or retention in skin. They can also be efficacious as reservoirs in SC being a main procedure to improve drug penetration into skin.[191]

#### 22.4.3.1 Nanocapsules

Nanocapsules, submicroscopic tiny bits, are polymeric capsules surrounded by a watery or oily core. Nanocapsules are employed in cosmetics to protect sensitive actives, decrease unwanted odors, and remove incompatibility between formulation components. One of the earliest nanocapsule-based products in the market was an antiwrinkle lotion with vitamin A nanocapsules that gradually discharge the active through time.[10] L'Oréal marketed Primordiale Intense and Hydra Zen Serum using nanocapsules to encapsulate various active ingredients.[192]

Application of nanocapsules has reduced the penetration of UV filter octyl methoxycinnamate in skin over customary mixtures.[10] Nanocapsules were examined as sunscreen carriers for octyl methoxycinnamate (OMC), octyl salicylate, and benzophenone-3. They generated a preservative layer on the skin surface and retarded the permeation of the actives in sunscreen to the viable layer. Polymer PCL was used to prepare OMC-loaded nanocapsules for efficient shielding to UVB radiation. OMC was simultaneously encapsulated in cellulose acetate phthalate nanocapsules and its penetration in the SC was compared to that from a nanoemulsion.[192] In this case, the nanocapsules were not as efficient in delivering OMC; the encapsulation of benzophenone-3 in some NPs containing PVA-fatty acid were more effective. The nanocapsules notably diminished the movement of oxybenzone through porcine ear skin.[193,194]

#### 22.4.3.2 Hydrogels

Hydrogels, 3D hydrophilic polymer networks, swell in biological fluids as a consequence of chemical or physical cross-link formation.[10] The cosmetic field is on the frontline of hydrogels for synthesizing a pH-sensitive material, P(MAA-co-EGMA) for discharge of cosmetics and drugs such as arbutin, niacinamide, and adenosine molecules. The hydrogels were sensitive to pH variations: at pH 4.0, they hold the drugs in the compound when in touching skin; at pH 6 and higher, penetrability increased and drugs were delivered. The compound was designed to be applied for skin-whitening and antiwrinkle purposes.[195]

#### 22.4.3.3 Chitosan

Chitosan, a linear polysaccharide composed of β-(1-4)-linked D-glucosamine and *N*-acetyl-D-glucosamine is a hydrocolloid that can be synthesized by treating the chitin shells of shrimp and other crustaceans with alkaline solutions. It becomes viscous on being neutralized by acids. Several benefits of chitosans, such as biocompatibility, biodegradability, biorenewability, bioadhesivity, and nontoxicity have made them important natural polymers for pharmaceutical and cosmetic industries. Chitosan and chitin are fungistatic and fungicidal in nature. Ultraviolet radiation absorber compounds can covalently conjugate to chitosan amino groups. Chitosan and other hydrocolloids-based compounds composed of antiallergics, antioxidants, and antiinflammatory substances of vegetable origin have been produced. Chitosans have also been examined for drug delivery purposes.[196–199] They have been used in skin care, oral care, and hair products as modifying viscosity, film forming and hydrating agents, and delivery system. Facial mask produced by curcuminoids reflected skin irritation but the incorporation of chitosan decreased the disadvantageous effect.[200]

#### 22.4.3.4 Liquid Crystals

Liquid crystal, a novel emulsion dissimilar to the conventional systems, is a divided structure of surfactant and oil molecules developed at oil-water interface. The ordered form has enabled further efficiency than traditional emulsions such as higher stability and moisturizing properties, and directed drug discharge. Liquid crystal properties not only depend on the emulsion composition but also on their preparation method. Liquid crystal emulsions break apart on skin following the evaporation of their water content, and the emulsion dissociation enhances the drug penetration into outer layers.[201,202]

Different features and potential application of liquid crystal emulsions have enticed a large number of scholars in pharmaceutical and makeup products to do intensive studies on emulsion structures. Numerous chemical suppliers have prepared emulsifiers such as nonionic surfactants like alkyl glycosides, polyglycerol esters, phosphates, and so forth for developing emulsions with liquid crystal structure. Research on liquid crystal emulsions mostly addresses the idea of special systems, like aligned construction of emulsifier molecules, steadiness and rheological behavior, and applications of emulsion systems.[202,203]

## 22.4.4 Nanoparticulate Systems

Nanoparticulate delivery systems have been established for superior healing outcome as well as low skin toxicity. They have offered novel features and utilizations.[204]

### *22.4.4.1 Nanospheres*

Nanospheres are microscopic particles that are used to deliver active components into deep layers of skin. The natural nano-sized lipid nanoparticles in nanospheres improve drug penetration into the skin and lead to enhanced stability and higher activity in makeup components.[205]

### *22.4.4.2 Nanotopes*

TINODERM Nanotopes, new ultrasmall unilamellar vehicle systems three to four times smaller than conventional liposomes for delivery of actives, was first produced by Ciba Specialty Chemicals. Their size is less than 50 nm and can easily pass through the intercorneocyte lipids and the intercorneocyte pores. Their small size causes an even distribution of actives on the skin surface. They produce the highest possible number of actives on skin and cause fast and efficient transport through the skin barrier. They can easily penetrate in deeper layers of the lipid barrier and deliver the ingredients closer to the epidermis. Their unilamellar membrane consists of cone-like and cylinder-like molecules. Numerous cone and cylinder sequences create high stable particles that can strongly protect the active ingredients. They show higher surfactant resistance than conventional liposomes. Their stability and particle size distribution are better than liposomes, nanospheres, nanoparticles, and nanoemulsions. Prescriptive Px D-Panthenol (P)-loaded Nanotopes demonstrated the highest effect on erythema reduction in a dose- and time-dependent manner. TINODERM P is suggested for use in after-sun products and products for irritated skin and day cream formulations.[206]

### *22.4.4.3 Nanocrystals*

Nanocrystals have recently been examined for dermal applications.[207,208] They are made from pure active substance and do not require the use of organic solvents. The mechanism of nanocrystal dermal penetration enhancement might be explained by three various effects:

1. Increased gradient concentration between dermal formulation and skin following increased saturation solubility of nanosized ingredients leads to greater drug diffusion into skin.
2. Large surface area of nanocrystals leads to increased dissolution velocity.
3. Due to their nanosized dimensions, they show higher adhesion to skin. Greater kinetic saturation solubility, in combination with large surface area, leads to fast dissolution.[207,208]

Curcumin nanocrystal was introduced as a promising carrier in dermal application. Penetration behavior of curcumin nanocrystals (200 nm) produced by smartCrystals process demonstrated that low nanocrystals viscosity caused more skin penetration.[209] Recently, rutin nanocrystals were produced for dermal application by the combination technology of smartCrystal process. In a human study, rutin nanocrystals exhibited a twofold increased SPF,[207] which means a 1000-fold higher bioactivity in skin compared to rutin raw drug powder and/or rutin derivatives.[210]

### *22.4.4.4 Nanofibers*

Fibers are small pore solid nanomaterials with diameters of 5−500 nm. They can be defined as the particles with one dimension less than 100 nm and a theoretically unlimited length. Nanofibers have a porous structure with a large surface area per unit mass. Their large surface area provides suitable active sites for reactions. Structural modification of nanofibers gives them improved properties, such as better mechanical strength and higher flexibility than any other form of the same material.

Electrospinning technique has been used to produce different fiber assemblies. A wide variety of polymers such as chitosan, polyvinyl alcohol, collagen, gelatin, and carboxymethylcellulose can be produced by this technique. Nanofibers have found their promising potential in various biomedical areas such as drug and gene delivery, artificial blood vessels, and artificial organs.

Functionalized or nonfunctionalized nanofibers prepared by electrospun polymer have been used as cosmetic skin care masks for skin healing and skin cleansing. Nonwoven nanofibers applied for wound dressing have

pore sizes ranging from 500 nm to 1 mm. Because of small interstices and high surface area (5−100 $m^2/g$), they can improve the penetration of active ingredients into skin and extremely increase drug efficiency.[211,212]

#### 22.4.4.5 *Nanopigments*

Nanopigments, naturally occurring minerals, such as titanium dioxide or zinc oxide, are widely being used in sunscreen formulations to protect skin against broad-spectrum sun ultraviolet radiation including UVA, UVB, and UVC. Even at nanometer size, they are able to reflect and scatter UV light. They can provide a three-fold improvement compared with traditional UV filters. Large clusters of nanopigments present in sunscreens in the size range of 300−600 nm ensure optimal protection of the skin. Sunscreens containing nanosized titanium dioxide or zinc oxide are more favored by consumers, since they are transparent and do not leave a white film on skin. They usually do not cause skin adverse side effects such as irritations and contact allergies. They can improve the durability of sunscreen, one application in a day may be enough. They are also able to prevent the degradation of other active ingredients present in the formulation. They also show antibacterial properties under UV light irradiation.

There are controversial discussions regarding the toxicity of $TiO_2$ and ZnO in the formulation of sunscreens. While some experiments describe that these two nanoparticles are inert and nontoxic and do not pass through the skin barrier (either healthy skin or compromised skin) after topical application, other reports demonstrate toxicity from long-term application. More experiments are needed to determine the safe limit of these nanoparticles for the total human body.[213,214]

### 22.4.5 Carbon-Based Nanoparticles

#### 22.4.5.1 *Fullerene*

Fullerene, a hollow cluster of $sp^2$ carbon atoms, is a polygon with 60 vertices and 32 faces resembling a soccer ball. Several higher-order fullerenes such as C70, 76, 84, 90, and 94 or lower-order fullerenes such as C28 and C36 have been discovered, all belonging to the same family of hollow cage carbon structure. Among them, fullerene C60 (pristine fullerene) has remained the most common and stable type.

Pristine fullerene is one of the nanomaterials that has valuable applications in the field of biomedicine. Its exceptional antioxidant activity has made it a promising core ingredient in many dermatological and skin care products including sunscreen, skin whitening, and antiaging products. The experiments have shown that different fullerene derivatives such as PVP/F, γ-CD/F, hydroxy-fullerene, LF, and fullerenol can reduce ROS, while CF, Radical Sponge, PVP/F, LF, and fullerenol are able to reduce apoptosis as well as cellular and morphological changes. Fullerene can increase the antioxidant capacity of the skin and protect the skin against UV damage.[7,215] Fullerene has recently been introduced for acne therapy due to its high antioxidant activity and high skin penetration ability into epidermis. It can act as a vehicle to enhance drug delivery. Studies on one of the fullerene derivatives (fullerenol, $C_{60}(OH)_{24}$) show that it can suppress sebum production and has antimicrobial activity against (Propionibacterium acnes) p. Acne. Fullerene can stimulate hair growth. The experiments on the effect of fullerene on live mice and human skin samples indicated that either intradermal injection or topical application of fullerene can accelerate hair growth and cause de novo hair follicle generation.

Different kinds of fullerene C60 and its derivatives have been applied for cosmetic usages. Molecular complexation of fullerenes with cyclodextrins, polyvinyl pyrrolidone (PVP), and liposomes are of special interest to the beauty industry. Incorporation of fullerene C60 and C60 adducts in liposomes made of phosphatidyl-ethanolamine were the primary studies on using liposomes to develop fullerenes.[216] Fullerene and LipoFullerene in squalane could prevent wrinkles caused by 2,4-nonadienal in 3D-human skin tissue model. Radical Sponge is able to recover the skin barrier. A significant improvement in transepidermal water loss was observed without any change in SC hydration. The effect of fullerene in decreasing facial pores using a lotion with 1% Radical Sponge indicated 17.6% reduction in conspicuous pores ($p < .05$) after 8 weeks of study.

There are many patents about miscellaneous uses of this newly emerging nanomaterial in dermatology and cosmetic technology. Japan manufactures the majority of fullerene-containing products; many of them use Radical Sponge or LipoFullerene, which are produced by vitamin C60 Corporation. Radical Sponge is water soluble, while LipoFullerene is lipid soluble. The company claims that fullerene can be used in whitening, pore tightening, antiwrinkle, antiacne, hair growth, and recovery of skin barrier products. There are currently more than 1500 clinics in Japan and more than 1000 products in the worldwide market that use fullerene as an active ingredient. Fullerene can be used in topical preparations without a major risk for dermatitis. However, more studies assessing different fullerene compositions and different skin conditions are needed to draw conclusive results about dermal absorbance and toxicity of fullerenes.[7,215−217]

#### 22.4.5.2 Nanodiamond

Nanodiamond with the size range of ~5 nm is an attractive nanoparticle for biomedical applications. It has a highly ordered diamond core covered by a layer of functional groups on the surface, which stabilizes the particle by terminating the dangling bonds. Conversion of $sp^3$ carbon to $sp^2$ carbon causes further surface stabilization. The $sp^2$ carbons form chains and graphitic patches. The majority of surface atoms are terminated with oxygen-containing groups. Each nanodiamond is made up of a highly ordered diamond core. Some nanodiamonds are faceted, whereas most have a rounded shape.

Nanodiamond shows important properties such as biocompatibility, tailorable surface chemistry, which facilitate bioconjugation and accessibility. Its unique optical, mechanical, and thermal properties with stable photoluminescence characteristics has made it a good candidate for a wide range of applications in tribology, drug delivery, and tissue engineering.[218,219] Nanodiamonds have recently been introduced as carriers for improving transdermal actives' administration for the treatment of skin diseases and application in cosmetic and health care products. They have been proposed as promising materials for wound healing and antiscarring applications.[220]

The surface of nanodiamond is able to be fluorine terminated to increase its superhydrophobic properties. This surface is very hungry of organic molecules. Fluorinated nanodiamond has a diamond core and Teflon surface, called dialon fragments. Dialon readily diffuses in organic media and can be utilized for numerous applications. Dialon nail oil is more resistant than common nail polish materials. Dialon face lift is a super cleaner for removing leftover cosmetics on the face. Due to its high binding potential to proteins, dialon exhibits great antibacterial activity.

Since nanodiamond is relatively minuscule over ordinary cells and can be captured via the membrane of the cell, it is not toxic for them. Excellent physical performance of diamond nanoparticles accompanied by their biocompatibility and nontoxicity have made them an attractive ingredient in cosmetics, however, the toxicological and environmental safety of nanodiamonds have to be considered using specific toxicological studies prior to a wider application of the new technology.[219]

### 22.4.6 Other Nanoparticles

#### 22.4.6.1 Cyclodextrins

Cyclodextrin technology is one of the most recent delivery technologies in the worldwide marketplace that is perfectly consistent with cosmeceutical needs. The technology is expected to emerge in many new cosmeceutical formulations in the near future. Cyclodextrins (CDs) are nontoxic cyclic polysaccharides comprised of six to eight d-(+)- glucopyranose units using α (1 → 4) glucosidic bonds. The three natural CDs—α, β, and γ—built from D-glucose units (α = 6, β = 7, γ = 8) vary in their ring diameter and solubility. They are naturally occurring and can be obtained during the enzymatic degradation of starch.

Cyclodextrins are ring- or cylindrically shaped structures creating an internal cavity that can encompass other molecules and form host-guest supramolecules. They can form inclusion complexes with numerous molecules, and thus can be used in a variety of fields. They enable controlled and sustained drug release in pharmaceutical products, stabilize molecules against light and oxygen degradation, and increase solubility of low-soluble molecules. α-CD commonly creates inclusion complexes with both aliphatic hydrocarbons and gases. β-CD makes complexes coupled with tiny aromatic molecules.[183,221] γ-CD is able to accept additional bulky mixtures such as vitamin D. Complexation with CDs stabilizes the active ingredient against oxidative, photolytic, as well as thermal degradation. It can maintain the molecules in a rigid form, inhibit occurrence of reactive conformation, separate the molecules from environment, and reduce the incompatibilities. The formulations including emulsions may cause dry or doll effect on skin, which can be reduced by the addition of cyclodextrins, preferably β- and α-types.[222]

Cyclodextrins can be found in a variety of personal care products such as antiaging treatment, facial moisturizer/lotion, sunscreen, cleanser, eye cream, deodorant/antiperspirant, and self-tanners. Based on host-guest interactions, they prevent the degradation of active ingredients such as antioxidants and vitamin A derivatives (aka retinoids), which are very sensitive to temperature and light. In the fragrance industry, their odor absorption capabilities stabilize fragrances.

There are a large number of commercially available cyclodextrin-based cosmeceutical products, and numerous applications of cyclodextrins in cosmetic and pharmaceutical are patented. The FDA has included this ingredient as a GRAS direct food additive, and both animal and human experiments have demonstrated nontoxicity of the compound.[221,222]

#### 22.4.6.2 Dendrimers

Dendrimers, artificial macromolecules with layered structures, consist of a central main part and an inner region comprised of repeating units and terminal groups. These multivalent nanostructures are highly symmetric around the core and often have a spherical three-dimensional structure. They have recently been developed for delivery of hydrophilic and hydrophobic drugs, nucleic acids, and imaging due to their interesting features like well-established dimensions and molecular weight, multivalency, monodispersity, number of available internal cavities, high degree of branching, and different surface functional groups. They have recently been utilized in personal care products and cosmetics such as antiacne products, shampoos, hair-styling gels, and sunscreens.[223–225] As an effective ingredient for improving the performance of bioactive dermocosmetic ingredients, they are able to improve the efficacy of actives by protecting their integrity, targeting cosmetics to different skin layers and molecular receptors, and increasing solubility of cosmetic ingredients. Rich functional surface groups of dendrimers and their viscosity characteristics have produced new claims of product superiority over conventional personal care products.

Recently, a novel dendrimer with hydroxyl functional groups has been used as a successful cosmetic additive that spreads uniformly on the skin, increases the adhesion, and forms a thin and soft layer that prevents the makeup from coming off the skin and has a cleaning effect. Dendritic macromolecules with polyhydric polyester alcohol or hyperbranched polyol functionalized groups have been patented for application in a hair-styling spray, gel, or mousse formulation.[223] Dendritic macromolecules with terminal hydroxyl functional group polyester in combination with film-forming polymers have created a superior cosmetic product with high performance and ease of use. The product has been patented by L'Oréal for application to the skin, keratinous fibers, nails, or mucous membranes. The combination of a dendritic polymer with a film-forming polymer created a low-viscous product that can form a dry film on skin capable of being peeled off after the application period. A conjugate of aminobutadiene with an amine-rich dendritic molecule offered UV-absorbing capabilities to the final product. Owing to the high molecular weight of the resulting molecule, the product is nonpenetrating into the skin and minimizes the risk of irritation or sensitization reactions when applied on the skin. Amine-terminated cationic dendrimers have been used as mildness agents in personal care cleansing products. They exhibited odor-absorbing properties and were considered as deodorant active agents. Formulations containing amine-terminated dendrimers and a tanning agent could increase the intensity and quality of skin coloration produced, as well as providing a shade that was closer to a natural tan. Cationic dendrimers can be used for lowering skin irritation of cosmetic formulations containing harsh anionic surfactants. They maintain the dispersion in salt solution and interact with anionic surfactants in the composition to prevent the reduction of skin lathering, skin conditioning, or cleansing, which can be caused by the precipitation of mildness agents (linear cationic polymers) upon interaction with anionic surfactants. Surface-modified dendrimers have also been used in drug delivery systems. Dendrimers containing free amino groups were used as carriers for improving delivery of antiacne agents.[223–225]

## 22.5 TOXICITY OF NANOPARTICLES

The different physical and chemical attributes of engineered NPs have produced several new and helpful applications to enhance our lives. Nonetheless, these same qualities have also allowed them to be introduced into the human body and cooperate with biological systems in unusual procedures. As a consequence, nanotoxicity is now a realistic issue and the field of nanotoxicology investigation has developed in recent years.[226]

Among the various potential routes of NP entry into the body, permeation in the skin with the help of topical skin products is a concern despite our conventional knowledge that such permeation amounts are low. Influence of skin types and integrity of the physical skin barrier on NP permeation have not been effectively addressed. The consequences of continued but diminished level NP penetrations during continuous application of topical skin products are simultaneously unmapped and under question.[226]

From the investigational point of view, considerable knowledge has been produced on the possible toxicity processes of NP–biological system interactions that are relating to nanotoxicity in skin. ROS production, oxidative stress induction, and long-term inflammation are all viable scenarios to investigate. Nevertheless, the interaction between these and their real effect on skin physiology and beyond will demand preserved investigation attempts to resolve. Unconventional discoveries like the induction of autophagy in keratinocytes are able to bring new knowledge and methods for managing distinguished risks. Recent investigations and models will be important in helping scientists advance the knowledge of nanotoxicity in skin that is quick enough to cope with the speed which new nanoparticles including topical skin manufactured articles are being introduced into the market.[226]

## 22.6 SAFETY REQUISITES FOR A BLOOMING BEAUTY

Cosmetic manufacturers with the help of nanotechnology meet an uncertain future from both client response and regulatory opinion. Prominent technical bodies like the Royal Society, Britain's most prestigious technical body, and the US Food and Drug Administration warn that the physical state risks of nanocosmetics need thorough experimentation prior to product commercialization. One of the greatest problems is that there is not much proof regarding how much or what kind of safety evaluations are done by the different cosmetic manufacturers on their products.[10]

Though there are increased numbers of cosmetics and personal care manufactured articles including nanomaterials in the market, there are no specific regulations with reference to their safety evaluation. In Australia, the National Industry Chemicals Notification and Assessment Scheme modulates the safety of components in makeup and personal care products and the Therapeutic Goods Administration modulates sunscreens. Nonetheless, these regulators fail to detect between NPs and larger sized particles. The European Parliament permitted the modified recast of the EU Cosmetics Directive, introducing the statement of "nanomaterials" into an EU legislation. As requested by the European Parliament, the novel regulation introduces a safety evaluation strategy for all products including nanomaterials as follows.[10,141]

- The ruling describes nanomaterial as "an insoluble or bio-persistent and intentionally manufactured material with one or more external dimensions, or an internal structure, on the scale from 1 to 100 nm."
- Responsible individual shall ensure compliance with safety, GMP, product information file, safety evaluation, sampling and assessment, notification, limitations for substances listed in Annexes, nanomaterial traces, CMR, animal experimentation and labeling, claims, communication of SUE, information to the public, information on substances.
- Before placing the cosmetic product on the market, the responsible person needs to submit the following information to the Commission:
  - The existence of substances in the form of nanomaterials;
  - Their identification containing the chemical name (IUPAC) and other descriptors;
  - The reasonably foreseeable revealing circumstances;
- In case the Commission has concerns about the safety of the nanomaterial, the Commission shall request the SCCS to give its opinion on the safety of these nanomaterials for the pertinent categories of cosmetic products and the reasonably foreseeable exposure circumstances;
- All components present in the form of nanomaterials shall be clearly stated in the list of ingredients. The names of such components shall be followed by the word "nano" in brackets;
- Specific consideration shall be given to any practical effects on the toxicological profile caused by:
  - Particle sizes, containing nanomaterials;
  - Impurities of the substances and raw material in use; and
  - Interplay of substances.[10,141]

## 22.7 NANOMATERIALS AND THE EU COSMETICS REGULATIONS

European regulations for the safety of cosmetics/personal care product (PCP) were established in 1976 by the EU Cosmetic Directive, which has been updated.[226a] In accordance with the EU definition, cosmetics are any substance or compound planned to be placed in contact with several parts of the human body (hair system, lips, nails, epidermis, and external genitals) and with the teeth or mucous tissues of the oral cavity. In the EU, cosmetic products do not need premarketing clearance; the safety of cosmetics and their components is the responsibility of the industrialist.[227]

Safety necessities for cosmetic components are listed in the "Notes of Guidance for the Testing of Cosmetic Ingredients and their Safety Evaluation" (SCCP, 2006). General safety requirements for a regulated cosmetic ingredient, such as hair dyes or UV filters are as follows:

- dermal absorption/penetration
- acute toxicity
- dermal irritation
- use and physical/chemical data
- mucous membrane irritation

- skin sensitization
- genetic toxicity
- subchronic toxicity
- phototoxicity and photogenotoxicity
- human data

The factory owners or importers in the EU of PCP have to provide safety sheet on each cosmetic product, containing composition, specifications, and a product safety evaluation on the final product and its ingredients; the safety evaluation has to be evaluated by a qualified expert.[227]

## 22.8 NANOCOSMECEUTICALS IN MARKET

Nowadays there are over 400 suppliers and industrialists of cosmeceutical products, and the industry is predicted to expand in future years. Results of a study of several nanotechnology-based cosmeceutical manufactured articles in the market have been tabulated in Table 22.2.[112,141]

**TABLE 22.2** Various Nanotechnology-Based Cosmeceutical Products in the Market

| Product | Proposed Use | Manufacturer | Marketing Claims |
|---|---|---|---|
| Hydra Flash Bronzer Daily Face moisturizer | Moisturizer | Lancôme | Nanocapsules of pure Vit E provide powerful antioxidant protection and ensure a natural, healthy glowing skin |
| Hydra Zen Cream | Moisturizer | Lancôme | Containing nanoencapsulated triceramides. It provides perfect comfort and softness, full hydration to skin; renews skin's health; and protects skin from signs of daily stress |
| Nano-in Hand and Nail Moisturizing Serum and Foot Moisturizing Serum | Moisturizer | Nano-Infinity Nanotech | Fine crystals of ZnO NPs penetrate skin tissue to prevent hands and nails from being hurt |
| Lancôme Renergie Microlift | Antiwrinkle | Lancôme | Formulated with colloidal silica and soy protein NPs to provide the best possible face-lift effect |
| RevitaLift Anti-Wrinkle, Firming Face, Neck Contour Cream | Antiwrinkle | L'Oréal | RevitaLift formula is enriched with Pro-Retinol A, encapsulated in nanosomes |
| RevitaLift Double Lifting | Antiwrinkle | L'Oréal | It contains nanosomes of Pro-Retinol A and has a unique dual action treatment that instantly retightens skin and effectively fights wrinkles |
| Eye Tender | Antiwrinkle | Kara Vita | It contains nanospheres, delivers 13 bioactives including wrinkle-reducing peptides to stimulate fibroblasts, build collagen, brighten skin, and reduce inflammation for a younger, healthier appearance |

*Continued*

**TABLE 22.2** Various Nanotechnology-Based Cosmeceutical Products in the Market—cont'd

| Product | Proposed Use | Manufacturer | Marketing Claims |
|---|---|---|---|
| Eye Contour Nanolift | Antiwrinkle, Antiaging | Euoko | Lifting nanocapsules join appropriate ingredients to remove fine lines, wrinkles, and puffiness. They provide instant and long-term smoothness, give the eye area more radiance, and diminish the appearance of dark circles |
| Soleil Soft-Touch Anti-Wrinkle Sun Cream SPF 15 | Antiwrinkle, sunscreen | Lancôme | It contains nanocapsules of vitamins to preserve skin's youth and create long-lasting effect. SPF-15 offers optimal protection against the sun |
| Nano Gold Firming Treatment | Antiaging | Chantecaille | Small NPs of pure gold bind to silk microfibers to firm and tone skin, causing incredible antiinflammatory, healing and antiaging effect |
| Nanosphere Plus | Antiaging | DermaSwiss | It contains stem cell (cells from a rare Swiss apple, Uttwiler Spatlauber) antiaging nanosphere to preserve and protect skin cells. Nanosphere Plus combats chronological aging |
| Zelens Fullerene C-60 Night Cream | Antiaging | Zelens | Containing fullerene C-60, which creates remarkable antioxidant properties |
| Clearly It! Complexion Mist | Antiacne | Kara Vita | This nanosphere-based product tackles acne conditions and balances sebum production. Nanosphere time-released bioactives stimulate capillary activity for all-day detoxifying results |
| DiorSnow Pure UV Base SPF 50 | Sunscreen | Dior | Contains nano-UV filters for ultraprotection against the damaging effects of UVA and UVB rays |
| Soleil Instant Cooling Sun Spritz SPF 15 | Sun protection spray | Lancôme | Contains vitamins in nanocapsules. Instant cooling sun spray SPF 15 offers a sensation of freshness. SPF 15 provides optimal protection against sun |
| Fresh As A Daisy Body Lotion | Body lotion | Kara Vita | This lotion uses nanospheres to quickly penetrate, moisturize, and nourish all types of skin |
| Cosil Nano Beauty Soap | Cleanser | Natural Korea | This product contains silver nanoparticles that act as an effective disinfectant |
| Cosil Whitening Mask | Face mask | Natural Korea | Made with nanocolloidal silver used for removing germs from face, compressing pores, soothing skin conditions, and keeping skin radiant and soft |

**TABLE 22.2** Various Nanotechnology-Based Cosmeceutical Products in the Market—cont'd

| Product | Proposed Use | Manufacturer | Marketing Claims |
|---|---|---|---|
| Nanorama—Nano Gold Mask Pack | Face mask | LEXON NanoTech | It contains pure nanosized gold, highly effective in penetrating small pores and disinfecting skin, helps to reduce pore size, prevents and treats acne |
| Primordiale Optimum Lip | Lip treatment | Lancôme | Delivers pure Vit E via nanocapsules to lips to reduce bleeding and feathering due to fine lines and wrinkles |
| Lip Tender | Lip moisturizer | Kara Vita | Ten bioactive ingredients loaded on lyphazomes cause long-lasting hydration for fast and dramatic lip repair |
| Nano Cyclic Cleanser Silver | Cleanser | Nano Cyclic | It is a blend of nanosilver and natural ingredients that kills harmful bacteria and fungi, treats acne, exfoliates dead skin on all parts of the body, diminishes age spots, deodorizes the body, and fights wrinkles |
| LifePak Nano | Face gel | Pharmanex | LifePak Nano is a nutritional antiaging formulation to nourish and protect cells, tissues, and organs against the ravages of aging. Nanoencapsulation increases bioavailability of coenzyme Q10 by 5—10 times |

*Reprinted from Cevc G. Lipid vesicles and other colloids as drug carriers on the skin. Adv Drug Deliv Rev 2004;**56**:675—711 from "Hindawi Publishing Corporation", Copyright 2016.*

## 22.9 FUTURE TRENDS IN NANOCOSMECEUTICALS

The utilization of beauty products has drastically increased in recent years. The global tendency in the cosmetic industry is in the direction of preparing "medicinally" active cosmetics, and in the pharmaceutical industry toward "cosmetically" oriented therapeutic products as part of a recent "lifestyle" ideology.[5,228,229]

The future promises to an increasing extent sophisticated formulations for skin care products and cosmetics. Cosmetic firms are developing methods to deliver small-dose components that do not need medical regulations and to introduce steroids and hormones in lip balms, which would lead to production of beauty products that are able to help balance body mass, nail, and hair growth. New calls will also be presented to government regulatory agencies as more chemicals with true biological undertaking are developed and put to the test. Claim substantiation and premarketing testing need to also evolve to accurately assess efficacy and safety issues with crucial implications for total body health. The innovative carriers and delivery systems combined with usual ingredients will affect percutaneous absorption, requiring reevaluation of substances with a presumed good safety profile. Biotechnology will simultaneously compete right with the medications and cosmetic firms. The most influential outlook in the coming 5 years will be the links among internal health, beauty, together with antiaging products.[228—232]

## 22.10 CONCLUSIONS

Dependent on the latest patents and the research-based literature on the application of nanotechnology in cosmetics, this emerging technology is about to turn into a vital tool for knowledge-based investigations of recent cosmetic products. Whereas nanotechnology is nowadays being established for both generating new packaging materials and manufacturing equipment for cosmetics, it is within the scope of cosmetic materials formulation that one currently finds the maximum number of nanotechnology-related patents and research-based reports. In formulations, nanomaterials are already being utilized or being proposed for coming applications as vehicles of active

substances, as more widespread formulation aids, and as active ingredients by themselves. The kinds of nanomaterials under consideration vary vastly in chemical and physical qualities and include NPs of biological substances such as amino acids, proteins, and peptides; metals like silver, gold, zinc, and titanium; oxides like alumina, silica, and titanium oxide; carbon nanomaterials like fullerenes, graphene, and CNTs; lipid-based NPs; as well as some modified and synthetic polymers.

The cosmeceutical nanomaterials are rapidly and widely developing, thus we can expect a range of novel nanotechnology-based cosmetic products on the shelves of our nearest drug stores in the near future. Precise toxicity evaluations of nanoparticles including life cycle, the human exposure routes, the behavior of nanoparticles in the body, and the risks for workers are needed. Safety regulations and guidelines for their production and application are mandatory.

## Acknowledgments

The authors appreciate the Department of Chemistry, Central Tehran Branch, IAU, Tehran, Iran and Department of Dermatology, University of California, San Francisco, CA, USA, for support of this work.

## References

1. Morganti P. Use and potential of nanotechnology in cosmetic dermatology. *Clin Cosmet Investig Dermatol* 2010;**3**:5–13.
2. Morganti P, Yuanhong L, Morganti G. Nano-structured products: technology and future. *J Appl Cosmetol* 2007;**25**:161–78.
3. Firooz A, Namdar R, Nafisi S, Maibach HI. Nano-sized technologies for miconazole skin delivery. *Curr Pharm Biotechnol* 2016;**17**:524–31.
4. Behtash A, Nafisi S, Maibach HI. New generation of fluconazole: a review on existing researches and technologies. *Curr Drug Deliv* 2016;**13**. Manuscript in Publication.
5. Firooz A, Nafisi S, Maibach HI. Novel drug delivery strategies for improving econazole antifungal action. *Int J Pharm* 2015;**495**:599–607.
6. Nassiri-Kashani M, Namdar R, Nafisi S, Maibach HI. Improved voriconazole topical delivery by nanoparticles (minireview). *Pharm Chem J* 2016;**50**:76–9.
7. Mousavi SZ, Nafisi S, Maibach HI. Fullerene nanoparticle in dermatological and cosmetic applications. *Nanaomedicine* 2016. Manuscript is submitted.
8. Nafisi S, Maibach HI. Silica nanoparticles: promising nanoparticles for increasing cosmetic ingredients/drugs efficacy. *Cosmet Toilet* 2015.
9. Nafisi S, Schäfer-Korting M, Maibach HI. Perspectives on percutaneous penetration: silica nanoparticles. *Nanotoxicology* 2015;**9**:643–57.
10. Raj S, Jose S, Sumod U, Sabitha M. Nanotechnology in cosmetics: opportunities and challenges. *J Pharm Bioallied Sci* 2012;**4**:186–93.
11. Morganti P, Morganti G. Nanotechnology and wellness. *SOFW J* 2007;**133**:22–7.
12. Alikhan A. Dermatology simplified: outlines and mnemonics. *J Am Acad Dermatol* 2016;**74**:e37.
13. Burns T, Breathnach S, Cox N, Griffiths C. *Rook's textbook of dermatology*. Oxford: Blackwell Science Ltd.; 2004.
14. Ginhoux F, Tacke F, Angeli V, Bogunovic M, Loubeau M, Dai X-M, et al. Langerhans cells arise from monocytes in vivo. *Nat Immunol* 2006;**7**: 265–73.
15. Marks JJG, Miller JJ, Lookingbill DP. *Lookingbill and Marks principles of dermatology*. Philadelphia (PA): Saunders Elsevier; 2006.
16. Ovaer P, Lippens S, Vandenabeele P, Declercq W. The emerging roles of serine protease cascades in the epidermis. *Trends Biochem Sci* 2009;**34**: 453–63.
17. James WD, Berger TG, Elston DM. *Andrews' diseases of skin, clinical dermatology*. Canada: Elsevier Saunders; 2006.
18. Wolff K, Johnson RA. *Fitzpatrick's color atlas and synopsis of clinical dermatology*. New York: McGraw-Hill Medical; 2009.
19. Ro BI, Dawson TL. The role of sebaceous gland activity and scalp microfloral metabolism in the etiology of seborrheic dermatitis and dandruff. *J Investig Dermatol Symp Proc* 2005;**10**:194–7.
20. Gawkrodger DJ, Ardern-Jones MR. *Dermatology: an illustrated colour text*. Edinburgh (Scotland): Elsevier Health Sciences. Churchill Livingstone/Elsevier; 2012.
21. Montagna W. *The structure and function of skin 3E*. Academic Press; 2012.
22. Bronaugh RL, Maibach HI. *Percutaneous absorption: mechanisms, methodology, drug delivery*. New York.: Marcel Dekker; 1989.
23. Hadgraft J. Skin, the final frontier. *Int J Pharm* 2001;**224**:1–18.
24. Toll R, Jacobi U, Richter H, Lademann J, Schaefer H, Blume-Peytavi U. Penetration profile of microspheres in follicular targeting of terminal hair follicles. *J Investig Dermatol* 2004;**123**:168–76.
25. Vyas SP, Khar RK. *Controlled drug delivery concepts and advances*, vol. 1. Vallabh Prakashan; 2002. p. 411–47.
26. Roberts MS, Walters KA. Human skin morphology and dermal absorption. In: Roberts MS, Walters KA, editors. *Dermal absorption and toxicity assessment*. New York: Informa Healthcare; 2008.
27. Liu X, Grice JE, Lademann J, Otberg N, Trauer S, Patzelt A, et al. Hair follicles contribute significantly to penetration through human skin only at times soon after application as a solvent deposited solid in man. *Brit Clin Pharmacol* 2011;**72**:768–74.
28. Grice JE, Ciotti S, Weiner N, Lockwood P, Cross SE, Roberts MS. Relative uptake of minoxidil into appendages and stratum corneum and permeation through human skin in vitro. *J Pharm Sci* 2010;**99**:712–8.
29. Flynn G. Cutaneous and transdermal delivery: processes and systems of delivery. *Drugs Pharm Sci* 1996;**72**:239–98.
30. Mccarley KD, Bunge AL. Pharmacokinetic models of dermal absorption. *J Pharm Sci* 2001;**90**:1699–719.
31. Morrow DIJ, McCarron PA, Woolfson AD, Donnelly RF. Innovative strategies for enhancing topical and transdermal drug delivery. *Open Drug Deliv J* 2007;**1**:36–59.
32. Scheuplein RJ. Permeability of the skin: a review of major concepts and some new developments. *J Investig Dermatol* 1976;**67**:672–6.

33. Flynn GL. Mechanism of percutaneous absorption from physicochemical evidence. In: Bronaugh RL, Maibach HI, editors. *Percutaneous absorption: mechanism-methodology-drug delivery*. New York: Marcel Dekker; 1989.
34. Hadgraft J. Modulation of the barrier function of the skin. *Skin Pharmacol Physiol* 2001;**14**:72–81.
35. Morganti P, Ruocco E, Wolf R, Ruocco V. Percutaneous absorption and delivery systems. *Clin Dermatol* 2001;**19**:489–501.
36. Price E. The mechanism of lymphatic obstruction in endemic elephantiasis of the lower legs. *Trans R Soc Trop Med Hyg* 1975;**69**:177–81.
37. Price E, Henderson W. The elemental content of lymphatic tissues of barefooted people in Ethiopia, with reference to endemic elephantiasis of the lower legs. *Trans R Soc Trop Med Hyg* 1978;**72**:132–6.
38. Teneralli MJ. Traditional skin care lines: improving looks with dietary supplements. *Neutraceuticals World* 2004;**7**:74–80.
39. Kuno N, Matsumoto M. *Skin beautifying agent, antiaging agent for skin, whitening agent and external agent for the skin*, US Patent No. 6682763 B2, 2004.
40. Arquette DJG, Brown J, Reinhardt J. *Dry emollient compositions*, US 6280746 B1, 2001.
41. Martin R, Belcour-Castro B. *Use of at least one extract of the genus Chrysanthemum for assisting skin and/or hair pigmentation*, US 6726940 B2, 2004.
42. Farage MA, Miller KW, Maibach HI. *Textbook of aging skin*. Springer Science & Business Media; 2009.
43. Kempers S, Katz HI, Wildnauer R, Green B. An evaluation of the effect of an alpha hydroxy acid-blend skin cream in the cosmetic improvement of symptoms of moderate to severe xerosis, epidermolytic hyperkeratosis, and ichthyosis. *Cutis* 1998;**61**:347–50.
44. Kurtzweil P. Alpha hydroxy acids for skin care. smooth sailing or rough seas? *FDA Consum* 1998;**32**:30–5.
45. Kolattukudy PE, Walton TJ. Structure and biosynthesis of the hydroxy fatty acids of cutin in *Vicia faba* leaves. *Biochemistry* 1972;**11**: 1897–907.
46. Gupta SK. *Hydroxy acids based delivery systems for skin resurfacing and anti-aging compositions*, US Patent 20040092482, 2004.
47. Stallings AF, Lupo MP. Practical uses of botanicals in skin care. *J Clin Aesthet* 2009;**2**:36–40.
48. Ganesan P, Choi DK. Current application of phytocompound-based nanocosmeceuticals for beauty and skin therapy. *Int J Nanomed* 2016;**11**: 1987–2007.
49. *Ancient cosmetics and fragrance; Egypt, Greece and Rome*. Available at: http://www.cyonic-nemeton.com/Cosmetics.html.
50. El Asbahani A, Miladi K, Badri W, Sala M, Aït Addi EH, Casabianca H, et al. Essential oils: from extraction to encapsulation. *Int J Pharm* 2015; **483**:220–43.
51. Munin A, Edwards-Lévy F. Encapsulation of natural polyphenolic compounds; a review. *Pharmaceutics* 2011;**3**:793–829.
52. Nanbu T. *Whitening cosmetic composition containing arbutin nanoparticles*, US 20090069253 A1, 2008.
53. Kafi R, Kwak HS, Schumacher WE, Cho S, Hanft VN, Hamilton TA, et al. Improvement of naturally aged skin with vitamin a (retinol). *Arch Dermatol* 2007;**143**:606–12.
54. Yoshioka A, Miyachi Y, Imamura S, Niwa Y. Anti-oxidant effects of retinoids on inflammatory skin diseases. *Arch Dermatol Res* 1986;**278**: 177–83.
55. Lippman SM, Shimm DS, Meyskens FL. Nonsurgical treatments for skin cancer: retinoids and α-interferon. *J Dermatol Surg Oncol* 1988;**14**: 862–71.
56. Mukherjee S, Date A, Patravale V, Korting HC, Roeder A, Weindl G. Retinoids in the treatment of skin aging: an overview of clinical efficacy and safety. *Clin Interv Aging* 2006;**1**:327–48.
57. Stefanaki C, Stratigos A, Katsambas A. Topical retinoids in the treatment of photoaging. *J Cosmet Dermatol* 2005;**4**:130–4.
58. Jenning V, Gysler A, Schäfer-Korting M, Gohla SH. Vitamin A loaded solid lipid nanoparticles for topical use: occlusive properties and drug targeting to the upper skin. *Eur J Pharm Biopharm* 2000;**49**:211–8.
59. Jenning V, Gohla SH. Encapsulation of retinoids in solid lipid nanoparticles (SLN). *J Microencapsul* 2001;**18**:149–58.
60. Shah KA, Date AA, Joshi MD, Patravale VB. Solid lipid nanoparticles (SLN) of tretinoin: potential in topical delivery. *Int J Pharm* 2007;**345**: 163–71.
61. Yamaguchi Y, Nagasawa T, Nakamura N, Takenaga M, Mizoguchi M, Kawai S, et al. Successful treatment of photo-damaged skin of nano-scale atRA particles using a novel transdermal delivery. *J Control Release* 2005;**104**:29–40.
62. Date AA, Naik B, Nagarsenker MS. Novel drug delivery systems: potential in improving topical delivery of antiacne agents. *Skin Pharm Physiol* 2005;**19**:2–16.
63. Weissmann B, Meyer K. The structure of hyalobiuronic acid and of hyaluronic acid from umbilical cord. *J Am Chem Soc* 1954;**76**:1753–7.
64. Weissmann B, Meyer K, Sampson P, Linker A. Isolation of oligosaccharides enzymatically produced from hyaluronic acid. *J Biol Chem* 1954; **208**:417–29.
65. Scott JE, Heatley F. Hyaluronan forms specific stable tertiary structures in aqueous solution: a 13C NMR study. *Proc Natl Acad Sci USA* 1999; **96**:4850–5.
66. Balazs EA. *Chemistry and molecular biology of the intercellular matrix*. New York: Academic Press; 1970.
67. Bates EJ, Harper GS, Lowther DA, Preston BN. Effect of oxygen-derived reactive species on cartilage proteoglycan-hyaluronate aggregates. *Biochem Int* 1984;**8**:629–37.
68. Turino GM, Cantor JO. Hyaluronan in respiratory injury and repair. *Am J Resp Crit Care Med* 2003;**167**:1169–75.
69. Meyer LJM, Stern R. Age-dependent changes of hyaluronan in human skin. *J Investig Dermatol* 1994;**102**:385–9.
70. Stern R, Maibach HI. Hyaluronan in skin: aspects of aging and its pharmacologic modulation. *Clin Dermatol* 2008;**26**:106–22.
71. Longas MO, Russell CS, He X-Y. Evidence for structural changes in dermatan sulfate and hyaluronic acid with aging. *Carbohydr Res* 1987;**159**: 127–36.
72. Fakhari A. *Biomedical application of hyaluronic acid nanoparticles*. Bioengineering and the Graduate Faculty, University of Kansas; 2012.
73. Jegasothy SM, Zabolotniaia V, Bielfeldt S. Efficacy of a new topical nano-hyaluronic acid in humans. *J Clin Aesthet Dermatol* 2014;**7**:27–9.
74. Kong M, Chen XG, Kweon DK, Parka HJ. Investigations on skin permeation of hyaluronic acid based nanoemulsion as transdermal carrier. *Carbohydr Polym* 2011;**86**:837–43.
75. Lim HJ, Cho EC, Lee JA, Kim J. A novel approach for the use of hyaluronic acid-based hydrogel nanoparticles as effective carriers for transdermal delivery systems. *Colloids Surf A Physicochem Eng Asp* 2012;**402**:80–7.
76. Harding CR, Moore DJ, Rawlings AV. Ceramides and the skin. In: Baran R, Maibach HI, editors. *Textbook of cosmetic dermatology*. New York: Informa Healthcare; 2010.

77. Garidel P, Fölting B, Schaller I, Kerth A. The microstructure of the stratum corneum lipid barrier: mid-infrared spectroscopic studies of hydrated ceramide:palmitic acid:cholesterol model systems. *Biophys Chem* 2010;**150**:144–56.
78. Popa I, Abdul-Malak N, Portoukalian J. The weak rate of sphingolipid biosynthesis shown by basal keratinocytes isolated from aged vs. young donors is fully rejuvenated after treatment with peptides of a potato hydrolysate. *Int J Cosmet Sci* 2010;**32**:225–32.
79. Ruddock V. *Are ceramides key to skin care?* Available at: http://skincare.lovetoknow.com/skin-care-treatments/are-ceramides-key-skin-care.
80. Tashiro T, Nakaune A, Kosugi T, Arakawa J, Mori H, Serizawa S, et al. *Development of functional cosmetics "ASTALIFT JELLY AQUARYSTA"*. Fujifilm Research & Development No. 056; 2011.
81. Kanthraj GR. Skin-lightening agents: new chemical and plant extracts-ongoing search for the holy grail! *Indian J Dermatol Venereol Leprol* 2010;**76**:3–6.
82. Shin JW, Park KC. Current clinical use of depigmenting agents. *Dermatol Sinica* 2014;**32**:205–10.
83. Morganti P, Del Ciotto P, Carezzi F, Guarneri F, Yeo YJ. Skin lightening efficacy of new formulations enhanced by chitin nanoparticles delivery system. Note I. *J Appl Cosmetol* 2014;**32**:57–71.
84. Buranajaree S, Donsing P, Jeenapongsa R, Viyoch J. Depigmenting action of a nanoemulsion containing heartwood extract of *Artocarpus incisus* on UVB-induced hyperpigmentation in C57BL/6 mice. *J Cosmet Sci* 2011;**62**:1–14.
85. Sharma B, Sharma A. Future prospect of nanotechnology in development of anti-ageing formulations. *Int J Pharm Pharm Sci* 2012;**4**:57–66.
86. Fu X, Qutubuddin S. Polymer-clay nanocomposites: exfoliation of organophilic montmorillonite nanolayers in polystyrene. *Polymer* 2001;**42**:807–13.
87. Feinstone W. *Means for removing cosmetics*, US 3795624 A, 1974.
88. Mammone T, Gan DC. *Methods of exfoliation using N-acetyl glucosamine*, US 6413525 B1, 2002.
89. Rosa MD. *Nano-structured thixotropic inorganic peeling gels*, US 20090196926 A1, 2009.
90. *Peptides for skin*. Available at: http://www.paulaschoice.com/expert-advice/anti-aging/_/peptides-for-skin.
91. *Peptides*. Available at: http://www.paulaschoice.com/cosmetic-ingredient-dictionary/definition/peptide.
92. Benabio. *Do peptides in skin care products work?* Available at: http://thedermblog.com/2008/06/23/do-peptides-in-skin-care-products-work/.
93. Buri P, Puisieux F, Doelker E, Benoit JP. *Formes pharmaceutiques nouvelles*. Paris: TEC & DOC Lavoisier; 1985. p. 44–70.
94. Ranade VV. Drug delivery systems. 6. Transdermal drug delivery. *J Clin Pharmacol* 1991;**31**:401–18.
95. Guy RH. Current status and future prospects of transdermal drug delivery. *Pharm Res* 1996;**13**:1765–9.
96. Vecchia BE, Bunge AL. Evaluating the transdermal permeability of chemicals. In: Guy R, Haghraft J, editors. *Transdermal drug delivery*. New York: Marcel Dekker; 2002.
97. Walters KA. *Dermatological and transdermal formulations*. New York, London: CRC Press; 2002.
98. Cullander C, Guy RH. (D) Routes of delivery: case studies: (6) Transdermal delivery of peptides and proteins. *Adv Drug Deliv Rev* 1992;**8**:291–329.
99. Chen Y, Shen Y, Guo X, Zhang C, Yang W, Ma M, et al. Transdermal protein delivery by a coadministered peptide identified via phage display. *Nat Biotechnol* 2006;**24**:455–60.
100. Foldvari M, Attah-Poku S, Hu J, Li Q, Hughes H, Babiuk LA, et al. Palmitoyl derivatives of interferon α: potential for cutaneous delivery. *J Pharm Sci* 1998;**87**:1203–8.
101. Robinson LR, Fitzgerald NC, Doughty DG, Dawes NC, Berge CA, Bissett DL. Topical palmitoyl pentapeptide provides improvement in photoaged human facial skin. *Int J Cosmet Sci* 2005;**27**:155–60.
102. Abdulghani AA, Sherr A, Shirin S, Gottlieb AB. Effects of topical creams containing vitamin C, a copper-binding peptide cream and melatonin compared with tretinoin on the ultrastructure of normal skin-A pilot clinical, histologic, and ultrastructural study. *Dis Manag Clin Outcomes* 1998;**1**:136–41.
103. Osborne R, Robinson L, Mullins L, Raleigh P. Use of a facial moisturizer containing palmitoyl pentapeptide improves the appearance of aging skin. *J Am Acad Dermatol* 2005;**52**:P96.
104. Blanes-Mira C, Clemente J, Jodas G, Gil A, Fernández-Ballester G, Ponsati B, et al. A synthetic hexapeptide (Argireline) with antiwrinkle activity. *Int J Cosmet Sci* 2002;**24**:303–10.
105. Draelos ZD. Therapeutic moisturizers. *Dermatol Clin* 2000;**18**:597–607.
106. Bikowski J. The use of therapeutic moisturizers in various dermatologic disorders. *Cutis* 2001;**68**:3–11.
107. Wertz PW. Lipids and barrier function of the skin. *Acta Dermato Venereologica-Supplement* 2000;**208**:7–11.
108. Hashizume H. Skin aging and dry skin. *J Dermatol* 2004;**31**:603–9.
109. Lee SG, Kim SR, Cho HI, Kang MH, Yeom DW, Lee SH, et al. Hydrogel-based ultra-moisturizing cream formulation for skin hydration and enhanced dermal drug delivery. *Biol Pharm Bull* 2014;**37**:1674–82.
110. http://www.ashfordlab.com/novel_drug.html.
111. Scientific Committee on Consumer Products SCCP. *Preliminary opinion on safety of nanomaterials in cosmetic products*. 2007. Available at: http://ec.europa.eu/health/ph_risk/committees/04_sccp/docs/sccp_o_099.pdf.
112. *A survey of ingredients in 25,000 personal care products reveals widespread use of nano-scale materials, Not assessed for safety, in everyday products*. Washington DC: Environmental Working Group. Available at: http://www.ewg.org/skindeep/2007/08/25/hundreds-of-personal-care-products-contain-poorly-studied-nano-materials/.
113. Wakefield G, Stott J, Hock J. Sunscreens and cosmetics containing manganese doped titanium oxide nanoparticles. *SOFW J* 2005;**131**:46–51.
114. Nordlund JJ, Halder RM. Sunscreens and cosmetics. In: Nordlund JJ, Boissy RE, Hearing VJ, King RA, Oetting WS, Ortonne JP, editors. *The pigmentary system: physiology and pathophysiology*. Wiley-Blackwell; 2006.
115. Pinnell SR, Fairhurst D, Gillies R, M.M A, Kollias N. Microfine zinc oxide is a superior sunscreen ingredient to microfine titanium dioxide. *Dermatol Surg* 2000;**26**:309–14.
116. Schlumpf M, Cotton B, Conscience M, Haller V, Steinmann B, Lichtensteiger W. In vitro and in vivo estrogenicity of UV screens. *Environ Health Persp* 2001;**109**:239–44.
117. Osmond MJ, McCall MJ. Zinc oxide nanoparticles in modern sunscreens: an analysis of potential exposure and hazard. *Nanotoxicology* 2010;**4**:15–41.
118. Gergely A, Coroyannakis L. Nanotechnology in the EU cosmetics regulation. *Househ Pers Care Today* 2009;**3**:28–30.

119. Rosen J, Landriscina A, Friedman AJ. Nanotechnology-based cosmetics for hair care. *Cosmet Toilet* 2015;**2**:211–24.
120. Hu Z, Liao M, Chen Y, Cai Y, Meng L, Liu Y, et al. A novel preparation method for silicone oil nanoemulsions and its application for coating hair with silicone. *Int J Nanomed* 2012;**7**:5719–24.
121. Sonneville-Aubrun O, Simonnet JT, L'alloret F. Nanoemulsions: a new vehicle for skincare products. *Adv Colloid Interface Sci* 2004;**108**:145–9.
122. Morganti P, Palombo M, Cardillo A, Del Ciotto P, Morganti G, Gazzaniga G. Anti-dandruff and anti-oily efficacy of hair formulations with a repairing and restructuring activity. The positive influence of the Zn-chitin nanofibrils complexes. *J Appl Cosmetol* 2012;**30**:149–59.
123. Sampaio S, Maia F, Gomes JR. Diffusion of coloured silica nanoparticles into human hair. *Color Technol* 2011;**127**:55–61.
124. Gangadharan B, Hayward MA. *Skin cleanser*. 1998. Google Patents.
125. Tittl JR, Wolf CA. *Compositions and methods for mitigating skin irritation and enhancing skin barrier function*, US Patent WO 2016007314 A1, 2016.
126. Gajbhiye S, Sakharwade S. Silver nanoparticles in cosmetics. *J Cosmet Dermatol Sci Appl* 2016;**6**:48–53.
127. Veraldi S, Barbareschi M, Micali G, Skroza N, Guanziroli E, Schianchi R, et al. Role of cleansers in the management of acne: results of an Italian survey in 786 patients. *J Dermatol Treat* 2016;**27**:439–42.
128. Duarah S, Pujari K, Durai RD, Narayanan VH. Nanotechnology-based cosmeceuticals: a review. *Int J Appl Pharm* 2016;**8**:8–12.
129. Chung BH, Lim YT, Kim JK, Jeong JY, Ha TH. *Cosmetic pigment composition containing gold or silver nano-particles*, US 20090022765 A1, 2009.
130. Hasenzahl S, Heike R, Meyer J, Neugebauer P. *Adsorber, carrier for cosmetics; melting, mixing* (2002) Google Patents. *Use of granulates based on pyrogenically-produced silicon dioxide in cosmetic compositions*, CA 2465615 C, 2003.
131. Baran R. Nail cosmetics. *Am J Clin Dermatol* 2002;**3**:547–55.
132. *Nail polish*. Nano Labs Corp., Form 10-K. Available at: http://www.otcmarkets.com/edgar/GetFilingPdf?FilingID=9555018.
133. Nasir A, Friedman A, Wang S. *Nanotechnology in dermatology*. New York: Springer-Verlag; 2012.
134. Uchegbu IF, Vyas SP. Non-ionic surfactant based vesicles (niosomes) in drug delivery. *Int J Pharm* 1998;**172**:33–70.
135. Muzzalupo R. Niosomes and proniosomes for enhanced skin delivery. In: Dragicevic N, Maibach HI, editors. *Percutaneous penetration enhancers chemical methods in penetration enhancement: nanocarriers*. Springer; 2016.
136. Beloqui A, Solinís MA, Rodríguez-Gascón A, Almeida AJ, Préat V. Nanostructured lipid carriers: promising drug delivery systems for future clinics. *Nanomed Nanotechnol* 2016;**12**:143–61.
137. Müller RH, Alexiev U, Sinambela P, Keck CM. Nanostructured lipid carriers (NLC): the second generation of solid lipid nanoparticles. In: Dragicevic N, Maibach HI, editors. *Percutaneous penetration enhancers chemical methods in penetration enhancement*. Springer; 2016.
138. Nasir A. The future of nanotechnology in dermatology. *US Dermatol* 2008;**3**:9–13.
139. Nasir A. Nanotechnology and dermatology: part II-risks of nanotechnology. *Clin Dermatol* 2010;**28**:581–8.
140. Souto E, Müller R. Cosmetic features and applications of lipid nanoparticles (SLN®, NLC®). *Int J Cosmet Sci* 2008;**30**:157–65.
141. Lohani A, Verma A, Jo shi H, Yadav N, Karki N. Nanotechnology-based cosmeceuticals. *ISRN Dermatol* 2014:1–14, 843687.
142. Allouche J. Synthesis of organic and bioorganic nanoparticles: an overview of the preparation methods. In: Brayner R, Fiévet F, Coradin T, editors. *Nanomaterials: a danger or a promise?* London: Springer; 2013.
143. Naseri N, Valizadeh H, Zakeri-Milani P. Solid lipid nanoparticles and nanostructured lipid carriers: Structure, preparation and application. *Adv Pharm Bull* 2015;**5**:305–13.
144. Kamble MS, Vaidya KK, Bhosale AV, Chaudhari PD. Solid lipid nanoparticles and nanostructured lipid carriers - an overview. *Int J Pharm Chem Biol Sci* 2012;**2**:681–91.
145. Pardeike J, Hommoss A, Müller RH. Lipid nanoparticles (SLN, NLC) in cosmetic and pharmaceutical dermal products. *Int J Pharm* 2009;**366**: 170–84.
146. Imbert D, Wickett RR. Topical delivery with liposomes, a critical review for the cosmetic scientist. *Cosmet Toilet* 1995;**110**:32–45.
147. Cevc G. Lipid vesicles and other colloids as drug carriers on the skin. *Adv Drug Deliv Rev* 2004;**56**:675–711.
148. Choi M, Maibach HI. Liposomes and niosomes as topical drug delivery systems. *Skin Pharmacol Physiol* 2005;**18**:209–19.
149. El Maghraby GM, Barry BW, Williams AC. Liposomes and skin: from drug delivery to model membranes. *Eur J Pharm Sci* 2008;**34**:203–22.
150. Castor TP. Phospholipid nanosomes. *Curr Drug Deliv* 2005;**2**:329–40.
151. Nohynek GJ, Lademann J, Ribaud C, Roberts MS. Grey goo on the skin? Nanotechnology, cosmetic and sunscreen safety. *Crit Rev Toxicol* 2007; **37**:251–77.
152. Madhav NVS, Saini A. Niosomes: a novel drug delivery system. *Int J Res Pharm Chem* 2011;**1**:498–511.
153. Makeshwar KB, Wasankar SR. Niosome: a novel drug delivery system. *Asian J Pharm Res* 2013;**3**:16–20.
154. Ramakrishna GA, Manohar SD, Bhanudas SR. Ethosomes: carrier for enhanced transdermal drug delivery system. *Circulation* 2014;**4**:380–7.
155. Meidan V, Alhaique F, Touitou E. Vesicular carriers for topical delivery. *Acta technologiae et legis medicamenti* 1998;**9**:1–8.
156. Leonarduzzi G, Testa G, Sottero B, Gamba P, Poli G. Design and development of nanovehicle-based delivery systems for preventive or therapeutic supplementation with flavonoids. *Curr Med Chem* 2010;**17**:74–95.
157. Verma P, Pathak K. Therapeutic and cosmeceutical potential of ethosomes: an overview. *J Adv Pharm Technol Res* 2010;**1**:274–82.
158. Kesarwani A, Yadav AK, Singh S, Gautam H, Singh HN, Sharma A, et al. Theoretical aspects of transdermal drug delivery system. *Bull Pharm Res* 2013;**3**:78–89.
159. Meenakshi D. Emulgel: A novel approach to topical drug delivery. *Int J Pharm Biol Sci* 2013;**4**:847–56.
160. Jain N. *Advances in controlled and novel drug delivery*. New Delhi (Delhi, India): CBS Publishers & Distributors; 2010.
161. Schatzlein A, Cevc G. Non-uniform cellular packing of the stratum corneum and permeability barrier function of intact skin: a high-resolution confocal laser scanning microscopy study using highly deformable vesicles (transfersomes). *Br J Dermatol* 1998;**138**:583–92.
162. Verma P, Ram A, Jha AK, Mishra A, Thakur A. Phosphatidylcholine: a revolution in drug delivery technology. *Int J Pharm Sci Res* 2010;**1**:1–12.
163. Langer R. Transdermal drug delivery: past progress, current status, and future prospects. *Adv Drug Deliv Rev* 2004;**56**:557–8.
164. Naik B, Nagarsenker M. Novel drug delivery systems: potential in improving topical delivery of antiacne agents. *Skin Pharmacol Physiol* 2005; **19**:2–16.
165. Jain S, Jain V, Mahajan S. Lipid based vesicular drug delivery systems. *Adv Pharm* 2014:1–12, 574673.
166. Khalifa MK. Miconazole nitrate based cubosome hydrogels for topical application. *Int J Drug Deliv* 2015;**7**:1–12.
167. Bhosale RR, Osmani RA, Harkare B, Ghodake PP. Cubosomes: the inimitable nanoparticulate drug carriers. *Sch Acad J Pharm* 2013;**2**:481–6.
168. Tenjarla S. Microemulsions: an overview and pharmaceutical applications. *Crit Rev Ther Drug Carr Syst* 1999;**16**:461–521.

169. Boonme P. Applications of microemulsions in cosmetics. *J Cosmet Dermatol* 2007;**6**:223–8.
170. Husein MM, Nassar NN. Nanoparticle preparation using the single microemulsions scheme. *Curr Nanosci* 2008;**4**:370–80.
171. Sharma S, Sarangdevot K. Nanoemulsions for cosmetics. *Int J Adv Res Pharm Biosci* 2012;**1**:408–15.
172. Özgün S. *Nanoemulsions in cosmetics***1**. Anadolu University; 2013. p. 3–11.
173. Gutiérrez J, González C, Maestro A, Nolla J. Nano-emulsions: new applications and optimization of their preparation. *Curr Opin Colloid Interface Sci* 2008;**13**:245–51.
174. Becher P. *Encyclopedia of emulsion technology: basic theory, measurement applications*. New York (Basel): Marcel Dekker; 1987.
175. Raynal S, Grossiord JL, Seiller M, Clausse D. A topical W/O/W multiple emulsion containing several active substances: formulation, characterization and study of release. *J Control Release* 1993;**26**:129–40.
176. Kumar R, Kumar MS, Mahadevan N. Multiple emulsions: a review. *Int J Adv Pharm Res* 2012;**2**:9–19.
177. Lee J-S, Kim JW, Han S-H, Suh KD. The stabilization of L-ascorbic acid in aqueous solution and water-in-oil-in-water double emulsion by controlling pH and electrolyte concentration. *J Cosmet Sci* 2004;**55**:1–12.
178. Chappat M. Some applications of emulsions. *Colloid Surf A Physicochem Eng Asp* 1994;**91**:57–77.
179. Khan AY, Talegaonka S, Iqbal Z, Ahmed FJ, Khar RK. Multiple emulsions: an overview. *Curr Drug Deliv* 2006;**3**:429–43.
180. Mataumoto S, Kang WW. Formation and applications of multiple emulsions. *J Dispers Sci Technol* 1989;**10**:455–82.
181. Hougeir FG, Kircik L. A review of delivery systems in cosmetics. *Dermatol Ther* 2012;**25**:234–7.
182. Patravale V, Mandawgade S. Novel cosmetic delivery systems: an application update. *Int J Cosmet Sci* 2008;**30**:19–33.
183. Arora N, Agarwal S, Murthy R. Latest technology advances in cosmeceuticals. *Int J Pharm Sci Drug Res* 2012;**4**:168–82.
184. Borowska S, Brzóska MM. Metals in cosmetics: implications for human health. *J Appl Toxicol* 2015;**35**:551–72.
185. Rai M, Yadav A, Gade A. Silver nanoparticles as a new generation of antimicrobials. *Biotechnol Adv* 2009;**27**:76–83.
186. Kokura S, Handa O, Takagi T, Yoshikawa T. Silver nanoparticles as a safe preservative for use in cosmetics. *Nanomed Nanotechnol Biol Med* 2010;**6**:570–4.
187. Taufikurohmah T, Sanjaya IGM, Syahrani A. Nanogold synthesis using matrix mono glyceryl stearate as antiaging compounds in modern cosmetics. *J Mater Sci Eng A* 2011;**1**:857–64.
188. Yapar EA, Inal O. Nanomaterials and cosmetics. *J Fac Pharm Istanbul Univ* 2012;**42**:43–70.
189. Pissuwan D, Niidome T. Gold nanoparticles for the development of transdermal delivery systems. In: Hepel M, Zhong CJ, editors. *Functional nanoparticles for bioanalysis, nanomedicine, and bioelectronic devices*; 2012.
190. Smijs TG, Pavel S. Titanium dioxide and zinc oxide nanoparticles in sunscreens: focus on their safety and effectiveness. *Nanotechnol Sci Appl* 2011;**4**:95–112.
191. Guterres SS, Alves MP, Pohlmann AR. Polymeric nanoparticles, nanospheres and nanocapsules, for cutaneous applications. *Drug Target Insights* 2007;**2**:147–57.
192. Wu X, Guy RH. Applications of nanoparticles in topical drug delivery and in cosmetics. *Drug Deliv Sci Technol* 2009;**19**:371–84.
193. Luppi B, Cerchiara T, Bigucci F, Basile R, Zecchi V. Polymeric nanoparticles composed of fatty acids and polyvinylalcohol for topical application of sunscreens. *J Pharm Pharmacol* 2004;**56**:407–11.
194. Olvera-Martínez BI, Cázares-Delgadillo J, Calderilla-Fajardo SB, Villalobos-García R, Ganem-Quintanar A, Quintanar-Guerrero D. Preparation of polymeric nanocapsules containing octyl methoxycinnamate by the emulsification-diffusion technique: penetration across the stratum corneum. *J Pharm Sci* 2005;**94**:1552–9.
195. Chirani N, Yahia LH, Gritsch L, Motta FL, Chirani S, Faré S. History and applications of hydrogels. *J Biomed Sci* 2015;**4**:1–23.
196. Agudelo D, Nafisi S, Tajmir-Riahi HA. Encapsulation of milk β-lactoglobulin by chitosan nanoparticles. *J Phys Chem B* 2013;**117**:6403–9.
197. Agudelo D, Sanyakamdhorn S, Nafisi S, Tajmir-Riahi HA. Transporting antitumor drug tamoxifen and its metabolites, 4-hydroxytamoxifen and endoxifen by chitosan nanoparticles. *PLoS One* 2013;**8**:e60250.
198. Gavhane Y, Gurav A, Yadav A. Chitosan and its applications: a review of literature. *Int J Biomed Pharm Sci* 2013;**4**:312–31.
199. Tajmir-Riahi HA, Nafisi S, Sanyakamdhorn S, Agudelo D, Chanphai P. Applications of chitosan nanoparticles in drug delivery. *Methods Mol Biol* 2014;**1141**:165–84.
200. Nawanopparatsakul S, Euasathien J, Eamtawecharum C, Benjasirimingokol P, Soiputtan S, Toprasri P, et al. Skin irritation test of curcuminoids facial mask containing chitosan as a binder. *Silpakorn Univ J* 2005;**5**:140–7.
201. Liu Y, Friberg SE. Role of liquid crystal in the emulsification of a gel emulsion with high internal phase fraction. *J Colloid Interface Sci* 2009;**340**:261–8.
202. Zhang W, Liu L. Study on the formation and properties of liquid crystal emulsion in cosmetic. *J Cosmet Dermatol Sci Appl* 2013;**3**:139–44.
203. Saulnier P, Anton N, Heurtault B, Benoit JP. Liquid crystals and emulsions in the formulation of drug carriers. *Comptes Rendus Chimie* 2008;**11**:221–8.
204. Kreuter J. Nanoparticulate systems for brain delivery of drugs. *Adv Drug Deliv Rev* 2001;**47**:65–81.
205. Letchford K, Burt H. A review of the formation and classification of amphiphilic block copolymer nanoparticulate structures: micelles, nanospheres, nanocapsules and polymersomes. *Eur J Pharm Biopharm* 2007;**65**:259–69.
206. Ciba Specialty Chemicals. *Ciba® Tinoderm™ Nanotopes™, Ultra small carriers*. Available at: http://showme.physics.drexel.edu/lucci/backup/temp/encapsulation/Encapsulation/Nanotopes_Ciba.pdf.
207. Petersen R. *Nanocrystals for use in topical cosmetic formulations and method of production thereof*, US Patent 12/514,621, February 25, 2010.
208. Lai F, Schlich M, Pireddu R, Corrias F, Maria Fadda A, Sinico C. Production of nanosuspensions as a tool to improve drug bioavailability: focus on topical delivery. *Curr Pharm Des* 2015;**21**:6089–103.
209. Pyo SM, Meinke M, Cornelia M, Keck CM, Müller RH. Rutin increased antioxidant activity and skin penetration by nanocrystal technology, (smart crystals). *Cosmetics* 2016;**3**:9.
210. Vidlářová L, Romero GB, Hanuš J, Štěpánek F, Müller RH. Nanocrystals for dermal penetration enhancement – Effect of concentration and underlying mechanisms using curcumin as model. *Eur J Pharm Biopharm* 2016;**104**:216–25.
211. Khan PA, Sasikanth K, Nama S, Suresh S, Brahmaiah B. Nanofibers – a new trend in nano drug delivery systems. *Pharm Innov* 2013;**2**:118–27.
212. Mehetre G, Pande V, Kendre P. An overview of nanofibers as a platform for drug delivery. *Inventi Rapid NDDS* 2015;**2015**:1–6.
213. Baez E, Quazi N, Ivanov I, Bhattacharya SN. Stability study of nanopigment dispersions. *Adv Powder Technol* 2009;**20**:267–72.

214. Munoz EB. Nanopigment development and dispersion in aqueous systems. In: *Civil Environmental & Chemical Engineering*. RMIT University; 2011.
215. Lens M. Recent progresses in application of fullerenes in cosmetics. *Recent Pat Biotechnol* 2011;**5**:67–73.
216. Lens M. Use of fullerenes in cosmetics. *Recent Pat Biotechnol* 2009;**3**:118–23.
217. Williams RM, Verhoeven JW, Crielaard W, Hellingwer KJ. Incorporation of fullerene-C60 and C60 adducts in micellar and vesicular supramolecular assemblies; introductory flash photolysis and photoredox experiments in micelles. *Recueil des Travaux Chimiques des PaysBas* 1996; **115**:72–6.
218. Korobov MV, Avramenko NV, Bogachev AG, Rozhkova NN, Ōsawa E. Nanophase of water in nano-diamond gel. *J Phys Chem C* 2007;**111**: 7330–4.
219. Mochalin VN, Shenderova O, Ho D, Gogotsi Y. The properties and applications of nanodiamonds. *Nat Nanotechnol* 2012;**7**:11–23.
220. Man HB, Ho D. Diamond as a nanomedical agent for versatile applications in drug delivery, imaging, and sensing. *Physica Status Solidi A* 2012:1–10.
221. Buschmann HR, Schollmeyer E. Applications of cyclodextrins in cosmetic products: a review. *J Cosmet Sci* 2002;**53**:185–91.
222. Tarimci N. Cyclodextrins in the cosmetic field. In: Bilensoy E, editor. *Cyclodextrins in pharmaceutics, cosmetics, and biomedicine: current and future industrial applications*. John Wiley & Sons; 2011.
223. Choi HH, Tolia GT. The role of dendrimers in topical drug delivery. *Pharm Technol* 2008;**32**:88–98.
224. Munir M, Hanif M, Ranjha NM. Dendrimers and their applications: a review article. *Pak J Pharm Res* 2016;**2**:55–66.
225. Tripathy S, Das MK. Dendrimers and their applications as novel drug delivery carriers. *J Appl Pharm Sci* 2013;**3**:142–9.
226. Owen R, Handy R. Viewpoint: formulating the problems for environmental risk assessment of nanomaterials. *Environ Sci Technol* 2007;**41**: 5582–8;
226a. EU. Council Directive of July 27, 1976 on the approximation of the laws of the Member States. *Relating to cosmetic products*. 2007. 76/768/EEC. Available at: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CONSLEG:1976L0768:20070508:EN:PDF.
227. Bowman DM, Van Calster G, Friedrichs S. Nanomaterials and regulation of cosmetics. *Nat Nanotechnol* 2010;**5**:92.
228. Brandt FS, Cazzaniga A, Hann M. Cosmeceuticals: current trends and market analysis. *Semin Cutan Med Surg* 2011.
229. Wanjari N, Waghmare J. A review on latest trend of cosmetics-cosmeceuticals. *Int J Pharm Res Rev* 2015;**4**:45–51.
230. Karimi M, Solati M, Amiri M, Mirshekari H, Mohamed E, Taheri M, et al. Carbon nanotubes part I: preparation of a novel and versatile drug-delivery vehicle. *Exp Opin Drug Deliv* 2015;**12**:1071–87.
231. Draelos ZD. New developments in cosmetics and skin care products. *Adv Dermatol* 1996;**12**:3–17.
232. Draelos ZD. Cosmetics, categories, and the future. *Dermatol Ther* 2012;**25**:223–8.

CHAPTER

# 23

# Wetting and Surface Characterization

*K. Tsujii*

**Hokkaido University (retired), Wakayama, Japan**

## 23.1 INTRODUCTION

Wetting phenomena are quite common in daily life and in many industrial processes. Let us show some typical examples of wetting phenomena in daily life. When you wake up in the morning, you will wash your face and hands, and then wipe up the water drops with a towel. You can wipe up your face and hands since the towel is wettable with water. If the towel is treated with a fabric softener, it is soft but absorbs fewer of the water drops. You may have a lot of experiences with such phenomena. Your wife makes a sunny-side-up egg for breakfast with a Teflon-coated frying pan. The Teflon-coated frying pan is hardly stained and is easily washed clean. This effect of Teflon coating is strongly related to the wetting phenomenon. Next, your wife starts to wash the clothes with a washing machine after you leave home for your office. Wetting is the key phenomenon for the first step of the washing.

There are many processes in industries where wetting phenomena play important roles. In the adhesion process, good wetting is an important key property to get good performance. In order to satisfactorily disperse the powders of organic pigments in the paint industries, the wetting of the powders with the medium is an essentially important first step for dispersion. If the wetting is not good enough, uniform and smooth surfaces cannot be obtained in any coating processes such as painting, duct tape making, photogravure paper manufacturing, and so on.

Skin care, makeup, and body-cleansing processes in daily life as well as the manufacturing processes of cosmetic products are, of course, not exceptions. For example, a water-in-oil (W/O)-type skin cream is sometimes not extended smoothly and uniformly on a wetted skin after bathing due to the poor wettability of the cream. Therefore, wetting is very important and useful in cosmetic science and technology. In this chapter, the principles of wetting and its application to cosmetics will be discussed.

## 23.2 WETTING ON THE FLAT SURFACES

The wettability of a liquid on a solid surface is governed by two factors. One is the chemical factor, and the other is the geometrical (roughness) factor of the solid surface. The chemical factor determines the wettability of a liquid on a flat surface, and depends upon the materials themselves of the solid surface and the liquid on it. This factor reflects the molecular interactions in the solid and liquid materials as well as those at the solid/liquid interface. The second geometrical (roughness) factor, on the other hand, represents the structure or shape of solid surface. Therefore, the study of wetting phenomena contributes to understanding both the microscopic molecular matters and the macroscopic surface characterization.

### 23.2.1 The Young's Equation

Fig. 23.1 shows a liquid droplet on a flat solid surface. The wettability can be represented quantitatively by the contact angle $\theta$, which is defined as the angle between the solid surface and the tangent line of the liquid surface

*Cosmetic Science and Technology: Theoretical Principles and Applications*
http://dx.doi.org/10.1016/B978-0-12-802005-0.00023-9



Copyright © 2017 Elsevier Inc. All rights reserved.

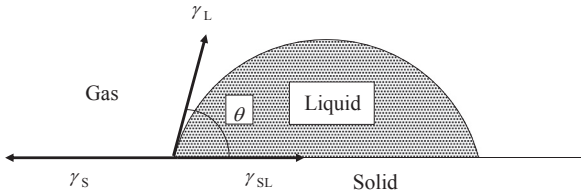



FIGURE 23.1 Wettability of a liquid droplet on a flat solid surface. The contact angle ($\theta$) is determined by the balance in horizontal direction of three surface and interfacial tensions of $\gamma_S$, $\gamma_L$, and $\gamma_{SL}$.

at the peripheral contact line. We can define a wettable (repellent) surface as one in which the contact angle is smaller (greater) than 90 degrees. The contact angle is determined by the balance in horizontal direction of three surface and interfacial tensions ($\gamma_S$, $\gamma_L$, $\gamma_{SL}$), where $\gamma_S$, $\gamma_L$, $\gamma_{SL}$ are the surface tensions of solid, liquid and the interfacial tension between them, respectively. This balance among the surface and the interfacial tensions in the horizontal direction is expressed by the well-known Young's equation as follows:[1]

$$\gamma_S = \gamma_{SL} + \gamma_L \cos\theta \text{ or}$$
$$\cos\theta = \frac{(\gamma_S - \gamma_{SL})}{\gamma_L} \tag{23.1}$$

When the surface tension of solid ($\gamma_S$) is greater than the solid–liquid interfacial tension ($\gamma_{SL}$), the contact angle becomes smaller than 90 degree and the surface is wettable. When the balance is opposite, the surface repels the liquid. A Teflon-coated frying pan, for example, has low surface tension and high interfacial tension for water, thus repels water well. The surface of clean metal and/or glass has high surface tension and low interfacial tension for water, and they are wettable with water.

### 23.2.2 Capillary Phenomena

Fig. 23.2 shows a capillary action phenomenon of a liquid. In this case, the liquid penetrates into a capillary of radius $r$ being driven by the imbalance of surface tension of solid and interfacial tension between solid and liquid. The force that pulls the liquid into the capillary is written as $2\pi r\,(\gamma_S - \gamma_{SL})$, since the surface (interfacial) tension is

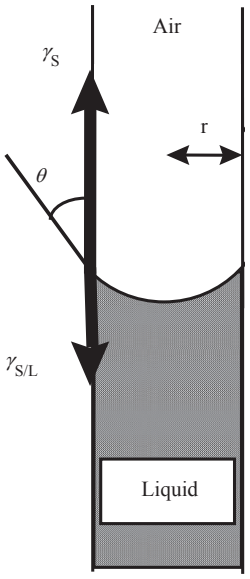



FIGURE 23.2 A capillary action phenomenon of liquid. The liquid penetrates into a capillary being driven by the imbalance of surface tension of solid and interfacial tension between solid and liquid.

defined as force/unit length. We can obtain the capillary pressure ($\Delta P$) by dividing the previous force by a cross-sectional area of the capillary. Then,

$$\Delta P = \frac{2\pi r(\gamma_S - \gamma_{SL})}{\pi r^2} = \frac{2(\gamma_S - \gamma_{SL})}{r} \tag{23.2}$$

Eq. (23.2) indicates that the pressure in the liquid side is lower than that in the air side by the value of $\Delta P$, when the meniscus is concave to the air. A curved liquid surface tends to become flat in order to make the surface area minimum. This action of the surface tension of liquid results in the lower pressure in the liquid side.

Combining Eq. (23.1) with Eq. (23.2), we obtain the next equation:[2]

$$\Delta P = \frac{2\gamma_L \cos\theta}{r} \tag{23.3}$$

One can understand that $\Delta P > 0$ when $\theta < 90°$, and $\Delta P < 0$ when $\theta > 90°$. Liquid penetrates into the capillary when $\theta < 90°$, and the liquid is pushed out of the capillary when $\theta > 90°$. Water does not penetrate into a Teflon and/or polyethylene capillary, but does penetrate into a glass one.

Surfactant enhances the wettability of water toward the hydrophobic solid surface with low surface tension.[3] The contact angle of water becomes smaller than 90 degrees on addition of surfactant, and then $\Delta P$ becomes positive. Consequently, water (liquid in general) is then allowed to penetrate into hydrophobic capillaries.[3] This enhancement of wettability by surfactant is utilized in a variety of application fields. Hydrophobic powders (say carbon black or organic pigments) cannot be dispersed into water because the water medium does not penetrate into their interparticle small spaces. Water also cannot penetrate into interfabric spaces when clothes with oily dirt are washed. In such cases, the surfactant works dramatically for the penetration of water into small spaces and contributes to disperse the powders and to wash the dirty clothes.

## 23.2.3 Estimation of Surface Tension of Solid

As mentioned earlier, the wetting property (contact angle) is governed by the surface tensions of liquid and solid as well as the interfacial tension between them. The surface tension of liquid can be easily measured experimentally, and some techniques are well known.[4] The surface tension of solid, however, is quite difficult to determine experimentally. There is almost no way to measure the solid surface tension precisely. Then, we adopt two alternative methods to obtain the substitute of the real solid surface tension, which are the critical surface tension and the calculation of approximate quantity.

### *23.2.3.1 The Critical Surface Tension*

The critical surface tension of solid is determined as follows: (1) the contact angles of various liquids are measured on a target solid surface; (2) the values of $\cos\theta$ for these contact angles are plotted against the surface tension of the liquid used; (3) an obtained straight line is extrapolated to unity (i.e., $\theta = 0°$); and (4) the value of the liquid surface tension at an intersection between the straight line and $\cos\theta = 1$ is taken as the critical surface tension of the solid ($\theta_C$).[5] An example of the created plot (called Zisman plot) is shown in Fig. 23.3. As understood from such a process, the critical surface tension means that a liquid having a lower surface tension than $\theta_C$ wets the solid surface completely. The critical surface tension is taken as a substitute for the real surface tension of the target solid.

Let us consider here why the critical surface tension can be a substitute for the surface tension of the target solid. Let us prove first that the critical surface tension is exactly the real surface tension of solid when the next approximate equation is valid for the interfacial tension between the liquid and the solid.

$$\gamma_{SL} = \gamma_S + \gamma_L - 2\sqrt{\gamma_S\gamma_L} \tag{23.4}$$

The Young's Eq. (23.1) can be expressed as Eq. (23.5) when the surface tension of liquid is the critical one.

$$\gamma_S = \gamma_{SL} + \gamma_C \cos 0° = \gamma_{SL} + \gamma_C \tag{23.5}$$

The above approximate interfacial tension Eq. (23.4) is employed for the $\gamma_{SL}$ in Eq. (23.5), we obtain Eq. (23.6).

$$\gamma_S = \gamma_S + \gamma_C - 2\sqrt{\gamma_S\gamma_C} + \gamma_C \tag{23.6}$$

From Eq. (23.6), we finally obtain the target equation, i.e., $\gamma_C = \gamma_S$

Now we know that the critical surface tension can be represented as the surface tension of solid, when the interfacial tension can be expressed by Eq. (23.4). What kind of condition(s) must be satisfied for this approximate

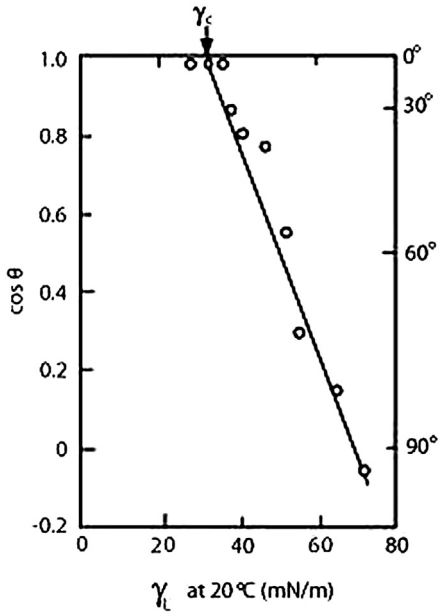



FIGURE 23.3 A Zisman plot on a polyethylene surface. The critical surface tension is determined as the surface tension of liquid at an intersection between the extrapolated straight line and $\cos\theta = 1$.

Eq. (23.4)? The condition is that the same kind of molecular interaction works in both solid and liquid as well as solid/liquid interface, say van der Waals attractive interaction. When the interaction is the same kind, the interaction energy is expressed by the same power law of the distance between molecules. If two interactions obey the same power law of distance, the geometric mean of them is also in the same power law, then, Eq. (23.4) is valid.

#### 23.2.3.2 *Calculation of the Approximate Surface Tension of Solid*

The critical surface tension is a good substitute of the surface tension of solid if molecular interaction is the same kind in the liquid, solid, as well as the liquid/solid interface. So if we determine the critical surface tension of polyethylene by using a series of hydrocarbons as the sample liquids, the obtained value may be close to the real surface tension of the polymer. But generally speaking, the kinds of interactions are, of course, different in the liquid and solid states. We are particularly interested in water as a liquid. As is well known, this liquid shows many kinds of molecular interactions such as van der Waals attraction, hydrogen bonding, dipole−dipole interaction, etc. In such a case we choose another approach to obtain a substitute of the solid surface tension, i.e., theoretical calculation method.

As mentioned previously, Eq. (23.4) is good approximation when the molecular interactions of solid and liquid are of same kind. Then, Eq. (23.4) was modified to be responsible for two kinds of interactions between molecules. There are two main theories for this purpose. One is given by Fowkes,[6] and an extended theory by Owens and Wendt.[7] The other is proposed by van Oss et al.[8] According to Fowkes−Owens−Wendt, the surface tension consists of the nonpolar component (corresponding to the London dispersion force or van der Waals interaction) and the polar component, i.e., $\gamma = \gamma^{\mathrm{d}} + \gamma^{\mathrm{P}}$, where $\gamma^{\mathrm{d}}$ and $\gamma^{\mathrm{P}}$ are the dispersion and the polar component of surface tension, respectively. On the other hand, van Oss et al. propose that the surface tension is expressed by the nonpolar component and the component of electron-donor/-acceptor (Lewis acid-base) interaction, i.e., $\gamma = \gamma^{\mathrm{d}} + \gamma^{\mathrm{AB}}$; where $\gamma^{\mathrm{AB}}$ is the acid-base component of the surface tension. According to these approaches, Eq. (23.4) is modified as follows.

$$\gamma_{\mathrm{SL}} = \gamma_{\mathrm{S}} + \gamma_{\mathrm{L}} - 2\left(\sqrt{\gamma_{\mathrm{S}}^{d}\gamma_{\mathrm{L}}^{d}} + \sqrt{\gamma_{\mathrm{S}}^{p}\gamma_{\mathrm{L}}^{p}}\right) \tag{23.7}$$

$$\gamma_{\mathrm{SL}} = \gamma_{\mathrm{S}} + \gamma_{\mathrm{L}} - 2\left(\sqrt{\gamma_{\mathrm{S}}^{d}\gamma_{\mathrm{L}}^{d}} + \sqrt{\gamma_{\mathrm{S}}^{+}\gamma_{\mathrm{L}}^{-}} + \sqrt{\gamma_{\mathrm{S}}^{-}\gamma_{\mathrm{L}}^{+}}\right) \tag{23.8}$$

where $\gamma^{+}$ and $\gamma^{-}$ are the electron-acceptor and the electron-donor components in $\gamma^{\mathrm{AB}}\left(=2\sqrt{\gamma^{+}\gamma^{-}}\right)$, respectively. Both of these equations are, of course, still approximate ones, since the molecular interactions are not limited to

two kinds, particularly for water. These theories were utilized to estimate the surface tension (surface free energy) of human skin and hair, as mentioned later.

Let us discuss here briefly the procedures of calculation of surface tension of solid from Eqs. (23.7) and/or (23.8). The first step is to determine each component of a liquid. When we take a liquid having only dispersion (van der Waals) force, say alkanes, fluoroalkanes and tetrachloromethane, etc., the measured surface tension consists of only a nonpolar component, i.e., $\gamma = \gamma^{\mathrm{d}}$. Next, the interfacial tension between this nonpolar liquid and another polar liquid is measured and Eq. (23.7) is applied for these two liquids (in this case subscript S refers to the polar liquid). The fourth term in the right side of Eq. (23.7) is zero, $\sqrt{\gamma_{\mathrm{S}}^{p}\gamma_{\mathrm{L}}^{p}} = 0$, since $\gamma_{\mathrm{L}}^{p} = 0$. Now, we obtain the nonpolar and polar components of the polar liquid, since $\gamma = \gamma^{\mathrm{d}} + \gamma^{\mathrm{P}}$. If we repeat this procedure, we can obtain the nonpolar and the polar components of any liquids as we want. When we use Eq. (23.8), three liquids (two nonpolar and one polar) are necessary to obtain each electron-donor/-acceptor component of the polar liquid. However, the procedures are essentially the same as those for Eq. (23.7).

Once we have a list of the nonpolar and the polar component of liquids, we can use these values to estimate the surface tension and each of its components of any solid with Eq. (23.7) by measuring the contact angles of the liquids on the solid surface. Combining the Young's Eqs. (23.1) and (23.7), we obtain the next Eq. (23.9),

$$\gamma_{\mathrm{L}}(1 + \cos\theta) = 2\left(\sqrt{\gamma_{\mathrm{S}}^{d}\gamma_{\mathrm{L}}^{d}} + \sqrt{\gamma_{\mathrm{S}}^{p}\gamma_{\mathrm{L}}^{p}}\right) \tag{23.9}$$

Here we have two unknown varieties, $\gamma_{\mathrm{S}}^{d}$ and $\gamma_{\mathrm{S}}^{p}$, and we can determine these values by employing two sample liquids of known nonpolar and polar components. Finally. we can also get the surface tension of solid, i.e., $\gamma_{\mathrm{S}} = \gamma_{\mathrm{S}}^{d} + \gamma_{\mathrm{S}}^{p}$.

Combining Eqs. (23.1) and (23.8), we obtain the next Eq. (23.10),

$$\gamma_{\mathrm{L}}(1 + \cos\theta) = 2\left(\sqrt{\gamma_{\mathrm{S}}^{d}\gamma_{\mathrm{L}}^{d}} + \sqrt{\gamma_{\mathrm{S}}^{+}\gamma_{\mathrm{L}}^{-}} + \sqrt{\gamma_{\mathrm{S}}^{-}\gamma_{\mathrm{L}}^{+}}\right) \tag{23.10}$$

By solving the three simultaneous equations, we can obtain the surface tension and its components, $\gamma_{\mathrm{S}}^{d}$, $\gamma_{\mathrm{S}}^{+}$, and $\gamma_{\mathrm{S}}^{-}$, using three liquids of known nonpolar and polar components.

It should be emphasized again here that the values of surface tension of solid and its components obtained herein are approximate ones and not the true values.

## 23.3 WETTING ON ROUGH SURFACES

The contact angle on a flat solid surface is expressed by the Young's Eq. (23.1) as mentioned previously. Let us move to the second factor of wetting, i.e., the roughness factor of the surface. The roughness of the solid surface enhances the wettability on the flat surface, i.e., a wettable surface becomes more wettable and a rough repellent surface does more repelling. There are three theories to explain the wettability of rough surfaces. When the roughness is not so extreme and the surface contacts completely with a liquid droplet on it, the Wenzel theory is applied. When the repellent surface is extremely rough, on the other hand, the liquid on it cannot penetrate into small spaces or pores of the surface due to the capillary effect and the air is left in the bottom of the space. In such cases the Cassie–Baxter theory is employed. One more theory is built up when the roughness is in fractal structures. This theory is a kind of unified one of the Wenzel and the Cassie–Baxter theories, although it is applicable only to the fractal surfaces. Let us discuss each theory in the following sections.

### 23.3.1 The Wenzel Theory

Wenzel proposed that the contact angle, $\theta_{\mathrm{r}}$, of a liquid droplet placed on the rough solid surface can be written as Eq. (23.11) when the surface contacted completely with the liquid even in the small spaces or pores.[9]

$$\cos\theta_{\mathrm{r}} = \frac{r(\gamma_{\mathrm{S}} - \gamma_{\mathrm{SL}})}{\gamma_{\mathrm{L}}} \tag{23.11}$$

where $r$ is the roughness (surface area magnification) factor that is defined as the ratio of actual surface area of a rough surface to the geometric projected area. Eq. (23.11) can be interpreted as showing that the surface (interfacial) free energies of the solid and the solid/liquid interface become larger $r$ times due to the increase of the surface area

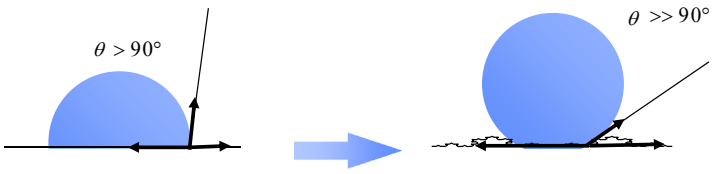



FIGURE 23.4 Schematic illustration to explain the Wenzel theory. Surface and interfacial free energies of solid and solid/liquid interface increase due to the surface area magnification with roughness.

(see Fig. 23.4). Then, the relationship between $\theta_r$ and $\theta$ (the contact angle on a flat surface of the same material) is given by Eq. (23.12) combining Eqs. (23.1) and (23.11).

$$\cos\theta_r = r\cos\theta \tag{23.12}$$

Eq. (23.12) indicates that the rough surface is more liquid repellent (more wettable) when $\theta$ is greater (smaller) than 90 degrees, i.e., the roughness of the surface enhances the wettability due to the surface area magnification.

### 23.3.2 The Cassie–Baxter Theory

In the Cassie–Baxter theory,[10] the solid surface is assumed to be constructed of two components of materials one and two in mixing microscopically as shown in Fig. 23.5. Suppose the contact angles of a liquid on the surface of the pure component 1 and 2 to be $\theta_1$ and $\theta_2$, respectively, and the surface area fraction of component 1 and 2 in the mixed solid surface to be $f_1$ and $f_2$, respectively, the contact angle of the liquid on the microscopically mosaic surface can be expressed as

$$\cos\theta_r = f_1\cos\theta_1 + f_2\cos\theta_2 \tag{23.13}$$

When a liquid-repellent surface is analyzed by the Cassie–Baxter equation, one component, say component 2, is assumed to be air, since the theory is employed when the air is left in the bottom of the small spaces or pores. Because the contact angle, $\theta_2$, on the air is 180 degrees, Eq. (23.14) is obtained, since $f_1 + f_2 = 1$.

$$\cos\theta_r = f - 1 + f\cos\theta \tag{23.14}$$

where $f_1$ and $\theta_1$ are rewritten as $f$ and $\theta$. The Cassie–Baxter theory is usually applied to the surfaces consisting of many pillars and/or needles aligning perpendicularly to the surfaces as shown in Fig. 23.6. Lotus and some other plant leaves repel water almost completely in this way.

### 23.3.3 A Theory of Wettability on the Fractal Surfaces

A fractal surface is an ideal one from the viewpoint of surface area magnification, since the surface consists of rough structure of a nest like a Russian nesting doll.[11] When the roughness of the surface is in fractal nature, the

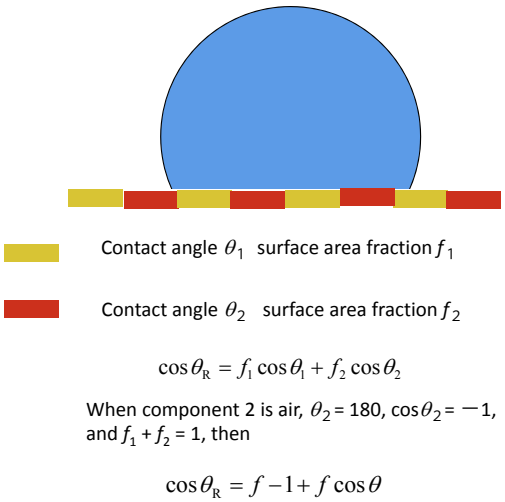



FIGURE 23.5 The Cassie–Baxter theory for the wetting of liquid on the solid consisting of two materials in small mosaic state.

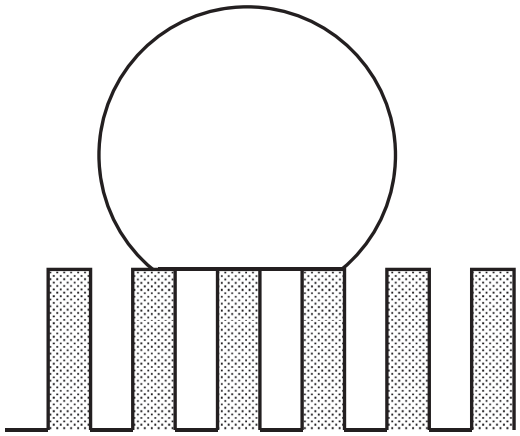


FIGURE 23.6 Schematic representation showing the wetting on a pillar-structured surface. Air is left in the bottom of the small spaces.

surface area magnification factor $r$ in Eq. (23.12) can be written as $(L/l)^{D-2}$. Then, the contact angle $\theta_f$ of liquid droplet placed on a fractal solid surface is given by Eq. (23.15):[12–14]

$$\cos\theta_f = \left(\frac{L}{l}\right)^{D-2}\cos\theta \tag{23.15}$$

where $L$ and $l$ are the upper and the lower limit lengths of fractal (self-similar) behavior, respectively; $D$ ($2 \le D < 3$) is the fractal dimension of the solid surface. It is assumed in the derivation of this equation that (1) $l$ is much larger than the diameter of molecules composing a liquid, (2) $L$ is much smaller than the diameter of a liquid droplet, and (3) the interfacial tension of a solid is isotropic being independent of crystal orientation. Eq. (23.15) indicates that the contact angle of a liquid droplet placed on the fractal surface changes dramatically when compared with nonfractal surfaces, since the surface area magnification factor $(l/L)^{D-2}$ can easily become large.

Eq. (23.15) was derived under the same assumption as that of the Wenzel theory, i.e., the full contact of liquid with the fractal solid surface. This is not true when the air is left in the bottom of the small pores. Taking this condition into consideration, the theory was modified.[12] Fig. 23.7 shows the relationship between $\cos\theta_r$ (or $\cos\theta_f$) and $\cos\theta$ for three theories explaining the wettability of rough surfaces. In the Wenzel and fractal theories, the curves pass through the original point, but not in the Cassie–Baxter one. In addition, the curve does not reach the line of $\cos\theta_r = 1$ in the Cassie–Baxter theory.

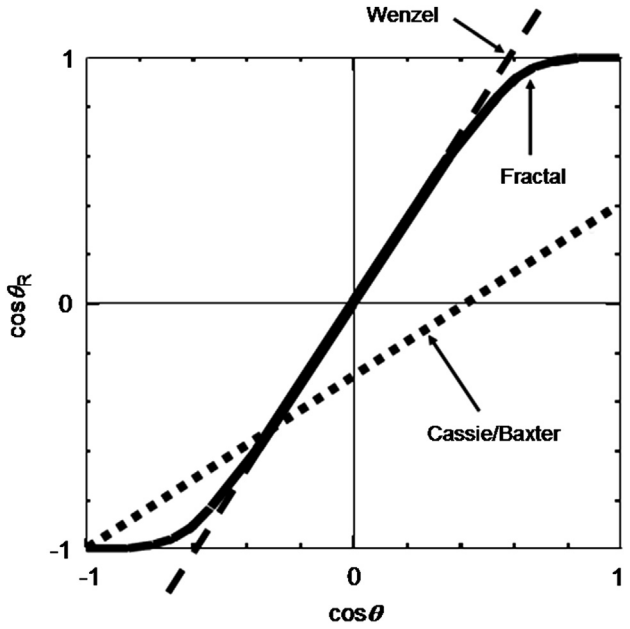



FIGURE 23.7 The theoretical curves of $\cos\theta_R$ versus $\cos\theta$ for the Wenzel, the Cassie–Baxter and the wetting of fractal surfaces.

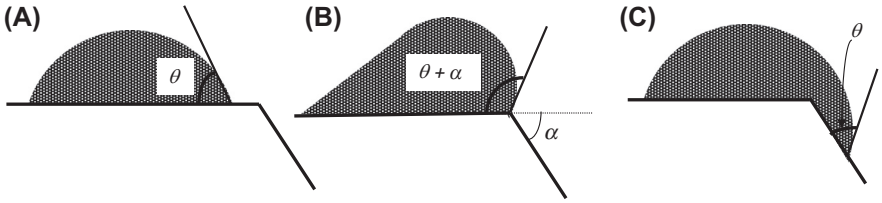



FIGURE 23.8 Schematic illustration to explain the pinning effect of wetting. Equilibrium contact angle of a liquid droplet on this solid surface is $\theta$ (A), the droplet does not move over an edge of solid surface until the contact angle becomes $\theta + \alpha$ (B), and finally moves over when the angle exceeds $\theta + \alpha$ (C).

### 23.3.4 Pinning Effect of Wetting

There is one more phenomenon to be noticed when we consider the wetting of a liquid on rough surfaces. This is the pinning effect.[15] Fig. 23.8 shows the contact angle change when a liquid droplet contacts an edge of a solid surface. Suppose the equilibrium contact angle of this liquid on the surface to be $\theta$ and the bending angle of the surface edge to be $\alpha$, the liquid droplet cannot move over the edge of the solid surface until the contact angle exceeds $\theta + \alpha$. If the front of the liquid droplet is to surpass the edge, the contact angle at the front has to be smaller than $\theta$, and this makes it possible for the drop to be pinned to the edge. If the droplet expands over the edge, the contact angle has in arbitrary value between $\theta$ and $\theta + \alpha$ in this situation, and can be much greater than the equilibrated value.

This pinning effect sometimes plays a very important role for super water repellency.[16] Super water-repellent surface can be obtained by the pinning effect even when a flat surface is wettable ($\theta < 90°$) with the liquid. It must be emphasized, however, that the super water repellency obtained by this mechanism is in a thermodynamically metastable state.[16] The wetting behavior of human hair with water can be governed by the pinning effect as discussed later.

## 23.4 SUPER WATER- AND OIL-REPELLENT SURFACES RESULTING FROM FRACTAL STRUCTURE

As discussed in Section 23.3.3, we can make a super liquid-repellent or a super wettable surface if we can make the surface fractal. But, how can we make it? Quite luckily, the author and his coworkers knew a material that formed a fractal structure spontaneously. A raw material of paper sizing agent, alkylketene dimer (AKD; Fig. 23.9), is such a material. The author and a coworker were developing the sizing agent utilizing AKD, and found one day that the AKD surface showed the very similar structure even when the magnification of electron microscopic observation was changed. When a coworker later established the theory on the wettability of fractal surface mentioned before, we remembered the fractal surface of the AKD. Then, this was a relatively easy way to realize the super water-repellent fractal surfaces experimentally.

### 23.4.1 Super Water-Repellent Fractal Surfaces Made of a Wax (Alkylketene Dimer)

AKD is a wax having the melting point of about 65°C. Super water-repellent surfaces were prepared by spontaneous solidification from the molten AKD.[12,13] After about 3 days from solidification, the contact angle of a water droplet on the AKD surface becomes greater than 170 degrees (Fig. 23.10A). Scanning electron microscope (SEM) observations indicate that the AKD surface just after the solidification has no special structure in the surface. After 3 days, however, the solid surface exhibits the extreme roughness with some stratified structures as shown in Fig. 23.11. One can see from the figure that there are two kinds of structures of roughness. One has a spherical shape like a flower of hydrangea having a size of roughness of about 30 μm, and the other is a flakelike structure the size of which is about 1 μm. This stratified structure was substantiated to be fractal by the box-counting method.[12,13]

The AKD sample with a flat surface was also prepared as a reference by mechanical cutting with a knife. The flat surface is, of course, not very water repellent, showing contact angle not larger than 109 degrees (Fig. 23.10B). One can understand consequently that the super water repellency of the surface can be realized by the surface roughness of the AKD.

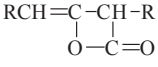



FIGURE 23.9 Molecular structure of alkyl ketene dimer (AKD), R = $C_{16}$.

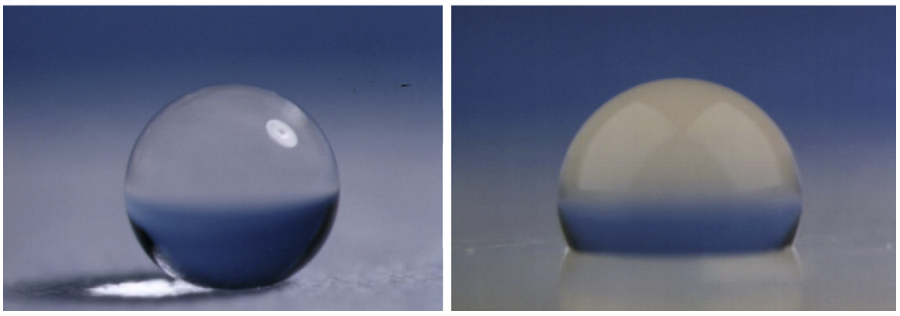



FIGURE 23.10 Water droplet (~1 mm size) on a super water-repellent AKD surface (A) and on a flat AKD surface (B).

The fractal parameters, $L$, $l$, and $D$, in Eq. (23.15) were determined by the box-counting method to be 34, 0.2 μm, and 2.29, respectively. Two critical sizes of $L = 34$ μm and $l = 0.2$ μm interestingly correspond quite well to the sizes of the flowerlike structure and the thickness of the flakelike crystal of the AKD (see Fig. 23.11). One can easily imagine that the surface appears flat (two dimensional) when observed on a larger scale than the spherical flowerlike structure. The surface is also flat for water droplets of smaller size than the thickness of the flakelike crystal. The mechanism of the spontaneous formation of fractal structure on wax surfaces was also made clear later.[17–19]

### 23.4.2 Super Oil-Repellent Fractal Surfaces Made of Anodically Oxidized Aluminum

We have applied the same theory, i.e., enhancement of wettability by fractal structure of surfaces, also to the novel super oil-repellent surfaces.[20,21] The highest barrier to obtain the super oil-repellent surface is to make a flat surface that has a contact angle greater than 90 degrees for oils. Let us estimate the surface tension of the solid to achieve such a condition. According to the Young's Eq. (23.1), the surface tension of solid surface ($\gamma_S$) must be equal to the interfacial tension of solid and liquid ($\gamma_{SL}$) when the contact angle is 90 degrees. If we use the approximate Eq. (23.4) for the interfacial tension, $\gamma_{SL}$, we obtain $\gamma_S = \gamma_L/4$ for the condition of $\theta = 90°$. Typical surface tensions of oils are 20–30 mN/m, and the value of $\gamma_S$ must be the order of several mN/m. Such a small surface tension of a solid can be provided by the trifluoromethyl group.[5] Accordingly, our strategy to make the super oil-repellent surfaces is to obtain a fractal surface of enough roughness and then cover the rough surface with trifluoromethyl groups by treating it with some fluorinated compound.[20,21]

An anodically oxidized aluminum surface was employed for such a purpose. A couple of aluminum plates of $100 \times 50 \times 1$ mm size were dipped into an aqueous 0.5 M $H_2SO_4$ solution. The distance between both aluminum plates was 5 cm. The anode oxidation was performed by a current density of 10 mA/cm$^2$ for 3 h at room temperature. The anodic plate was washed thoroughly with deionized water after the oxidation treatment to remove the

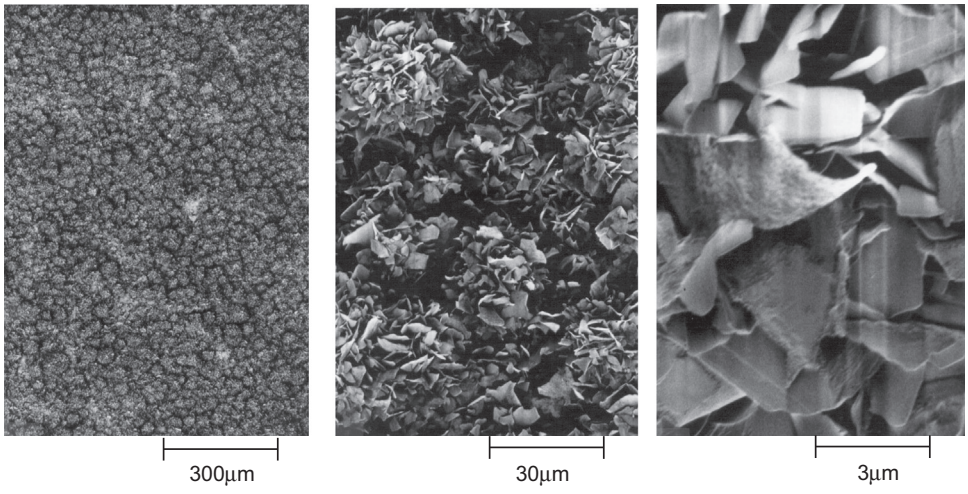



FIGURE 23.11 SEM images with different magnification of a fractal AKD surface.

residual $H_2SO_4$ on the surface, and was dried well at 353K. The surface structure of the anodically oxidized surface was observed by an FE-SEM apparatus, and the fractal analysis (the box-counting method) was performed for the surface. The fractal dimension $D$ was estimated to be 2.19, and the upper $L$ and the lower limit scale $l$ of fractal parameters unfortunately could not be determined in this case.

The anodically oxidized aluminum surface of the previous example was hydrophobized by treatment with fluorinated monoalkylphosphates ($n$-$CF_3(CF_2)_mCH_2CH_2OP(=O)(OH)_2$, m = 7 and 9; abbreviated as $F_{m+1}$-MAP). The anodically oxidized aluminum plate was then washed with pure water and then immersed in 2.0 wt% ethanol solution of $F_8$-MAP or $F_{10}$-MAP for 1 week at room temperature. The treated plate was washed well with chloroform and dried, and then washed again with distilled water. An oil droplet of rapeseed put on the treated anode-oxidized aluminum surface is demonstrated in Fig. 23.12.[20,21] One can see a beautiful spherical shape of the oil droplet having a very high contact angle of 150 degrees. The oil droplet having such a high contact angle rolls around without attaching on the surface when tilted slightly.

The contact angles of various oils or organic solvents were measured on the previously mentioned super oil-repellent surfaces, and those greater than 120 degrees were obtained for the oils with higher surface tension than approximately 24 mN/m of decane.[20,21] The critical surface tension ($\gamma_C$) values were roughly estimated from the Zisman plots. They are 14−15 mN/m for the flat surfaces treated with $F_8$-MAP and $F_{10}$-MAP. These values are in between the $\gamma_C$ of Teflon (18.5 mN/m) and that of trifluoromethyl group (∼6 mN/m). Our oil-repellent surfaces are still far from ideal. This work demonstrates the guiding principle for making super oil-repellent surfaces by combining both effects of the high fractal dimension of the solid surface and the compact packing of trifluoromethyl groups on it.

## 23.5 WETTING PHENOMENA IN COSMETIC SCIENCE AND TECHNOLOGY

### 23.5.1 Estimation of the Surface Tensions of Human Hair and Skin

As mentioned previously, the surface and interfacial tensions of solid and liquid are basic quantities that govern the wetting properties between them. So, in order to understand the wetting phenomena of human hairs and skins, their surface tensions are essentially important physical quantities. However, no direct method to determine their surface tension exists and we have to use some substitutes. As discussed in Section 23.2.3, we have two kinds of estimation methods to obtain the substitute of solid surface tension, i.e., the critical surface tension and the theoretical calculation for approximate values. These two methods have been applied to human hair and skin, and some papers have been published that give the substitutes of their surface tensions. Following are the results of these works.

Some examples of the reported substitute values of surface tension (critical surface tensions and theoretically calculated values) of human hair are listed in Table 23.1. These values are unbelievably small. Some data are around 20 mN/m, which are smaller than the critical surface tension of methyl group and close to that of Teflon (∼18 mN/m[5])! Even if the hair cuticle surface is covered with 18-methyleicosanoic acid molecules,[24,25] the reported values look too small to be accepted for the present author. Something may be wrong.

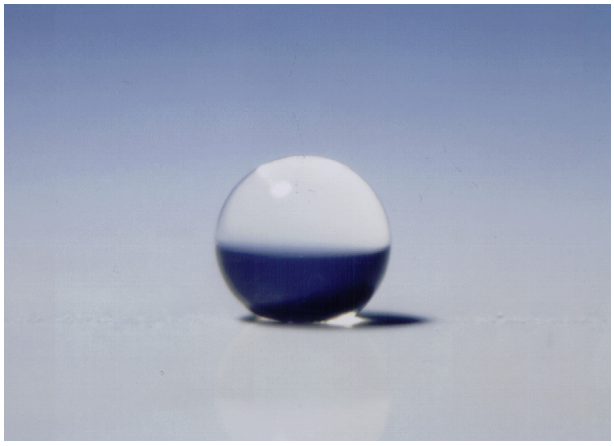


FIGURE 23.12 A droplet of rapeseed oil on a super oil-repellent surface.

**TABLE 23.1** Some Examples of Reported Surface Tension and Its Components Values of Human Hair

| Critical Surface Tension ($\gamma_c$) ($mNm^{-1}$) | Calculated Values of Surface Tension ($mNm^{-1}$) | | | References |
|---|---|---|---|---|
| | $\gamma$ | $\gamma^d$ | $\gamma^p$ | |
| $19.4 \pm 1.0$[a] | | | | 22 |
| $20.9 \pm 2.4$[b] | $26.8 \pm 1.4$[b] | $24.8 \pm 2.2$[b] | $2.6 \pm 1.3$[b] | 22 |
| $20.0 \pm 2.0$[c] | $26.5 \pm 1.0$[c] | $23.9 \pm 2.2$[c] | $2.5 \pm 1.5$[c] | 22 |
| $24.8 \pm 3.9$[d] | | | | 22 |
| $26.0 \pm 6.9$[e] | $31.0 \pm 1.6$[e] | $19.5 \pm 1.9$[e] | $11.5 \pm 1.7$[e] | 22 |
| $24.9 \pm 3.0$[f] | $29.6 \pm 2.2$[f] | $19.5 \pm 2.4$[f] | $10.0 \pm 2.0$[f] | 22 |
| | 18.89[g] | 16.41[g] | 2.48[g] | 23 |
| | 18.47[g] | 17.83[g] | 0.64[g] | 23 |
| | 29.83[h] | 27.65[h] | 2.18[h] | 23 |
| | 26.90[h] | 25.03[h] | 1.87[h] | 23 |

[a] *Using advancing contact angle, ignoring hair scale direction.*
[b] *Using advancing contact angle, against direction of hair scale.*
[c] *Using advancing contact angle, with direction of hair scale.*
[d] *Using "equilibrium" contact angle, ignoring hair scale direction.*
[e] *Using "equilibrium" contact angle, against direction of hair scale.*
[f] *Using "equilibrium" contact angle, with direction of hair scale.*
[g] *Virgin hair, no other information is given.*
[h] *Bleached hair, no other information is given.*

In order to determine the substitute of surface tensions of solids, we must employ the contact angle measurements of two or three liquids on the target solid surface (see Section 23.2.3). So, the contact angle measurement must be made properly to obtain the reasonable substitute values. From this point of view the contact angle data of human hair reported so far are quite questionable, since the hair shows the complex wetting behavior due to its rough surface with cuticles. As discussed fully in the next section, the contact angle data of water on human hair may be too large and may not the thermodynamically equilibrated values.

Some examples of the reported substitute values of surface tension (critical surface tensions and theoretically calculated values) of human skin are listed in Table 23.2. We can see some characteristic features in this table as follows: (1) again, some critical surface tension ($\gamma_C$) data are surprisingly small; (2) the $\gamma_C$ value of forehead is very much greater than that of forearm; and (3) the $\gamma_C$ and the surface tension and its components are considerably different from each other by the researchers. These results may be owing to the procedures for contact angle measurements as discussed later.

## 23.5.2 Wetting Behaviors of Human Hair and Skin

As mentioned in the previous section, contact angle data is necessary to obtain the substitutes of surface tension of human hair and skin. So let us see, in this section, the wetting behaviors (contact angle measurements) of human hair and skin.

### *23.5.2.1 Wetting Behaviors of Human Hair With Water*

The contact angle of a human hair fiber was measured by the Wilhelmy microbalance method.[22,25] The experiment was made as follows. A hair fiber was glued to a small wire hook mounted on the beam of an electromicrobalance and counterbalanced in air. A vessel containing a liquid was raised to contact the liquid surface with a tip of the hair fiber. The hair fiber was pulled into or pushed out of the liquid by the surface tension of liquid depending upon the wettability of the fiber surface. The force exerting on the hair fiber was measured with a microbalance equipped in the apparatus. The contact angle of the hair fiber with the liquid was obtained from the next equation,

$$F = \gamma P \cos\theta + W - \rho g y A \tag{23.16}$$

**TABLE 23.2** Some Examples of Reported Surface Tension and Its Components Values of Human Skin

| Critical Surface Tension ($\gamma_c$) ($mNm^{-1}$) | Calculated Values of Surface Tension ($mNm^{-1}$) | | | | | References |
|---|---|---|---|---|---|---|
| | $\gamma$ | $\gamma^d$ | $\gamma^p$ or $\gamma^{AB}$ | $\gamma^+$ | $\gamma^-$ | |
| $27.5 \pm 2.4$[a] | | | | | | 26 |
| $21.6 \pm 2.5$[b] | | | | | | 26 |
| $23.7 \pm 1.0$[c] | | | | | | 26 |
| $21.6 \pm 3.4$[d] | | | | | | 26 |
| >50.7[e] | | | | | | 26 |
| $29.3 \pm 1.7$[f] | | | | | | 26 |
| 18.80[g], 20.42[g] | $44.78 \pm 0.66$[g] | $38.82 \pm 0.93$[g] | $5.96 \pm 1.01$[g] | $1.61 \pm 0.44$[g] | $6.09 \pm 2.63$[g] | 27 |
| 22.26[g], 19.25[g] | $42.85 \pm 0.68$[h] | $37.31 \pm 0.87$[h] | $5.55 \pm 0.87$[h] | $1.26 \pm 0.38$[h] | $6.71 \pm 2.71$[h] | 27 |
| | $36.05 \pm 1.18$[i] | $34.09 \pm 1.47$[i] | $1.96 \pm 0.48$[i] | $0.89 \pm 0.39$[i] | $1.30 \pm 0.70$[i] | 27 |
| | $34.65 \pm 1.12$[j] | $32.74 \pm 1.41$[j] | $1.91 \pm 0.45$[j] | $0.68 \pm 0.33$[j] | $1.61 \pm 0.76$[j] | 27 |
| $27.3 \pm 3.6$[a] | $38.5 \pm 3.5$[a] | $27.6 \pm 4.1$[a] | $10.6 \pm 1.1$[a] | | | 28 |
| $21.3 \pm 3.9$[b] | $38.3 \pm 4.2$[b] | $21.1 \pm 2.7$[b] | $17.3 \pm 1.5$[b] | | | 28 |
| $23.8 \pm 3.0$[d] | $31.7 \pm 5.3$[d] | $25.1 \pm 0.5$[d] | $6.6 \pm 4.5$[d] | | | 28 |
| $30.9 \pm 3.9$[c] | $29.1 \pm 7.0$[c] | $20.3 \pm 3.7$[c] | $8.8 \pm 3.4$[c] | | | 28 |

[a] *On volar forearm, casual condition.*
[b] *On volar forearm, after cleaning with ether.*
[c] *On volar forearm, after cleansing with soap.*
[d] *On volar forearm, after occlusion with a polyethylene sheet for 1 h.*
[e] *On forehead, casual condition.*
[f] *On forehead, after cleaning with ether.*
[g] *On forearm, casual condition, at 293K, $\gamma_c$ values depending on surfactant used.*
[h] *On forearm, casual condition, at 308K.*
[i] *On forearm, after cleaning with ethanol solution, at 293K.*
[j] *On forearm, after cleaning with ethanol solution, at 308K.*

where $F$, measured force; $\gamma$, surface tension of the liquid; $P$, wetted perimeter of the fiber at liquid/air interface; $\theta$, contact angle on the fiber surface; $W$, weight of the fiber; $\rho$, density of wetting liquid; $y$, immersion depth; and $A$, cross-sectional area of the fiber.

The wetting behavior of human hair is quite curious. Fig. 23.13 shows a typical wetting force curve when a single hair fiber is immersed into water.[22] This curve was observed when the liquid surface contacted with and then immersed the hair fiber 1 mm at a time up to an immersed length of 5 mm. The fiber was then allowed to remain immersed in the liquid for ~15 min during which time the force on the electromicrobalance reached an almost constant level. Advancing wetting forces at immersion depths of 1−5 mm and the force reached at a constant level were read from the chart. One can see some characteristic wetting behaviors from Fig. 23.13 as follows:(1) At the first contact with the water surface, an upward (negative) force is experienced by the fiber, which quickly reduces with time. This pattern is observed during the immersion of each millimeter of the fiber up to a depth of 5 mm. These results indicate that the human hair behaves as a water-repellent material. (2) When the fiber is left in the water, the upward force slowly decreases, and in most cases, the direction of the force changes to the downward (positive) one, which implies that the hair surface is intrinsically hydrophilic. (3) The force then reaches an approximately constant value at ~15 min. This value is referred to as the "equilibrium" wetting force by the authors.[22] But it is clearly not in the true equilibrium since the force is still slightly increasing as seen from the figure.

It is a typical phenomenon of pinning effect of wetting that the intrinsically hydrophilic surface behaves as if it was water-repellent in a thermodynamically metastable state[16] (see Section 23.3.4). This pinning effect takes place frequently when the surface is rough, particularly when the surface consists of a lot of pillar-like structures. The hair surface is rough enough to show the pinning effect, since the cuticles completely cover the surface of the hair. In such cases, the equilibrium contact angle is hardly obtained because it is attained only when all the small spaces or trenches on the surface of the hair are filled with water. Then, the substitute of surface tension of human

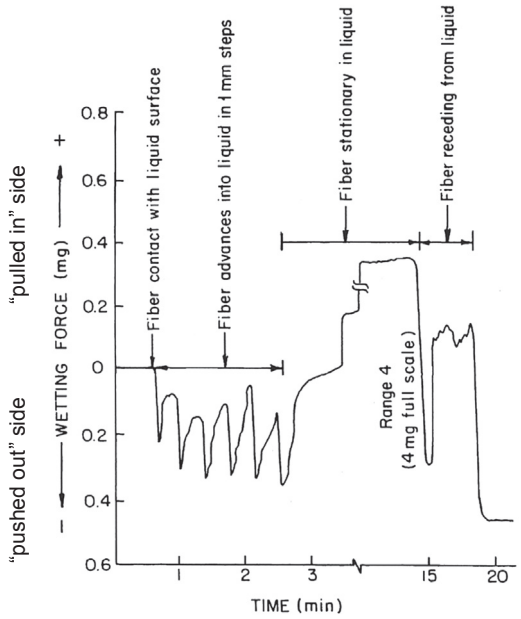



**FIGURE 23.13** A typical wetting force curve for human hair fiber in water. *Modified from Kamath YK, Dansizer CJ, Weigmann HD.* J Soc Cosmet Chem *1977;**28**:273–84.*

hair (critical surface tension and/or theoretically calculated value) obtained by utilizing the contact angle data is quite questionable.

#### *23.5.2.2 Wetting Behaviors of Human Skin*

Human skin is a relatively flat structure and the contact angles can be measured with a common sessile drop method.[26–28] Although the roughness of the human skin is much more moderate compared with that of human hair, it should be taken into account to obtain the correct contact angle data (see Section 23.3.1). Unfortunately, however, no published papers consider the roughness factor of the skin.

In the experiments of the contact angle measurements for human skin, there is another difficulty to obtain the equilibrium contact angle. The skin is a living tissue and shows various physiological functions such as secretion of sebum and sweat, insensible perspiration, etc. These physiological functions change the surface conditions of the skin momentarily. In such situations, it is quite difficult to understand what is the equilibrium condition. For example, the sebum membrane (the outermost thin membrane on the human skin) consists of an emulsion changing its type of O/W and W/O in response to the water content on the skin.[26] Water may completely wet the O/W type sebum membrane, and oil may do the same for a W/O type membrane. Furthermore, some liquids put on the surface of the skin to measure the contact angle can change the conditions of the sebum membrane. The present author cannot believe that the equilibrium contact angle is obtained in such conditions, and dares to say that the contact angle data and the surface tension substitutes calculated from these data are quite questionable.

As shown in Table 23.2, the critical surface tension of forehead skin is much greater than that of the forearm.[26] The authors mentioned in their paper that the high critical surface tension of the forehead was due to the high levels of sebum and sweat. If this is the case, the standard liquids used to determine the critical surface tension were put on a sebum membrane (a kind of emulsion). Then, the liquid (polar or nonpolar) might be miscible with the continuous phase or incorporated into it as emulsion droplets with time. In both cases, the contact angle must be time dependent, and finally becomes zero (complete wetting). The time-dependent measurement of the contact angle is considered to be essentially important. However, no attempt to do such experiment was made.

The forearm has the lowest sebum secretion on the human skin, and is considered to give more reasonable contact angle data.[26–28] But the data shown in Table 23.2 are not in very good agreement with each other. Some critical surface tensions are surprisingly small (18.80, 19.25, 20.42 mN/m). Although the reason is not clear why such small critical surface tensions are obtained, the problem may be in the method of contact angle measurements. The

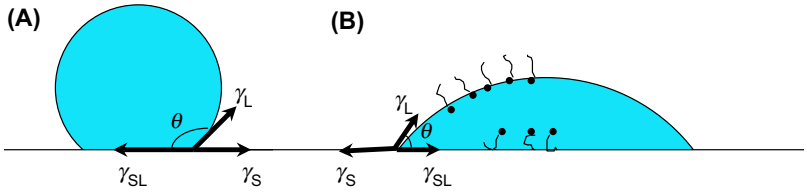



FIGURE 23.14 Enhancement of wetting by the adsorption of surfactant at the air/water and water/solid interfaces.

possible problems in obtaining the equilibrium contact angle include neglecting the roughness of the skin surface, the physiological functions of skin even if the lowest sebum secretion, and the time-dependent contact angle value.

#### 23.5.2.3 *Wetting of Cosmetic Materials on the Human Hair and Skin*

Wetting of human hair and skin with water is not a simple phenomenon as discussed before. However, our main interest is not the wetting of them with simple water but with cosmetic materials. Human skin and hair are easily wetted with most cosmetic materials, since they contain surfactants and some oils. Surfactants enhance the wettability of hydrophobic surfaces with water as shown in Fig. 23.14. Surfactant molecules adsorb on the solid/water and air/water interface and reduce their interfacial tensions, which results in the enhancement of wetting according to the Young's Eq. (23.1). Surfactants also enhance the penetration of water into capillaries (see Section 23.2.2). This capillary effect is important in the shampooing process, since the small spaces between hair fibers can be regarded as the capillaries. It is well known that hair shampoos and conditioners, shaving foams, skin-washing liquids, etc. contain a significant amount of surfactants. Even in skin creams, foundations, hair colors, etc. surfactants are used as the emulsifiers. These formulated surfactants enhance the wetting of cosmetic materials on human skin and hair.

Oils are materials having relatively low surface tension, and they easily wet solid surfaces. Lipsticks, skin creams, foundations, and any other emulsion products, of course, contain a sizable amount of some oils. These oils help the cosmetic materials to wet on the skin.

It should be emphasized again that the wetting behavior of human skin and hair with water is somewhat complicated, but their wetting with cosmetic materials is in no problem due to the formulated surfactants and oils.

### 23.5.3 Wetting Phenomena in Cosmetic Technologies

Wetting phenomena are also important in the formulation and the manufacturing processes of the cosmetic products. Some examples of such phenomena are discussed in this section.

#### 23.5.3.1 *Water-Repellent Treatments of Cosmetic Components*

Most of the inorganic powders are of intrinsically hydrophilic nature, and wettable with water. This property of the powders is sometimes inconvenient to use for cosmetic products. For example, the inorganic powders used for the foundations should be water repellent and even oil repellent, if possible, since the makeup is hopefully long lasting. If the powders are hydrophilic, the foundation flows away with sweat, and the makeup is broken. If the powders are oil repellent, it becomes durable even for the sebum secretion too. Therefore, inorganic powders are often treated with some hydrophobic compounds.

Fig. 23.15 shows a schematic illustration for the water-repellent treatment. Hydrophobic compounds like cationic surfactants and silane-coupling agents are bound to the surface of the inorganic powders. Cationic surfactant molecules adsorb on the negatively charged powder surface, orienting the hydrophobic group outward. The silane-coupling agents form a covalent bond with the hydroxyl group existing on the surface of the powders, and the hydrophobic chains cover the powder surface. Then, water-repellent powders are obtained. When the hydrophobic groups are fluorocarbons, one can expect even an oil-repellent property for the treated powders.

#### 23.5.3.2 *Wetting in the Formulation Technologies of Cosmetics*

Some cosmetic products are in suspension state. Foundations, mascaras, lipsticks, manicures, sunscreens, etc. contain some solid powders of organic or inorganic pigments. When the hydrophobic powders like organic pigments are dispersed in aqueous phase, wetting is the most important first step. If the powders are not wetted with the aqueous phase, undissolved lumps are formed and not dispersed well. Small spaces among the powder particles are regarded as capillaries, and the capillary effect works (see Section 23.2.2). Water cannot penetrate

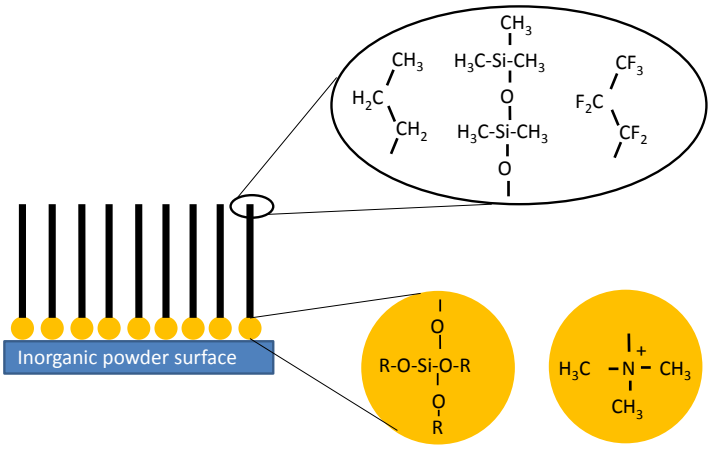



FIGURE 23.15 Schematic illustration of the water-repellent treatments of cosmetic materials.

into small spaces between hydrophobic powder particles. In order to change the wettability of the powders the addition of surfactants is quite useful. Surfactants enhance the wettability and decrease the contact angle down to 90 degrees. Then, the water phase penetrates into small spaces, and the powders turn from lump state to dispersed one.

## 23.6 FUTURE PERSPECTIVES ON THE WETTING TECHNOLOGIES IN COSMETICS

The final section of this chapter describes future perspectives on the wetting technologies in cosmetics including some dreamy ones. Let us discuss some technologies in the order from the most realistic one to the dreamier ones.

### 23.6.1 New Emulsion Technologies Utilizing the Wetting Phenomena

There have recently appeared some new emulsion technologies utilizing wetting phenomena. A pickering emulsion is an emulsion stabilized with small particles adsorbed at the oil/water interfaces.[29,30] The key property of this technology is the wetting of the small particles with water and oil. The particle must be properly wettable with both water and oil in order to adsorb at the oil/water interface. If this is the case, the interfacial free energy for the small particles reaches the lowest value at the oil/water interface rather than in both bulk phases of oil and water. In addition, this adsorption free energy of the particles is very much larger than that of surfactant (ordinary emulsifier) molecules. Consequently, the adsorbed particles tend to reside at the oil/water interface and the emulsions are quite stable.

One more new technique is the active interfacial modifier (AIM)-stabilizing emulsion.[31] In this case, an amphiphilic liquid polymer consisting of a silicone backbone modified with hydrocarbon chains and hydrolyzed silk peptides is present at the oil (silicone oil)/water interface and stabilizes the emulsion. The liquid AIM polymer penetrates spontaneously into the oil/water interface, and the driving force of this penetration is the wetting. The added value of two interfacial tensions at the oil/AIM and the water/AIM interfaces must be lower than that at the oil/water interface.

Both emulsion technologies just mentioned are conceptually new, since the small particles and the AIM polymer molecules are not soluble into either oil or water. When we use some surfactants as the emulsifiers, they dissolve more or less in the oil and/or the water phase. The hydrophile-lipophile-balance (HLB) concept is, then, necessary as an index for the most efficient adsorption of the emulsifier at the oil/water interface. In these new technologies, however, the HLB concept is nonsense because all the particles or the polymer molecules come to exist spontaneously at the oil/water interface. These technologies will be discussed fully in the other chapter of emulsions.

### 23.6.2 Some Dreamy Technologies of Cosmetics Utilizing the Wetting Phenomena

Let us move to some dreamy technologies or products of cosmetics made by utilizing the wetting phenomena. Even the author does not know that these technologies or products will be realized in the future or not. But any dreamy technologies or products will not be realized without having any dreams.

Super quick-dry shampoos and/or conditioners are one dreamy product for the present author. Even when a dog is caught in a shower, it gets dry by just shaking its body. If we could do the same thing after shampooing, how convenient and wonderful this would be! Human hair surface consists of cuticles and is quite rough. As mentioned previously, the surface roughness enhances the wetting property. This is a good sign to develop the super quick-dry shampoos and/or conditioners. If we can make the hair surface hydrophobic with some components of shampoos or conditioners, the hair surface becomes super water repellent automatically. The author wishes anybody to try to make the above dreamy products!

The second dreamed-of technology is the control of tactile feeling. According to a recent study on the tactile impression for recognition of water, the stick-slip motion of a fingertip on a solid surface coated with a thin water film is the most important factor for the above recognition.[32] Quite interestingly, the subject people recognized clearly a 3% aqueous surfactant solution as a different liquid from water in spite of the almost same viscosity. On the other hand, an aqueous solution of 25% sodium chloride could not be distinguished from water. The stick-slip motion of a fingertip took place on the sodium chloride solution but not on the aqueous surfactant one. It seems reasonable to the present author that the stick-slip motion might originate from the partial (adhesive) wetting of the forefinger with water, since the contact angle of water on the human forearm skin is reported to be 70°−90°.[27]

As is well known, silicone (polydimethylsiloxane) oil shows very unique slippery feeling, and is very water-repellent material. It could be possible that the unique feeling might be due to the dewetting phenomena between the silicone oil and the forefinger. The relationship between the feeling and the wettability is just speculation by the present author, and there is no evident experimental and/or theoretical result. If this would be the case, however, we could expect a lot of new technologies developed by utilizing the wetting property.

## References


1. Adamson AW, Gast AP. *Physical chemistry of surfaces*. 6th ed. New York: John Wiley & Sons, Inc.; 1997. p. 353.
2. Tsujii K. *Surface activity — principles, phenomena, and applications*. Boston: Academic Press; 1998. p. 51.
3. Tsujii K. *Surface activity — principles, phenomena, and applications*. Boston: Academic Press; 1998. p. 49−52.
4. For examples, Mulqueen M, Huibers PDT [Chapter 11]. In: Holmberg K, editor. *Handbook of applied surface and colloid chemistry*, vol. 2. John Wiley and Sons; 2002. p. 10−40. Adamson AW, Gast AP. *Physical chemistry of surfaces*. 6th ed. New York: John Wiley & Sons, Inc.; 1997. p. 353.
5. Adamson AW, Gast AP. *Physical chemistry of surfaces.* 6th ed. New York: John Wiley & Sons, Inc.; 1997. p. 367−68 Holmberg K. In: Holmberg K, editor. *Handbook of applied surface and colloid chemistry*, vol. 1. John Wiley and Sons; 2002. p. 120−1.
6. Fowkes FM. *J Phys Chem* 1962;**66**:382.
7. Owens DK, Wendt RC. *J Appl Polym Sci* 1969;**13**:1741.
8. As a good review article, van Oss CJ, Chaudhury MK, Good RJ. *Chem Rev* 1988;**88**:927.
9. Wenzel RW. *Ind Eng Chem* 1936;**28**:988.
10. Cassie ABD, Baxter S. *Trans, Faraday Soc* 1944;**40**:546.
11. Mandelbrot BB. *The fractal geometry of nature*. San Francisco: Freeman; 1982.
12. Onda T, Shibuichi S, Satoh N, Tsujii K. *Langmuir* 1996;**12**:2125.
13. Shibuichi S, Onda T, Satoh N, Tsujii K. *J Phys Chem* 1996;**100**:19512.
14. Hazlett RD. *J Colloid Interface Sci* 1990;**137**:527.
15. de Gennes PG, Brochard-Wyart F, Quere D. *Capillarity and wetting phenomena: drops, bubbles, pearls, waves*. New York: Springer; 2003 [Chapter 9].
16. Kurogi K, Yan H, Tsujii K. *Colloids Surfaces A* 2008;**317**(1−3):592−7.
17. Fang W, Mayama H, Tsujii K. *J Phys Chem B* 2007;**111**:564−71.
18. Fang W, Mayama H, Tsujii K. *Colloids Surfaces A* 2008;**316**:258−65.
19. Minami T, Mayama H, Nakamura S, Yokojima S, Shen J-W, Tsujii K. *Soft Matter* 2008;**4**:140−4.
20. Tsujii K, Yamamoto T, Onda T, Shibuichi S. *Angew Chem Intl Ed* 1997;**36**:1011.
21. Shibuichi S, Yamamoto T, Onda T, Tsujii K. *J Colloid Interface Sci* 1998;**208**:287.
22. Kamath YK, Dansizer CJ, Weigmann HD. *J Soc Cosmet Chem* 1977;**28**:273−84.
23. Gao T, He Y, Landa P, Tien J-M. *J Cosmet Sci* 2011;**62**:127−37.
24. Robbins CR. *Chemical and physical behavior of human hair*. 4th ed. New York: Springer-Verlag; 2002 [Chapter 1].
25. Lodge RA, Bhushan B. *J Appl Polym Sci* 2006;**102**:5255−65.
26. Elkhyat A, Mavon A, Leduc M, Agache P, Humbert P. *Skin Res Technol* 1996;**2**:91.
27. Krawczyk J. *Skin Res Technol* 2015;**21**:214.
28. Elkhyat A, Agache P, Zahouani H, Humbert P. *Int J Cosmet Sci* 2001;**23**:347.
29. Pickering SU. *J Chem Soc* 1907:2001−21.
30. Ngai T, Bon S, editors. *Particle-stabilized emulsions and colloids: formation and applications*. Royal Society of Chemistry; 2015.
31. Sakai K, Ikeda R, Sharma SC, Shrestha RG, Ohtani N, Yoshioka M, Sakai H, Abe M, Sakamoto K. *Langmuir* 2010;**26**:5349−54.
32. Nonomura Y, Fujii T, Arashi Y, Miura T, Maeno T, Tashiro K, Kamikawa Y, Monchi R, Colloids, Surfaces B. *Biointerfaces* 2009;**69**:264−7.

CHAPTER

# 24

# Molecular Structure and Phase Behavior of Surfactants

M. Miyake[1], Y. Yamashita[2]

[1]Lion Corporation, Tokyo, Japan; [2]Chiba Institute of Science, Choshi, Japan

## 24.1 INTRODUCTION

Cosmetics and personal care products require effective surfactants that are able to produce a homogeneous and stable mixture of other ingredients in a formula accompanied with greater availability. We often encounter many issues such as the melting temperature of raw materials, handling performance (e.g., viscosity), stability of mixed and dispersed state at given storage temperatures for an examined period, and so on, when manufacturing such products. Then, understanding the phase behavior of surfactant coordinated by critical packing parameter (CPP) should help us predict and control a molecularly self-assembled state appropriate for work efficiency, handling, and dispersion stability. The phase behavior of surfactant system refers to types of the hydrophilic and lipophilic groups as well as the kind of counterion(s) for ionic surfactants. This chapter first describes the fundamental concept and interpretation of phase diagrams in surfactant system, and secondly reviews the effect of the molecular structure of surfactants on the phase behavior and physicochemical properties such as melting temperature.

## 24.2 NOTATIONS IN PHASE DIAGRAM

W: water phase or molecularly dispersed solution phase in water, $L_1$: micellar solution, $I_1$: discontinuous cubic liquid crystal, $H_1$: hexagonal liquid crystal, $V_1$: bicontinuous cubic liquid crystal, L$\alpha$: lamellar liquid crystal, $V_2$: reversed bicontinuous cubic liquid crystal, $H_2$: reversed hexagonal liquid crystal, $I_2$: reversed discontinuous cubic liquid crystal, $L_2$: reversed micellar solution, O: oil phase or molecularly dispersed phase in oil, D: surfactant phase or bicontinuous microemulsion, $L_3$: sponge phase, S: solid.

## 24.3 PHASE DIAGRAM IN SURFACTANT SYSTEM

Surfactants are amphiphilic substances having hydrophilic and lipophilic groups in the molecule, that show different dissolution behavior within common solutes. In aqueous media, the hydrophilic group interacts with water molecules (hydration), while the lipophilic group is excluded from the aqueous environment because of the entropically unfavorable ordered structure of water surrounding the lipophilic group (see Chapter 12). This results in interfacial adsorption and self-assembled structures phenomena that are characteristic properties of surfactant systems. Phase diagrams demonstrate the self-assembling phenomena as functions of composition, temperature, etc., and provide information on the dissolution state of surfactants and the phase transitions under certain specific physical conditions.

### 24.3.1 Binary System

As a consequence of their amphiphilicity surfactants assemble into a wide variety of self-organized structures such as micelles and lyotropic liquid crystals because of hydrophobic interaction in water. As a result the phase

*Cosmetic Science and Technology: Theoretical Principles and Applications*
http://dx.doi.org/10.1016/B978-0-12-802005-0.00024-0



Copyright © 2017 Elsevier Inc. All rights reserved.

diagram of the surfactant system depicts the different "phases" by the kind of self-organized structures. Such phase behavior can be found not only aqueous solvent but also in other ones. Furthermore complicated phase diagram are sometimes found in mixed solvents.

Fig. 24.1 demonstrates a schematic phase diagram in a binary surfactant/water system.[1] In the lower surfactant concentration region, W and adjacently $L_1$ are present. This phase boundary between $L_1$ and W is the so-called critical micellar concentration (CMC), generally found in the range $10^{-4} \sim 10^{-2}$ mol/L for common surfactants. The CMC is an important characteristic of a surfactant, useful in consideration of the practical uses of the surfactant. In addition, the solubility of surfactant dramatically increases at the CMC. Additionally, the solubility may be very low at low temperatures and then increase by orders of magnitude in a relatively narrow temperature range. This phenomenon is denoted as the Krafft phenomenon, and the temperature corresponding to the onset of the strongly increasing solubility is known as "Krafft point" or "Krafft temperature." The solubility curve becomes almost independent of the surfactant concentration above the Krafft point because micellization takes place at the corresponding concentration and temperature, and thus the Krafft point is also defined as the intersection point of the solubility curve and the CMC curve.

With increasing surfactant concentration, structural transitions from $L_1$ to lyotropic liquid crystals are observed. There are many kinds of lyotropic liquid crystals, for example, $I_1$, $H_1$, $V_1$, and $L_\alpha$ (Fig. 24.2). Except for $L_\alpha$, which is symmetrical around the middle of the bilayer, the different liquid crystal structures have a reversed counterpart in which the polar and nonpolar parts have changed roles and the reversed structures are abbreviated as $I_2$, $H_2$, and $V_2$. The liquid crystals have bilateral character of liquid-like disorder and the solid-like order, and their structures are determined by the kind of surfactant, temperature, additive, composition, and so on.

The other distinctive behavior in surfactant system is the coexistence (clouding) curve. Clouding phenomenon is one example of a thermodynamically-driven temperature effect, and some systems, typically aqueous polyethylene-oxide (PEO)-type surfactant solutions, phase separate above a critical temperature. The temperature at which this occurs is referred to as "cloud point." The clouding phenomenon could be attributed to dehydration of PEO chain

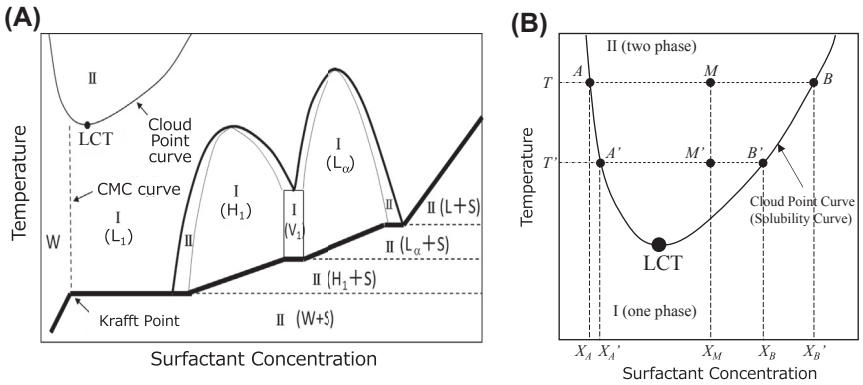



FIGURE 24.1 Schematic phase diagram as functions of surfactant concentration and temperature of a representative surfactant/water binary system.[1] I and II denote one-phase and two-phase respectively. The phase diagram on the right side represents the magnification of the phase coexistence curve in (a). $M$ and $M'$ are the sample conditions at (temperature, composition) = ($T$, $X_M$) and ($T'$, $X_M$). $X_A$, $X_A'$, $X_B$, $X_B'$ indicate the composition at the points $A$, $A'$, $B$, $B'$, respectively.

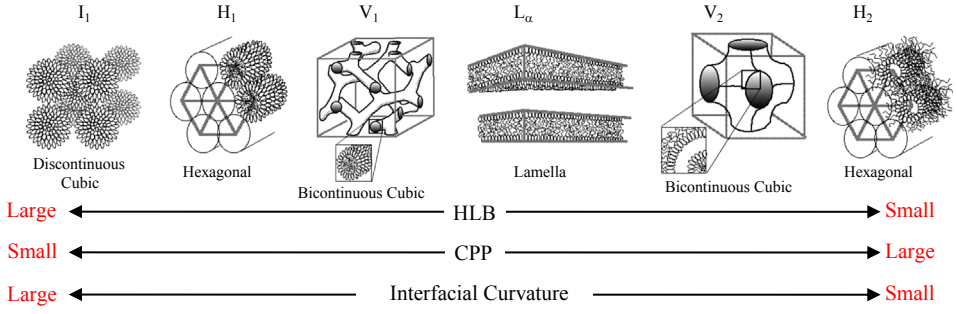



FIGURE 24.2 Self-organized structures and various relevant parameters determining their structures: hydrophile-lipophile balance (HLB), critical packing parameter (CPP), and interfacial curvature.

and thereby growth of the micelle size. Above the cloud point, shown in Fig. 24.1, dilute surfactant phase, W, and concentrated surfactant phase, denoted D, coexist in the two-phase region above the cloud point. Likewise, various two-phase regions between the single phases are present. Then the phase rule indicates that the two-phase region always consists of the adjacent single phases.

The notation of multiple phase, even two phase, seems to be difficult and sometimes incorrect. The typical case is two phase above cloud point. To understand the separated two phases above the cloud point, the respective W and D phase should be identified on the basis of the tie-line in the two phase region(II). Let us consider the two-phase solution at the point *M* in Fig. 24.1B. The W phase consists of the monomeric surfactant dispersed in water without any aggregate, which can be referred to the solution below CMC. On the other hand, the D phase is formed by the surfactant aggregate of composition $X_B'$. The composition of the W and D phases at temperature *T* corresponds to the intersections between the solubility curve and tie-line, that is, $X_A$ and $X_B$, respectively. The phase fractions of the W and D phases are proportional to the lengths *B*-*M* and *A*-*M* according to the principle of leverage. The decrease in temperature from *T* to *T*′ causes different composition, $X_A'$, and fraction, *B*′-*M*′, for the W phase, $X_B'$ and *A*′-*M*′ for the D phase. It can be noticed from this figure that the fraction of the D phase in the system should increase with lowering temperature, suggesting that the larger amount of water is included in the D phase at the lower temperature. Eventually, the separated two phases turn to the single $L_1$ phase below lower critical temperature. From this point of view, the clouding phenomenon can be understood to arise from the phase separation of the W phase from the D phase.

### 24.3.2 Ternary System

Many products for daily use such as cosmetics, toiletries, and foods are composed basically of surfactant, water, and oil, and therefore ternary phase diagrams would be useful for understanding formulation technology and finding out causes of trouble. On the other hand, the phase diagram become complicated when the number of components increases, and the phase diagram in a system consisting of more than three components is depicted under certain fixed conditions, for example, temperature, pressure, and mixing ratio of components. With three components, at constant pressure the maximum of degree of freedom is three, i.e., temperature and two concentration variables. Therefore, the overall image of a phase diagram in a ternary system can be expressed by a triangular prism (Fig. 24.3), but the diagram is not executable to be drawn. Instead, a two-dimensional representation can be made, depending on the system and purpose, namely fixing the temperature, fixing one concentration, or fixing the mixing ratio of two components.

Fig. 24.4[2] is a Gibbs triangle, which is commonly used to represent the phase behavior at a constant temperature. The apices represent three pure components, meaning that the concentration of each component decreases as the distance from each apex. The self-organized structures formed in a ternary system are similar to a binary system, while a three-phase region often appears as a two-dimensional area in the ternary system and cannot be observed in binary systems. To include the mutually immiscible components such as water and oil in the ternary system, emulsion and microemulsion are formed and tie-lines in the multiphase are complicated but important to understand the phase state, guiding applications such as solubilization and emulsification.

The solution state in the multiphase region depends on physicochemical properties of each component, in particular, surfactant. The phase behaviors can be classified using hydrophile-lipophile balance (HLB) of a surfactant, which indicates the degrees of hydrophilicity and lipophilicity. High HLB means a hydrophilic surfactant and low HLB a lipophilic surfactant, and thus the HLB of surfactant relates to affinity with solvents, and is related to the phase behavior.

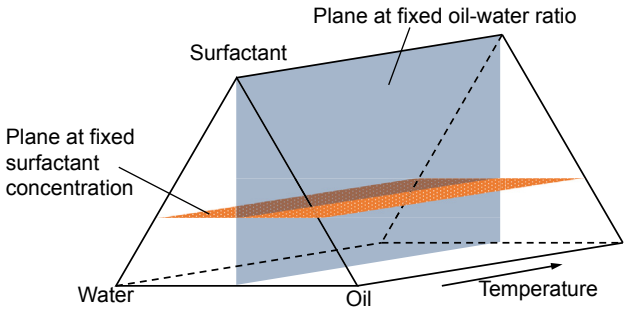



**FIGURE 24.3** Triangular prism to express an overall phase diagram in a water/surfactant/oil ternary system as functions of their compositions and temperature.

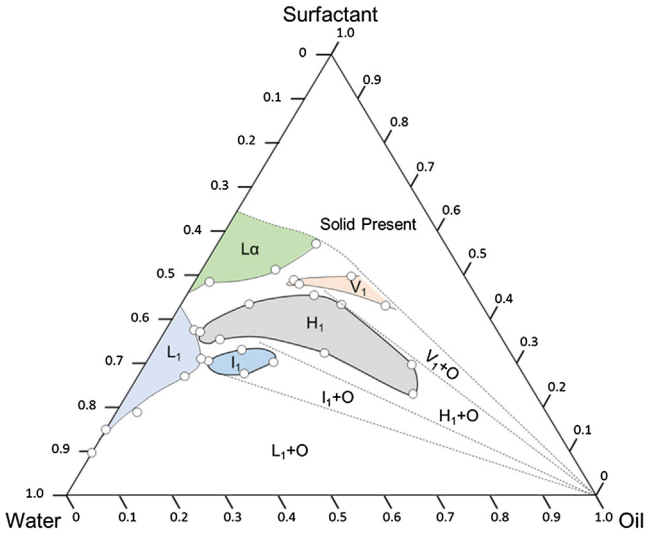



**FIGURE 24.4** Gibbs triangle phase diagram in a water/surfactant/oil system at a constant temperature.[2]

Fig. 24.5 illustrates schematic diagrams when HLB changes from high (hydrophilic) to low (lipophilic).[3] The influence of HLB on the phase behavior can be clearly seen in their multiphase regions: two-phase $L_1 + O$ (oil-in-water, O/W, emulsion, Fig. 24.5A) for the high HLB, three-phase $W + D + O$ (Fig. 24.5B) for the middle HLB, and two-phase $L_2 + W$ (water-in-oil, W/O, emulsion, Fig. 24.5C) for the low HLB. Apparently Fig. 24.5A and C seem to be similar, but the tie-lines and emulsion type are quite different. When the degrees of hydrophilicity and lipophilicity are balanced, the bicontinuous microemulsion (D) phase can be formed as depicted in Fig. 24.5B. This D phase is a thermodynamically stable microemulsion in the ternary system, referring to a large amount of oil or water or both solubilized in the surfactant aggregates, and should not be regarded as emulsions with very small droplet size.

For a ternary system, other depictions of phase diagrams are used to evaluate surfactant properties. The diagram is expressed as functions of temperature and composition, where one composition variable, i.e., oil/water ratio or surfactant concentration, is fixed then. Fig. 24.6 shows typical phase diagrams at (a) a constant oil/water ratio and (b) a constant surfactant concentration in the case of POE nonionic surfactants, which exhibit strong temperature dependence and become lipophilic with increasing temperature. Therefore, an O/W emulsion formed at lower temperature turns to a W/O emulsion with elevation in temperature, and the three-phase composition, including the D phase, is present at the middle temperature, the so-called "HLB temperature" or "phase inversion temperature (PIT)."[4] PIT can be estimated by both the phase diagrams in Fig. 24.6, and the respective diagram provides significant information on solubilization and emulsification processes.

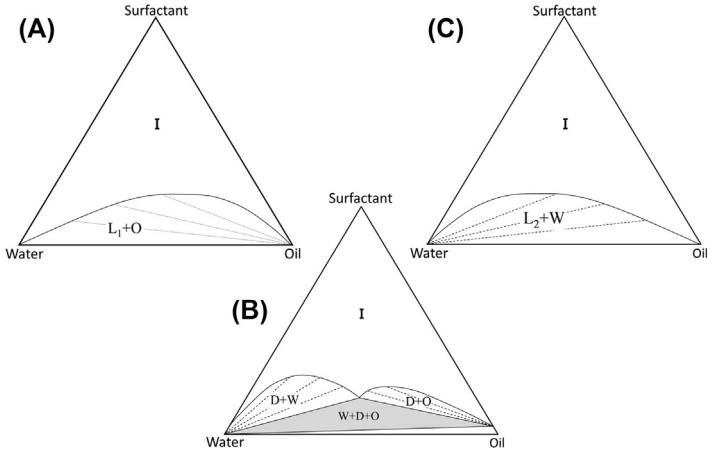



**FIGURE 24.5** Ternary phase diagrams consisting of various surfactants with different HLBs: (A) higher HLB (hydrophilic surfactant), (B) intermediate HLB, and (C) lower HLB (hydrophobic surfactant).[3]

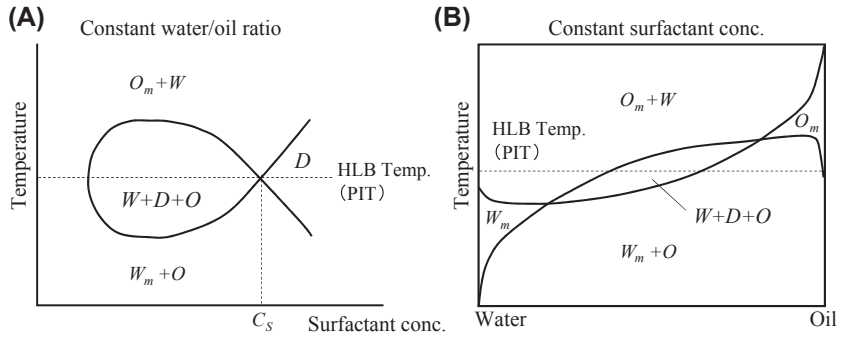



**FIGURE 24.6** Schematic phase diagrams as functions of (A) the surfactant concentration and (B) water-to-oil ratio in a water/POE nonionic surfactant/oil system. These diagrams are referred to each plane depicted in Fig. 24.3.

## 24.4 SELF-ORGANIZED STRUCTURE

With reference to micellization, one fundamental property of surfactants is that unimers in solution tend to spontaneously form aggregates by intermolecular interaction. This phenomenon is called "self-organization" and the aggregate composed of a number of molecules is a "self-organized structure." The general prerequisites of self-organized solutes are[5]:

1. low affinity with solvent
2. the presence of amphipathic molecular structure that causes the molecules to self-assemble into multimolecular aggregates
3. liquid or liquid crystal states can result from the molecular self-assembly

The self-organization can take place only if the previous requirements are fully satisfied, otherwise unstable organized structures such as solid deposition and separation of two liquid phases can be observed. Table 24.1 represents comparison between molecularly dispersed solutions and self-organized solutions.[5] Besides the self-organized strucutres formed in the surfactant solution (micelle, liposome, liquid crystal, microemulsion), the protein solution and functional polymer solutions can construct self-organized structures. This is relevant because complexed and multifunctional activities in living systems are based on self-organization structures and phenomena in many cases.

Various self-organized structures are known in surfactant systems, being controllable by solvent, composition, additive, temperature, as well as the chemical structure of surfactant. Subsequently, three important parameters—interfacial curvature, critical packing parameter, and HLB number—are applied to understanding and controlling self-organized structures and phase transition phenomena.

**TABLE 24.1** Comparison Between Molecular Dispersion and Self-Organized Solution[5]

| Molecular Dispersion (Disordered Mixture) | Self-Organized Solution (Functional Solution, Biological System) |
|---|---|
| Diluted solution | Micellar solution |
| Electrolyte solution | Liposome |
| Regular solution | Liquid crystal |
| Regular polymer solution | Solubilized solution (Microemulsion) |
| Molten salt | Protein solution |
| | Functional polymer solution |
| Solutions can be idealized and described by regular solution theory | Solutions are characterized by orientation, assembly, organization, and behaves biologically, organically, functionally |

### 24.4.1 Interfacial Curvature

Self-organized structures are characterized by their interfacial curvature (main curvature). In principle, overall area of the interface can be defined as the mean curvature (c) and Gaussian curvature (κ) using the radii of the main curvatures, $R_1$ and $R_2$, as shown in Fig. 24.7.

$$\text{Mean Curvature:} \quad c = \frac{1}{2}\left(\frac{1}{R_1} + \frac{1}{R_2}\right)$$

$$\text{Gaussian Curvature:} \quad \kappa = \frac{1}{R_1} \times \frac{1}{R_2}$$

When a spherical micelle is formed at low-surfactant concentration, the mean curvature corresponds to $c = 1/R$ ($R = R_1 = R_2$) and the Gaussian curvature is $\kappa = 1/R^2$ because of its isotropic structure. On the other hand, anisotropic structures such as cylindrical micelles and bilayer structures lead to other different values: $c = 1/(2R_1)$ and $\kappa \sim 0$ for the cylindrical structure; $c \sim 0$ and $\kappa \sim 0$ for the bilayer structure. The curvatures corresponding to the respective aggregate structure are summarized in Table 24.2. The conventional representation of interfacial curvature is that positive curvature means convex toward the water phase, and contrarily negative curvature indicates concave. Therefore, the curvature becomes smaller in the order corresponding to $L_1$, $I_1$, $H_1$, $V_1$, $L_\alpha$, $V_2$, $H_2$, $I_2$, and $L_2$ as shown in Fig. 24.2.

### 24.4.2 Critical Packing Parameter

The ordered self-organized structures are determined geometrically by the volume of the self-organized structure occupied in space of the system and the molecular structure of surfactant composed in the system. The surfactant molecules can be arranged in a geometric structure under given condition so that the interfacial area per molecule will be minimized. The morphology of the self-organized structure is governed by the balance of two opposing forces, hydrophobic interaction at the alkyl chain−water interface and repulsive interaction between the head

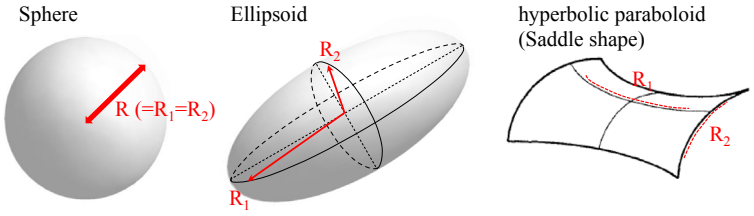



**FIGURE 24.7** Schematic representation of the radii of two main curvatures, $R_1$ and $R_2$.

**TABLE 24.2** Mean and Gaussian Curvatures of Various Self-Organized Structures

| Structure/Phase | Mean Curvature | Gaussian Curvature |
|---|---|---|
| Spherical micelle | $+1/R$ | $+1/R^2$ |
| Cylindrical micelle | $1/(2R)$ | 0 |
| Bicontinuous cubic phases | $0 \sim 1/(2R)$ | $-1/R^2 \sim 0$ |
| Lamellae (planar bi1ayer) | 0 | 0 |
| Inverse bicontinuous cubic phase | $-1/(2R) \sim 0$ | $-1/R^2 \sim 0$ |
| Inverse cylindrical micelle | $-1/(2R)$ | 0 |
| Inverse spherical micelle | $-1/R$ | $1/R^2$ |

groups of surfactants (ionic repulsion, hydration force, steric hindrance, etc.), leading to the interfacial free energy per surfactant molecule ($\mu_N^0$).[6]

$$\mu_N^0 = \gamma a + \frac{K}{a}$$

where K is constant, $\gamma$ the interfacial tension, $a$ the cross-sectional area of the surfactant head group at the interface, and the first and second terms represent attraction and repulsion, respectively. On the basis of the assumption that these interactions would operate within the same interfacial area, the minimum $\mu_N^0$ gives the optimized effective cross-sectional area per molecule ($a_S$), which is known to be an important factor determining the self-organized structure.

Furthermore, Israelachivili proposed a "critical packing parameter" relating the molecular structure of surfactant to the morphology of the self-organized structure. CPP has nondimensional units and can be calculated using the volume of alkyl chain ($V_L$), and the length of the extended alkyl chain ($l$), and $a_S$:

$$\text{CPP} = \frac{V_L}{a_S l}$$

CPP gives a geometric characterization of a surfactant molecule and is useful when discussing the type of self-organized structure formed by a given amphiphile. Considering which surfactants fall into the different categories of the self-organized structures of Fig. 24.2, we note that CPP characterizes the self-organized structure, for example, the CPP $< 1/3$ for the spherical micelles ($L_1$, $I_1$), $1/3 \sim 1/2$ for the cylindrical micelles ($H_1$), $\sim 1$ for the bilayer structure ($L_\alpha$).

### 24.4.3 HLB Number

As mentioned previously, the concept of HLB is often used when we discuss phase behavior. The term seems to be preferentially utilized in the industrial field because the commercial surfactants with chain length distribution may not be simply characterized by CPP. HLB denotes the inner nature of surfactant in terms of hydrophilicity and lipophilicity, and Griffin codified the HLB number as a useful parameter. If the molecular structure of a surfactant is known, the HLB number can be calculated from the hydrophilic and lipophilic portions of the molecule (see Chapter 28). The HLB number is a tool for selection of surfactants suitable for various application (e.g., emulsifier, solubilizer, wetting agent, antifoamer).

## 24.5 ANIONIC SURFACTANTS

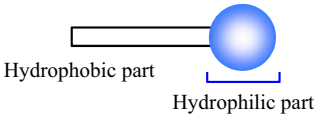
Anionic surfactants have mostly been applied in detergents, such as soaps, due to their soil removal ability through emulsification, solubilization, and dispersion processes. Table 24.3 shows the molecular structure of typical anionic surfactants used in industry. Carboxylate, sulfonate, sulfate, and phosphate salts are commonly used as the hydrophilic head groups, while $C_{12}$ to $C_{18}$ hydrocarbons act as the hydrophobic alkyl chains.

### 24.5.1 Molecular Structure of the Hydrophilic Groups and Their Phase Behavior

The phase behavior of anionic surfactants widely used in body soaps and shampoos has been compared within similar $C_{12}$ alkyl chains and sodium salts. Fig. 24.8 shows the phase diagrams of sodium laurate ($C_{12}$Soap),[7] sodium dodecyl sulfate (SDS),[8] sodium laurylbenzene sulfonate (LAS),[9] and sodium dodecyl tetraoxyethylene sulfate ($C_{12}E_4S$)[10] in surfactant/water two-component systems. The melting temperature of the solid phase for $C_{12}$Soap is higher than that for SDS at all concentrations. The molecular packing of the carboxylate moiety, the head group of the soap, is more compact than the sulfate moiety of SDS because of the dipole−dipole interactions operative between the carbonyl groups. The molecular orientation of the soap is thus favored; the molecules are closely packed in the solid state, which results in a higher melting point for the soap. On the other hand, there is no solid phase for $C_{12}E_4S$ and the melting point is below 0°C until the surfactant concentration is over 50 wt%. The crystallization of $C_{12}E_4S$ is inhibited at low-surfactant concentrations, as the cross-sectional area per molecule ($a_S$) of the sulfate group is expanded by the hydrated ethylene oxide (EO) units. This difference in their melting points is the reason why soap is mostly applied in solid products and alkyl ethoxylate sulfate (AES) in liquid products.

$C_{12}$Soap, SDS, and $C_{12}E_4S$ have liquid crystal phases at higher concentrations above the melting temperature. For $C_{12}$Soap and SDS, the $H_1$ phase appears at around 30−40 wt% of surfactant concentration, and the L$\alpha$ phase at

**TABLE 24.3** Molecular Structure of Typical Anionic Surfactants




| | | |
|---|---|---|
| Carboxylate | Sodium laurate ($C_{12}$Soap) | $C_{11}H_{23}COONa$ |
| Sulfonate | Sodium dodecylsulfonate | $C_{12}H_{25}SO_3NA$ |
| | Sodium dodecylbenzene sulfonate (LAS; x + y = 11) | $C_xH_{2x+1}$ / $C_yH_{2y+1}$ CH ⟨O⟩ $SO_3Na$ |
| Sulfate | Sodium dodecyl sulfate (SDS) | $C_{12}H_{25}SO_3Na$ |
| | Sodium dodecylethoxylate sulfate (SLES) | $C_{12}H_{25}O(EO)_pSO_3Na$ |
| Phosphate | Sodium dodecylphosphate | $C_{12}H_{25}OPO_32Na$ |

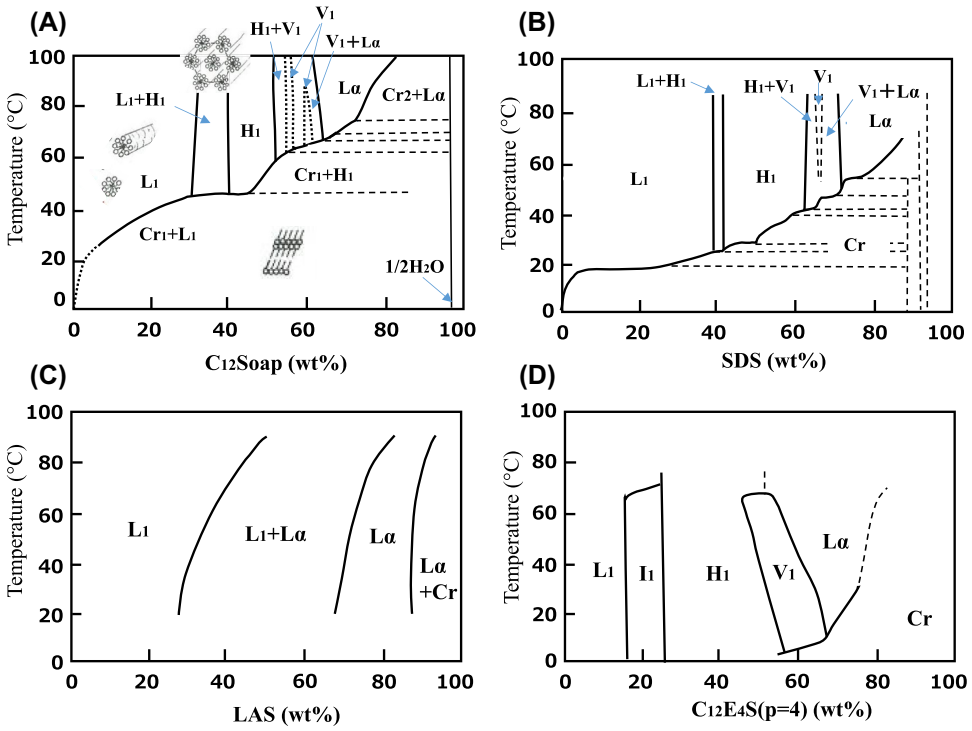



**FIGURE 24.8** Phase diagrams of typical anionic surfactants: (A) $C_{12}$Soap,[7] (B) SDS,[8] (C) LAS,[9] and (D) $C_{12}E_4S$.[10]

around 60–70 wt% of surfactant concentration. $C_{12}E_4S$ exhibits an $I_1$ phase and a $V_1$ phase at the adjacent $H_1$ phase, respectively. However, commercial AES does not form a cubic liquid crystal phase due to the EO units' distribution. The phase transition of $C_{12}$Soap and SDS from $H_1$ to Lα means that the CPP increases from 1/3–1/2 to 1/2, as the cross-sectional area per molecule decreases with the increasing surfactant concentration. The appearance of the $I_1$ phase in the $C_{12}E_4S$ system suggests that the CPP is 1/3 or lower, due to the bulky hydrophilic group consisting of the EO units and sulfate group, leading to CPP $\leq$ 1/3. This way, phase behavior is controlled by the CPP based on the molecular structure of the surfactant.

## 24.5.2 Alkyl Chain Length and Melting Temperature

The melting temperature of the hydrated solid phase gradually rises with the increasing surfactant concentration and reaches a constant value above the CMC, corresponding to the Krafft point as mentioned previously. In order to

compare Krafft points among different surfactants, the measurement conditions must be noted, since many Krafft point data may be obtained under convenient conditions that are not sometimes responsible for the definition of the actual Krafft point.

Tables 24.4 and 24.5 show the effect of the alkyl chain length and counterion on the Krafft point of soap and alkyl sulfate (AS), respectively.[11–13] The Krafft point of both soap and AS increases with increasing alkyl chain length. The Krafft points of $C_{12}$AS and $C_{14}$AS are lower than that of soap, whereas they are similar to that of soap for alkyl chain lengths over $C_{16}$. Compared to the sodium salts, the Krafft points of the potassium salts are higher for AS but much lower for soap. This is a result of the contribution from the ion radius and the hydration of the counterion. The larger potassium ion presents a lower hydration degree, as it has a lower charge density on its surface. This leads to the promotion of counterion binding and the stabilization of the solid state. On the other hand, the size of the potassium ion affects the interactions between the carbonyl groups of soap, and therefore disturbs the molecular orientation of the solid. Thus, the type of salt affects the cross-sectional area per molecule and controls the solubility of the surfactants. As a result, it is necessary to consider the effect of calcium salts when using tap water, since calcium salts have generally a high melting temperature, which reduces their solubility.[14]

### 24.5.3 Surfactant Mixtures and Their Melting Temperature

In order to maintain the stability of surfactant solutions at low temperatures, it is necessary to lower their Krafft point by mixing different surfactants. The changes in the Krafft point as a result of surfactant mixing follow three patterns, as shown in Fig. 24.9.[15] The first case is a mixture with a eutectic point, the second one is a solid solution, and the third one represents an intermolecular compound.

In the first case, the melting temperature of the solid decreases with the mixing ratio of surfactants, and reaches a minimum at the eutectic point. The crystals of the pure components are mixed below the eutectic point. Many mixtures of surfactant present this behavior. The melting point can be effectively decreased by mixing surfactants with low Krafft points. On the other hand, the solid solution is a molecular mixture. The melting point changes with the mixing ratio. This type of mixture is very uncommon, except for the example in Fig. 24.9B. Lastly, intermolecular compounds are formed between surfactants that interact with each other, for example, anionic and amphoteric

**TABLE 24.4** Krafft Point Variation With the Alkyl Chain Length of Soap[11] and AS[12]

| | R | Krafft Point (°C) |
|---|---|---|
| Soap | $C_{12}$ | 20 |
| | $C_{14}$ | 34 |
| RCOONa | $C_{16}$ | 45 |
| | $C_{18}$ | 54 |
| AS | $C_{12}$ | 9 |
| $ROSO_3Na$ | $C_{14}$ | 21 |
| | $C_{16}$ | 45[a] |
| | $C_{18}$ | 56[a] |

[a]*Melting temperature of a 1 wt% surfactant solution.*

**TABLE 24.5** Krafft Point Variation With the Counterion for DS[11] and $C_{12}$Soap[12]

| | Counterion | Krafft Point (°C) |
|---|---|---|
| $C_{12}H_{25}OSO_3^-$ | $Na^+$ | 9 |
| | $K^+$ | 34 |
| $C_{11}H_{23}COO^-$ | $Na^+$ | 20 |
| | $K^+$ | <0 |

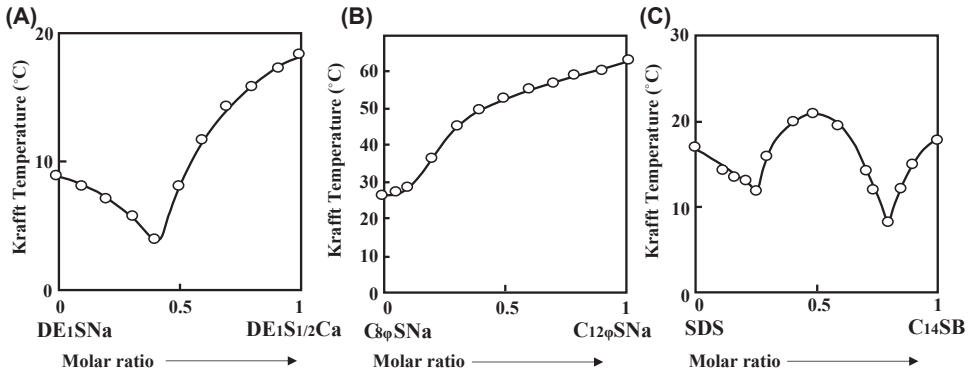



FIGURE 24.9 Change of melting temperature with surfactant mixing. (A) Mixed system of sodium dodecyloxyethlene sulfate ($DE_1S$ Na) and ½ calcium dodecyloxyethlene sulfate ($DE_1S$ 1/2Ca), (B) mixed system of sodium octylbenzene sulfonate ($C_8\phi S$ Na) and sodium dodecylbenzeneslufonate ($C_{12}\phi S$ Na), and (C) mixed system of sodium dodecyl sulfate (SDS) and palmitoylsulfobetaine ($C_{14}SB$).[15]

surfactants. The melting temperature in this case presents a maximum in the solubility–composition curve (Fig. 24.9C). In order to obtain the desired liquid state, it is important to know how the melting point changes with the surfactant composition.

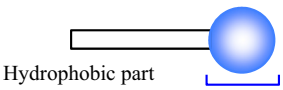
## 24.6 CATIONIC SURFACTANTS

Cationic surfactants are applied for surface modification in softeners or hair conditioners, since most of the targeting product surfaces have anionic charge. Moreover, cationic surfactants can have bactericidal action and are essential in antibacterial and hygiene products. The hydrophilic group of most cationic surfactants is the ammonium cation. Other groups are the pyridinium and guanidinium (derived from the basic amino acid arginine) cations (Table 24.6). Hydrogen bonding related to the nitrogen atom and the number of methyl groups on that nitrogen atom in the hydrophilic head has a great influence in the phase behavior of cationic surfactants.

### 24.6.1 Structure of the Hydrophilic Group and Phase Behavior

Fig. 24.10 shows the phase diagrams of alkyl ammonium cationic surfactants with different number of methyl groups.[16,17] For the widely used dodecyltrimethyl ammonium chloride (DTAC) surfactant, the melting point is

TABLE 24.6 Molecular Structure of Typical Cationic Surfactants




| | | |
|---|---|---|
| Alkyl ammonium salt | $C_{12}N(H)a(Me)bCI$ | |
| a = 3, b = 0 | Dodecyl ammonium chloride | $C_{12}H_{25}NH_3CI$ |
| a = 0, b = 3 | Dodecyltrimethyl ammonium chloride | $C_{12}H_{25}N(CH_3)_3CI$ |
| Dialkyl ammonium salt | $R_2N(Me)_2CI$ | |
| R = l8 | Dioctadecyldimethyl ammonium chloride | $C_{18}H_{37}$ $C_{18}H_{37}$ $N(CH_3)_2$ Cl |
| Alkyl pyridinium salt | $C_{12}NPyCI$ | |
| | Dodecyl pyridinium Chloride | $C_{12}H_{25}N$ ⬡ Cl |
| Alkyl guanidinium salt | $C_{12}AmGCI$ | |
| $m = 0$ | Dodecylguanidinium Chloride | $C_{12}H_{25}NHC(=NH)\,Cl$, $NH_2$ |
| $m = 4$ | Dodecylaminobutyl guanidinium chloride | $C_{11}H_{23}CNH(CH_2)_mNHC(=NH)\,Cl$, O, $NH_2$ |

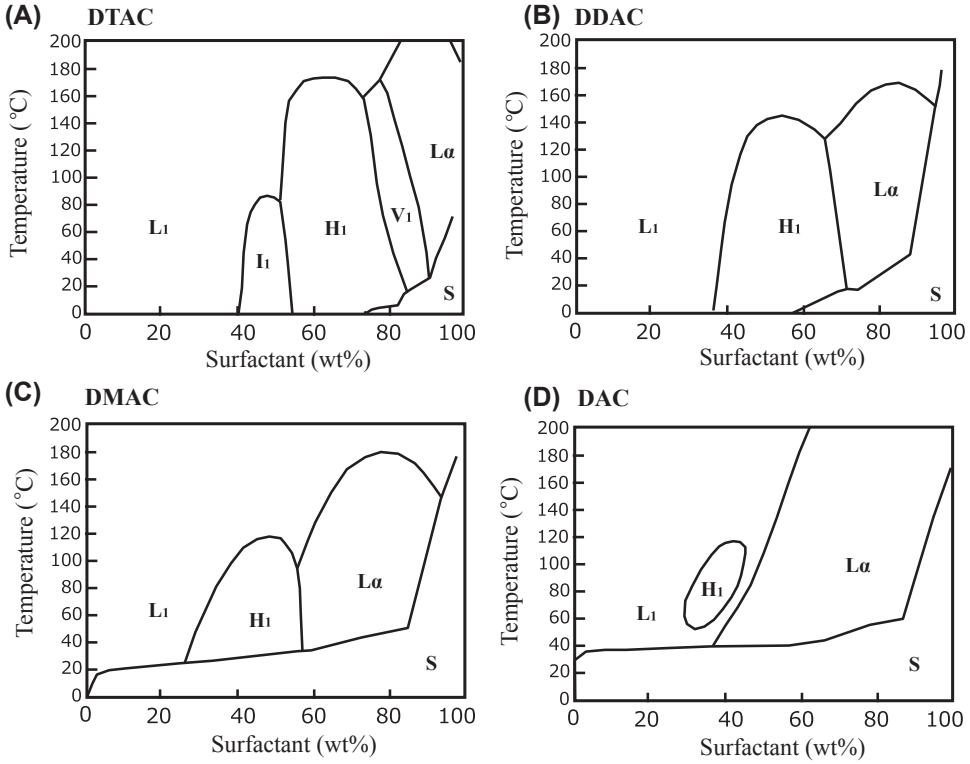



FIGURE 24.10 Phase diagram of alkyl ammonium salts.[16,17] (A) Dodecyltrimethyl ammonium chloride (DTAC), (B) dodecyldimethyl ammonium chloride (DDAC), (C) dodecylmethyl ammonium chloride (DMAC), and (D) dodecyl ammonium chloride (DAC).

below 0°C at low-surfactant concentrations. The liquid crystals of DTAC exhibit, in order, $I_1$, $H_1$, $V_1$, and L$\alpha$ at a higher surfactant concentration than $L_1$. As the three methyl groups of DTAC increase the cross-sectional area per molecule, the molecular orientation relaxes, the melting point decreases, and the appearance of a $I_1$ phase means that the CPP is small. A decrease in the number of methyl groups greatly changes the phase behavior. An $H_1$ phase appears first for dodecyldimethyl ammonium chloride (DDAC), and further decrease in the number of the methyl group bonding to the N atom, namely dodecylmethyl ammonium chloride (DMAC) and dodecyl ammonium chloride (DAC), induces the $H_1$ region to reduce and the L$\alpha$ region to expand. In addition, the decreasing number of methyl groups allows higher molecular orientation of the surfactant and increases the Krafft points of the ammonium salts with small $a_S$ (Table 24.7). Furthermore, for dodecyltributyl ammonium chloride, which has a larger $a_S$ than DTAC, solid and liquid crystal phases do not form as the molecular orientation is disturbed (Fig. 24.11), while the cloud point and phase separation region exist at higher temperatures due to the hydrophobicity of the butyl groups.[18]

On the other hand, guanidine surfactants belong to a novel cationic surfactant family that is highly adsorbed onto hair.[19] Fig. 24.12 shows the phase diagrams of guanidine surfactants. The phase behavior of dodecyl guanidinium chloride ($C_{12}G$) differs greatly from that of DTAC with the same alkyl chain length. The melting point of the solid

TABLE 24.7 Krafft Points of Alkyl Ammonium Salts

| | | Krafft Point (°C) |
|---|---|---|
| DTAC | $C_{12}H_{25}N(CH_3)_3Cl$ | −16 |
| DDAC | $C_{12}H_{25}NH(CH_3)_2$ Cl | −5 |
| DMAC | $C_{12}H_{25}NH_2CH_3Cl$ | 23 |
| DAC | $C_{12}H_{25}NH_3Cl$ | 32.5 |

These are the melting point at a concentration at which the boundary of the solid phase is flat.

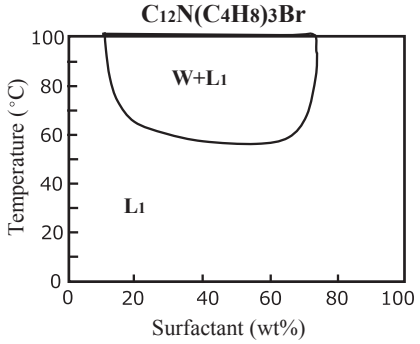



FIGURE 24.11 Phase behavior of dodecyltributyl ammonium bromide.[18]

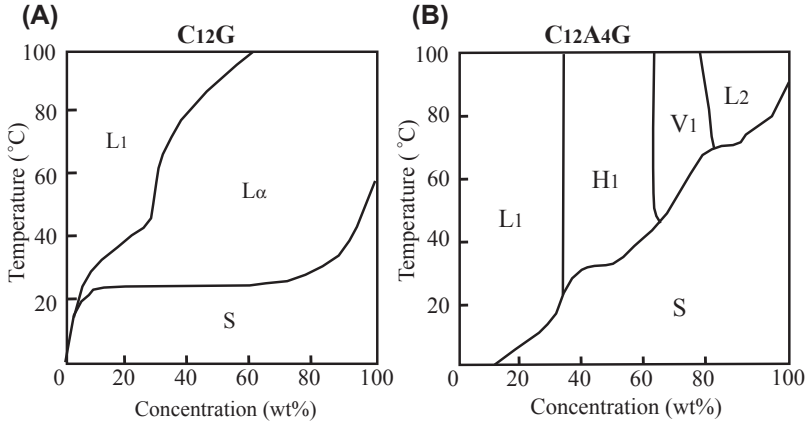



FIGURE 24.12 Phase behavior of guanidine cationic surfactants.[19]

phase is higher, and the Lα phase appears at a lower surfactant concentration.[20] This is due to the presence of hydrogen bonding between the oriented guanidine groups, which results from the flatter and more compact guanidine group as the surfactant head and eventually a CPP value of almost one. For dodecyl amidobutyl guanidinium chloride ($C_{12}A_4G$), with an amidobutyl ($A_4$) spacer between the alkyl chain and the head group, the melting point is low at low surfactant concentrations, where $L_1$ and $H_1$ phases with a positive curvature appear. It is suggested that a spacer group expands the cross-sectional area and leads to a decrease in the CPP. However, the melting point at high concentrations rises abruptly with increasing surfactant concentration, since the spacer group contributes to the molecular orientation in the solid phase. The effect of a spacer group on the Krafft point of guanidine cationic surfactants is shown in Table 24.8.[2] Inserting a short amidoalkyl ($A_m$) spacer group lowers the Krafft point and the melting temperature reaches a minimum, 0°C, for $m = 4$. This lowering effect by the number of carbon atoms is greater with even-numbered $m$ values ($m = 2$ and 4) compared to that with an odd-numbered value ($m = 3$). On the contrary, an increase in $m$ from 2 to 3 raises the Krafft point. The $A_m$ group not only increases $a_S$ but also changes the molecular shape of the guanidine surfactant. An even-numbered $m$ value causes the guanidine group to bend toward the alkyl chain, and the spacer with an odd-numbered $m$ value extends the alkyl chain straight. As a result, the molecular orientation of $C_{12}A_3G$ is promoted compared to that of $C_{12}A_2G$. As the amidoalkyl chain is lengthened up to $m = 6$, the hydrophobicity increases and the Krafft point increases again. A spacer group plays two roles: (1) disturbing the molecular orientation and expanding the cross-sectional area, and (2) enhancing the hydrophobicity of the alkyl chain. Therefore, the $A_m$ group in guanidine surfactants has a great influence in the melting temperature of solid phases.

## 24.6.2 Phase Behavior and Melting Temperature Dependence on the Alkyl Chain

Fig. 24.13 shows the phase diagrams of hexadecyltrimethyl ammonium bromide ($C_{16}$TAB) and hexadecylpyridinium bromide ($C_{16}$PyB).[22] $C_{16}$TAB and $C_{16}$PyB exhibit various liquid crystal phases: $H_1$, $V_1$, and Lα. The larger volume of the hydrophobic group of these two surfactants than DTAC increases the CPP, leading to the absence of an $I_1$

**TABLE 24.8** Krafft Points of Guanidine Type Cationic Surfactants[21]

| Surfactant | Carbon Number *m* of Spacer | Krafft Point (°C) |
|---|---|---|
| $C_{12}$TAC | | <0 |
| $C_{12}$G | 0 | 20 |
| $C_{12}A_2$G | 2 | 4.0 |
| $C_{12}A_3$G | **3** | 9.5 |
| $C_{12}A_4$G | 4 | <0 |
| $C_{12}A_6$G | 6 | 21.6 |

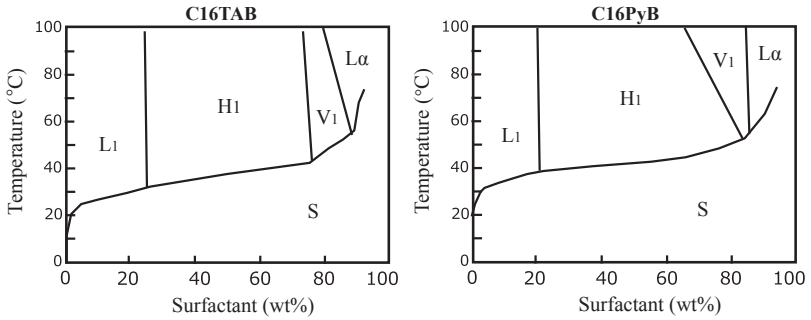



**FIGURE 24.13** Phase behavior of hexadecyltrimethyl ammonium bromide ($C_{16}$TAB) and hexadecylpyridinium bromide ($C_{16}$PyB).[22]

**TABLE 24.9** Krafft Points of Typical Cationic Surfactants[21,23–25]

| Surfactant | Krafft Point (°C) |
|---|---|
| $C_{12}$TAC | <0 |
| $C_{14}$TAC | <0 |
| $C_{16}$TAC | <0 |
| $C_{18}$TAC | 7 |
| $C_{12}$TAB | <0 |
| $C_{14}$TAB | 9.5–10.5 |
| $C_{16}$TAB | 25 |
| $C_{18}$TAB | 35–37 |
| $C_{12}$PyB | <0 |
| $C_{14}$PyB | 14–15 |
| $C_{16}$PyB | 32 |

phase. The relationship between the alkyl chain length and the Krafft point is shown in Table 24.9. The Krafft point rises with increasing alkyl chain length for all cationic surfactants. Among the trimethyl ammonium surfactants with identical alkyl chain lengths, the Krafft points of the bromide species[23] are higher than those of the chloride ones,[21] and the Krafft points of the pyridinium surfactants are a little higher than those of the trimethyl ones.[23–25] This is due to the aromatic ring of the pyridinium group, which favors the relatively higher molecular orientation in the solid phase.

Lastly, the phase diagram of dioctadecyldimethyl ammonium chloride, which is used in softeners and as a surface-modifying agent, is shown in Fig. 24.14.[26] For the double chain surfactant, an Lα phase appears over almost

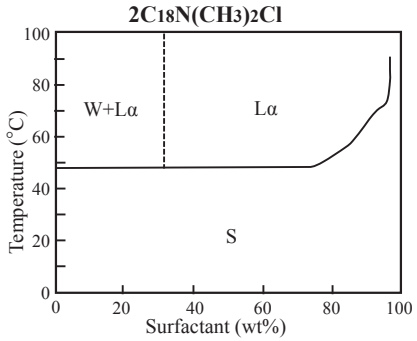



**FIGURE 24.14** Phase behavior of dioctadecyldimethyl ammonium chloride.[26]

the whole concentration range because the CPP is approximately 1. In particular, vesicles consisting of lamellar bilayers are dispersed in the W + Lα phase at low surfactant concentration.

## 24.7 NONIONIC SURFACTANTS

Nonionic surfactants are widely used as detergents, emulsifiers, and dispersants. The hydrophilic part usually consists of noncharged polyethyleneoxide (PEO) or polyglycerin chains (Table 24.10). For alcohol ethoxylate (AE), the size of the hydrophilic head is tunable by the degree of polymerization of the EO unit, and the hydration volume of PEO depends on various conditions such as the concentration and temperature. In other words, the ambient condition controls the hydrophile-lipophile balance (HLB) as well as the CPP. Formulation of real applications essentially requires understanding the relationship between the CPP and the phase behavior. In addition, polyglycerin fatty acid esters, having high hydrophilicity through the hydroxyl group of glycerin, and triblock polymer surfactants (PEO blocks polymerized with polypropylene blocks) are frequently used to control dispersion and thickening properties in the personal care industry.

### 24.7.1 PEO Surfactants

#### *24.7.1.1 Phase Behavior in PEO Surfactant System*

PEO surfactants have been widely used in industry because HLB and CPP can be varied simply by varying the hydrophilic PEO chain length. Fig. 24.15 shows the phase diagrams for pure dodecylalcohol ethoxylates ($C_{12}EO_m$) with a single EO chain.[27] In comparison with anionic surfactants having a solid phase over broad concentration and temperature ranges, the solid phase of nonionic surfactants only appears at high surfactant concentrations, and the

**TABLE 24.10** Molecular Structure of Typical Nonionic Surfactants

| | | Hydrophobic part / Hydrophilic part |
|---|---|---|
| Polyethoxylate type | Polyoxyethylene dodecylether ($C_{12}EOp$) | $C_{12}H_{25}O(CH_2CH_2O)pH$ |
| | Polyoxyethylene Nonylphenylether (NPEOp) | $C_9H_{19}C_6H_4O(CH_2CH_2O)_pH$ |
| | Lauroyl methylester Ethoxylate ($C_{12}MEEp$) | $C_{11}H_{23}CO(CH_2CH_2O)_pMe$ |
| Polyglycerin type | Polyglycerin Laurate | $C_{11}H_{23}CO(CH_2CHCH_2O)_pH$ (OH) |
| Block copolymer type | Diblock AB | PEOa-PPOb |
| | Triblock ABA | PEOa-PPOb-PEOa |

*A*, polyoxyethylene; *B*, polypropylene.

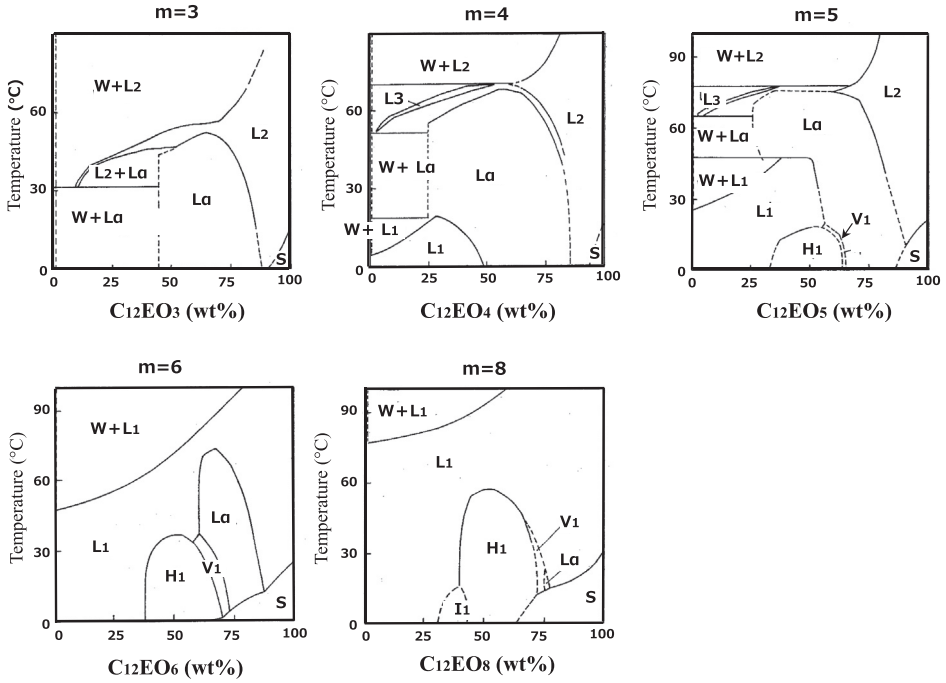



**FIGURE 24.15** Phase diagrams of polyoxyethylene dodecylether ($C_{12}EO_m$)[27]. $m$ is the single molar number of EO.

melting temperature at low surfactant concentrations is low. Looking at the solution state and phase sequence as a function of the surfactant concentration, the L$\alpha$ phase appears at low concentrations for $m = 3$. For $m = 4$, following the $L_1$ phase. For $m = 5$, $H_1$ and L$\alpha$ phases appear after the $L_1$ phase. For $m = 6$ and 8, the $L_1$ and $H_1$ phases are wider, and the L$\alpha$ phase becomes smaller. This phase behavior results from CPP changes with the number of EO units. The CPP at $m = 3$ and 4 is approximately one at low concentrations, and the CPP decreases with the increasing number of EO units.

Phase behavior of nonionic surfactants often shows temperature dependency and typically the PEO type presents a two-phase separation region at high temperatures. The onset temperature for phase separation is called the cloud point or lower critical solution temperature, and the boundary is a mutual solubility curve. Above the cloud point, the monomer dispersed solution (W) and surfactant phase (D) are separated, and the composition and volume fraction of the separated two phases can be followed by the phase rule and the tie-lines (see Section 1.1). For example, as the boundary for $m = 6$ and 8 abuts a thick $L_1$ solution (D phase), the two-phase region becomes a W + $L_1$(D) phase. For $m = 3$, W and $L_2$(D) are separated because the boundary meets an $L_2$ phase at a higher concentration than the L$\alpha$ phase. Even more, the two phase regions for $m = 4$ and 5 are W + $L_1$(D) and W + $L_2$(D) phases at the lower and upper sides of the temperature at which the lamellar phase appears, CPP = 1, respectively. Before the W + L$\alpha$ phase converts into the W + $L_2$(D) phase, an $L_3$ phase appears, which is an isotropic liquid due to torn-off lamellar phases, called sponge phase.

On the other hand, the nonionic surfactants commonly used have a polymerization degree distribution with respect to the EO chain. For example, commercial AE, whose the unit number of the EO chain ($p$) is 7, has EO chains between $m = 0$ and 15, and the actual content of $m = 7$ is about 10%. The HLB number of such a commercial surfactant can be theoretically calculated from the mass fraction of constituent raw materials, but is strongly affected by the EO chain distribution and composition, in particular the presence of unreacted alcohol ($m = 0$). Fig. 24.16 shows the phase diagrams of commercial AEs having a molecular weight distribution of EO chains ($C_{12}EO_p$).[28] In comparison with the phase diagram of $C_{12}EO_m$ having a single EO chain in Fig. 24.15, the $p = 5$ diagram is similar to that of $C_{12}EO_4$, and the $p = 7$ and 10 diagrams are similar to those of $C_{12}EO_6$ and $C_{12}EO_8$. The phase diagram can be a reliable tool for knowing the real cloud point and the region of liquid crystal formation for commercial surfactants, since CPP and HLB cannot be easily determined.

### *24.7.1.2 Effect of Methyl Caps and Ester Groups*

Fatty acid methyl ester ethoxylate (MEE), derived from a plant raw material, has an ester group and a methyl group at the end of the EO chain, and displays a characteristic phase behavior (Fig. 24.17).[29] The cloud point and

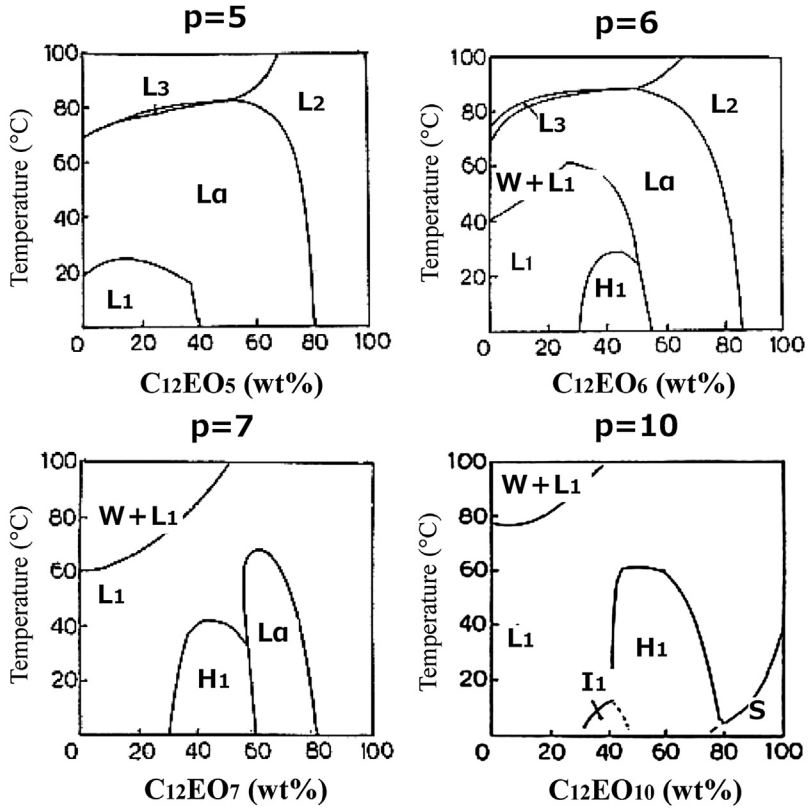



FIGURE 24.16 Phase diagrams of polyoxyethylene dodecylether ($C_{12}EO_p$) in which the EO chain presents a molecular weight distribution.[28] *p* is the averaged addition molar number of EO.

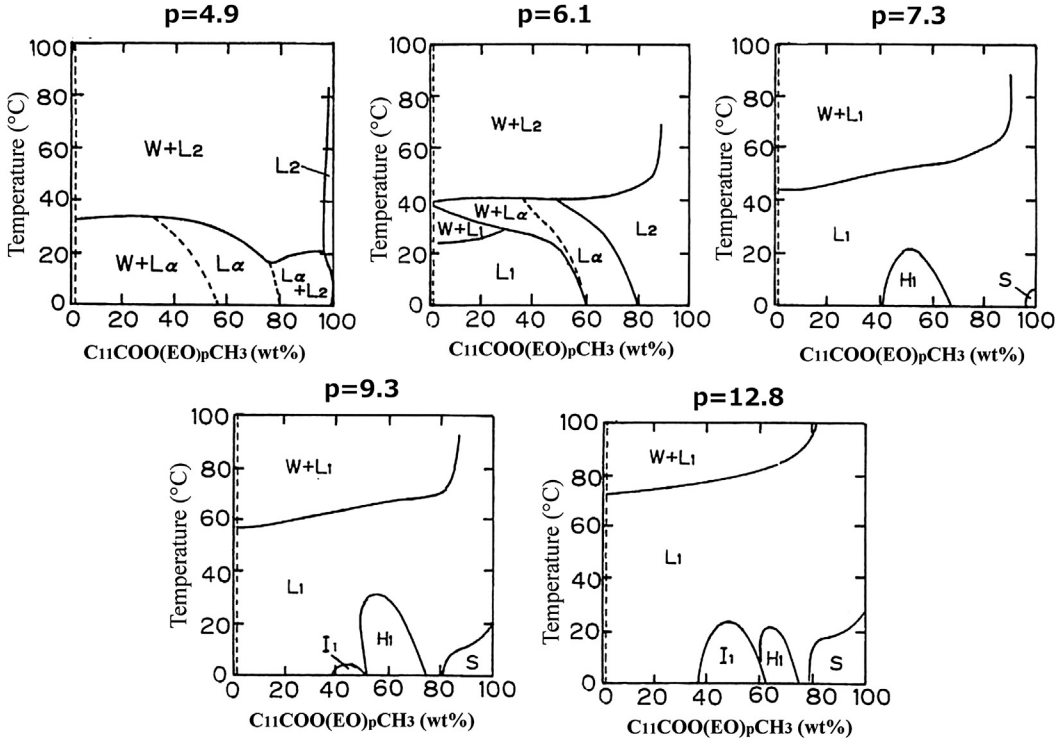



FIGURE 24.17 Phase behavior of lauroyl methylester ethoxylate ($C_{12}MEE_p$).[29] *p* is the averaged addition molar number of EO.

melting point of the liquid crystal phases (upper limit temperature of I1 and $H_1$) are very low. This can be interpreted as follows: the cloud point is low due to the dehydration promoted by the hydrophobicity brought onto the hydrophilic group by the terminal methyl group, and the melting point decreases due to the hindrance of the alkyl chain orientation by the bulky ester group. This is clearly observed when comparing the phase diagrams of $C_{12}MEE_{12.8}$ in Fig. 24.17 and $C_{12}EO_{12.9}$ in Fig. 24.18.[29]

### 24.7.1.3 *Effect of the Alkyl Chain*

An increase in the alkyl chain length expands the temperature and concentration regions of the liquid crystal and solid phases. Fig. 24.19 shows the phase diagrams for $m = 4$ and 8 with alkyl chain lengths of $C_{12}$ and $C_{16}$.[27] Compared to $C_{12}EO_4$, $C_{16}EO_4$ has a wider solid phase. Furthermore, $C_{16}EO_8$ has $V_1$ and L$\alpha$ phases whose CPP is

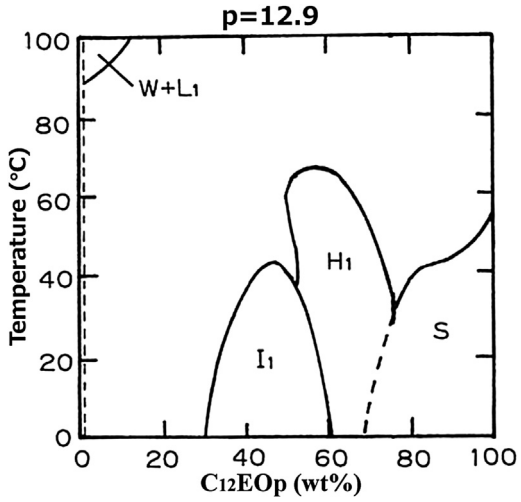



FIGURE 24.18 Phase behavior of $C_{12}EO_{12.9}$ having a sharp EO distribution.[29]

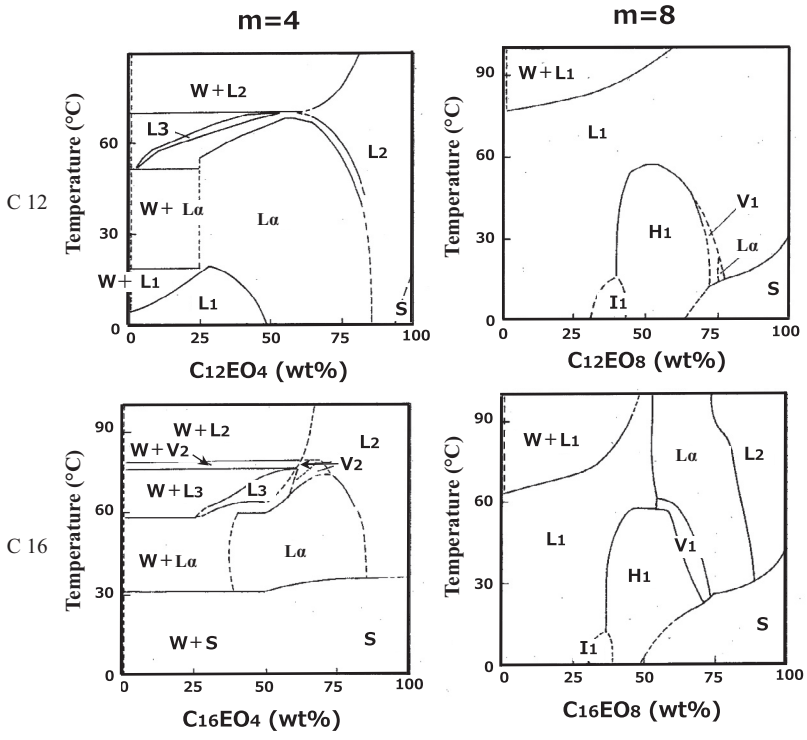



FIGURE 24.19 Phase behavior of PEO dodecyl ether ($C_{12}EO_m$) and PEO hexadecyl ether ($C_{16}EO_m$).[27]

larger than that of the $H_1$ phase at high concentrations. The CPP becomes larger by increasing the volume of the hydrophobic part of the surfactant.

#### 24.7.1.4 EO Chain and Cloud Point

The cloud point of an alcohol ethoxylate is controlled by the HLB related to its molecular structure. The changes in the cloud point by the alkyl and EO chains are summarized in Table 24.11.[30–32] An increase in the alkyl chain length and a decrease in the EO chain length reduce the HLB, therefore, the cloud point is lowered. This means that the cloud point is controlled by the number of EO units and their hydration state.

The cloud point of MEE is considerably lower than that of AE (Table 24.12), as observed in Figs. 24.16 and 24.17. This is an effect of the terminal methyl group of the EO chain and the ester group. The cloud point of $C_{12}EO_6Me$,[33] that is, methyl-capped $C_{12}EO_6$, is 35°C, while that of $C_{12}EO_6$ is 46°C.[34] The terminal methyl group lowers the cloud point by about 10°C. The ester group also has a lowering effect on the cloud point, and the cloud point of $C_{11}COOEO_{6.3}Me$[29] is more than 10°C lower than that of $C_{12}EO_6Me$. It is known that the micelle association number of MEE is smaller than that of AE, as the association is disturbed by the bulky ester groups.[35,36] Nuclear magnetic resonance and small-angle X-ray scattering (SAXS) measurements have demonstrated that the unstable hydration structure in the hydrophilic layer of the MEE micelle can disturb the association of the MEE molecules.[37] It has been suggested that the unstable hydration structure contributes to a lower cloud point, which results from dehydration.

The hydration of the EO chains in nonionic surfactants is influenced by the inorganic salts present. Fig. 24.20 shows the lowering effect of electrolytes on the cloud point of $C_{12}EO_7$.[38] The cloud point decreases in the order of potassium salt anions: $SO_4^- > Cl^- > Br^- > NO_3^-$. This is due to a salting-out effect following the lyotropic series. $SCN^-$ and urea increase the cloud point by breaking the hydration structure of the bulk water. The anions weaken the hydrophobic hydration formed by water surrounding the alkyl chain and promote the hydration of the ether oxygen of the EO chain. On the other hand, the effect of the cations within the chloride family is in the order: $Na^+ > K^+ > Li^+$. The lithium ion does not obey the lyotropic series due to a salting-in effect, by which $Li^+$ forms a complex with the ether oxygen atom weakening the dehydration of the EO chain.

**TABLE 24.11** Effect of Alkyl Chain Length ($n$) and Addition Molar Number of EO ($p$) on the Cloud Point of AE[30–32]

| | $n$ | $p$ | Cloud Point (°C) |
|---|---|---|---|
| $Cn(EO)_8H$ | 10 | 8 | 84.5[28] |
| | 12 | 8 | 77.9[28] |
| | 14 | 8 | 70.5[28] |
| | 16 | 8 | 65.0[29] |
| | 12 | 5 | 28.9[30] |
| $C_{12}(EO)pH$ | 12 | 6 | 51.0[30] |
| | 12 | 7 | 64.7[30] |
| | 12 | 8 | 77.9[30] |

**TABLE 24.12** Effect of the Substituted Group on the Cloud Point of Nonionic Surfactants

| | $p$ | Cloud Point (°C) |
|---|---|---|
| $C_{12}O(EO)_6H$ | 6 | 46[32] |
| $C_{12}O(EO)_6Me$ | 6 | 35[31] |
| $C_{11}COO(EO)pMe$ | 6.3 | 25[26] |

$p$ is the averaged addition molar number of EO.[26,31,32]

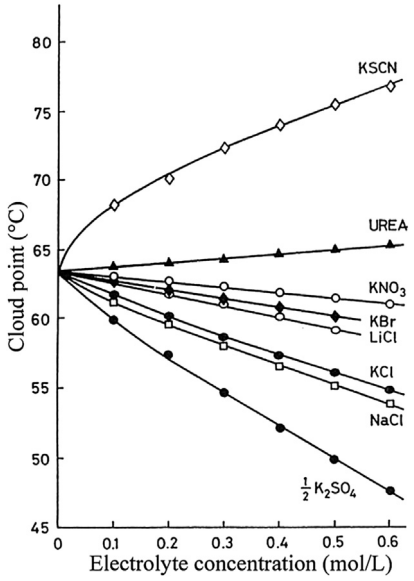



FIGURE 24.20 Effect of electrolytes on the cloud point of C12EO7 (5 mmol/L).[38]

## 24.7.2 Polyglycerin Surfactants

Polyglycerin fatty acid esters or polyglycerin alkyl ethers have a higher hydrophilic fragment than polyethylenoxide. Fig. 24.21 shows the phase diagram of tetraglycerol lauryl ether ($C_{12}Gly_4$)[39] where the wide $L_1$ and $H_1$ phases exist but the L$\alpha$ phase is absent. The phase behavior and sequence in the $G_{12}Gly_4$ system remarkably differs from those in the $C_{12}EO_4$ system having the same polymerization degree of the hydrophilic chain. The biggest difference is that the micellar solution of $C_{12}Gly_4$ has less dependence on temperature and does not have a cloud point. Furthermore, for the $H_1$ phase, the melting point is $\geq$100°C, and the boundary presents little temperature dependence. From SAXS measurements, it was found that the volume fraction of the hydrophilic part of $C_{12}Gly_4$ becomes large with hydration, and that the size of the core–shell structure does not change between 25°C and 85°C. The greater contribution of the Gly unit to hydrophilicity, relative to the EO unit, is clearly demonstrated by the phase diagram[40] and also by the recent chromatography method.[41]

With increasing the Gly chain length, glycerol surfactants have structural diversity because of several possibilities of reactive points in the synthetic process. In addition to polymerization degree distribution of the hydrophilic chain, the Gly chain can be in the linear form or cyclic form, which to some extent can be refined by synthetic methods. Fig. 24.22 shows the phase diagrams of commercial polyglycerin fatty acid esters, pentaglyceryl laurate ($C_{12}Gly_5$),

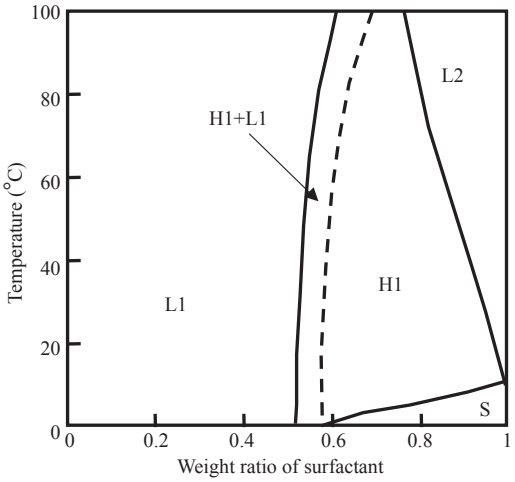



FIGURE 24.21 Phase behavior of the tetraglycerol lauryl ether ($C_{12}Gly_4$)/water system.[39]

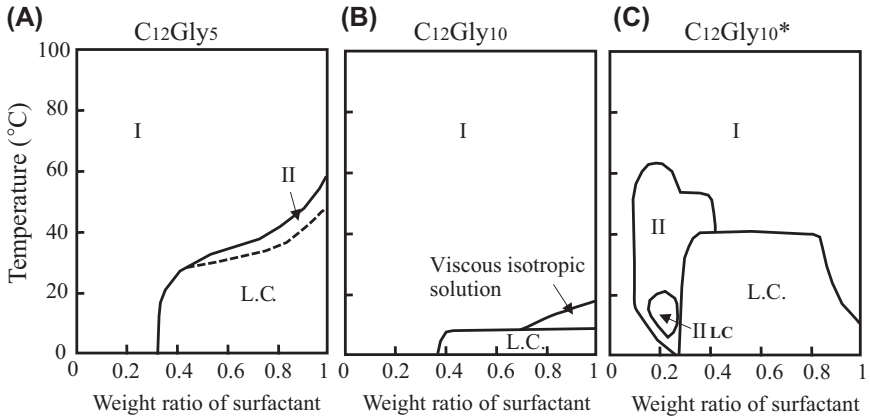



**FIGURE 24.22** Phase behavior of (A) pentaglyceryl laurate ($C_{12}Gly_5$) and (B), (C) decaglyceryl laurate ($C_{12}Gly_{10}$).[42] $C_{12}Gly_{10}$* in (C) contains a large amount of cyclic polyglycerol esters. I is the isotropic solution phase, II is the two phase region, and L.C. is a liquid crystal phase.

and decaglyceryl laurate ($C_{12}Gly_{10}$, $C_{12}Gly_{10}$*).[42] $C_{12}Gly_5$ has less distribution of Gly chain length, but wide distribution for $C_{12}Gly_{10}$ and $C_{12}Gly_{10}$*. The estimated HLB numbers are 17.1 for $C_{12}Gly_{10}$, 15.8 for $C_{12}Gly_5$, and 16.1 for $C_{12}Gly_{10}$*. The difference in the HLB numbers is attributed to not only the polymerization degree but also the content of cyclic form of the Gly chain, for example, $C_{12}Gly_{10}$* contains a large percentage of the cyclic Gly chain, ca. 40%, than $C_{12}Gly_{10}$, resulting in the lower HLB number. Comparing the phase diagrams of $C_{12}Gly_{10}$ and $C_{12}Gly_{10}$* in Fig. 24.22B and C, the former shows lower stability of the liquid crystal phases than the latter. The phase diagram of (c) $C_{12}Gly_{10}$* is substantially similar to that of $C_{12}Gly_5$, compatible with similarity of the HLB numbers. It can be expected from these phase diagrams including Fig. 24.21 that the liquid crystal formation apparently depends on the HLB number. For $C_{12}Gly_{10}$* with more cyclic Gly chain than $C_{12}Gly_5$ and $C_{12}Gly_{10}$, the two-phase separation region appears at a low surfactant concentration. This is due to the increased hydrophobicity by decreasing the number of hydroxyl groups.

In the case of polyglycerin lauric acid diesters, $(C_{11})_2Gly_n$,[43] having double alkyl chains, the solubilized states at 10 wt% are micellar solutions at temperatures above 100°C when $m \geq 8$, and at the phase separation region when $m < 8$ (Fig. 24.23). This phase diagram indicates that the glycerol surfactant with the greater hydrophilic Gly chain shows clouding phenomenon with increasing temperature, whereas the phase behavior is greatly dependent HLB rather than temperature. This is a significant property of the glycerol surfactant.

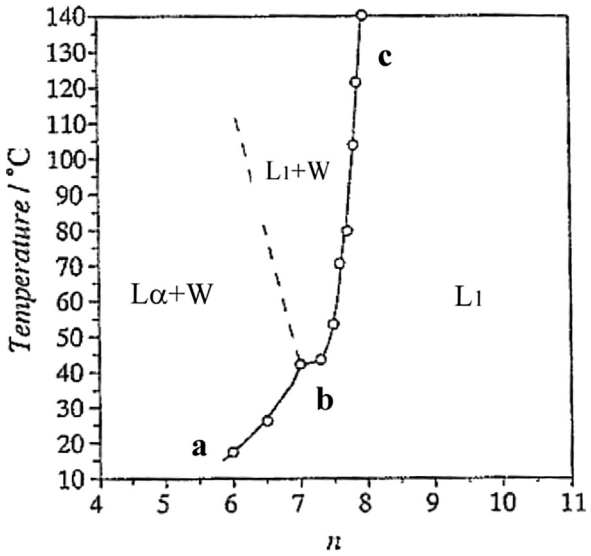



**FIGURE 24.23** Effect of temperature on the phase behavior of $(C_{11})_2Gly_n$ at 10 wt%.[43] The Lα phase separates at low $n$ values in the a-b line, whereas the $L_1 + W$ separation region appears at low $n$ values in the b-c line. The b-c line represents the cloud temperature.

### 24.7.3 Block Polymer Surfactants

As a representative polymeric surfactants, block copolymers consisting of a PEO chain (A) and a polypropylene (PPO) chain (B) have been thoroughly investigated. There exist various combinations of A and B, typically diblock AB and triblock ABA. A range of molecular structures can be tuned by the degree of polymerization of A and B. Hydrophilic ABA-type polymer surfactants are used in commercial products. The monodispersed molecules called monomer micelles, in which a coil of PPO is surrounded by PEO chains, are soluble in water at low concentrations. The dehydration of the PPO chain is sensitive to increasing temperature and concentration, and this leads monomer micelles to aggregate. Thus, ABA-type polymer surfactants have a critical micellar temperature, in addition to a critical micellar concentration. Fig. 24.24 shows the phase behavior of an ABA polymer surfactant, in which $x$ and $y$ are the degree of polymerization for PEO and PPO, respectively.[44] PE6400 ($EO_{13}PO_{30}EO_{13}$; $x = 13$ and $y = 30$) has a wide micellar phase below 60°C and up to 40−60 wt% of surfactant. The micellar phase narrows with the increasing temperature as the dehydration of the PPO chain is promoted, and it is separated above 60°C. The micellar phase converts to $H_1$ and Lα phases at high concentrations. For P65 ($x = 20$ and $y = 30$; $EO_{20}PO_{30}EO_{20}$), the micellar phase is larger than for PE6400. F68 ($x = 80$ and $y = 30$; $EO_{80}PO_{30}EO_{80}$), does not separate at high temperatures, and has a cubic phase. On the other hand, for F127 ($x = 106$ and $y = 70$; $EO_{106}PO_{70}EO_{106}$), the micellar phase becomes narrow due to the hydrophobicity of the large PO chain and changes to a cubic phase at low concentrations. It was confirmed by SAXS measurements that this phase is a micellar cubic phase in which micelles are closely packed.[45] The long PEO chains of the ABA-type polymer surfactants lead to a dissolved state and display a steric hindrance effect. This contributes to prevent the formation of colloid particles from flocculation and coalescence, and to increase viscosity.

## 24.8 SUGAR-BASED SURFACTANTS

Sugar-based surfactants and lipids have gained attention in the fields of cosmetics and pharmaceutics due to their biodegradability, environmental adaptability, biological safety, and their use as naturally derived surfactants. Table 24.13 shows the name and molecular structure of various sugar-based surfactants; the most typical ones are sucrose fatty acid ester and alkyl glycoside. The sugar unit of the hydrophilic part possesses a large number of hydroxyl groups and displays higher hydrophilicity than the PEO chain of nonionic surfactants. The polymerization degree, stereostructure, and shape of the sugar greatly affect their molecular interactions by hydrogen bonding,[46,47] and coniderably change their phase behavior.

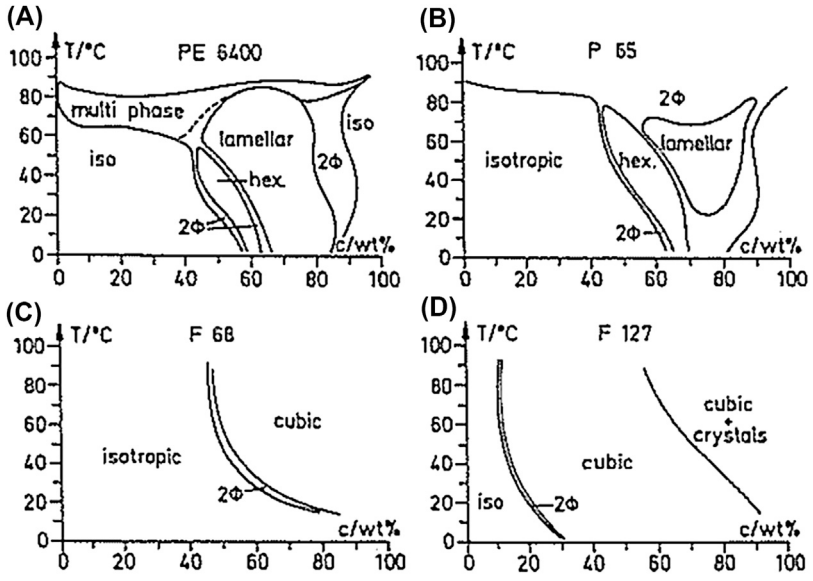



FIGURE 24.24 Phase behavior of triblock polymer surfactants ($EOxPOyEOx$).[44] (A) PE6400: $EO_{13}PO_{30}EO_{13}$, (B) P65: $EO_{20}PO_{30}EO_{20}$, (C) F68: $EO_{80}PO_{30}EO_{80}$, and (D) F127: $EO_{106}PO_{70}EO_{106}$.

**TABLE 24.13** Molecular Structure of Typical Sugar-Based Surfactants

| | |
|---|---|
| Sucrose fatty acid ester (R = H or Alkyl) | Alkyl polyglucoside (R = Alkyl) |
| Methylglucoside Fatty acid ester (R = Alkyl) | Alkyl glucoside (R = Alkyl) |
| Sorbitan Fatty acid ester (R = H or Alkyl) | Acyl sugar alcohol (R = Alkyl) |
| Biosurfactant ($R_1$, $R_2$ = Alkyl) | |
| Mannosylerythritol lipid | Sophorolipid |

## 24.8.1 Effect of Alkyl Chain Length

Alkyl-β-*D*-glycoside ($C_mGlyco_1$) has the simplest molecular structure among cyclic sugar-based surfactants, in which the hydrophobic group binds to the hydroxyl group of $C_1$ in the pyranose ring. Fig. 24.25 shows the phase diagrams of $C_mGlyco_1$ having different alkyl chain lengths. $C_8Glyco_1$ and $C_9Glyco_1$ transition from an $L_1$ to an $H_1$, a $V_1$, and an Lα with the increasing surfactant concentration.[48,49] For $C_{10}Glyco_1$, a two-phase region (W + $L_1$(D)) appears at low surfactant concentrations, and $H_1$ and $V_1$ phases do not form. The two-phase region of alcohol ethoxylate (AE) is determined by the surfactant concentration and temperature, while that of $C_{10}Glyco_1$ only depends on the surfactant concentration. This suggests that the hydration state of the hydroxyl group does not change with the temperature.

Generally, with PEO nonionic surfactants, the effective cross-sectional area per molecule, $a_S$, at the interface between the hydrophilic and hydrophobic groups is influenced by the ratio of water to surfactant, which depends

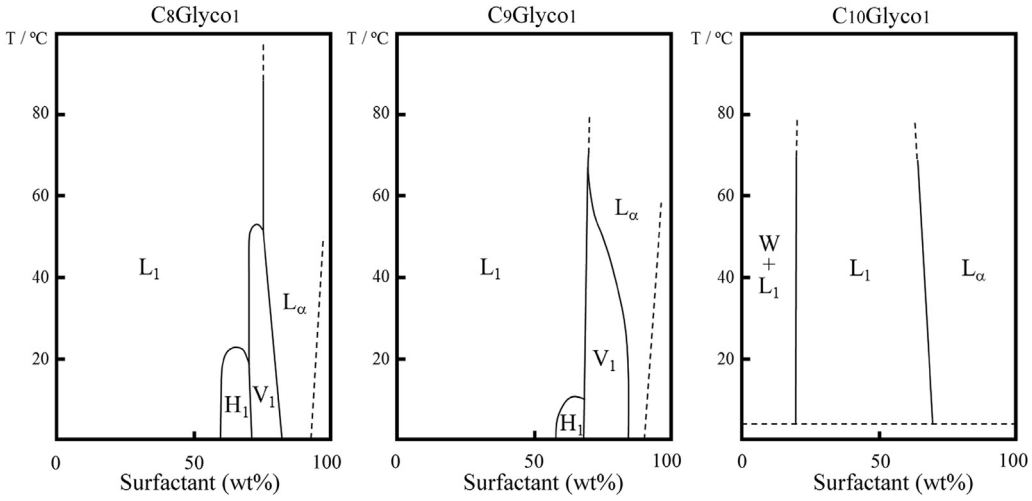



**FIGURE 24.25** Phase behavior of alkyl-β-*D*-glycoside ($C_mGlyco_1$).[48,49]

on the concentration, and then, the CPP value changes.[50] On the contrary, it has been reported that the $a_S$ of the $C_8G_1$/water system is constant regardless of the liquid crystal structure and the surfactant concentration.[48] The $L_1$ phase of $C_{10}Glyco_1$ begins at around 20 wt% and contains enormous micelles connected by wormlike micelles. The giant micelles can easily transform to the Lα phase, because they have an optimal $a_S$ near CPP = 1. Conversely, it is thought that $a_S$ is not able to expand with the increasing water ratio; thus, the micelles are separated from excess water. On the other hand, the addition of 15–20 wt% of $C_9Glyco_1$ to $C_{10}Glyco_1$ changes the two phase to a homogeneous $L_1$ phase at low temperatures.[50] Accordingly, one characteristic of sugar-based surfactants is that a slight difference in the alkyl chain length causes a drastic change in their phase behavior.

## 24.8.2 Effect of the Polymerization Degree of the Sugar

Industrially produced alkyl glycoside presents a glycoside polymerization degree distribution. Fig. 24.26 shows the phase diagrams of dodecyl polyglycoside ($C_{12}Glyco_\alpha$) in relation with the polymerization degree of the glycoside, α.[51] The melting point of the solid phase of $C_{12}Glyco_\alpha$ is 42°C for $\alpha = 1.1$ and 38°C for $\alpha = 1.38$–1.8, which is higher than that of $C_{10}Glyco_1$. The phase behavior is slightly changed by the α value, however, it greatly depends on the alkyl chain length. In the two-phase region, the giant micelle phase, $L_1$, and another micellar phase, L′, formed near the CMC, are separated. This is the case of sugar-based surfactants in which the small micelles formed near the CMC are separated after growing.[49]

For $\alpha \geq 1.6$, the two-phase region ($L' + L_1$) disappears. It is suggested that the micelles change to a structure able to coexist with the surfactant monomer phase (W). Thereby, the $L_1$ phase widens and the lamellar phase expands toward low concentrations.

## 24.8.3 Effect of the Conformation of the Hydrophilic Group

Fig. 24.27 shows the phase diagrams of sugar-based surfactants that have been methyl-etherified in the first carbon and esterified in the sixth carbon through the fatty acid in the pyranose ring.[52] The conformation of the

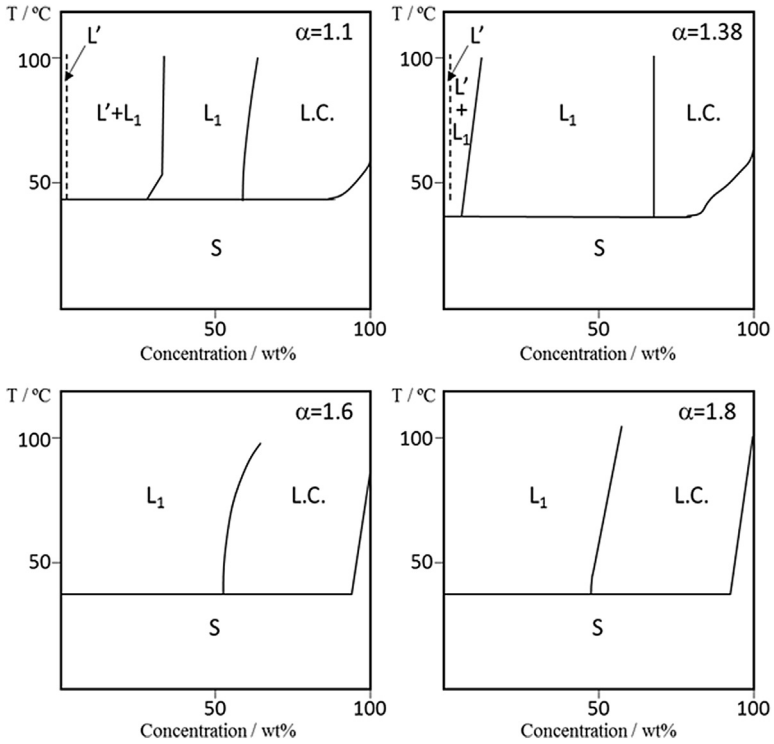



FIGURE 24.26 Effect of the averaged degree of glycoside polymerization (α) on the phase behavior of dodecyl polyglycoside ($C_{12}Glyco_\alpha$).[51] L′ and $L_1$ are the micellar phases, L.C. is the liquid crystal.

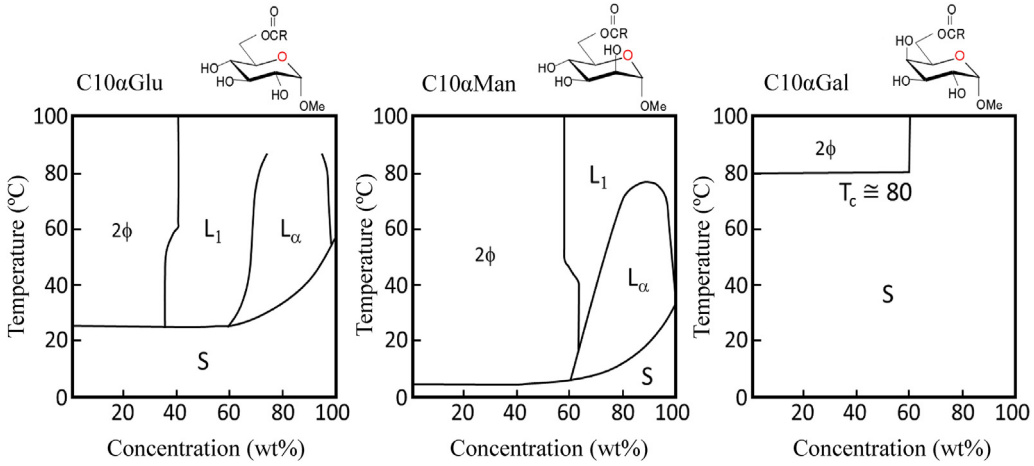



FIGURE 24.27 Phase behavior of α-methylglucoside ester ($C_{10}$αGlu), α-methylmannoide ester ($C_{10}$αMan), and α-methylgalactoside ester ($C_{10}$αGal).[52] 2ϕ denotes the two-phase region.

hydroxyl groups at the second and fourth carbons is different, while the alkyl chain length is the same, $C_{10}$. The phase behavior of the methyl glycoside ester ($C_{10}$αGlu) is relatively similar to that of $C_{10}Glyco_1$. In the case of methyl mannoside ester ($C_{10}$αMan), whose hydroxyl group at the second carbon points upward over the sugar ring, the melting temperature of the solid phase is considerably reduced, although the two-phase region expands at high concentrations of 50 wt% and more. On the other hand, for methyl galactoside ester ($C_{10}$αGal), whose hydroxyl group at the fourth carbon points upward over the sugar ring, the melting temperature is spectacularly increased. From the analysis of their crystal structures, it is found that the conformation of the hydroxyl groups determines the distance of hydrogen bonding and its chain architecture in the solid state, and the $C_{10}$αGal crystal has infinite chain architecture of hydrogen bonding.[53–55] This hydrogen bonding continuity causes an extremely high melting point in the phase diagram (Fig. 24.27). Furthermore, it has been suggested that the melting points of the solid and liquid crystal phases for $C_{10}$αMan are low because mannoside has a conformation that disturbs continuous hydrogen bonding.

There are many reports related to aggregation states and phase behavior that result from the conformation of sugar-based surfactants. Alkyl glucoside, whose etherified alkyl chain at the first carbon is referred to as the α type, has a smaller CMC and a larger association number of micelles than the β type.[56,57]. On the other hand, for dodecyl-*D*-maltoside ($C_{12}$M), the α type forms spherical micelles, and the β type, bigger flat ellipsoidal micelles.[58] The effect of the conformation is different with the number of sugar molecules. The association properties of the α type are superior to those of the β type among monosaccharide surfactants, but the β type is superior to the α type among disaccharide surfactants.

Furthermore, the conformation of the glucoside linkage in the polyglucoside affects the association state. Malto-oligosaccharide lipid ($Mal_N(C_{12})_2$) has β-1,4 bonding, and cello-oligosaccharide ($Cel_N(C_{12})_2$) has α-1,4 bonding. With increasing alkyl chain length, the melting point of $Cel_N(C_{12})_2$ increases, while that of $Mal_N(C_{12})_2$ decreases (Fig. 24.28).[59] These differences are reflected in the CPP values. The $a_S$ value of $Cel_N(C_{12})_2$ does not change with the increasing number of glucoside units ($N$), and the CPP is almost one, whereas $a_S$ of $Mal_N(C_{12})_2$ increases proportionally to $N$, and then CPP decreases.[60]

## 24.8.4 Effect of Shape, Ring or Chain Structure

The phase behavior of a surfactant with a sugar alcohol chain differs from that of one with a sugar ring. The chemical formula of the hydrophilic fragment of *N*-methyldecanoylglucamide ($C_{10}$MEGA) is $C_6O_5H_{13}$, similar to that of $C_{10}Glyco_1$, and their HLB values are equal. However, the phase diagram of $C_{10}$MEGA (Fig. 24.29)[53] differs greatly from that of $C_{10}Glyco_1$ (Fig. 24.25), indicating that the CPP is influenced by the sugar structure. $C_{10}$MEGA forms various liquid crystals phases, $H_1$, $V_1$, and Lα, as the concentration increases. This means that the CPP changes with the concentration. Even more, for sugar-based surfactants having a sugar alcohol chain, the CMC increases with the number of hydroxyl groups, in other words, with the HLB value.[61]

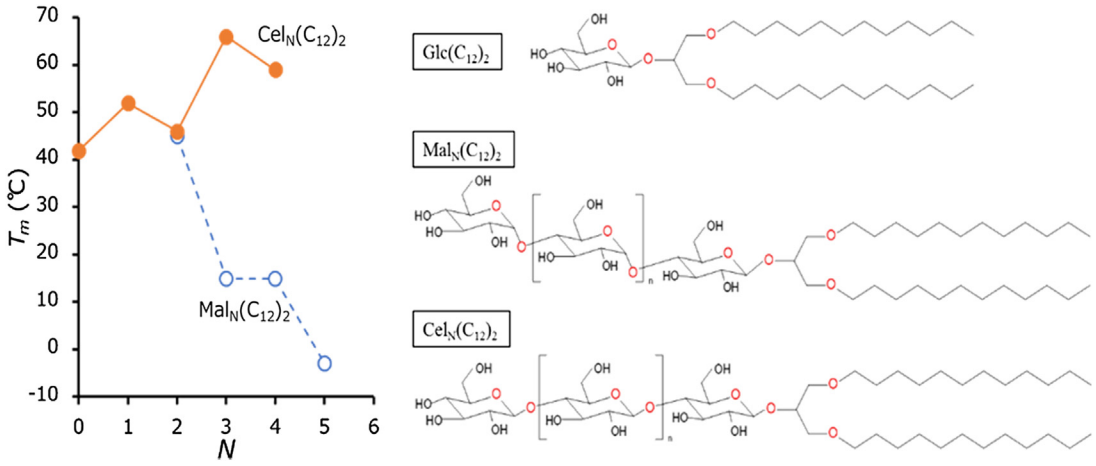



**FIGURE 24.28** Change of melting temperature with the degree of sugar polymerization ($N$) for malto-oligosaccharide ($Mal_N(C_{12})_2$) and cello-oligosaccharide ($Cel_N(C_{12})_2$) lipids.[59]

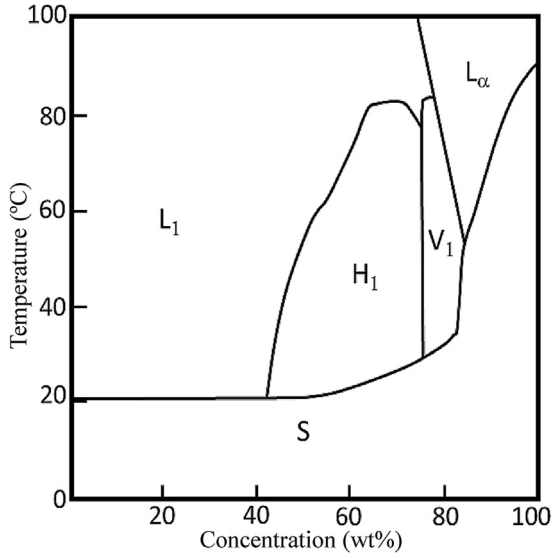



**FIGURE 24.29** Phase behavior of *N*-methyldecanoyl glucamide ($C_{10}$MEGA).[53]

## 24.9 CONCLUSIONS

We have investigated a variety of phase diagrams for different types of surfactants and we substantially feel that surfactant properties cannot be predicted simply by numerical parameters such as the HLB number. On the other hand, phase diagrams provide accurate information on surfactant properties including intermolecular interactions and offer a powerful and reliable tool to understand the real behavior of surfactant molecules in solution, even in the solid state, which significantly relates to industrial applications. In particular, we demonstrated comparison between "pure" and "crude" (commercial grade) surfactants in this chapter, and whoever reads through this chapter will notice the apparent difference, which may possibly be a key clue to troubleshoot cosmetic formulations.

## References

1. Japan Oil Chemists' Society, editor. *Handbook of oil chemistry.* 4th ed. Maruzen; 2002. p. 564.
2. Yamashita Y, Sato T, Nagasawa T, et al. *Chem Lett* 2013;**42**(4):433–5.
3. Aramaki K. In: Japan Oil Chemists' Society, editor. *Interfaces and surfactant*; 2009. p. 101–2.
4. Shinoda K, Arai H. *J Phys Chem* 1964;**68**:3485–90.

5. Shinoda K. In: *Solution and solubility*. 3rd ed. Maruzen; 1991. p. 2.
6. Israelachvili JN, Mitchell DJ, Ninham BW. *J Chem Soc Faraday Trans I* 1976;**72**:1525–68.
7. Small DM. *Handbook of lipid research 4. The physical chemistry of lipids, Chapter 9 Substituted aliphatic hydrocarbons: soap and acid-soaps*. New York: Plenum Press; 1986. p. 325.
8. Kekicheff P, Grabielle-Madelmont C, Ollivon M. *J Colloid Int Sci* 1989;**131**:112–32.
9. Sein A, Engberts JBFN. *Langmuir* 1996;**12**:2913–23.
10. Phase diagram of sodium dodecyl tetraoxyethylene sulfate (C12E4S) is unpublished data offered by the authors.
11. Shinoda K, Minegishi Y, Arai H. *J Phys Chem* 1976;**80**:1987–8.
12. Tsunoda M. *Function and application technology of surfactant*. CMC; 2006. p. 51.
13. Small DM. *Handbook of lipid research 4. The physical chemistry of lipids, Chapter 9 substituted aliphatic hydrocarbons: soap and acid-soaps*. New York: Plenum Press; 1986. p. 329.
14. Japan Oil Chemists' Society. *The handbook of oil chemistry, 4th ed., Lipids and surfactant*. Maruzen; 2001. p. 543.
15. Tsujii K. *J Jpn Oil Chem Soc* 1982;**31**(12):981–7.
16. Broome FK, Hoerr CW, Harwood HJ. *J Am Chem Soc* 1951;**73**:3350–2.
17. Balmbra RR, Clunje JS, Goodman JF. *Nature* 1969;**222**:1159–60.
18. Buckingham SA, Garvey CJ, Warr GG. *J Phys Chem* 1993;**97**:10236–44.
19. Mitamura J, Suzuki N, Ohnuma K, Miyake M, Nakamura T, Kiyomiya A. *J Soc Cosmet Chem Jpn* 1996;**30**(1):84–93.
20. Miyuki M, Yamada K, Oyama N. *Langmuir* 2008;**24**(16):8527–32.
21. Miyake M, Oyama N. *J Colloid Interface Sci* 2009;**330**:180–5.
22. Laughlin RG. In: *Aqueous phase science of cationic surfactant salts, surfactant science series*, vol. 37. Marcel Dekker, Inc; 1991. p. 1–40.
23. Davey TW, Ducker WA, Hayman AR, Simpson J. *Langmuir* 1998;**14**:3210–3.
24. Perche T, Auvray X, Petipas C, Anthore R. *Langmuir* 1996;**12**:863–71.
25. Bakshi MS, Sood R. *Colloids Surf A: Physicochem Eng Aspects* 2004;**237**:125–32.
26. Laughlin RG, Munyon RL. *J Phys Chem* 1990;**94**:2546–52.
27. Mitchell DJ, Tiddy GJT, Waring L, et al. *J Chem Soc Faraday Trans* 1983;**79**:975–1000.
28. Wormuth KR, Geissler PR. *J Colloid Interface Sci* 1991;**146**(2):320–9.
29. Fujiwara M, Miyake M, Hama I. *Colloid Polym Sci* 1994;**272**:797–802.
30. Ueno M, Takasawa Y, Tabata Y, et al. *J Jpn Oil Chem Soc (Yukagaku)* 1981;**30**(7):421–7.
31. Tamura T, Takeuchi Y, Kaneko Y. *J Colloid Interface Sci* 1998;**206**(1):112–21.
32. Deguchi K, Meguro K. *J Colloid Interface Sci* 1972;**38**(3):596–600.
33. Controy JP, Hall C, Leng CA, et al. *Progr Colloid Polym Sci* 1990;**82**:253–62.
34. Nakagawa T, Kuriyama K, Tori K. *Nippon Kagaku Zasshi* 1958;**79**:1194–8.
35. Becher P. *J Phys Chem* 1960;**64**:1221–3.
36. Nakagawa T, Kuriyama K, Tori K. *Nippon Kagaku Zasshi* 1958;**79**:345–8.
37. Miyake M, Kobayashi C, Ogura T, Takeuchi Y, Glatter O. In: *Abstracts in International Association of Colloid and Interface Scientists, Conference in Sendai*; 2012. S1P17–04.
38. Meguro K, Muto K, Ueno M. *Nippon Kagaku Kaishi* 1980;**1980**(3):394–9.
39. Shrestha LK, Strzelczyk KM, Shrestha RG, Ichikawa K, Aramaki K, Hill JP, Ariga K. *Nanotechnology* 2015;**26**:204002. 11 pp.
40. Sagitani H, Hayashi Y, Ochiai M. *JAOCS* 1989;**66**(1):146–52.
41. Yamashita Y, Sakamoto K. *The University Bulletin of Chiba Institute of Sci* 2013;**6**:89–92.
42. *Ingredient catalog for cosmetics*. Taiyou Kagaku Co., Ltd; 2015. p. 8.
43. Kunieda H, Akahane A, Feng J, Ishitobi M. *J. Colloid Interface Sci* 2002;**245**:365–70.
44. Wanka G, Hoffmann H, Ulbricht W. *Macromolecules* 1994;**27**:4145–59.
45. Mortensen K, Batsberg W, Hvidt S. *Macromolecules* 2008;**41**:1720–7.
46. Sculte J, Enders S, Quitzsch K. *Colloid Polym Sci* 1999;**277**:827–36.
47. Matsumura S, Imai K, Yoshikawa S, et al. *J Am Oil Chem Soc* 1990;**67**:996–1001.
48. Nilsson F, Soederman O. *Langmuir* 1996;**12**:902–8.
49. Nilsson F, Soederman O, Reimer J. *Langmuir* 1998;**14**:6396–402.
50. Israelachvili JN. In: *Intermolecular and surface forces with applications to colloidal and biological systems*. 2nd ed. McGraw-Hill Publishing Co; 1993. p. 255–9. 17.
51. Fukuda K, Soederman O, Lindman B, et al. *Langmuir* 1993;**9**:2921–5.
52. Ohbu K, Fujiwara M. *INFORM* 1995;**6**(10):1122–30. Phase diagrams of mannoside ester and galactoside ester are unpublished data.
53. Abe Y, Harata K, Fujiwara M, Ohbu K. *Carbohydr Res* 1995;**269**:43–51.
54. Abe Y, Fujiwara M, Ohbu K. *Carbohydr Res* 1995;**275**:9–16.
55. Abe Y, Harata K, Fujiwara M, Ohbu K. *Langmuir* 1996;**12**:636–40.
56. Fukada K, Kawasaki M, Seimiya T, et al. *Colloid Polym Sci* 2000;**278**:576–80.
57. Focher B, Savelli G, Torri G, et al. *Chem Phys Lett* 1989;**158**(6):491–4.
58. Dupuy C, Auvray X, Petipas C, et al. *Langmuir* 1997;**13**:3965–7.
59. Minamikata H, Hato M. *J Jpn Oil Chem Soc (Yukagaku)* 1996;**45**(10):1001–11.
60. Tamada K, Minamikawa H, Hato M, et al. *Langmuir* 1996;**12**:1666–74.
61. Piao J, Kishi S, Adachi S. *Colloids Surf A: Physicochem Eng Aspects* 2006;**277**:15–9.

CHAPTER

# 25

# Lamellar Gel Network

*T. Iwata*

**Procter & Gamble, Singapore Innovation Center, Singapore, Singapore**

## 25.1 INTRODUCTION

A lamellar gel network is a multiphase colloidal structure that exhibits opaque cream appearance with a highly viscous shear-thinning rheological property. It was already one of the most widely used colloidal systems in such cosmetics as facial creams, hair conditioners and treatments, and pharmaceutical creams long before the scientific understanding of the lamellar gel network had emerged.[1–3] Crude fatty alcohols that have a certain chain-length distribution, mainly C16 and C18, have been widely used to stabilize various oil-in-water emulsions. In most cases, such formulations are lamellar gel networks, although they are still called 'emulsion' orerroneously called 'lamellar liquid crystal.' Various emulsifying waxes are commercially available. These materials work as emulsifiers by themselves or together with a separate emulsifier to stably emulsify the oil in water, and results in a semisolid oil-in-water emulsion cream. Such emulsifying waxes are usually a mixture of cetostearyl alcohol and a surfactant, which by itself can form a lamellar gel network at a certain ratio to water. In such a semisolid gel network, many types of liquid oil can be physically stabilized, thus these ingredients fall under the designation "emulsifying" wax.

The opaque appearance of lamellar gel network is due to the multiphase nature of its colloidal structure. This includes a lamellar gel ($L_\beta$) phase that consists of regularly spaced bilayers of surfactant and fatty alcohols with an interlamellar water layer, an oil phase stabilized by a monolayer of surfactant and fatty alcohols, often with hydrated crystals of fatty alcohols, and a bulk water phase, as described by Junginger[1] (Fig. 25.1).

The highly viscous shear-thinning rheological property is the result of the three-dimensionally interconnected nature of a lamellar gel network, and the rigidity of the bilayers themselves. The bilayer of the $L_\beta$ phase consists of a hexagonally packed crystal (called $\alpha$-gel or $\alpha$-crystal) of surfactants and fatty alcohols having melting points above ambient temperature (Fig. 25.2). The alkyl chains in a hexagonal crystal are all in trans conformation (Fig. 25.3).

The high viscosity at resting condition allows the lamellar gel network to be kinetically stable enough for use in cosmetic products, although it is thermodynamically metastable. However, to develop good formulations with desired texture, performance, and stability, understanding the physical chemistry of the lamellar gel network is crucial. Common challenges with lamellar gel network-based formulations include: obtaining the desired texture and acceptable stability for product shelf life, accommodating large fractions of oil or lipophilic compounds as benefit agents, or ionic compounds such as polymers, acids, or salts, often as benefit agents, and stabilizing separately emulsified benefit agents in the lamellar gel network.

Although the lamellar gel network has been used widely in cosmetics and pharmaceutical industries for many years, not much of the science itself has been published. Rather, the technology has been mostly kept as a trade secret by each manufacturer. This chapter has been put together based on relevant publications to discuss the physicochemical aspect of lamellar gel networks.

## 25.2 UNIQUE ADVANTAGES OF LAMELLAR GEL NETWORKS

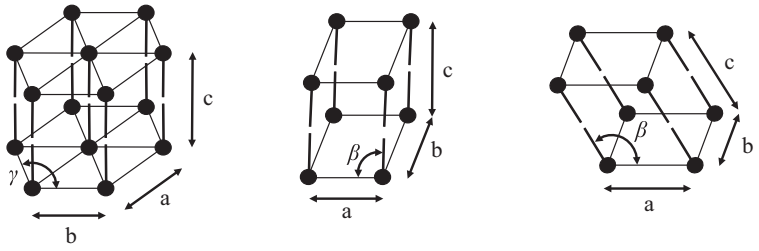
In brief, a lamellar gel network has five major advantages as the base of various cream formulae.

1. *Rich and creamy texture with very low amphiphiles*. Stable creams can be formulated with as low as 5 wt% of amphiphiles (fatty alcohols and surfactants). Because the lamellar phase forms an interconnected network

*Cosmetic Science and Technology: Theoretical Principles and Applications*
http://dx.doi.org/10.1016/B978-0-12-802005-0.00025-2



Copyright © 2017 Elsevier Inc. All rights reserved.




| $\alpha$-form (hexagonal) | $\beta$-form (orthorhombic) | $\gamma$-form (monoclinic) |
|---|---|---|
| $a = b \neq c$ | $a \neq b \neq c$ | $a \neq b \neq c$ |
| $\alpha = \beta = 90°$ | $\alpha = \gamma = 90° \neq \beta$ | $\alpha = \gamma = 90° \neq \beta$ |
| $\gamma = 120°$ | $\beta = 91\sim92°$ | $\beta = 122\sim123°$ |

**FIGURE 25.1** Lamellar gel network structure of water containing hydrophilic ointment. (a) Mixed crystal bilayer of cetostearyl alcohol and surfactant, (b) interlamellar water layer, (a+b) lamellar gel phase, (c) cetostearyl alcohol hydrated crystal, (d) bulk water phase, and (e) dispersed-oil phase.

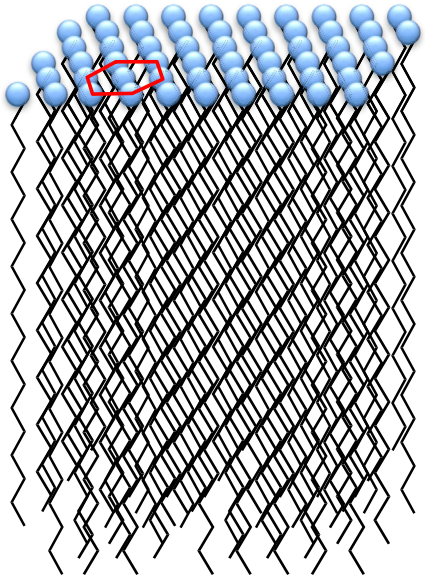


**FIGURE 25.2** Schematic representation of α-gel crystal structure of amphiphile. Blue ball *(light gray in print version)* indicates hydrophilic head group. All alkyl chains are packed in hexagonal lattice as indicated by red hexagon *(gray in print version)*.

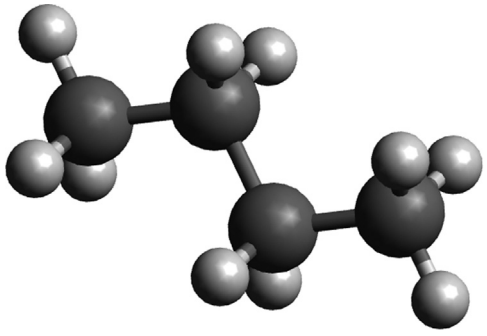


**FIGURE 25.3** Representation of all trans-alkyl chain conformations by *n*-butane.

structure, the lamellar gel network is usually elastic rather than viscous at its resting state, and there is usually a distinctive yield point at which the cream does not flow under the stress below the yield point, but suddenly becomes very flowable above the yield point. Besides this valuable rheological property, the alkyl chains of the amphiphiles that consist of bilayers are in the solid state, which is the same as paraffin wax. When this forms a lamellar structure alternating the "wax" and water, combined with the unique rheological properties, the lamellar gel network is perceived as possessing a rich and creamy texture.

2. *It provides an oily tactile sensation despite the low concentration of oily compounds*. There are two reasons. Even though the amphiphiles are as low as 5 wt% in a lamellar gel network, they are water insoluble, thus much more hydrophobic than typical surfactants used to form oil-in-water emulsions. Those amphiphiles are thus difficult to rinse off. When used as rinse-off cosmetic products, the amphiphiles deposit on the substrate surface to deliver unique tactile feel and cosmetic benefit. In addition, the lamellar phase is a bicontinuous structure, which allows the amphiphiles to contact skin more than typical oil-in-water emulsions.
3. *Its slippery behavior itself is an in-use benefit*. Lamellar gel network is typically very shear thinning as compared to most of the swollen cross-linked ionic polymer gels such as those obtained by thickening with Carbomer. This rheological property itself contributes to slippery behavior, and together with the solid amphiphilic bilayers, which resist more than any swollen polymer gel, the gel network remains slippery even under high pressure, such as is encountered upon scrubbing the face or combing to untangle wet hair.
4. *Relatively low cost* due to the low concentration of oily/solid compounds, cetostearyl alcohol is a commodity that can be derived from many natural resources cost-effectively.
5. *Practically stable and versatile to include water-soluble, oil-soluble, and insoluble materials*. Compared to other colloidal systems such as micelle phase ($L_1$) or emulsions, lamellar gel network is very stable and phase separation over time is usually not at all a concern, because lamellar gel network is an interconnected lamellar phase. Therefore, it is robust when including water-soluble materials in the water phase (either interlamellar water or bulk water phase, or both), oil-soluble materials in bilayers, or kept as a separate phase while surrounded by network and insoluble materials dispersed elsewhere in the lamellar gel network.

All of these advantages come from the fact that the lamellar gel network is mainly an extended, highly interconnected lamellar structure of surfactant bilayers and interlamellar water layers, which is called lamellar gel ($L_\beta$) phase. The bilayer consists of crystalline state of hydrophobic amphiphilic molecules of very low solubility. This typically results high storage modulus, $G'$, low $G''/G'$ ratio which is loss tangent, and high yield point, respectively. An example is shown in Fig. 25.4.

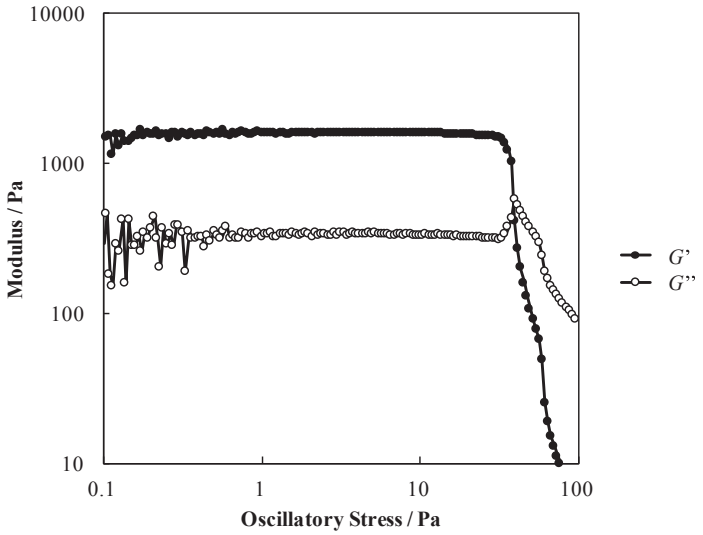



**FIGURE 25.4** Behentrimonium methosulfate (BTAMS) lamellar gel network rheological profile showing high solid-like property. *Redrawn from Iwata T, Aramaki K. Effect of the behenyl trimethyl ammonium counterion on the lamellar gel property.* IFSCC Mag *2013;**16**:249–54.*

## 25.3 α-GEL

α-Gel is a unit structure of the surfactant bilayer in the lamellar gel phase. Understanding the physicochemical aspect of this unit structure is important to understand, make, and work with a lamellar gel network. In α-gel, all alkyl chains are packed hexagonally. Each alkyl chain is solid state in an all-trans configuration. This means these molecules have their melting temperature, or Krafft temperature, higher than ambient temperature or the temperature at which the product is intended to be used. This is almost equivalent to defining that the alkyl chains must be fully saturated linear hydrocarbons with lengths C13 or longer.

The hexagonal crystal is formed mainly by enthalpy, ΔH, as main driving force. The hydrophobic alkyl chain is favorable to aggregate with other alkyl chains, rather than to be surrounded by water. This initially driven by hydrophobic interaction. The head group of the surfactant is favorable in the water phase.

The distance between the alkyl chains (lattice constant) is 0.41−0.42 nm. This distance allows the alkyl chains to freely rotate driven by thermal energy in accordance with the Maxwell−Boltzmann Statistical Distribution Law, whereas Van der Waals and hydrophobic interactions attract those alkyl chains together. This free rotation is thought to prevent further crystallization of the alkyl chains towards even tighter packing such as orthorhombic crystals, in which alkyl chains do not rotate.

Cetostearyl alcohol alone does not form α-gel, but immediately forms orthorhombic or monoclinic crystals. When a surfactant such as polyoxyethylene (15) oleyl ether (Oleth-15),[5] sodium dodecyl sulfate (SDS),[10] cetyltrimonium chloride (CTAC),[53] stearamidopropyl dimethylamine (SAPDMA)-citrate,[52] behentrimonium chloride (BTAC),[19,53] or behentrimonium methosulfate (BTAMS)[19] is mixed with cetostearyl alcohol at a certain ratio, the mixture stays as α-gel. This effect is due to lateral repulsion between the surfactant head groups due to their effective large hydrodynamic radius. This allows the surfactant molecules to freely rotate, which prevents the six cetostearyl alcohol molecules right next to the surfactant from forming a tighter pack, thus kept rotating. The propagation of rotational movement from surfactant to fatty alcohol within the hexagonal lattice may only be to the fatty alcohol directly next to the surfactant, because the surfactant-to-fatty alcohol ratio of 1:6 is a practical low limit. The ratio of 1:2 to 1:6 surfactant/fatty alcohol is shown schematically in Fig. 25.5.

Table 25.1 summarizes the number of surfactant molecules and fatty alcohol molecules that ideally surround each fatty alcohol molecule in the hexagonal lattice. In other word, this table shows the number of surfactant molecules that "drive" fatty alcohol molecule rotation. At a 1:3 ratio, each fatty alcohol is surrounded by two surfactants and four fatty alcohols. The two surfactants are "driving" one fatty alcohol to prevent crystallization. At a 1:6 ratio, this number goes down to 1. This means each fatty alcohol is "driven" by only one surfactant. At a lower ratio, some fatty

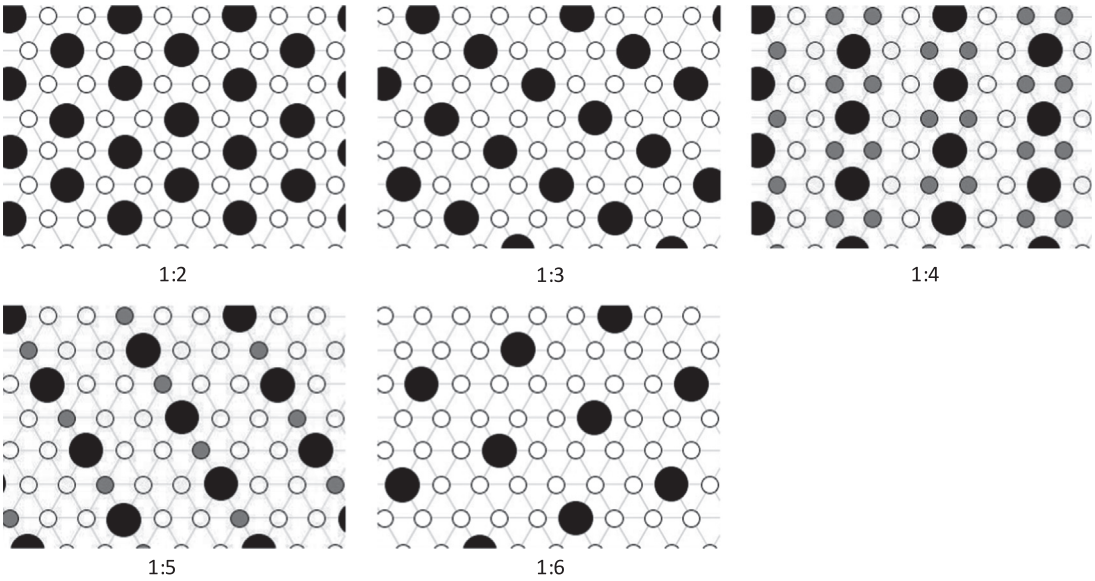



**FIGURE 25.5** Hexagonal packed surfactant (black) and fatty alcohol (white and gray) at molar ratio 1:2 to 1:6. At ratio 1:2, each and every fatty alcohol is surrounded by three surfactants and three fatty alcohols. At 1:3, each and every fatty alcohol is surrounded by two surfactants and four fatty alcohols. At 1:4 to 1:5 ratios, fatty alcohol is either surrounded by one surfactant and five fatty alcohols (white) or two surfactants and four fatty alcohols (gray). At 1:6, each and every fatty alcohol is surrounded by one surfactant and five fatty alcohols.

**TABLE 25.1** Average Number of Surfactants, $n_S$, and Fatty Alcohols, $n_{FA}$, That Surround Each Fatty Alcohol at Surfactant-to-Fatty Alcohol Molar Ratio, S:FA.

| S:FA | $n_S$ | $n_{FA}$ |
|---|---|---|
| 1:2 | 3 | 3 |
| 1:3 | 2 | 4 |
| 1:4 | 1.5 | 4.5 |
| 1:5 | 1.2 | 4.8 |
| 1:6 | 1 | 5 |

alcohol molecules are surrounded by six fatty alcohol molecules. The fatty alcohol at the center of the hexagon of six fatty alcohols is in danger not being "driven" to keep rotating, thus it might crystallize within an orthorhombic or a monoclinic crystal. This is why 1:6 is roughly the practical low limit of surfactant-to-fatty alcohol ratio. This low limit of surfactant-to-fatty alcohol ratio is important in practice to make a stable lamellar gel network regardless of surfactant type, as well as the critical packing parameter of surfactant and fatty alcohols involved (discussed later).

## 25.4 CETOSTEARYL ALCOHOL

Cetostearyl alcohol is a mixture of cetyl alcohol (1-hexadecanol) and stearyl alcohol (1-octadecanol). Depending on the quality, it includes low levels of shorter and longer linear alcohols, unsaturated alcohols, or fatty acids. Usually >99% of the composition is even-number fatty hydrocarbons. This may be related to natural selection of the even-number fatty acid synthesis process. The phase behavior of even-number and odd-number hydrocarbons is known to be different.[11] Most of our understanding of the physicochemical properties of cetostearyl alcohol is important for formulating a good lamellar gel network. Fukushima et al. found that mixtures of cetyl alcohol and stearyl alcohol are required to increase viscosity enough to stabilize the emulsion made with Oleth-15, liquid paraffin, and Vaseline in water, whereas cetyl alcohol or stearyl alcohol alone results in a low-viscosity emulsion and phase separation of the fatty alcohol crystals. The fatty alcohol in such cases separates out as β (orthorhombic) crystal or γ (monoclinic) crystals[6] (Fig. 25.7). Eccleston et al. clearly show microscopic evidence that the cetyl alcohol phase separates into a mixture of monoclinic crystals and water over time, whereas a cetostearyl alcohol system remains as a lamellar gel network (Fig. 25.8).[48] Fukushima et al. presented the phase diagram of the ternary system of Oleth-15, cetostearyl alcohol, and water without internal oil phase (Fig. 25.6), and identified the presence of α-gel.[4,5] Although the authors called the it α-phase and lamellar liquid crystal, it is lamellar gel phase by today's definition.

Furthermore, the hexagonal lattice is a nonspecific chain packing, in which each alkyl chain has freedom to rotate along the alkyl chain axis. The direction of rotation of each alkyl chain like "meshed gears" was proposed by Andrew.[7] In contrast, orthorhombic and monoclinic are specific crystals, in which all alkyl chains (all trans conformation) are tightly packed and no rotation is allowed due their shorter lattice constants (Fig. 25.9). Although the hexagonal lattice constant measured by Small is 4.2 Å, Larsson measured it as 4.15 Å.[8] In the case of surfactant system $L_\beta$ phases, 4.15 to 4.2 Å is generally agreed range.

The phase-transition temperature to β- or γ-form is lower than ambient temperature when the weight fraction of stearyl alcohol in total cetostearyl alcohol is roughly 10−70%. By adding cetostearyl alcohol to emulsion, one can easily thicken and stabilize emulsion, by turning the emulsion into a lamellar gel network. This explains why cetostearyl alcohol became a popular material for cosmetics and pharmaceutical formulations.

The relatively better stability of cetostearyl alcohol than pure cetyl or pure stearyl alcohol is considered due to the chain-length mismatch. The alkyl end of stearyl alcohol has higher degree of freedom due to the chain-length mismatch, and this part has increased gauche conformation.[9] This irregularity compared to all-trans conformation of alkyl chain prevents formation of orthorhombic or monoclinic crystals, thus the hexagonal phase is maintained. Awad et al. show the melting thermodynamics of pure cetyl and stearyl alcohol and the mixture thereof by differential scanning calorimetry (DSC).[10] They suggest that the chain-length mismatching by mixing cetyl alcohol and stearyl alcohol reduces the melting enthalpy more than pure cetyl or pure stearyl alcohol, and the phase shift of cetostearyl alcohol is simply solid to liquid (one step). On the other hand, pure cetyl and pure stearyl shows two-step melting: first is solid to rotator phase (hexagonal or near hexagonal), and second is rotator phase to liquid

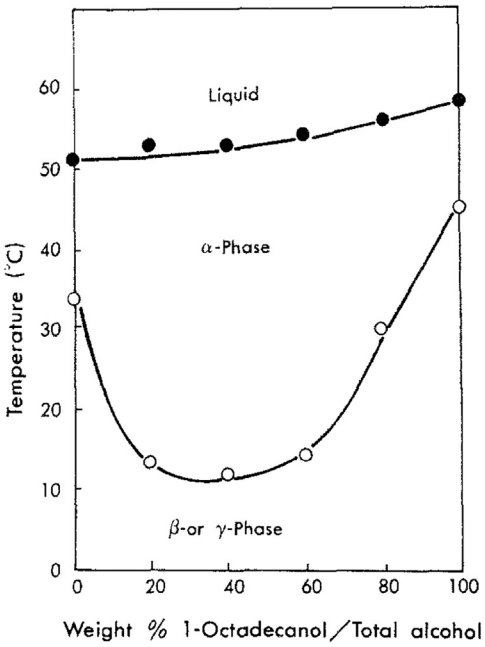
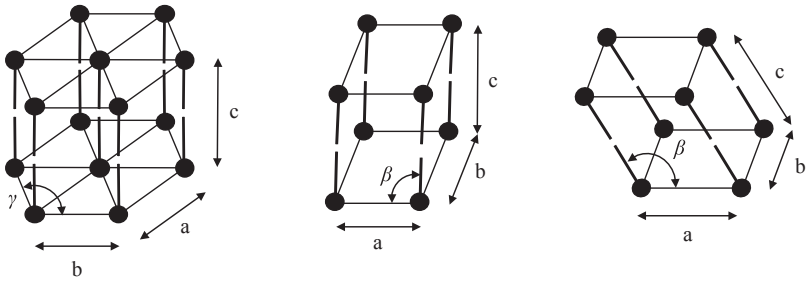



**FIGURE 25.6** Influence of 1-octadecanol (stearyl alcohol) on the melting point and transition point of 1-hexadecanol (cetyl alcohol) in the ternary system with Oleth-15 and water. *Reprinted from Fukushima S, Yamaguchi M, Harusawa F. Effect of cetostearyl alcohol on stabilization of oil-inwater emulsion II. Relation between crystal form of the alcohol and stability of the emulsion.* J Colloid Interface Sci *1977;**59**:159–65 with permission from publisher.*




| α-form (hexagonal) | β-form (orthorhombic) | γ-form (monoclinic) |
|---|---|---|
| a = b ≠ c | a ≠ b ≠ c | a ≠ b ≠ c |
| $\alpha = \beta = 90°$ | $\alpha = \gamma = 90° \neq \beta$ | $\alpha = \gamma = 90° \neq \beta$ |
| $\gamma = 120°$ | $\beta = 91\sim92°$ | $\beta = 122\sim123°$ |

**FIGURE 25.7** Hexagonal, monoclinic, and orthorhombic crystal forms of fatty alcohols. The diffraction peaks by WAXS are $\alpha = 0.42$ nm, $\beta = 0.38$, 0.42 nm, $\gamma = 0.46$ nm. *Based on Fukushima S, Yamaguchi M. The effect of cetostearyl alcohol in cosmetic emulsions.* Cosmet Toilet *1983;**98**:89–102.*

(Fig. 25.10). However, when the chain-length mismatch is six carbons or greater, they tend to segregate into two different crystals.[11]

A similar stability phenomenon has been well known for fatty acid α-crystal. Pure stearic acid or pure palmitic acid soap, regardless of their counterions, are not stable, but an approximately 45% stearic acid and 55% palmitic acid mixture is stable.[2]

## 25.5 SURFACTANTS FOR LAMELLAR GEL NETWORKS

The typical lamellar gel network uses water-soluble surfactants together with cetostearyl alcohol. Pure cetostearyl alcohol would stay as hydrated crystals, and phase-separate immediately upon cooling. The primary role of such

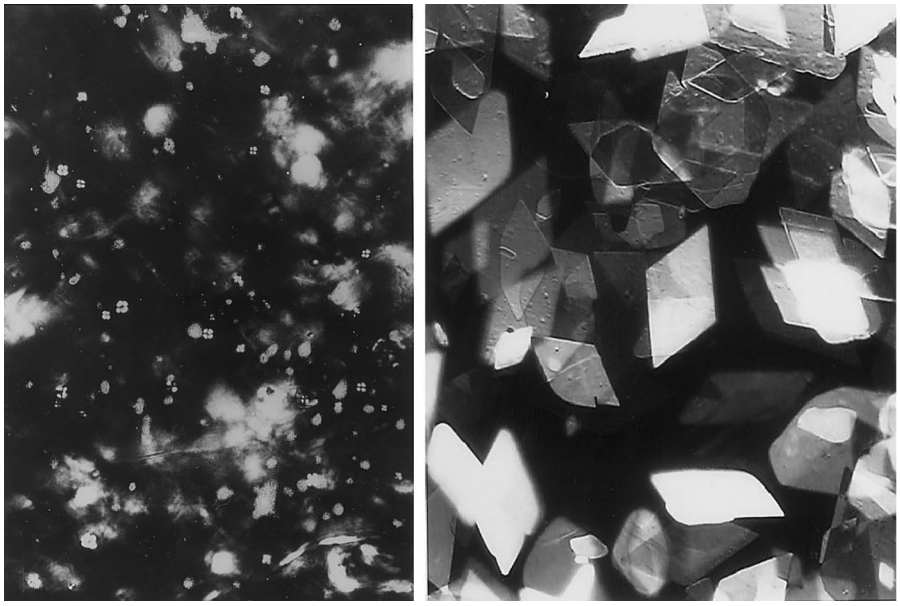


**FIGURE 25.8** Polarized microscopy photographs of cetrimide/cetostearyl alcohol gel network (left), and cetrimide/cetyl alcohol system separated after extended period. *Reprinted from Eccleston GM, Behan-Martin MK, Jones GR, Towns-Andrews E. Synchrotron X-ray investigations into the lamellar gel phase formed in pharmaceutical creams prepared with cetrimide and fatty alcohols.* Int J Pharm *2000;**203**:127–39 with permission from publisher.*

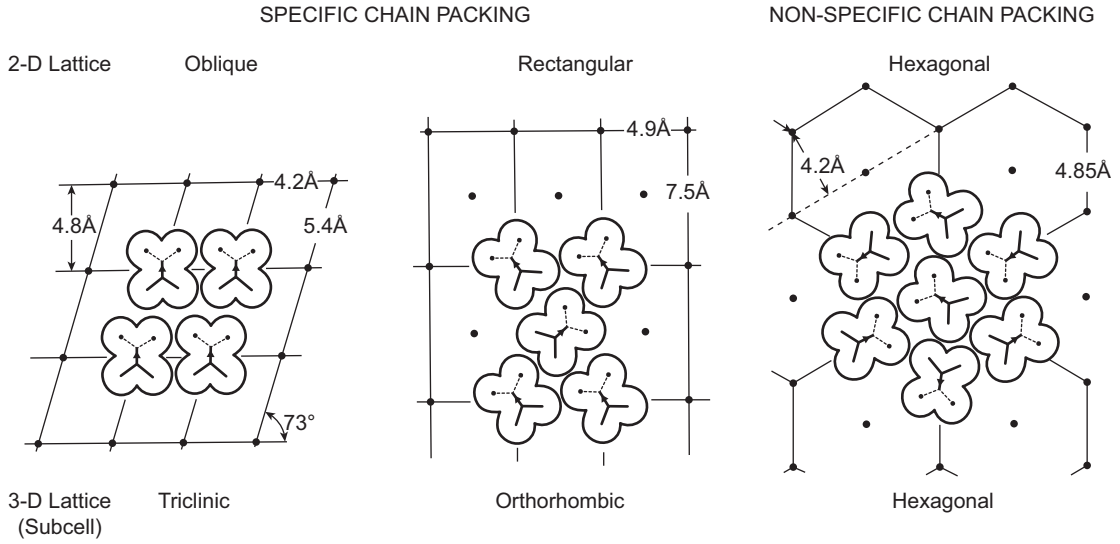



**FIGURE 25.9** Hydrocarbon chain packing viewed from alkyl chain axis (perpendicular to base plane). Area per alkyl chain in triclinic, orthorhombic, and hexagonal is 20.2, 18.4, and 20.4 $Å^2$, respectively. *Based on Small DM. Lateral chain packing in lipids and membranes.* J Lipid Res *1984;**25**:1490–500.*

surfactants is to "emulsify" cetostearyl alcohol at the temperature above chain-melting temperature, and form lamellar gel phase together with fatty alcohol upon cooling. The relatively larger head groups surfactants compared to the OH head group of fatty alcohols occupy a larger hydrodynamic space. This is an important contribution in two ways. One is to keep the neighboring molecule (either fatty alcohol or surfactant) relatively away. The balance between Van der Waals force among alkyl chains and this hydrodynamic force sets the alkyl chain to alkyl chain distance to be 4.15 to 4.2 Å, allowing rotational freedom for each molecule, to form hexagonal $\alpha$-gel. Second contribution arises from the hydrodynamic space in the direction normal to the lamellar plane. This brings more water from outside to hydrate all the head groups of surfactants and fatty alcohols to increase interlamellar distance. As mentioned earlier, a fatty

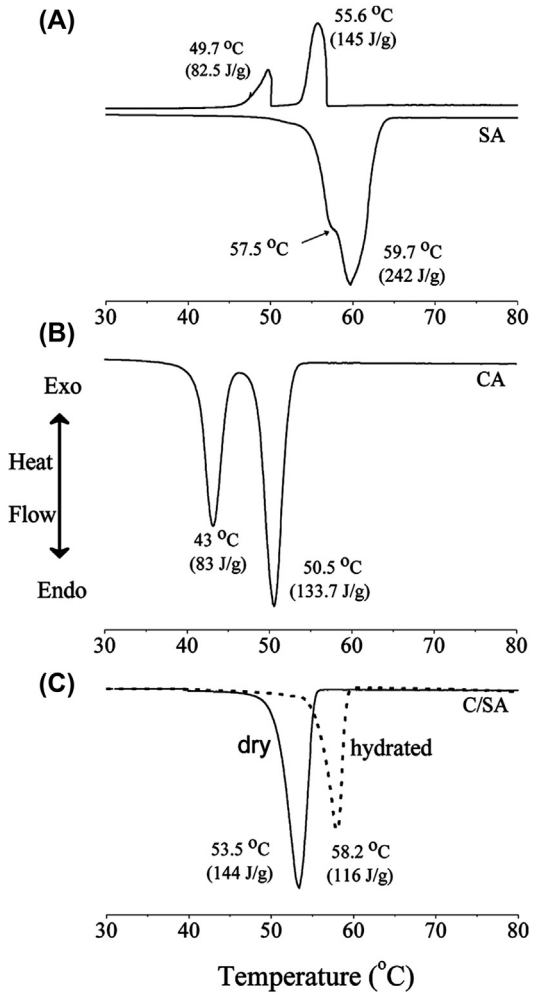



FIGURE 25.10 Differential scanning colorimetry of (A) pure stearyl alcohol, (B) pure cetyl alcohol, and (C) dry (*solid line*) and hydrated (*dotted line*) mixtures of cetostearyl alcohol. *From Awad TS, Johnson ES, Bureiko A, Olsson U. Colloidal structure and physical properties of gel networks containing anionic surfactant and fatty alcohol mixture.* J Dispersion Sci Tech *2011;32:807–15.*

alcohol unit crystal (four molecules) holds one water molecule via hydrogen bonding.[6] However, with surfactant mixed with fatty alcohol, the interlamellar distance can be significantly widen and 40 nm is not unusual.

The water-soluble surfactants include not only the ones that are water soluble at ambient temperature, such as cetrimonium chloride, but also the ones that become water soluble at elevated temperature, such as behentrimonium chloride. The key criterion for the selection is again that the melting temperature of the mixed surfactant system with cetostearyl alcohol should be higher than the temperature at which the product is intended to be stored and used. The melting temperature of a surfactant is largely affected by the chain length, number of alkyl chains, saturation, and branching of the alkyl chain. In general, straight-chain single-tail surfactants are preferred for the formation of lamellar gel phases. Unsaturated or branched surfactants are not used as primary surfactants to form the gel phase, because they result in a lower melting temperature of the mixed system or broadening of the liquid crystal temperature range, which causes product viscosity changes by slight temperature change. Double-tail (saturated) surfactants require special considerations and handling, which is discussed in the following section.

The critical packing parameter (CPP) of a surfactant mixture is a very important parameter for the formation a good gel phase. The CPP of the mixture needs to be as close to 1.0 to form a lamellar gel phase. Usually, this value is achieved by judicious choice of a surfactant having large head group (small CPP) and fatty alcohol having a small head group (large CPP). For instance, the hydrated state of cetyl alcohol (hydrated), monoglyceryl ether of cetyl alcohol, and N-(3-hexadecyloxi-2-hydroxypropyl)-N-2-hydroxyethyl hexadecanamide are 1.07, 0.633, and 1.37, respectively. [12]The CPP can be calculated in several different ways, and the numbers obtained may differ from one other. The CPP has had a hypothetical value for a long time. In practical formulation work, the molar concentration ratio of surfactant to

cetostearyl alcohol 1:3 is a good starting point, and, generally considered, this reaches a CPP of about 1.0. However, most recently, a method based on quantum mechanics is shown to be widely applicable[13]; thus, this is expected to be useful as an empirical calculation to predict mixture ratios without experimentation. In the case of triethanolamine stearate (soap), 35 mol% neutralization of stearic acid by triethanolamine will result in a lamellar phase.[2] This is due to both the creation of electric double layer by deprotonation of the carboxylic group, and adjustment of the packing parameter by bringing in larger triethanolamine as a counterion. Recently, monocetyl phosphate has been reported to form a lamellar gel phase when the monocetyl phosphate is neutralized with arginine, triethanolamine, or amino methyl propanol. This is probably the result of the hydrodynamic radius of its phosphate head group with those specific counterions being just right to form the hexagonal crystal lattice.[14]

### 25.5.1 Alkyl Monoglycerides

Monoglycerides, such as glycerol monostearate (GMS) and glycerol monooleate (GMO), provide good moisturized feel. These monoglycerides are known to form a lamellar gel phase in water in a wide range of surfactant concentrations.[15–17] Understanding their phase behavior without additional surfactant or fatty alcohol is useful for cosmetic formulation.

Cassin et al. showed that mixed C18/16-saturated monoglyceride forms $L_\beta$ phase over a 5–20% range in water and a temperature range of 45–55°C. α-Gel is maintained in this temperature range due to the energy balance between the relatively weak hydrogen bonds among head groups due to their mobility and Van der Waals attraction among alkyl chains.[16] Below 45°C, β-crystal becomes predominant.

Alfutimie et al. summarized the phase diagram of 50/50 (wt/wt) mixture of GMS and GMO, showing there is no lamellar gel network region in the phase diagram, but $L_\beta$ + cubic + water mixed phase is present at surfactant concentrations below 50%.[17] This is highly viscous material. Further opportunity may exist here at higher GMS-to-GMO ratio with various % water, based on the phase diagram of GMS + GMO without water.[18]

### 25.5.2 Quaternary Ammonium Salts

Quaternary ammonium salts, such as cetyl trimethyl ammonium chloride and behenyl trimethyl ammonium chloride, are widely used conditioning actives in various cosmetic formulations because of their unique lubricated and conditioned feel. The trimethylammonium head group, as well as its counterion such as chloride, is considered bulky and "pushes away" the fatty alcohol or surfactant head group next to it. This enables the molecule to have space to rotate that prevents crystallization of all alkyl chains around. This class of materials is widely used in hair conditioners and treatments due to their cationic charge to selectively bind to the negatively charged damaged hair surface. Historically, C16 alkyl chain was mainly used in hair conditioners but C22 has become mainstream in most recent years. This is driven by the trend is to provide a richer, heavier, more conditioned feel. Such feel is a function of hydrophobicity of the bilayer due to longer alkyl chains. More recently, the methosulfate counterion has been used to further increases the hydrophobicity and rigidity of bilayer compared to the chloride counterion.[19]

### 25.5.3 Alkyl Amidoamines

Alkyl amidoamines become ammonium salts when the pH is neutral to acidic. SAPDMA has been widely used as a conditioning agent in various cosmetic formulations, particularly in hair conditioners. Amidoamines are indicated to better reduce static flyaway of hair than monoalkyl quaternary ammonium chlorides.[20] This is likely due to the hydration capability of the amidoamine head group which may hold a few water molecules bound via hydrogen bonding, whereas the trimethyl ammonium head group does not have such hydrogen-bonding sites. Various acids are used, such as lactic acid, citric acid, glutamic acid, and hydrochloric acid to protonate alkylamidoamines. The CPP changed by the choice of counterion, but this area seems to be kept as a trade secret and few publications are found, except in a few cases, SAPDMA with lactic acid phase diagram,[52] which will be discussed later, and the phase behavior of behenyl amidopropyl dimethylamine (BAPDMA).[20] BAPDMA HCl is shown to be very unique in terms of its two-step aggregation behavior. This surfactant is shown to be 10 times or more water soluble than shorter-chain (C18 and C20) analogs having the same head group and counterion, whereas all of these surfactant solutions must be metastable state as the chain-melting temperature is above ambient. The two-step aggregation is suggested to be vesicle-like aggregation above $C_1$, and lamellar-like above $C_2$ (Fig. 25.11). The authors suggest that this surfactant maybe used to for clear hair-care formulations.

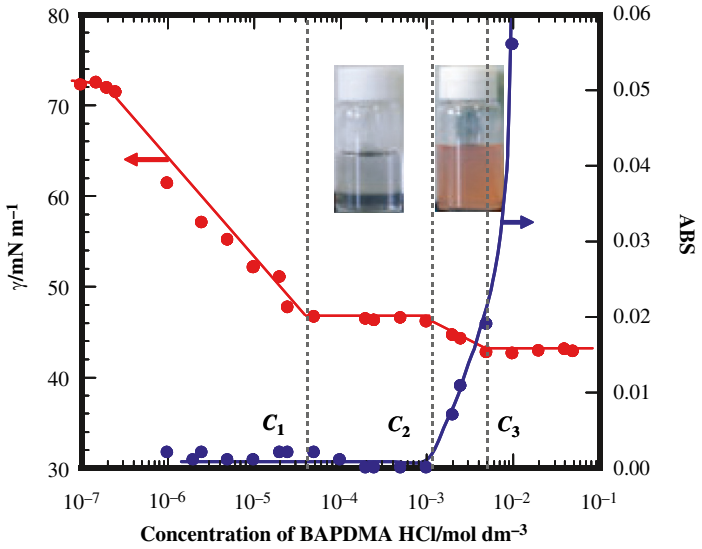



FIGURE 25.11 Surface tension and the solubilization of *o*-toluene-azo-*β*-naphthol by BAPDMA HCl. *From Minguet M, Subirats N, Castán P, Sakai T. Behenamidopropyl dimethylamine: unique behavior in solution and in hair care formulations.* Int J Cosmet Sci *2010;**32**:246–57.*

## 25.5.4 Double-Tail Surfactants

So far, mainly single-tail (monoalkyl) surfactants have been discussed. Double-tail (dialkyl) surfactants, such as distearyldimonium chloride (dioctadecyldimethylammonium chloride, DSDMAC) or di(2-stearoyloxyethyl) dimethylammonium chloride (DEEDMAC), are also widely used as part of lamellar gel networks. Phospholipids and their derivatives such as phosphatidylcholine, phosphatidylglycerol, or phosphatidic acid, are also known to form $L_\beta$ phase and are popularly used in cosmetic products. A special consideration though is justified for the use these double-tail surfactants in $L_\beta$ phase. Most often, these double-tail surfactants cannot be used as emulsifiers to form lamellar phase with fatty alcohol, because the CPP of these double-tail surfactants are about 1.0 by themselves. Primary emulsifiers comprising single tail surfactants with smaller CPP is needed to accommodate double-tail surfactants with fatty alcohols in α-gel. DSDMAC is well known to form hydrated crystals in water at below 40°C.[21] The two C18 alkyl chains crystallize together to form a hydrated crystal. This is because the alkyl chains of double-tail surfactant cannot rotate because they are connected each other via head group. Another possible explanation for this is that the dimethylammonium chloride head group is too small compared to the cross-section of two alkyl chains. The double-tail surfactant as a whole is less likely to rotate neither, because of the geometrical constraints to rotation within the hexagonal packing (Fig. 25.12).

DSDMAC forms as a translucent gel at above 5 wt% in water at room temperature. Laughlin et al. indicated in a phase diagram, however, the equilibrium state is hydrated crystal rather than hexagonal (Fig. 25.13) although it appears to be like a lamellar gel network macroscopically.[22]

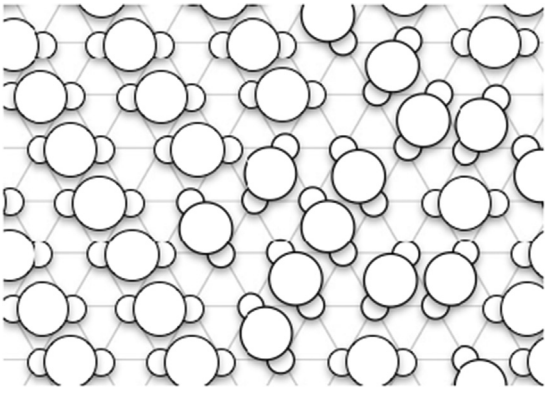


FIGURE 25.12 Geometrical constraints to rotate double-tail surfactant in hexagonal packing. *Small circles* indicate each alkyl chain. *Large circles* are the head group.

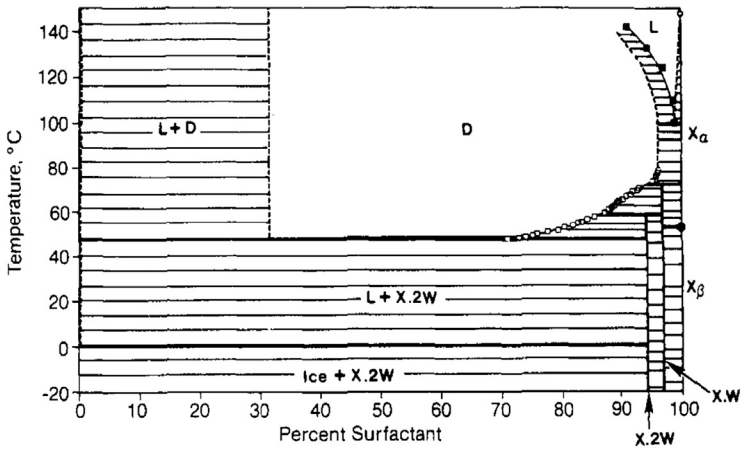



**FIGURE 25.13** Phase diagram of dioctadecyl diammonium chloride (DODAC)/water system; L: liquid; X.2W: equilibrium dehydrate of DODAC; X.W: equilibrium monohydrate of DODAC; and D: lamellar liquid crystal. *Reprinted from Laughlin RG, Munyon RL, Fu YC, Fehl AJ. Physical science of the dioctadecyldimethylammonium chloride − water system. 1. Equilibrium phase behavior.* J Phys Chem *1990;**94**:2546−52 with permission from the publisher.*

## 25.6 MULTIPHASE NETWORK STRUCTURE

Lamellar gel network is a multiphase colloidal system that includes at least lamellar gel ($L_\beta$) phase. However, it is not necessary that lamellar gel phase is present in high concentration. Most often, the majority of remaining fraction is bulk water phase. Many cosmetic products based on lamellar gel network include an oil phase. The oil can be selected from a wide variety of possible candidates, such as ester oil, natural extract, mineral oil, liquid paraffin, perfume accord, silicone oil. Lastly, fatty alcohol semihydrated crystals as coagel ($L_c$) phase are present in many lamellar gel networks. This is the result of an incomplete phase transition from lamellar liquid crystal above Krafft point to $L_\beta$ phase, but rather directly crystallized to coagel. This is considered due to the presence of a fatty alcohol-rich/surfactant-poor portion in emulsion.

The volumetric fraction of $L_\beta$ phase in lamellar gel networks of cosmetic products ranges very widely, i.e., 20−80%. The low end, such as below 30% $L_\beta$ phase, is a dispersed phase and typically requires thickening polymer to be added to confer homogeneity and stability; otherwise, these formulations quickly phase separate. The density of α-gel crystal is 0.846 g/cm$^3$, using C16 alkyl chains (all *trans*) length 2.174 nm and the lattice constant 0.42 nm. The high end, such as above 50% $L_\beta$ phase, forms extended networks of interconnected $L_\beta$ phase, and usually this is mixture of small multilamellar vesicles and largely extended and interconnected domains of lamellar phase. From a mechanical property standpoint, it is made up of a "pillars and beams" structure. Vesicles induce yield stress, whereas lamellar sheet structure prevents gravitational flowability.[37] The rheological character is the result of these mixtures. α-Gel is very stiff material. The Young's moduli of typical gel state bilayers and fluid state bilayers are about 50 and 200 MPa, respectively.[23] Two hundred MPa is about twice as high as typical low-density polyethylene! These structures of $L_\beta$ phase physically trap bulk-water phase to stabilize it from being separated. Hence, lamellar gel network stabilizes against phase separation. A lamellar gel network confers metastable or kinetically stable systems rather than thermodynamically stable compositions.

In a well-formulated lamellar gel network, there are no "free" surfactants that migrate to the air−water or water−oil interfaces. Therefore, the surface tension of lamellar gel networks can be as high as water, and dilution and mixing of lamellar gel network with water does not usually generate foam.

In following sections, each phase that are parts of lamellar gel network are discussed in further details.

## 25.7 LAMELLAR GEL ($L_\beta$) PHASE

$L_\beta$ phase is the major constituent of a lamellar gel network. It consists of regularly spaced bilayers of hexagonally packed solid state surfactants, in which the space in between bilayers is usually filled with aqueous phase. Lamellar gel phase may be spherical multilamellar vesicles, or infinitely bicontinuous lamellar sheets. Unilamellar vesicles or liposomes are not as lamellar gel phase included in this chapter. In this section, unique physicochemical aspects of lamellar gel phase are discussed. These are very important points to understand in order to develop formulations, and to troubleshoot.

### 25.7.1 $L_\beta$ Phase Is Built With Solid Amphiphiles Above the Solubility Limit and Below Krafft Point

In most colloidal phases, the surfactant concentration needs to be below the solubility limit, otherwise surfactants precipitate out of solution. In addition, these colloidal products are stored and used at temperatures well above the Krafft point of surfactants in the system. This allows high concentrations of surfactants in the mixture and still keeps the system intact without phase separation. The condition that the surfactants are above Krafft temperature means that the alkyl chains of the surfactants are in a flexible liquid state. However, $L_\beta$ phase breaks these two conventional rules of thumb of colloidal systems (Fig. 25.14).

In the case of $L_\beta$ phase, the total surfactants (including fatty alcohols) concentration is well above the solubility limit, and the surfactants and fatty alcohols have much higher Krafft temperature than the temperature at which the product is designed to be used. When the micelle solution of high Krafft point surfactant and fatty alcohol mixture is cooled down to cross the solubility limit, the surfactants "freeze", and change their CPP, thus no longer forms stable spherical micelle and converts to various crystals and phase separate from water. When the CPP of surfactant is about 1.0, the surfactant forms a bilayer. When a cetostearyl alcohol dispersion is cooled down, the straight alkyl chain are solidified to form highly packed lamellar structures of fatty alcohol bilayers with very small water layers in between, and this solid phase spontaneously phase separates. This is called coagel ($L_c$) phase, hydrated crystal, or fatty alcohol semihydrate. To form an $L_\beta$ phase instead of coagel phase, a hydrophilic surfactant of high Krafft point needs to be mixed with cetostearyl alcohol. Then the solidified bilayers hold large amounts of water in between bilayers ($L_\beta$ phase) instead becoming an $L_c$ phase. The $L_\beta$ phase with those surfactants, regardless whether they are either ionic or nonionic, most often have large swelling capacity due to the repulsive force between two bilayers. The repulsive forces arise from electrical double layer repulsion in the case of ionic surfactants, and steric repulsion for the case of nonionic surfactants. In the presence of bulk-water phase, there is always a "positive pressure" inside $L_\beta$ phase to swell and mutually push the bilayers apart.

The alkyl chains of the surfactants in $L_\beta$ phase are essentially in the solid state. They are fully extended all *trans* conformation chains in one plane. The alkyl chains are packed in hexagonal arrangement with regular lattice constant (distance between two alkyl chains) of 0.415 nm, which can be measured as a sharp peak by wide-angle X-ray scattering (WAXS). This is the diameter of all-*trans* conformation of alkyl chain.[24] This distance remains constant regardless to the head group of the surfactant or the length of alkyl chain or the temperature. Although the hexagonal packing is a "crystal," the surfactants are freely rotating around the alkyl chain. The difference of $L_\beta$ from $L_\alpha$ (lamellar liquid crystal) phase is the highly regular hexagonal lattice structure in $L_\beta$ whereas the alkyl chain packing in $L_\alpha$ is more disordered and average lattice constant is about 0.44 nm or larger, and shows a broader peak by WAXS. This was clearly displayed by Quinn et al. using dipalmitoylphosphatidylcholine $L_\beta$ to $L_\alpha$ transition using real-time X-ray diffraction (Fig. 25.15).[25]

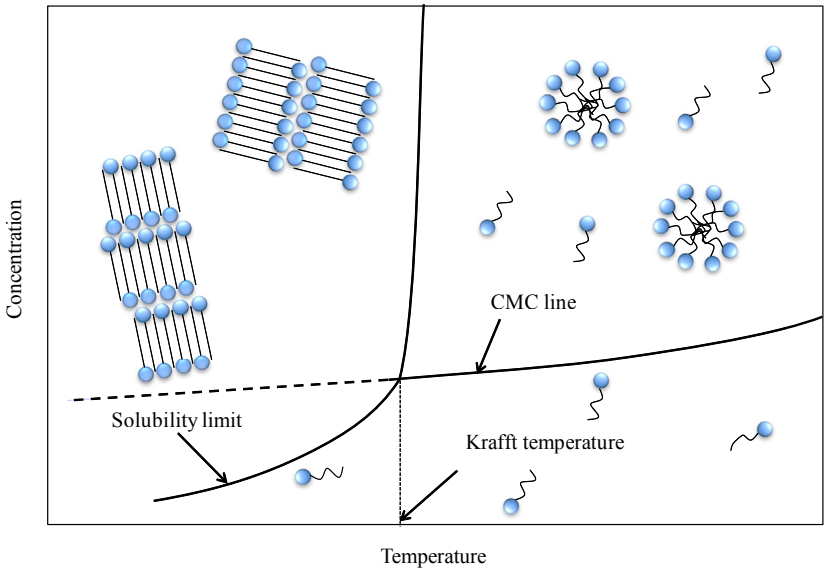



FIGURE 25.14 Schematic phase diagram of surfactant. Usual surfactant solutions are above the critical micelle concentration (CMC) line and above Krafft temperature. However, $L_\beta$ phase is an exception. It is below Krafft temperature and above the hypothetical CMC line (*dotted*).

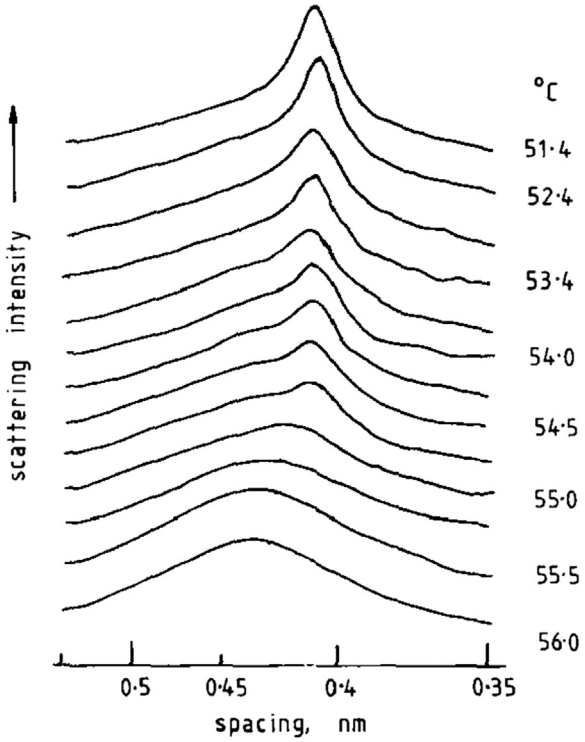



**FIGURE 25.15** X-ray diffraction pattern converted to real scale during dipalmitoyl phosphatidylcholine (DPPC) $L_\beta$ to $L_\alpha$ transition. *Reprint from Quinn PJ, Koynova RD, Lis LJ, Tenchov BG. Lamellar gel − Lamellar liquid crystal phase transition of dipalmitoylphosphatidylcholine multilayers freeze-dried from aqueous trehalose solutions. A real-time X-ray diffraction study.* Biochim Biophys Acta *1988;**942**:315–23 with permission from publisher.*

## 25.7.2 Domain Size and Shape of $L_\beta$ Phase in a Lamellar Gel Network

While one may want to form an extended network of $L_\beta$ phase in product design, another may want to form discrete multilamellar vesicles of $L_\beta$ phase in a product. In this section, several research papers that are relevant to this topic are discussed.

Nagai et al. used a mixed surfactant system of $C_{16}E_6$ and $C_{16}E_7$ at the temperature below the phase transition to $L_\beta$. Increasing the $C_{16}E_7$ fraction leads to a broader WAXS peak at $q = 15\ nm^{-1}$ which means the larger head group leads to more disordered alkyl chain packing, even as the lattice constant remains constant. The domain shape change due to the $C_{16}E_6/C_{16}E_7$ ratio change is clearly shown by optical and confocal microscopy, indicating that a higher fraction of larger head groups ($C_{16}E_7$) leads to a more spherical domain, and a lower fraction of larger head groups leads to a more extended network structure (Figs. 25.16 and 25.17).[47]

Nakagawa et al. used a distearoyl phosphatidylcholine (DSPC), distearoyl phosphatidylglycerol (DSPB), and 1-hexadecanol (HD) mixture to study the mesoscale structure transformation. At 0.66 HD molar fraction with DSPC + DSPG molar fraction of 0.34, all compositions are in $L_\beta$ phases. By varying the DSPC/DSPG molar ratio from 10:0 to 5:5, a drastic mesoscale structural change (Fig. 25.18) and viscosity change are revealed.[27] DSPC/DSPG of molar ratio 10:0 shows lamellar sheets. As phosphatidylcholines are well known to form a tightly packed lamellar phase due to their zwitterionic nature, a DSPC/HD 0.34:0.66 composition should be expected form such a closely stacked lamellar phase (Fig. 25.18A). Increasing the DSPC/DSPG ratio changes two things due to decreasing zwitterionicity and increasing anionicity of the mixture; one is to increase the repulsive force between bilayers, which can cause increased interlamellar *d*-spacing; the second is to decrease the bilayer bending modulus and increase curvature due to the increasing repulsive force between DSPGs in same layer. The mesoscale change from B to F in Fig. 25.18 with ratios between 9:1 and 5:5 suggests this hypothesis. The high viscosity with ratio 9:1 to 7:3 should be due to the balance between space filling by swollen lamellar phase domain and their relative size. In such size, bulk water could be included inside the swollen large vesicles. The low viscosity with ratios of 6:4 to 5:5 should be due to the vesicle becoming too small, leading to low inclusion rate of bulk water inside the vesicle, thus more bulk water is outside vesicles, so the vesicles become dispersed in water.

Lamellar domain shape and size is influenced not only by the chemical composition—the static condition per se, but also dynamic conditions such as shear rate which has a large effect in the case of $L_\alpha$ phase. Kawabata et al.

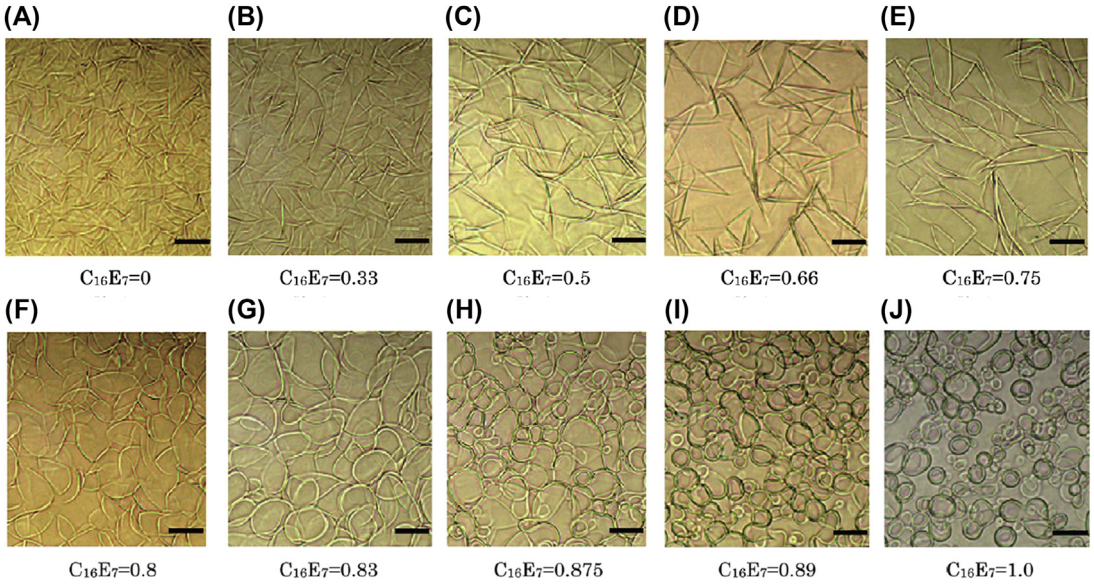



FIGURE 25.16 Optical microscope images of the $C_{16}E_6/C_{16}E_7$/water system. The numbers are mole fraction of $C_{16}E_7$ in total of $C_{16}E_6 + C_{16}E_7$. Scale bar indicates 20 μm. *Reprinted from Nagai Y, Kawabata Y, Kato T. Microscopic investigation on morphologies of bilayer gel structure in the mixed polyoxyethylene-type nonionic surfactant systems.* J Phys Chem B *2012;**116**:12558–66 with permission from publisher.*

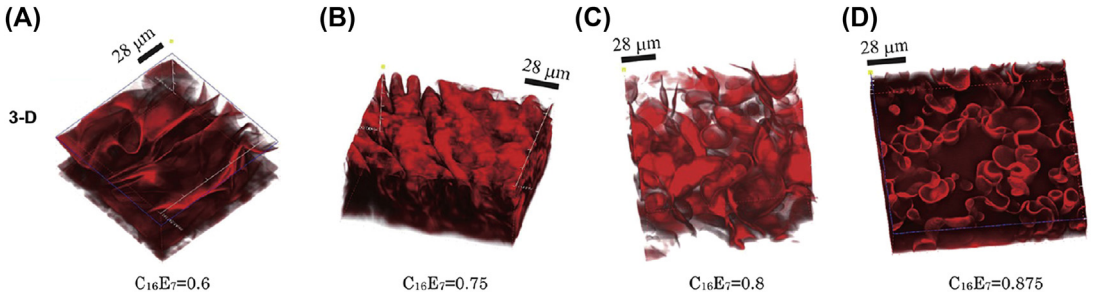



FIGURE 25.17 Three-dimensional synthesis of confocal microscope images of the $C_{16}E_6/C_{16}E_7$/water system. The numbers are mole fraction of $C_{16}E_7$ in total of $C_{16}E_6 + C_{16}E_7$. *Reprinted from Nagai Y, Kawabata Y, Kato T. Microscopic investigation on morphologies of bilayer gel structure in the mixed polyoxyethylene-type nonionic surfactant systems.* J Phys Chem B *2012;**116**:12558–66 with permission from publisher.*

demonstrated this with $C_{16}E_7$ at the temperature range above both its Krafft temperature of 12°C and its melting point (40°C).[716][28] Ito et al. demonstrated that 48% $C_{16}E_7$ in water changes the lamellar phase (sheet dominant) to packed multilamellar vesicle phase (onion), and vice versa by changing temperature or shear rate ([716]Fig. 25.19).[29,30]

Zilman and Granek suggest a coherent buckling mechanism. Their assumption is that neighboring bilayers collide with each other even under zero shear, and built a model of undulation under the influence of shear forces. They point out that when the shear force exceeds the dynamic stability of undulation, the undulating lamellar breaks up and curls further to become multilamellar vesicles having a structure that is reminiscent of the concentric layers of onions.[31] Although much experimental data of $L_\alpha$ systems of nonionic systems support this model, whether charged bilayers and $L_\beta$ behave the same way has not been established and is not well understood.

### 25.7.3 Counterion—Bending of Bilayer

The counterions of a surfactant head groups have strong influence on surfactant packing and thermodynamic behavior, and consequently upon lamellar gel network structure. Different cations cause structural changes due mainly to differences in the binding energy of each particular type of counterion to the respective head group. Just by changing the counterion from $Cl^-$ to $Br^-$, the melting point of dioctadecyl dimethylammonium chloride (DODAC) changes from 49°C to 45°C for dioctadecyl dimethylammonium bromide (DODAB). At 1.0 mM dioctadecyl dimethylammonium ($X = Cl^-$ and $Br^-$) (DODAX) concentration, both DODDAC and DODAB form unilamellar vesicles; the DODAC vesicle is larger than the DODAB vesicles.[32] This suggests that the DODAC bilayer is more densely packed

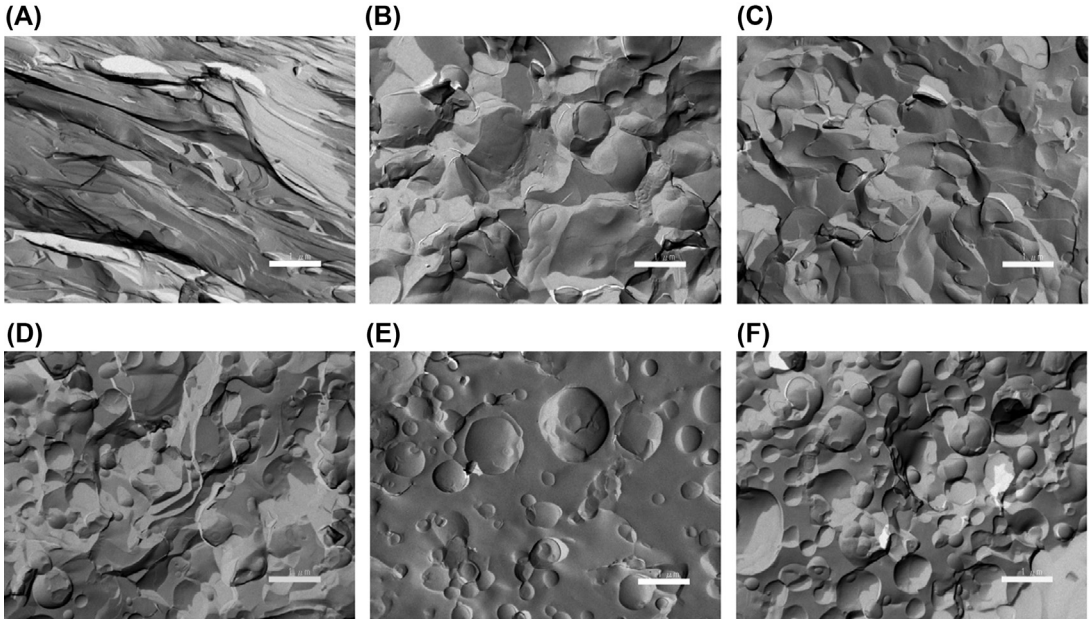



FIGURE 25.18 Cryo-Scanning Electron Microscopy (SEM) picture of DSPC/DSPG/HD gel phase, at HD molar fraction 0.66; A to F represents DSPC/DSPG mole fraction 10:0, 9:1, 8:2, 7:3, 6:4, and 5:5. *Reprinted from Nakagawa Y, Ohta M, Nakazawa H, Kato S. Requirement of charged lipids for the hexadecanol-induced gelation in the phospholipid bilayer system.* Colloids Surf A *2014;**443**:272–79 with permission from publisher.*

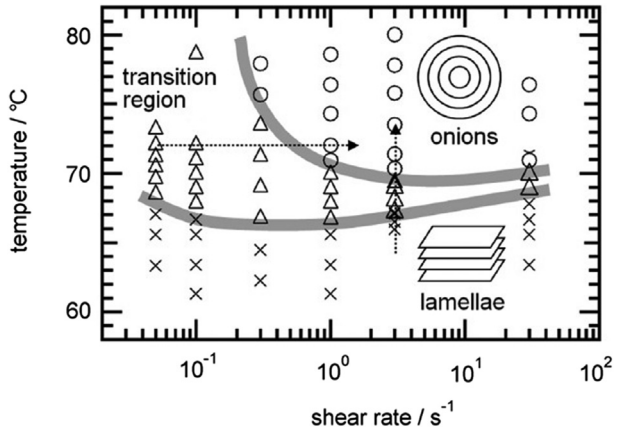



FIGURE 25.19 Temperature–shear-rate phase diagram of 48% $C_{16}E_7$ in deuterium oxide ($D_2O$) showing lamellar to multilamellar packed vesicle ('onion') transition. Cross, triangle, and circle indicate lamellar, transition zone, and onion, respectively. *Reprinted from Ito M, Kosaka Y, Kawabata Y, Kato T. Transition processes from the lamellar to the onion state with increasing temperature under shear flow in a nonionic surfactant/water system studied by Rheo-SAXS.* Langmuir *2011;**27**:7400–9 with permission from publisher.*

than the DODAB bilayer. The reason could be that $Cl^-$ is smaller than $Br^-$ and/or $Cl^-$ is more dissociated (further away from head group) than $Br^-$. Berr et al. found that the aggregation number of alkyl trimethylammonium surfactant micelles increases in the order of $NO_3 > Br > CH_3SO_4 > Cl >> OH$ using C16, C14, and C12 quaternary ammoniums.[33] Iwata et al. compared the two widely used counterions of alkyltrimethylammonium in cosmetic formulations for their influence on the structure of lamellar gel network and cosmetic sensorial aspects. $L_\beta$ phase of BTAC and fatty alcohol swells more than BTAMS when additional water is available. The bilayer of BTAC with fatty alcohol is suggested to be more flexible than BTAMS due to stronger repulsive force among neighboring BTAC head groups (Fig. 25.20).[19]

## 25.7.4 Swelling, Hydration, and Interbilayer Forces

Lamellar gel phase swells by the osmotic pressure of counterion in the case of ionic surfactants. This can be described by DLVO theory. In the case of nonionic surfactant systems, the hydrodynamic space occupied by the hydrophilic head group provides a force affecting swelling. However, a complex situation in lamellar gel network,

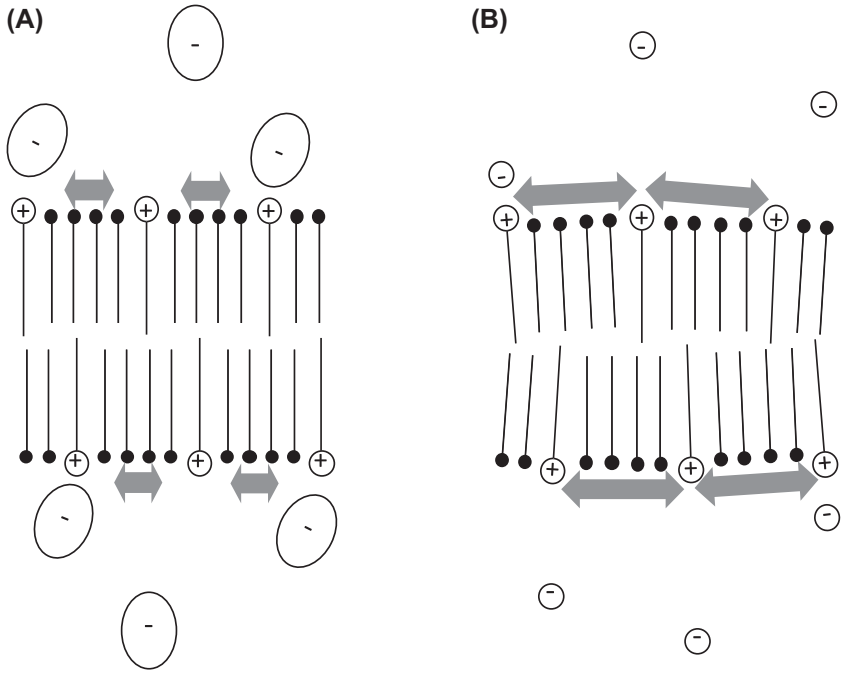



FIGURE 25.20 (A) Behentrimonium methosulfate (BTAMS) surfactants are more neutralized due to closer bound counterions. Thus the repulsive force between neighboring surfactants are weaker. (B) Behentrimonium chloride (BTAC) surfactants are less neutralized. Thus, the repulsive force is stronger, and the bilayer more flexible. *From Iwata T, Aramaki K. Effect of the behenyl trimethyl ammonium counterion on the lamellar gel property.* IFSCC Mag *2013;**16**:249–54.*

unlike simple micelle phase, is that the network structure by itself prevents swelling. Thus it is not easy to quantitatively predict swelling by DLVO theory alone.

Eccleston et al. showed changes in interlamellar *d*-spacing as a function of percent water with the lamellar gel network of CTAC + cetyl alcohol, and cetrimide (mainly C14 alkyl trimethyl ammonium bromide) + cetostearyl alcohol (Fig. 25.21).[48] The cetrimide + cetostearyl alcohol gel network was swollen to its theoretical maximum *d*-spacing, $d_{max}$ but the swelling of the CTAC + cetyl alcohol system could not be calculated due to its unknown commercial composition.

Iwata et al., compared various compositions of lamellar gel network made with either BTAC or BTAMS and fatty alcohol. Based on the changes in interlamellar *d*-spacing and viscoelasticity as a function of concentration of amphiphiles, the $L_\beta$ phase of BTAC system swells more with addition of water, whereas the additional water mainly goes to bulk water phase in the BTAMS system (Table 25.2). As the result, BTAC gel network does not change in viscoelasticity by changing the concentration of amphiphiles, whereas BTAMS gel network decreases both storage modulus and loss modulus as amphiphile concentration decreases (Fig. 25.22).[19] This difference is due to the difference in binding the counterion to its ammonium head group. Methyl sulfate is more bound to a head group than is chloride. Therefore, a BTAMS gel network is less repulsive between opposing bilayers, which reduces swelling when water is added.

The nature of high swelling in cetrimide + fatty alcohol system by Eccleston et al.[48] compared to BTAC or BTAMS systems by Iwata et al.[19] may be due to the relative flexibility of the bilayer due to the presence of shorter chain length. The cetrimide composition is 20% C12, 68% C14%, and 10% C16.

Inclusion of salt such as NaCl has significant effect by shielding electrostatic repulsion between opposing bilayers made of ionic surfactants and fatty alcohols. Eccleston et al. showed the impact of NaCl up to 2% in cetrimide/cetostearyl alcohol lamellar gel network.[48] NaCl directly impacts the interlamellar *d*-spacing reduction (Fig. 25.23). In general 0.1 M salt concentration is enough to shield electrostatic repulsion sufficiently to cause immediate phase separation in the case of micelle phase. Similarily, the interlamellar spacing of lamellar gel phase is also significantly reduced at around 1 M already.

Fairhurstet al. demonstrated that lamellar gel networks made of BTAC and fatty alcohols swell or shrink, when they contact polymer solution. The process is driven by osmotic pressure, and the rate of swelling or shrinking is a function of polymer concentration. With a lamellar gel network of 6 wt% total amphiphile concentration with 1:3 BTAC/stearyl alcohol molar ratio, and polyethylene glycol (PEG)-10,000 polymer solution, polymer concentrations up to 7.6% (wt/wt) show swelling of the lamellar gel network, while 10.0% and above cause shrinkage. The authors assumed this

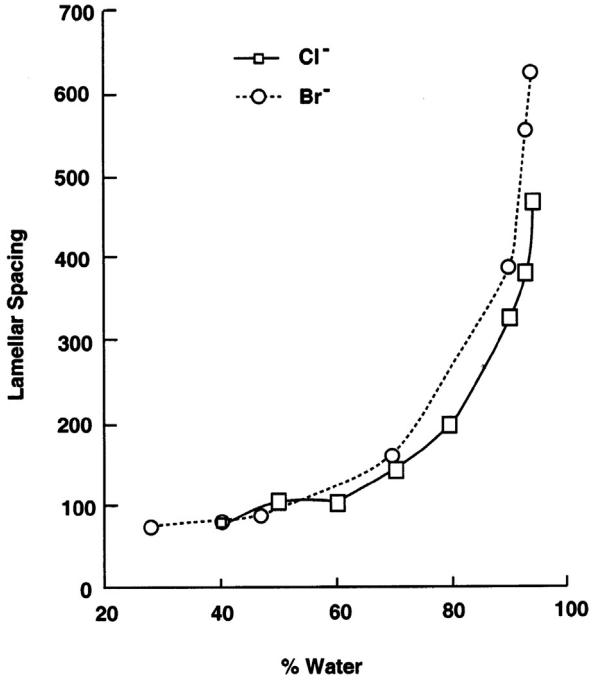



FIGURE 25.21 Interlamellar *d*-spacing of cetyltrimonium bromide (CTAB) or cetyltrimonium chloride (CTAC) plus cetostearyl alcohol lamellar gel network as a function of water concentration. *Reprinted from Eccleston GM, Behan-Martin MK, Jones GR, Towns-Andrews E. Synchrotron X-ray investigations into the lamellar gel phase formed in pharmaceutical creams prepared with cetrimide and fatty alcohols.* Int J Pharm *2000;**203**:127–39 with permission from publisher.*

TABLE 25.2 Calculated %Swelling of $L_\beta$ Phase in Gel Networks

| Surfactant | Concentration Factor | Theoretical Maximum *d* (nm) | Measured $d_1$ (nm) | %Swelling |
|---|---|---|---|---|
| BTAC | 1.10 | 50.6 | 29.2 | 57.7 |
| | 1.05 | 53.1 | 31.1 | 58.6 |
| | 1.00 | 55.7 | 32.1 | 57.6 |
| BTAMS | 1.10 | 51.6 | 31.1 | 60.2 |
| | 1.05 | 54.1 | 31.1 | 57.5 |
| | 1.00 | 55.7 | 31.1 | 55.8 |

*From Iwata T, Aramaki K. Effect of the behenyl trimethyl ammonium counterion on the lamellar gel property.* IFSCC Mag *2013;**16**:249–54.*

result arose from the diffusion between $L_\beta$ phase and isotropic polymer solution.[34] However, the diffusion of polymer may have been into the bulk water phase of the lamellar gel network rather than into the interlamellar water of $L_\beta$ phase, because the sample was quite opaque suggesting it was not $L_\beta$ single phase; also PEG-10,000 is quite bulky in water and might not penetrate into the interlamellar water layer.

Lastly, ionic surfactant systems may be quite sensitive to the cooling rate and mixing during cooling from $L_\alpha$ phase to $L_\beta$ phase. Eccleston indicates that $L_\alpha$ phase does not swell like $L_\beta$ phase.[3] This may be due to the higher mobility of counterions at such a high temperature. Counterions are more spread into bulk water phase, thus the osmotic pressure to swell interlamellar space is weaker for the $L_\beta$ phase in which the counterion is more bound closely to the surfactant head group. As $L_\alpha$ cools down to $L_\beta$, counterion mobility is reduced and the counterion comes closer to surfactant head group, which causes an osmotic pressure gradient that is more favorable to move water from the bulk water phase to the interlamellar spaces.

### 25.7.5 Spontaneous Curvature: Multilamellar Vesicle, Unilamellar Vesicle, and Lamellar Network

Spontaneous curvature of a bilayer is of primary importance in controlling mesoscale structure of a lamellar gel network from a network dominant structure to a discrete multilamellar vesicle dominant structure. Earlier discussions in this chapter were primarily directed to the control of the CPP of amphiphiles. However, this did not address the

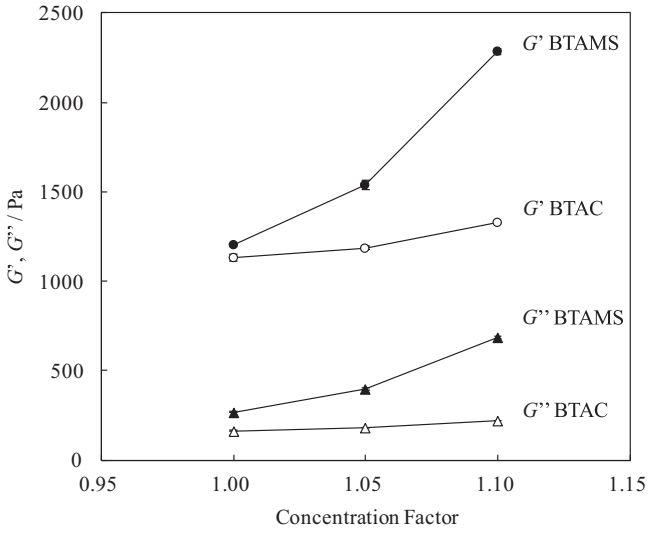



**FIGURE 25.22** Storage and loss moduli of BTAC and BTAMS gel networks at different concentration factors. *From Iwata T, Aramaki K. Effect of the behenyl trimethyl ammonium counterion on the lamellar gel property.* IFSCC Mag *2013;**16**:249–54.*

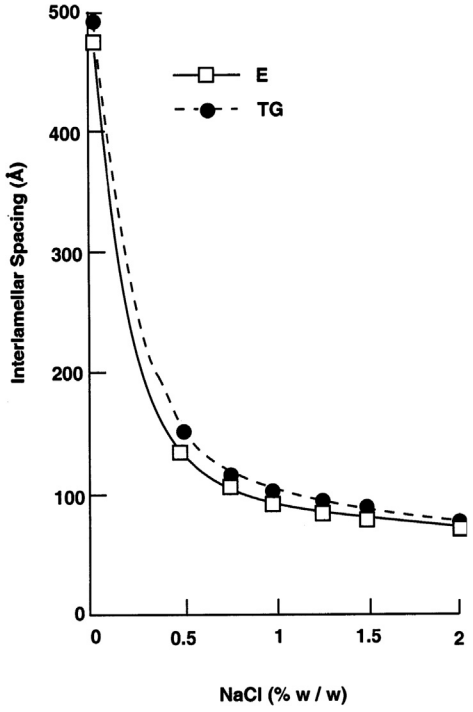



**FIGURE 25.23** Impact of adding NaCl in lamellar gel network. Phase separated water was gently mixed in before measurement. *Reprinted from Eccleston GM, Behan-Martin MK, Jones GR, Towns-Andrews E. Synchrotron X-ray investigations into the lamellar gel phase formed in pharmaceutical creams prepared with cetrimide and fatty alcohols.* Int J Pharm *2000;**203**:127–39 with permission from publisher.*

question of "how to get positive curvature in one side of bilayer and negative curvature in the other side of the bilayer?" Research articles which attempt to answer this question will now be considered.

In the dilute condition, the bilayer tends to curve to close the open edge. This can be explained as the energy required to curve a bilayer is less than having an open edge of a bilayer. The energy per unit area, $E/A$, is related to the bending modulus of bilayer, $\kappa$.

$$\frac{E}{A} = \frac{1}{2}\kappa(c_1 + c_2 - c_S)^2 \tag{25.1}$$

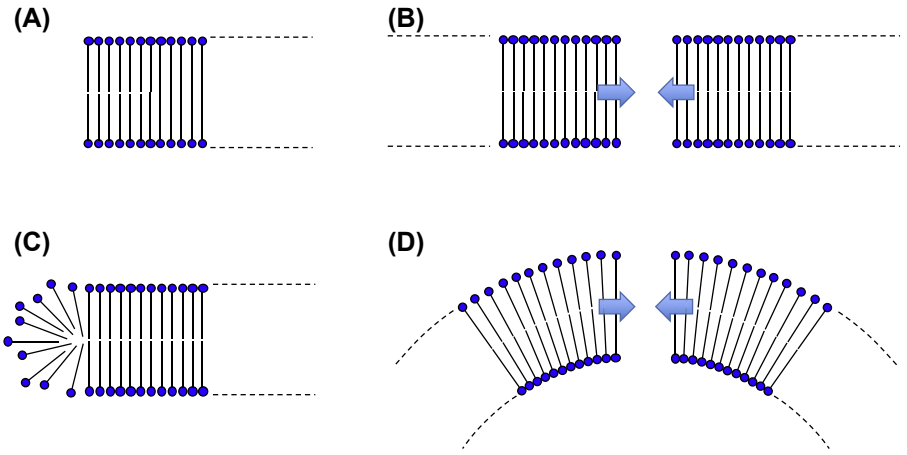



FIGURE 25.24 Growing disk micelle with two patterns of unstable edges, (A) exposed hydrophobic edge and (B) unstable amphiphile aggregation. (C) Edge adjoining with other disk micelle and (D) edge closing by itself to form vesicle.

in which $c_1$ and $c_2$ are the two principal curvatures of Gaussian curvature, and $c_S$ is the spontaneous curvature of the system. Kawabata et al. proposed that vesicles are formed as a result of the disk-like bilayer structure growing too large to be stable due to the edge energy being higher than bending energy for $C_{16}E_7$.[35] The transition of the disk-like bilayer structure to vesicle is concentration dependent. This theory supports the following hypothesis on why a network becomes predominant rather than discrete vesicles in highly concentrated systems, this is due to the mitigation of edge energy by adjoining the open edge of bilayer to another open edge of bilayer nearby, as a favorable way of eliminating the bilayer edge energy, because there is higher probability of connecting two growing bilayer disks to each other than for one bilayer disk to grow, curve and close by itself to form a vesicle (Fig. 25.24).

Spontaneous curvature of a bilayer is the result of the spontaneous curvature of two monolayers that consist a bilayer. When the two monolayers are identical in compositions, then the curvatures cancel out each other, and the spontaneous curvature of bilayer becomes 0, or it will require energy to increase the curvature of either side. In the case of mixed surfactant systems, the spontaneous curvature of the inner monolayer may be different from the outer monolayer due to a composition difference. In this case, Kaler et al. rewrote Eq. (25.1) as

$$\frac{E}{A} = \frac{1}{2}\kappa\left[(c - c_o)^2 + (c - c_i)^2\right] \tag{25.2}$$

in which $c$ is the curvature of spherical vesicle, $c_o$ and $c_i$ are the spontaneous curvature of the outer and inner monolayer, respectively.[36] However, the mechanism of generating inhomogeneity in a composition between outer and inner monolayers is not well understood. This can happen if environmental factors inside and outside the vesicle are different.[37] One may explain that during the bilayer formulation, which already starts to curve in one direction vs. the other, the composition of inner monolayer restricts the molecule with relatively smaller packing parameter to join, or on the other hand, the outer monolayer prefers to acquire the molecule with relatively smaller packing parameter.

Coldren et al. suggests that spontaneous bilayer curvature and low bending elasticity of bilayers are responsible for the spontaneous formation of vesicles from a cetyltrimethylammonium tosylate (CTAT) and sodium dodecylbenzene sulfonate (SDBS) mixture.[37] They used Caillé line shape analysis of small-angle X-ray scattering (SAXS) peaks to determine the elastic constant, $\kappa$ of the Helfrich equation which "determines the energy needed to bend the bilayer away from its spontaneous radius of curvature," the bulk compression modulus, $B$ and single crystal domain size, $L$.

### 25.7.6 Various Lamellar Gel Phases ($P_\beta$, $L_\beta$, $L_{\beta'}$, $L_{\beta i}$) and Phase Transition Thermodynamics

In natural lipid bilayers, such as cell membranes, or intercellular lamellar complexes, research shows that $L_\beta$ phases actually exist in several different conformations (Fig. 25.25). Discussions so far in this chapter have considered an $L_\beta$ structure in which the alkyl chains are perpendicular to the bilayer plane. However, in nature, this is not the case for many $L_\beta$ phases. $L_{\beta'}$ is a tilted gel phase, which the alkyl chain is tilted versus the bilayer plane. The distinction between $L_\beta$ and $L_{\beta'}$ can be measured by dynamic light scattering. The tilt orientation of alkyl chains in one bilayer of $L_{\beta'}$ is likely to be uniform. However, different bilayers have different orientations. This reduces the

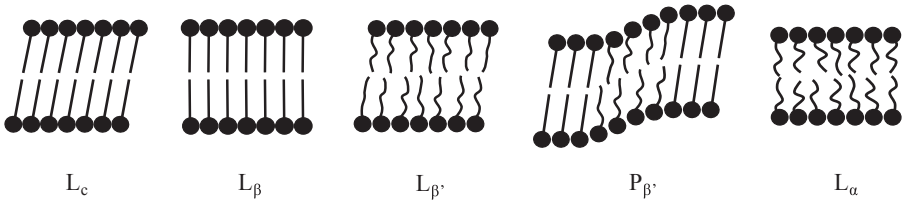



**FIGURE 25.25** Schematic drawings of various bilayer phases.

uniformity of $L_\beta$ phase as a whole causing the strength of birefringence to be weaker in $L_{\beta'}$ than $L_\beta$. Mishima et al. revealed that pure dipalmitoyl phosphatidylcholine (DPPC) $L_\beta$ phase is tilted, whereas DPPC with cholesterol mixed at 6–15 mol% becomes less tilted.[38] Kranenburg et al. suggest various phase transition modes between various phases of lipid bilayer based on modeling.[39] The phase transition from $L_c$ to $L_\alpha$ occurs through $L_\beta$ when the head group-to-head group repulsion is weak. However, when head-to-head repulsion is strong, the phase transition goes through a rippled phase, $P_{\beta'}$ instead of through $L_\beta$. In the case of typical cosmetic formulae that use surfactants (ionic or nonionic) and fatty alcohols, the head-to-head repulsion can be categorized as weak, hence the phase transition typically occurs $L_c > L_\beta > L_\alpha$.

## 25.7.7 Interdigitated Bilayer

In lamellar phases, regardless of $L_\beta$ or $L_\alpha$, interdigitation of surfactant alkyl chains can occur when a certain set of conditions are met. When interdigitation occurs, the total area of the bilayer is doubled, and the theoretical maximum interlamellar *d*-spacing becomes half. Therefore, making interdigitated $L_\beta$ phase an interesting way accommodate bulk water into the lamellar phase to potentially make the rheological properties of lamellar gel networks very different from typical lamellar gel networks. Short-chain alcohols are known to contribute to the formation of an interdigitated bilayer of phospholipids.[40–42] The mechanism is simple. To prevent exposure of the hydrophobic end of an alkyl chain to water, the hydrophobic end of the short-chain alcohol interacts with it (Fig. 25.26).

Adachi et al. measured the thickness of interdigitated bilayers of a phosphatidylcholine and alcohol system by X-ray diffraction as a mean to gain direct evidence that the bilayer is interdigitated.[43] Similar to alcohol, Makai et al. indicated that glycerin helps form interdigitated liquid crystal bilayers of Trideceth-10, and at a ratio of glycerin to Trideceth-10 of 3.2 the highest *d*-spacing and storage modulus were observed.[44] This suggests that 3.2 glycerin molecules together behave like an "endcap" of one alkyl chain end. Interdigitation seems to happen even without such short-chain alcohol or polyols. Nagai et al. suggested the existence of an interdigitated bilayer in a mixed $C_{16}E_6$ and $C_{16}E_7$ surfactant system by plotting interlamellar spacing vs. volume fraction of hydrophobic portion of the bilayer.[26]

## 25.7.8 Thermal History and Formation of $L_\beta$ Phase

Thermal history influences the phase behavior of colloidal systems in general. $L_\beta$ is not an exception. As a rule of thumb, to make $L_\beta$ phase reliably, all the amphiphiles need to be melted by raising temperature above their melting point, either in hot water or by the amphiphiles themselves in an oil mixture. Goto et al. studied various thermal histories in the dioctadecyl dimethylammonium chloride (DODAC) system.[45] 5.0 mmol/kg DODAC shows $L_c$ to $L_\beta$ transition at 19.7°C and $L_\beta$ to $L_\alpha$ transition at 39.9°C when the solution was prepared by suspending in water

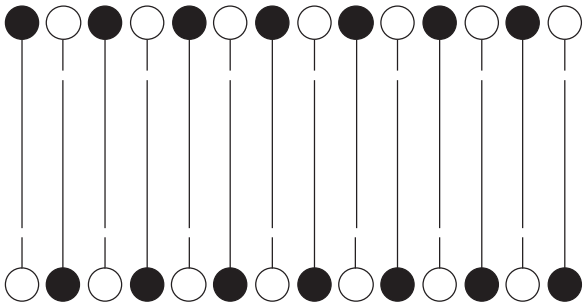


**FIGURE 25.26** Schematic representation of short-chain alcohol (*white head group*) and long-chain surfactant (*black head group*) together form an interdigitated bilayer.

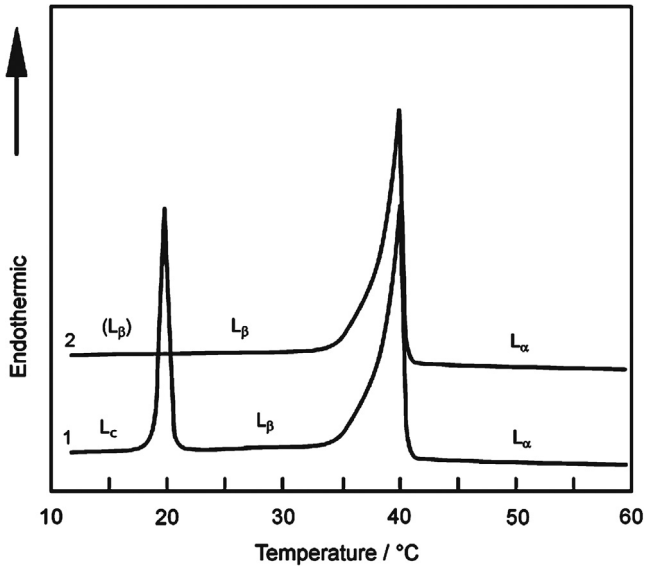



FIGURE 25.27 Differential scanning calorimetry thermograms of DODAC bilayer membranes prepared by different methods. *Reprinted from Goto M, Ito Y, Ishida S, Tamai N, Matsuki H, Kaneshina S. Hydrostatic pressure reveals bilayer phase behavior of dioctadecyldimethylammonium bromide and chloride.* Langmuir *2011;**27**:1592–8 with permission from publisher.*

with sonication and freeze–thaw cycles (Fig. 25.27-1), whereas the same solution prepared through melting at 60°C followed by freezing by liquid nitrogen then melting shows one transition from $L_\beta$ to $L_\alpha$ at 39.9°C only (Fig. 25.27-2). Kodama et al. found that metastability or stability of $L_\beta$ phase depends on the concentration of surfactant and the temperature history in the case of dioctadecyl dimethylammonium bromide.[46] They suggest that metastable supercooled liquid crystal phase exists when system is once cooled down to as low as −20°C. In the range of 67–93 wt% water, $L_c$ phase directly phase transitioned to $L_\alpha$ phase, when the system was cooled to −20°C, whereas the phase changes go from $L_\beta + L_c$ to $L_\alpha + L_c$, then to $L_\alpha$, when system was not cooled down to subzero °C. These papers suggest that thermal history of lamellar gel network is quite complex, and further study is encouraged, to help understand not only the thermal history during production of cosmetic products, but also the impact of various thermal histories during transportation and storage conditions.

### 25.7.9 Identification of $L_\beta$ phase

The presence of lamellar gel phase in lamellar gel network is verified by combination of several analytical methods. Crossed-polarizer microscopy gives the easiest signature of the presence of lamellar phase, when it shows so-called "Maltase cross" or "flow streaks." However, the crossed polarizer microscope does not distinguish lamellar gel ($L_\beta$) phase from lamellar liquid crystal ($L_\alpha$) phase or coagel ($L_c$) phase, as these three are all lamellar phases.

To understand if it is $L_\beta$ or $L_\alpha$, after confirming it is lamellar phase, differential scanning calorimetry (DSC) is a convenient tool as it gives the phase transition (melting or freezing) temperature of bilayer, as well as the thermal energy of melting and freezing. DSC also reveals the inhomogeneity of a multicomponent lamellar gel network, showing separate peaks that often suggest the presence of unintegrated fatty alcohol as separate hydrated crystals or coagel ($L_c$) phase. However, when one wants to use low melting point component(s) together with high melting point components to form lamellar gel network, the peak of melting can become very wide, thus it becomes difficult to conclude $L_\beta$ or $L_\alpha$.

Another way to identify $L_\beta$ phase is to use X-ray scattering in wide-angle to small-angle ranges. SAXS provides the evidence for lamellar phase, when the ratio of $d_1{:}d_2{:}d_3{:}d_4\ldots = 1{:}1/2{:}1/3{:}1/4\ldots$ SAXS also directly indicates the interlamellar spacing as $d_1$. WAXS provides the evidence for α-gel crystal presence by a sharp peak at $d = 0.42$ nm ($q = 15$ nm$^{-1}$) (Fig. 25.28).

## 25.8 BULK WATER PHASE

Juninger proposed that the distinction between bulk water and interlamellately fixed water was measurable by thermogravimetric analysis showing two distinctive peaks.[1] This method needs to be run very slowly, as it relies

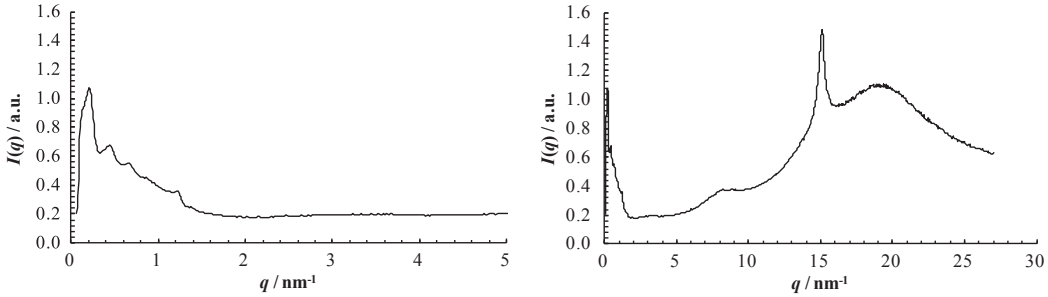



**FIGURE 25.28** SAXS (left) and WAXS (right) charts of BTAMS and cetostearyl alcohol lamellar gel network. *From Iwata T, Aramaki K. Effect of the behenyl trimethyl ammonium counterion on the lamellar gel property.* IFSCC Mag *2013;**16**:249–54.*

on a structural transition (such as melting fatty alcohol, or bilayer) at a certain temperature to effect release of entrapped water for release and evaporation.

Another method is to measure the interlamellar *d*-spacing by SAXS and calculate the bulk water phase. The calculation assumes that all amphiphiles are in α-gel. The cross-sectional area of one acyl chain is given as

$$\frac{2}{\sqrt{3}}\, a^2 \tag{25.3}$$

in which $a =$ the interacyl lattice constant measured by WAXS [nm], which is a constant 0.415 nm. The unit volume of two acyl chains + interlamellarely fixed water, assumed to be fully swollen, is the unit volume times theoretical maximum *d*-spacing, *d* [nm] (Fig. 25.29). The number of this unit volume in 1 liter is $CR/2$, in which $C =$ total acyl chain concentration [mol/l], and $R =$ Avogadro constant. Therefore, the theoretical maximum interlamellar *d*-spacing, $d_{\max}$, is given as

$$d_{max} = \frac{\sqrt{3} \times 10^{24}}{a^2 CR} \tag{25.4}$$

By comparing, the calculated theoretical maximum *d*-spacing and measured *d*-spacing, the volume ratio of $L_\beta$ phase and bulk water phase is obtained. A typical lamellar gel network, for example, using 0.3 M of surfactant and fatty alcohol, has a theoretical maximum *d*-spacing of 55.7 nm. If the measured *d*-spacing by SAXS turns out to be 25 nm, the swell is 44.9%. This means 55.1% of water is in bulk water phase. A *d*-Spacing of 55 nm with

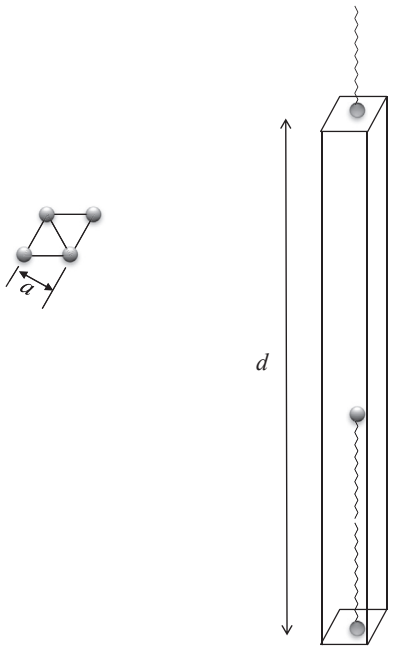



**FIGURE 25.29** The unit dimension of α-gel crystal (left), in which *a* is measured by WAXS, and the unit dimension of $L_\beta$ phase (right), in which *d* is measured by SAXS.

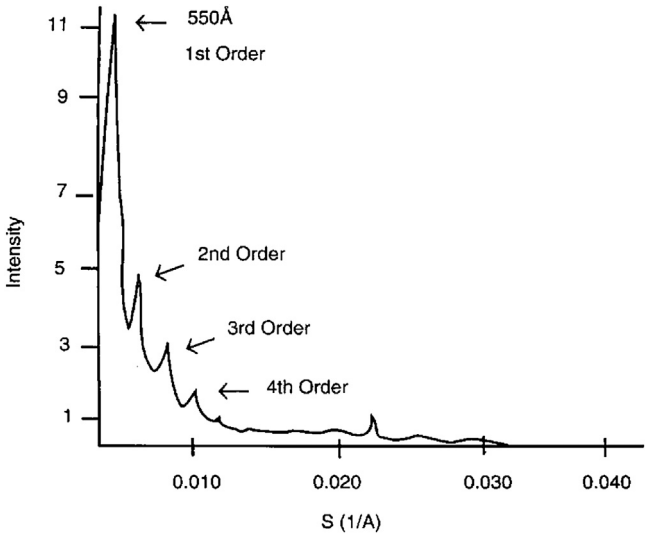



FIGURE 25.30 SAXS data of model cetrimide/cetostearyl alcohol/water ternary system containing 94% water showing 55.0 nm *d*-spacing. *Reprinted from Eccleston GM. Functions of mixed emulsifiers and emulsifying waxes in dermatological lotions and creams.* Colloids Surf A *1997;**123–124**: 169–82 with permission from publisher.*

cetrimide and cetostearyl alcohol system with 94% water has been reported (Fig. 25.30). Assuming the mole ratio of cetyl alcohol:stearyl alcohol:CTAB = 8:12:5, total amphiphile concentration is 0.21 M, the theoretical maximum *d*-spacing is 78.4 nm. Thus, 55.0 nm measured *d*-spacing means 70.1% swelling and 29.9% bulk water phase.

It is interesting that such large fraction of bulk water is physically surrounded by highly viscoelastic $L_\beta$ phase domains, and phase separation is prevented in practical time scale. The $L_\beta$ domains physically support each other and are connected each other as shown in Figs. 25.8, 25.17, and 25.18.

The cause that makes it difficult for $L_\beta$ phase to fully swell is primarily the rigidity of the α-gel bilayer. Once the bilayer becomes α-gel, bending of the bilayer to conform to the available space, driven by the osmotic pressure of water coming from the bulk water phase to the inter-lamellar space, may not be large enough (Fig. 25.31). In fact, the $L_\beta$ phase of ionic surfactant and fatty alcohol usually swells very well when diluted with water and the network structure is disentangled. Swelling as a function of total water depends upon the surfactant used in lamellar gel network. Even changing the counterion of the surfactant can cause significant difference in the swelling behavior.[19] This will be discussed later.

However, when ionic substances other than the ionic surfactants exist in the interlamellately fixed water phase, electrostatic repulsive forces between bilayers are shielded, thus swelling capability is limited. This can lead to phase separation.

In the case of nonionic surfactant lamellar gel networks, swelling is more limited than for ionic systems. The swelling capacity is dependent on the hydrodynamic diameter of the hydrophilic head groups of nonionic surfactants, and their concentration. Junginger demonstrated that a larger proportion of total water leads to unstable dispersions of $L_\beta$ phase in continuous water phase, which causes uneven *d*-spacing (Fig. 25.32).[1] However, even with

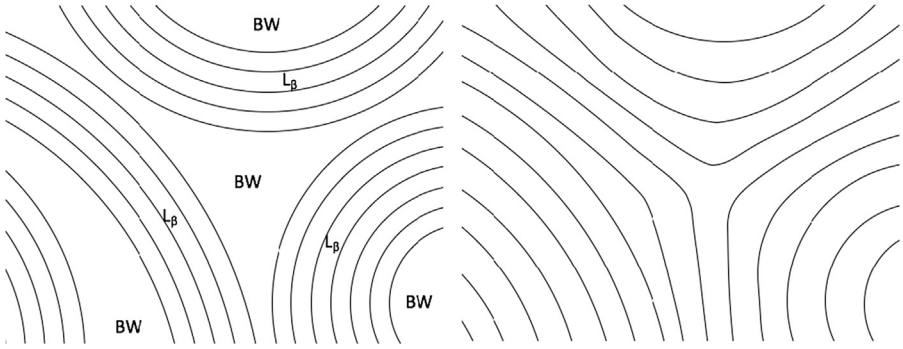



FIGURE 25.31 Schematic drawing of lamellar gel network consisting of $L_\beta$ phase and bulk water phase (BW) (left). To accommodate bulk water into $L_\beta$ phase, bilayers have to have much larger curvature to fill the space, which requires high energy (right).

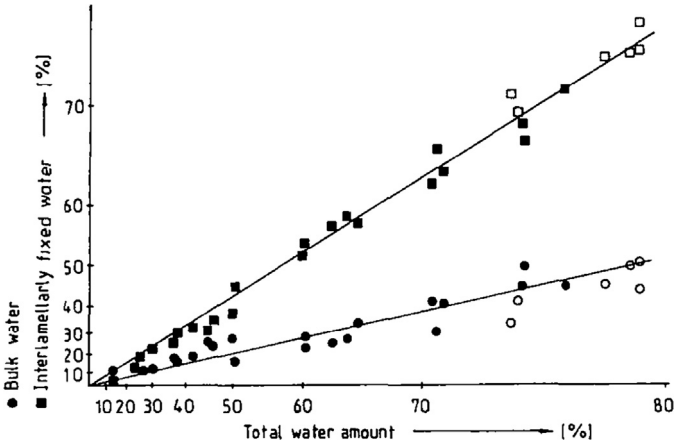



FIGURE 25.32 Interlamellar water and bulk water along with swelling behavior of nonionic lamellar gel network. *White square and circle* represent unstable systems. *From Junginger HE. Colloid structures of O/W creams.* Pharm Weekblad Sci Ed *1984;6:141–49.*

nonionic surfactants, Nagai et al. has shown that the mixture of $C_{16}E_6$, $C_{16}E_7$ and water, at high surfactant concentration, forms fully swollen $L_\beta$ phase. The phase boundary between $L_\beta$ and $L_\beta + W$ is dependent on the $C_{16}E_6/C_{16}E_7$ ratio. The higher $C_{16}E_7$ mole fraction, the lower the total surfactant concentration required to sustain $L_\beta$ phase without leaving the bulk water phase. At $C_{16}E_7$ mole fractions 0.5 and 0.83, the phase boundary is about $58-60_{716}$ wt% and 46–50 wt% total surfactant, respectively.[47] This is probably due to the larger hydrophilic head group size requiring more water for hydration.

## 25.9 OIL PHASE

Cosmetic products based on lamellar gel network can contain various oil phases. These oil phases include various emollients, liquid paraffin, mineral oil, fragrance, silicone, etc. These oil materials are not amphiphilic in strict sense and they exist as separate liquid oil phases surrounded by the hydrophobic side of amphiphiles (fatty alcohols and surfactants). See Fig. 25.1. Adding such liquid oil materials requires physicochemical understanding of the oil material and amphiphiles used. Best results are obtained by adding liquid oil materials after the formation of the lamellar gel network, if the oil materials have minimal compatibility with amphiphiles. In this case, the resultant mixture is more toward the dispersion of oil in a highly viscous lamellar gel network rather than emulsification of the oil. Silicone is typically such a material. On the other hand, when considerable interaction between oil material and amphiphiles is expected, the best result is obtained by mixing the oil materials with surfactants and fatty alcohols at the temperature at which everything can melt together, and then emulsifying in hot water. In this way, the liquid oil phase and bilayer are in equilibrium with amphiphiles partitioned between solid α-gel and solubilized in liquid oil phase. In the practice of cosmetic formulation, the mixture of surfactant and fatty alcohols (usually cetostearyl alcohol) is considered as an emulsifier for variety of oil materials, and such a mixture is often called an *emulsifying wax*. Schematically drawn, oil droplets are surrounded by monolayer of α-gel, and surrounded by $L_\beta$ phase (Fig. 25.33).

The easy and reliable way to confirm whether the oil phase is emulsified by the lamellar gel system is by polarized microscopy. An oil droplet surrounded by a Maltese cross indicates an oil droplet emulsified by multilamellar layers. Eccleston et al. showed this clearly when using a cetrimide/cetostearyl alcohol system to emulsify liquid paraffin (Fig. 25.34).[48] They also showed that addition of liquid paraffin into a lamellar gel network does not have much effect on lamellar *d*-spacing (Fig. 25.35). This is because the water-to-amphiphile ratio remained unchanged.

## 25.10 FATTY ALCOHOL HYDRATED CRYSTAL

Fatty alcohol hydrated crystals are usually present in lamellar gel networks. The crystals are orthorhombic or monoclinic crystal of fatty alcohols, or fatty alcohol-rich mixture with surfactant. Such crystals remain in the lamellar gel network, because these crystals are thermodynamically more stable than the α-gel that constitute $L_\beta$ phase. However, fatty alcohol hydrated crystals are often considered to be residual material that was not incorporated into the lamellar structure. Fatty alcohol hydrated crystal is left for two reasons: (1) there is not enough surfactant to emulsify

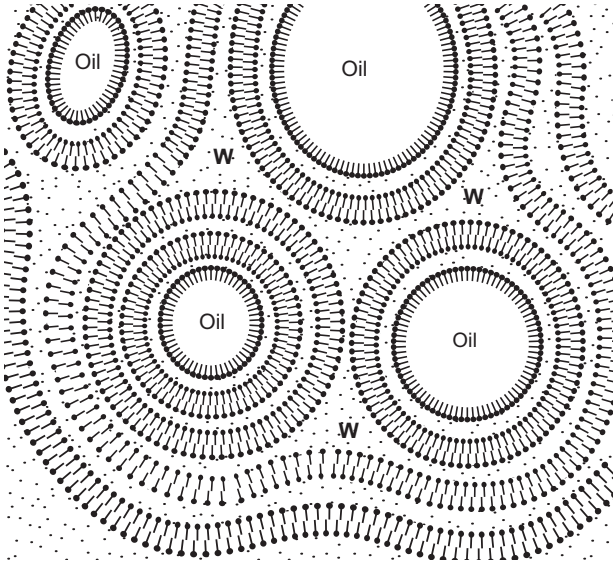



**FIGURE 25.33** Schematic representation of liquid oil emulsified by lamellar gel network.

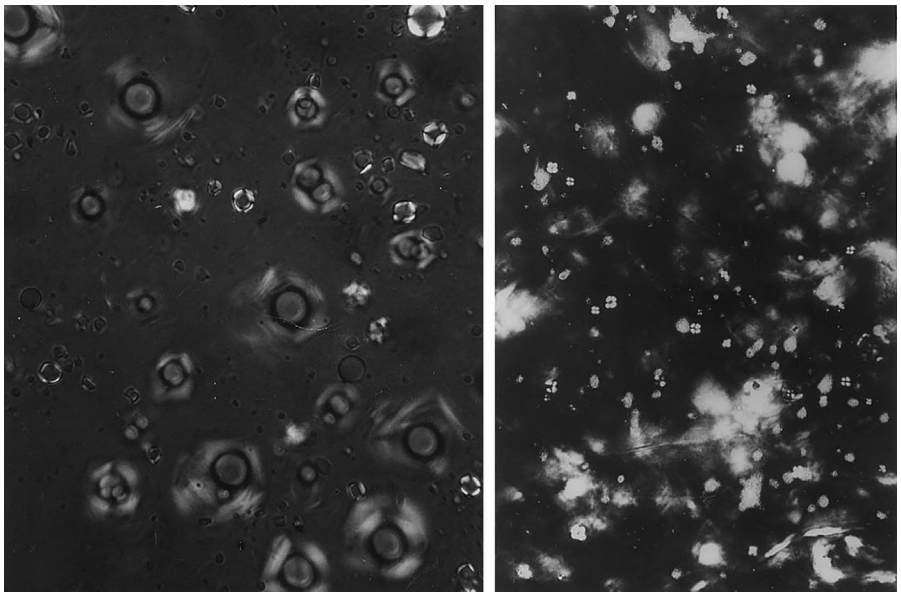


**FIGURE 25.34** Polarized microscopy photographs of cetrimide/cetostearyl alcohol/liquid paraffin gel network (left), cetrimide/cetostearyl alcohol gel network (right). *Reprinted from Eccleston GM, Behan-Martin MK, Jones GR, Towns-Andrews E. Synchrotron X-ray investigations into the lamellar gel phase formed in pharmaceutical creams prepared with cetrimide and fatty alcohols.* Int J Pharm *2000;**203**:127–39 with permission from publisher.*

the fatty alcohol entirely or locally at a molecular level. The former is due to lack of optimization in formulation. The latter is due to lack of enough mixing either in time or due to fluid dynamics. (2) Cooling after emulsification is too rapid, causing the surfactant having higher melting point to "escape" from crystal formation together with the fatty alcohol. This is typically due to large temperature deviation at the center of mixing tank versus the outer edge due to cooling water in jacket being too cold while inside the tank the temperature is still high.

The structure of fatty alcohol hydrated crystal is usually orthorhombic, for which an X-ray diffraction peak appears at 0.38 nm (Fig. 25.36). The unit of the hydrated crystal of cetostearyl alcohol consists of four hydroxyl groups trapping one water molecule via hydrogen bonding (Fig. 25.37), as suggested by Fukushima.[6] This crystal consists of multiple bilayers with only one molecule of water per four molecules of fatty alcohols in between the bilayers. This is *unswollen* lamellar phase and it is called coagel ($L_c$) phase. The bilayers of coagel phase do not slip past each other unlike the ones in $L_\beta$ phase, because they are hydrogen bonded. Thus, fatty alcohol hydrated crystals do not

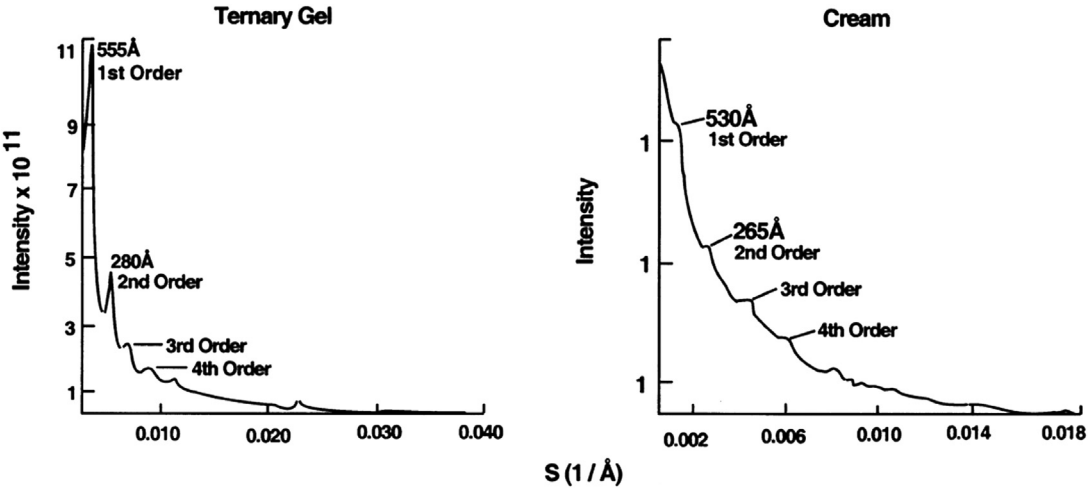



FIGURE 25.35 SAXS pattern of cetrimide/cetostearyl alcohol gel network (ternary gel) and the same gel network which includes liquid paraffin (cream). *Reprinted from Eccleston GM, Behan-Martin MK, Jones GR, Towns-Andrews E. Synchrotron X-ray investigations into the lamellar gel phase formed in pharmaceutical creams prepared with cetrimide and fatty alcohols.* Int J Pharm *2000;**203**:127–39 with permission from publisher.*

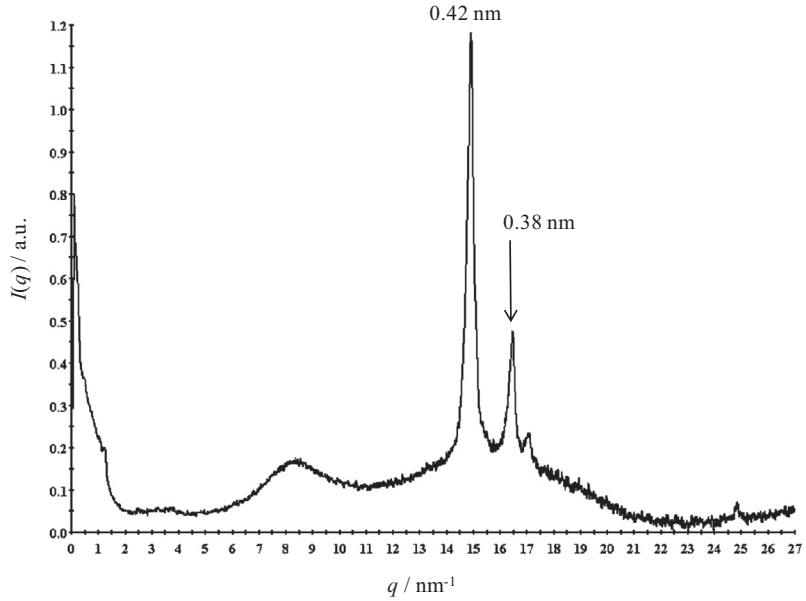



FIGURE 25.36 Example WAXS chart of lamellar gel network indicating the presence of orthorhombic crystals at 0.38 nm, whereas the major constituent is hexagonal (0.42 nm).

contribute to a conditioning benefit or to slipperiness of the composition, and for this reason these crystals are considered *residual*. As mentioned earlier, the alkyl chains are in all *trans* conformation, and not rotating.

## 25.11 STABILITY OF LAMELLAR GEL NETWORK

The lamellar gel network is a complex system and there are at least six mechanisms of instability: (1) α-Gel transforms to β-crystal, expelling interlamellar water to bulk water; (2) water movement to or from the bulk water phase to lamellar gel phase swells or shrinks the lamellar gel phase; (3) relaxation of the entangled lamellar gel network structure; (4) equilibration of liquid oil phase and α-gel bilayer. (5) If the composition includes water-soluble polymer that is solubilized post-lamellar gel network formation, the diffusion of the polymer takes an enormously long time. (6) If the composition includes other emulsions such as silicone microemulsion, added post-lamellar gel

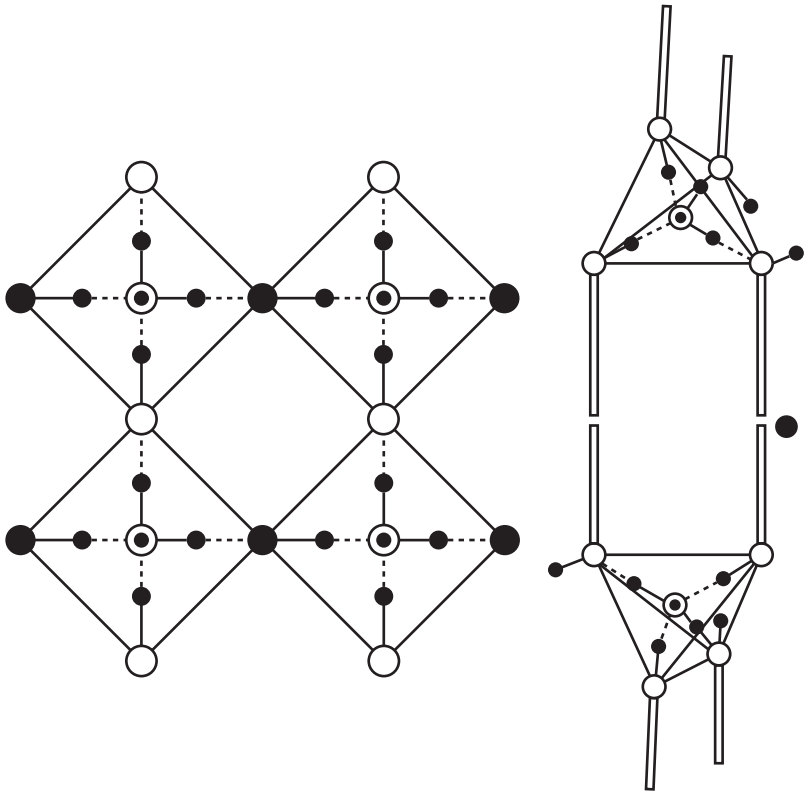


**FIGURE 25.37** Crystal structure of hydrated fatty alcohol. *Based on Fukushima S, Yamaguchi M. The effect of cetostearyl alcohol in cosmetic emulsions.* Cosmet Toilet *1983;**98**:89–102.*

network formation, surfactant exchange between the α-gel bilayer and the oil–water (O/W) emulsion is inevitable because most often such emulsion use high hydrophilic–lipophilic balance (HLB) emulsifiers at very high concentration. Let us look at each different mechanism of instability in more detail.

### 25.11.1 α-Gel Transforms to β-Crystal, Expelling Interlamellar Water to Bulk Water

Hexagonally packed rotator phase (α-gel) is not thermodynamically stable; it is metastable. There is always driving force to morph to orthorhombic crystal (β-crystal). This tendency becomes more apparent at lower temperature, because the thermal motion (rotation of amphiphiles) becomes less intense. As shown in Fig. 25.9, alkyl chains in orthorhombic crystals are more densely packed than in hexagonal phase, in which alkyl chains rotate freely. Using a C16 alkyl chain (all *trans*) length 2.174 nm, and the lattice constants in Fig. 25.9, the density of the alkyl chains part of orthorhombic crystal can be obtained as 1.079 g/cm$^3$. This means that β-crystals sink and water is expelled upward. This is the major cause of the water separation on top of lamellar gel network compositions observed after aging at low temperature.

This is the most prevalent practical stability problem across cosmetics formulations utilizing lamellar gel networks, because the phase transition temperature of cetostearyl alcohol + surfactant mixture can be as low as 12°C (Fig. 25.6). There may be a way to reduce the phase transition temperature from $L_\beta$ to $L_c$, by adding impurities to prevent alkyl chain morphing to orthorhombic crystallization. Such impurities can be branched, unsaturated, or shorter alkyl chain fatty alcohols, but none is known nor practiced widely in the industry. Instead, in reality, the stability of $L_\beta$ is managed kinetically, by setting shelf life on the product. For storage times longer than the shelf life (let us say 3 years), there will be a higher probability that products are phase separated. Therefore, a practically important question is how to slow down the kinetics of phase transition from $L_\beta$ to $L_c$ phase under various storage conditions, with emphasis on lower temperatures.

Salt increases the $L_\beta$ to $L_c$ transition temperature of ionic surfactant lamellar gel networks. Berr et al. showed that the $L_\beta$ to $L_c$ transition temperature of di(2-stearoyloxyethyl) dimethylammonium chloride (DEEDMAC) increases as NaCl concentration increases, whereas the $L_\beta$ to $L_\alpha$ transition temperature remains the same (Fig. 25.38).[49] This is

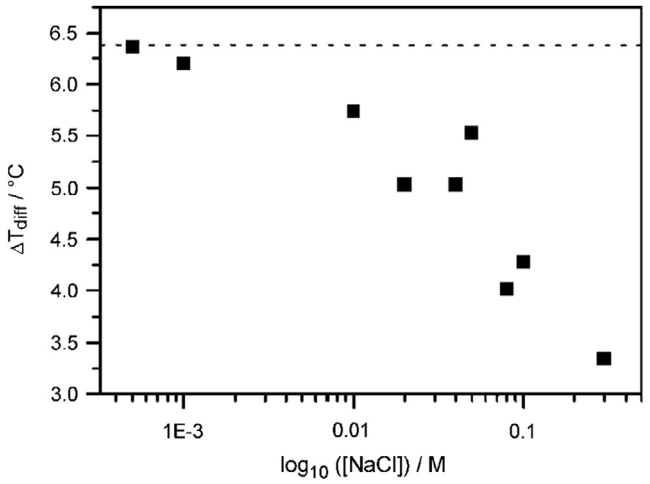



FIGURE 25.38 The temperature difference between $L_\beta - L_c$ transition and $L_\beta - L_\alpha$ transition, as a function of NaCl concentration. *From Shearman GC, Ugazio S, Soubiran L, Hubbard J, Ces O, Seddon JM, et al. Factors controlling the stability of a kinetically hindered lamellar–lamellar transition.* J Phys Chem B *2009;**113**:1948–53.*

probably due to reduced electrostatic repulsive force between adjacent surfactant head group on the same side of a bilayer.

In the case of glycerol monostearate $L_\beta$ phase, Cassin et al. suggests that the phase transition to β-crystal is concentration dependent. At 20% surfactant, crystal growth is three-dimensional whereas at 5% it is two-dimensional. Two-dimensional crystal growth means growth that is longitudinal throughout the monolayer (one side of the bilayer). Three-dimensional growth means growth that occurs two dimensionally as well as radically across water layers. Cassin et al. explains this arises from β-crystal formation due to segregation of D and L forms within the monolayer and the formation of hydrogen bonds among glycerol head group. At higher surfactant concentration, they argue there must be sporadic nucleation at a defined distance across the water layer to form hydrogen bonding across water layer.[16]

### 25.11.2 Water Movement to or from Bulk Water Phase to Lamellar Gel Phase to Swell or Shrink the Lamellar Gel Phase

For now, let us use a simple lamellar gel network made of ionic surfactant, fatty alcohol, and water, and that forms lamellar gel phase and bulk water phase. Assume that the lamellar gel phase was made by rapidly cooling while stirring the mixture, as in most cases of economical production of cosmetic products. When α-gel bilayers start to form, they lose the flexibility that is needed to flow, move, and deform. Therefore, often a portion of water is left behind from being trapped inside the lamellar gel phase. This is the bulk water phase. In such an ionic lamellar gel network, there is always an osmotic pressure drive to move water from the bulk water phase into the interlamellar spaces due to the difference in counterion concentration. If this osmotic pressure-driven exchange of water occurs, the lamellar phase swells over time (one day to over a few week period). This can be seen as a viscosity increase over time.[48] The rule of thumb to minimize the change during storage proposed by Eccleston is to provide vigorous mixing at a temperature close to the phase transition temperature, to maximize equilibration of bulk water and interlamellar water, followed by slow cooling while minimizing excessive mixing below the transition temperature. Ideally, it should be cooled undisturbed to minimize disintegration of the swollen lamellar gel structure.[2]

### 25.11.3 Relaxation of Entangled Lamellar Gel Network Structure

During mixing of lamellar gel network, or even in the process of filling the package, α-gel bilayers are deformed in various ways. Bending exerts stress on the bilayers. Sharp kinks may be more stable to separate into two pieces rather than to relax back to a straight single piece. Again, imagine thermoplastics. The annealing process after the plastic is molded is to release molecular-level residual stresses, and to complete deformation is completed. Processing of a lamellar gel network is the similar to such polymer processing.

### 25.11.4 Equilibration of Liquid Oil Phase and α-Gel

Many of the amphiphiles that constitute α-gel are soluble in many of the liquid oil phases that are formulated into lamellar gel networks. This can create a problem. A commonly used solution is to melt the liquid oil and amphiphiles together at high temperature to make a single-phase oil mixture, and then mix with hot water to make an emulsion, then cool it down to form lamellar gel network. This process allows equilibrium to be reached for amphiphiles partitioning between a solid monolayer and solution in oil phase. However, some liquid oil materials are not suitable to process in this manner, and have to be postadded to the lamellar gel network. In this case, the liquid oil phase has the capacity to solubilize the amphiphiles when they contact each other. This causes the network to be "eaten up" by liquid oil over time. In another case, the liquid oil molecules penetrate into α-gel bilayers, loosening packing, or turning into liquid crystal-like, or even triggering segregation of fatty alcohol and surfactant leading to coagel formation.

### 25.11.5 The Diffusion of the Polymer Takes an Enormously Long Time

Various water-soluble polymers, such as hydroxyethyl cellulose and polyacrylamide, are often included in lamellar gel network-based products. They are added with the purpose of modifying tactile sensory properties, improving stability, etc. When polymers are dissolved before the lamellar gel network is formed, they are distributed equally in interlamellar water and bulk water. However, many polymers can separate by a depletion mechanism. This process can cause the polymer to partition from the interlamellar water space to the bulk water phase. In the other case in which the polymer is dissolved after the lamellar gel network is formed, most of the polymer is first dissolved into the bulk water phase. Polymer addition shifts the osmotic balance to move water from the lamellar gel phase to the bulk water (polymer solution) phase.

### 25.11.6 Surfactant Exchange Between the α-Gel Bilayer and Oil−Water Emulsion

Post-adding an oil-in-water (O/W) emulsion into a lamellar gel network presents a huge challenge to formulation stability, because the emulsifiers used in O/W emulsions are usually high in HLB so they can easily mix with bilayers and "emulsify" the bilayer, which means they destroy the lamellar gel network structure. Also high concentrations of these O/W emulsion particles themselves drive the osmotic pressure to squeeze water out of the lamellar gel phase to the bulk water phase, which is now actually an O/W emulsion phase.

## 25.12 FORMULATION SPACES OF VARIOUS LAMELLAR GEL NETWORKS

Although manipulating the network structure of a gel network is quite an important aspect of delivering sensorial experience and product performance to consumers, this area is mostly kept as trade secrets rather than being proactively published by each company and, as a consequence, limited disclosures are available. This section will summarize formulation spaces of various lamellar gel network compositions from published phase diagrams, and rheological characteristics when available. Rheological properties are major contributors of tactile sensation.

Okuma et al. formulated 36 compositions that were used to construct a pseudoternary phase diagram of surfactant, oil, and water, to show the composition limits of the lamellar gel phase (LGP in Fig. 25.39) region. The surfactant was a mixture of Ceteth-2/Steareth-20 (0.93/0.07 wt/wt). They identified a composition of 10% surfactant mixture/15% oil/75% water (point F in Fig. 25.39) that demonstrated practical stability with minimum surfactant concentration and highest active-oil concentration.[50]

Benton et al. studied the system of stearyl dimethyl benzyl ammonium chloride and 60:40 (wt/wt/) mixture of cetyl alcohol and stearyl alcohol.[51] They indicate that spherical vesicles of lamellar gel phase are predominant at lower surfactant-to-fatty alcohol ratio, whereas needle-like crystals of surfactants become apparent at higher surfactant-to-fatty alcohol ratio such as 2:3 (wt/wt).

Similarly, Kudra, et al. showed a phase diagram of stearamidopropyl dimethylamine (SAPDMA) and fatty alcohol at a constant 9.5% total amphiphile concentration (Fig. 25.40). Lactic acid was used as the counterion. The weight ratio of cetyl alcohol:stearyl alcohol was 1:2 (w/w). At surfactant fractions below 0.1 (mol/mol), fatty alcohol crystals start to appear. At a surfactant fraction of 0.4 or above, needle-like crystals of surfactant start to appear.[52] Lamellar gel network is predominant at surfactant fractions from 0.1 to 0.4. Whether this region is single $L_\beta$ phase or lamellar gel network is not clear.

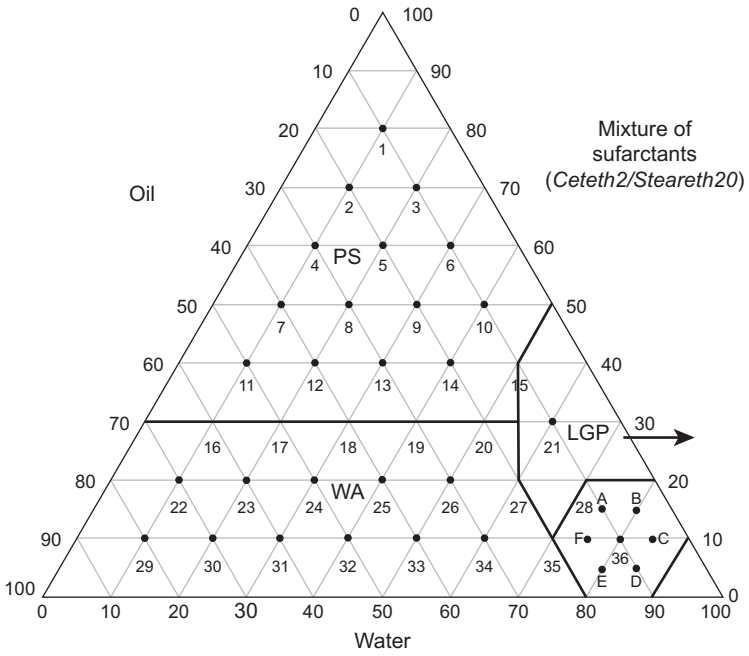



**FIGURE 25.39** Pseudo-ternary phase diagram of oil, mixture of Ceteth-2 and Steareth-20, and water based only on 36 mixtures in the diagram. The bold lines suggest the approximate phase boundaries. *LGP*, lamellar gel phase; *PS*, phase separated; *WA*, waxy. *From Okuma CH, Andrade TAM, Caetano GF, Finci LI, Maciel NR, Topan JF, et al. Development of lamellar gel phase emulsion containing marigold oil (*Calendula officinalis*) as a potential modern wound dressing.* Eur J Pharm Sci *2015;**71**:62–72.*

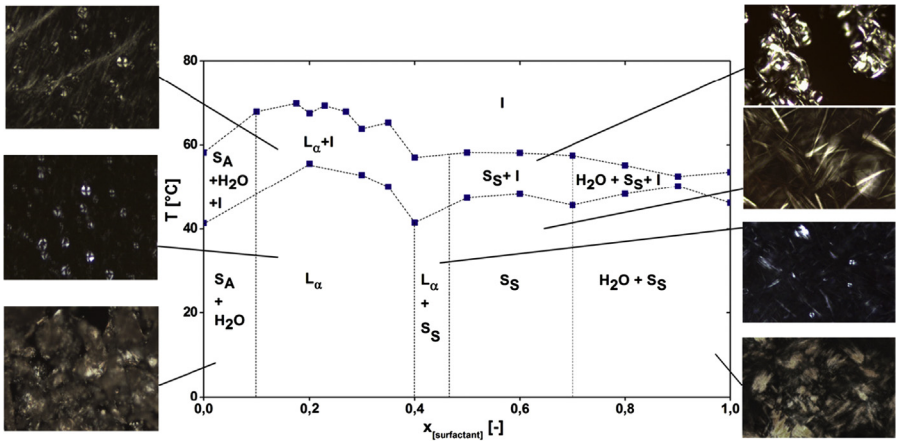



**FIGURE 25.40** Stearamidopropyl dimethylamine (SAPDMA)-Lactate + fatty alcohol phase diagram. *I*, isotropic phase; $L_\alpha$, lamellar phase; $S_A$, fatty alcohol crystal; $S_S$, surfactant crystal; $x_{[surfactant]}$ is molar ratio of surfactant and fatty alcohol. *From Kudra P, Sokolowski T, Blümich B, Wittern KP. Phase behavior of liquid–crystalline emulsion systems.* J Colloids Interface Sci *2010;**349**:554–59.*

Nakagawa et al. show phase structure changes by altering the ratio between 1-hexadecanol (HD), DSPC, and DSPG at a constant 5% total amphiphile concentration.[27] A HD fraction of 0.66, with a DSPC: DSPG ratio from 9: 1 to 7:3 results swollen lamellar gel phase (Fig. 25.41), although interlamellar *d*-spacing was not clearly measured by WAXS. At a DSPC: DSPG ratio of 10:0, bilayers are proposed to stack tightly, due to the zwitterionic nature of the head group, causing separation of large bulk water from lamellar phase. At 6:4 or lower ratios, the compositions are is proposed to consist of spherical vesicles, resulting in low viscosity.

Nakarapanich et al. showed a variation of lamellar gel network structure by comparing CTAC and BTAC and at various surfactant-to-fatty alcohol ratios (see Fig. 25.42). The surfactant concentration was kept at 1 wt%. The fatty alcohol was a mixture of 15% cetyl alcohol and 85% stearyl alcohol. At 2% fatty alcohol, the majority of the structure consists of vesicles in both CTAC and BTAC[53] (A and B). At 4% fatty alcohol, both CTAC and BTAC systems reveal a network structure (C and D). At 6% fatty alcohol, the CTAC system still shows the network structure dominating with several few discrete particles, which are likely fatty alcohol β-crystals (E). The BTAC system left large

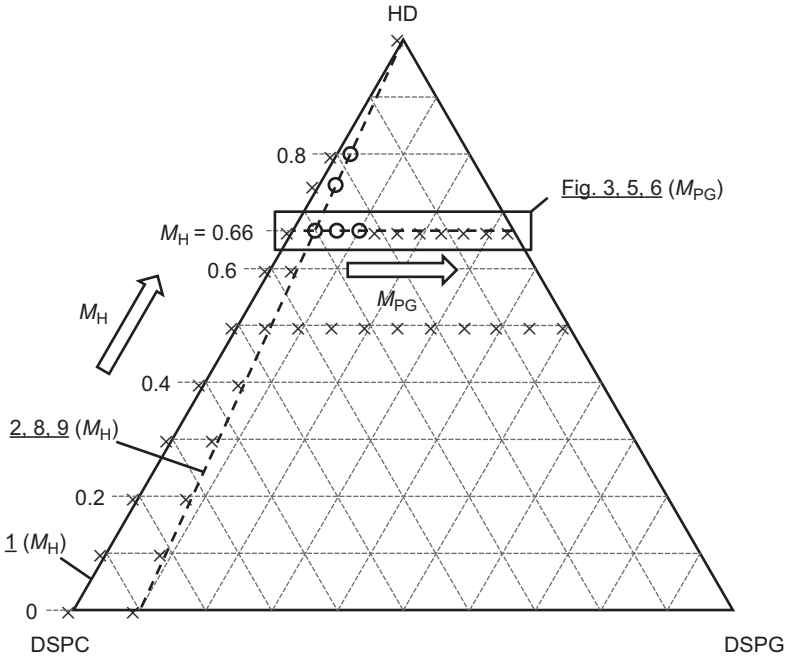



**FIGURE 25.41** State diagram of DSPC/DSPG/HD ternary bilayer system in water. Total concentration is 50 mg/mL. *Circles* indicate thick gel state. *Crosses* indicate low viscous/liquidity state. *Reprinted from Nakagawa Y, Ohta M, Nakazawa H, Kato S. Requirement of charged lipids for the hexadecanol-induced gelation in the phospholipid bilayer system.* Colloids Surf A *2014;**443**:272–79 with permission from publisher.*

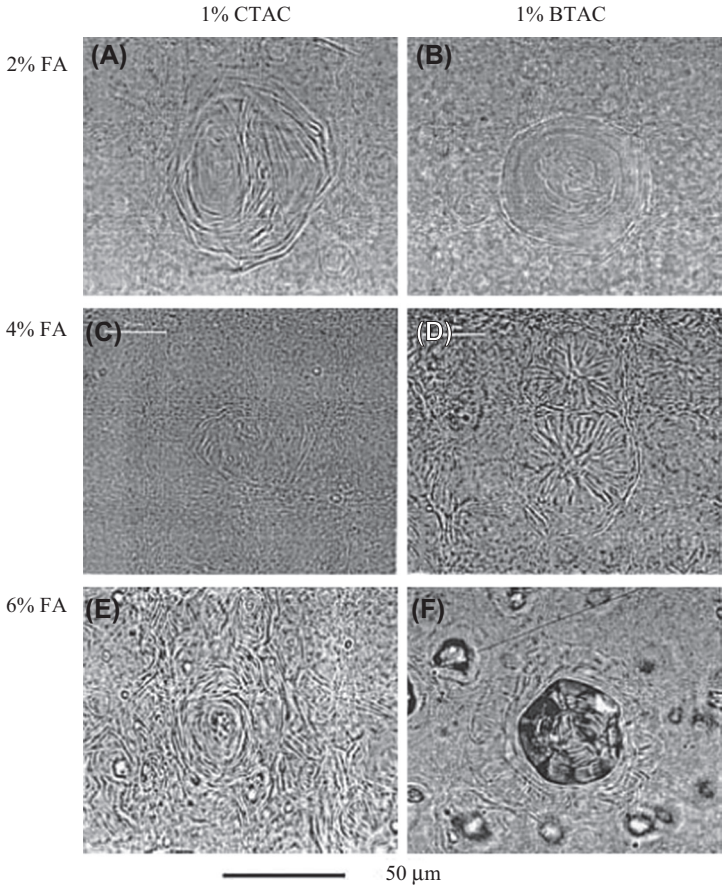



**FIGURE 25.42** Optical micrographs of various gel network samples at room temperature. Samples were made of CTAC or BTAC with various amount of fatty alcohol. Mole fraction of surfactant is (A) 0.293, (B) 0.247, (C) 0.172, (D) 0.141, (E) 0.121, and (F) 0.099. *From Nakarapanich J, Barameesangpet T, Suksamranchit S, Sirivat A, Jamieson AM. Rheological properties and structures of cationic surfactants and fatty alcohol emulsions: effect of surfactant chain length and concentration.* Colloid Polym Sci *2001;**279**:671–7.*

unintegrated fatty alcohol crystals (f).[53] This is considered due to the low mole fraction of BTAC (0.099) in the total amphiphile compared to the CTAC system (mole fraction 0.121). BTAC also has larger CPP compared to CTAC, and this makes it less capable of emulsifying fatty alcohol.

## 25.13 SUMMARY

Lamellar gel networks have been used in various cosmetics and pharmaceutical products for many years.

Lamellar gel network is a multiphase colloidal structure. The network is made of $L_\beta$ phase, and the network contains bulk water phase, and most often oil phase as well. $L_\beta$ phase is a lamellar phase built with solid state surfactants below their Krafft temperature and at much higher concentration than the solubility limit. The mechanical strength of the surfactant bilayer is much higher than liquid crystals. With this property and due to the network structure, lamellar gel network is sufficiently stable in practice, by physically holding bulk water phase and oil phase which otherwise phase separate immediately. In general, the $L_\beta$ phase of cosmetics formulations utilize combinations of fatty alcohol and surfactants. These amphiphiles together form hexagonally packed $\alpha$-gel structure as the unit crystalline structure of the bilayer, which builds lamellar phase. $\alpha$-Gel has the property of a crystal, as the molecules are restricted from translational diffusion, However, it is not pure crystal as the alkyl chains can revolve around the alkyl chain axis. For this reason it is called gel rather than a crystal.

## References


1. Junginger HE. Colloid structures of O/W creams. *Pharm Weekblad Sci Ed* 1984;**6**:141–9.
2. Eccleston GM. The microstructure and properties of fluid and semisolid lotions and creams. *IFSCC Mag* 2010:167–74.
3. Eccleston GM. Functions of mixed emulsifiers and emulsifying waxes in dermatological lotions and creams. *Colloids Surf A* 1997;**123–124**: 169–82.
4. Fukushima S, Yamaguchi M, Harusawa F. Effect of cetostearyl alcohol on stabilization of oil-in-water emulsion II. Relation between crystal form of the alcohol and stability of the emulsion. *J Colloid Interface Sci* 1977;**59**:159–65.
5. Fukushima S, Takahashi M, Yamaguchi M. Effect of cetostearyl alcohol on stabilization of oil-in-water emulsion I. Difference in the effect by mixing cetyl alcohol with stearyl alcohol. *J Colloid Interface Sci* 1976;**57**:201–6.
6. Fukushima S, Yamaguchi M. The effect of cetostearyl alcohol in cosmetic emulsions. *Cosmet Toilet* 1983;**98**:89–102.
7. Andrew ER. Molecular motion in certain solid hydrocarbons. *J Chem Phys* 1950;**18**:607–18.
8. Larson K. Arrangement of rotating molecules in the high-temperature form of normal paraffins. *Nature* 1967:383–4.
9. Snyder RG, Maroncelli M, Strauss HL, Elliger CA, Cameron DG, Casal HL, et al. Distribution of Gauche bonds in crystalline *n*-$C_{21}H_{44}$ in phase II. *J Am Chem Soc* 1983;**105**:133–4.
10. Awad TS, Johnson ES, Bureiko A, Olsson U. Colloidal structure and physical properties of gel networks containing anionic surfactant and fatty alcohol mixture. *J Dispers Sci Tech* 2011;**32**:807–15.
11. Small DM. Lateral chain packing in lipids and membranes. *J Lipid Res* 1984;**25**:1490–500.
12. Orita M, Uchiyama M, Hanamoto T, Yamashita O, Naitou S, Takeuchi K, et al. Formation of pseudo-intercellular lipids membrane on the skin surface by the alpha-gel holding a large amount of water. *J Soc Cosmet Chem Jpn* 2012;**46**:25–32.
13. Khalil RA, Zrari AA. Theoretical estimation of the critical packing parameter of amphiphilic self-assembled aggregates. *Appl Surf Sci* 2014;**318**: 85–9.
14. Tanaka K, Kamako S, Li J, Hashimoto S, Suzuki T. Unique self-assembling properties of linear-type long chain mono alkyl phosphate and its application in cosmetic formulations. *J Soc Cosmet Chem Jpn* 2015;**49**:16–21.
15. Krog N, Larsson K. Phase behaviour and rheological properties of aqueous systems of industrial distilled monoglycerides. *Chem Phys Lipids* 1968;**2**:129–43.
16. Cassin G, de Costa C, van Duynhoven JPM, Agterof WGM. Investigation of the gel to coagel phase transition in monoglyceride – water systems. *Langmuir* 1998;**14**:5757–63.
17. Alfutimie A, Curtis R, Tiddy GJT. The phase behavior of mixed saturated and unsaturated monoglycerides in water system. *Colloid Surf A* 2015;**465**:99–105.
18. Alfutimie A, Curtis R, Tiddy GJT. Gel phase ($L_\beta$) formation by mixed saturated and unsaturated monoglycerides. *Colloid Surf A* 2014;**456**: 286–95.
19. Iwata T, Aramaki K. Effect of the behenyl trimethyl ammonium counterion on the lamellar gel property. *IFSCC Mag* 2013;**16**:249–54.
20. Minguet M, Subirats N, Castán P, Sakai T. Behenamidopropyl dimethylamine: unique behavior in solution and in hair care formulations. *Int J Cosmet Sci* 2010;**32**:246–57.
21. Kunieda H, Shinoda K. Solution behavior of dialkyldimethylammonium chloride. In: *Water. Basic properties of antistatic fabric softeners*. *J Phys Chem*, **82**; 1978. p. 1710–4.
22. Laughlin RG, Munyon RL, Fu YC, Fehl AJ. Physical science of the dioctadecyldimethylammonium chloride – water system. 1. Equilibrium phase behavior. *J Phys Chem* 1990;**94**:2546–52.
23. Israelachvili JN. *Intermolecular and surface forces*. 3rd ed. Elsevier; 2011. p. 447.
24. Sagnella SM, Conn CE, Krodkiewska I, Drummond CJ. Nonionic diethanolamide amphiphiles with unsaturated C18 hydrocarbon chains: thermotropic and lyotropic liquid crystalline phase behavior. *Phys Chem Chem Phys* 2011;**13**:13370–81.

25. Quinn PJ, Koynova RD, Lis LJ, Tenchov BG. Lamellar gel − Lamellar liquid crystal phase transition of dipalmitoylphosphatidylcholine multilayers freeze-dried from aqueous trehalose solutions. A real-time X-ray diffraction study. *Biochim Biophys Acta* 1988;**942**:315−23.
26. Nagai Y, Kawabata Y, Kato T. Microscopic investigation on morphologies of bilayer gel structure in the mixed polyoxyethylene-type nonionic surfactant systems. *J Phys Chem B* 2012;**116**:12558−66.
27. Nakagawa Y, Ohta M, Nakazawa H, Kato S. Requirement of charged lipids for the hexadecanol-induced gelation in the phospholipid bilayer system. *Colloids Surf A* 2014;**443**:272−9.
28. Kawabata Y, Matsuno A, Shinoda T, Kato T. Formation process of bilayer gel structure in a nonionic surfactant solution. *J Phys Chem B* 2009;**113**: 5686−9.
29. Ito M, Kosaka Y, Kawabata Y, Kato T. Transition processes from the lamellar to the onion state with increasing temperature under shear flow in a nonionic surfactant/water system studied by Rheo-SAXS. *Langmuir* 2011;**27**:7400−9.
30. Kosaka Y, Ito M, Kawabata Y, Kato T. Lamellar-to-onion transition with increasing temperature under shear flow in a nonionic surfactant/water system. *Langmuir* 2010;**26**:3835−42.
31. Zilman AG, Granek R. Undulation instability of lamellar phases under shear: A mechanism for onion formation? *Eur Phys J B* 1999;**11**:593−608.
32. Feitosa E, Alves FR. The role of counterion on the thermotropic phase behavior of DODAB and DODAC vesicles. *Chem Phys Lipids* 2008;**156**: 13−6.
33. Berr S, Jones RRM, Johnson Jr JS. Effect of counterion on the size and charge of alkyltrimethylammonium halide micelles as a function of chain length and concentration as determined by small-angle neutron scattering. *J Phys Chem* 1992;**96**:5611−4.
34. Fairhurst DJ, Baker ME, Shaw N, Egelhaaf SU. Swelling and shrinking kinetics of a lamellar gel phase. *Appl Phys Lett* 2008;**92**:174105.
35. Kawabata Y, Ichiguchi K, Ando T, Kato T. Vesicle formations at critical vesicle concentration in a polyoxyethylene type nonionic surfactant system. *Colloid Surf A* 2014;**462**:179−85.
36. Kaler EW, Herrington KL, Kamalakara Murthy A. Phase behavior and structures of mixtures of anionic and cationic surfactants. *J Phys Chem* 1992;**96**:6698−707.
37. Coldren BA, Warriner H, van Zanten R, Zasadzinski JA, Sirota EB. Flexible bilayers with spontaneous curvature lead to lamellar gels and spontaneous vesicles. *Proc Natl Acad Sci* 2006;**103**:2524−9.
38. Mishima K, Satoh K, Suzuki K. Optical birefringence of multilamellar gel phase of cholesterol/phosphatidylcholine mixtures. *Colloid Surf B* 1996;**7**:83−9.
39. Kranenburg M, Smit B. Phase behavior of model lipid bilayers. *J Phys Chem B* 2005;**109**:6553−63.
40. McIntosh TJ, McDaniel RV, Simon SA. Induction of an interdigitated gel phase in fully hydrated phosphatidylcholine bilayers. *Biochim Biophys Acta* 1983;**731**:109−14.
41. Simon SA, McIntosh TJ. Interdigitated hydrocarbon chain packing causes the biphasic transition behavior in lipid/alcohol suspensions. *Biochim Biophys Acta* 1984;**773**:169−72.
42. Rowe ES. Thermodynamic reversibility of phase transitions. Specific effects of alcohols on phosphatidylcholines. *Biochim Biophys Acta* 1985; **813**:321−30.
43. Adachi T, Takahashi H, Ohki K, Hatta I. Interdigitated structure of phospholipid-alcohol systems studied by X-ray diffraction. *Biophys J* 1995; **68**:1850−5.
44. Makai M, Csányi E, Németh Z, Pálinkás J, Erős I. Structure and drug release of lamellar liquid crystals containing glycerol. *Int J Pharm* 2003; **256**:95−107.
45. Goto M, Ito Y, Ishida S, Tamai N, Matsuki H, Kaneshina S. Hydrostatic pressure reveals bilayer phase behavior of dioctadecyldimethylammonium bromide and chloride. *Langmuir* 2011;**27**:1592−8.
46. Kodama M, Kunitake T, Seki S. Thermal characterization of the mode of phase transition in the dioctadecyldimethylammonium bromide − water system in relation to the stability of its gel phase. *J Phys Chem* 1990;**94**:1550−4.
47. Nagai Y, Kawabata Y, Kato T. *J Phys Chem B* 2012;**116**:12558−66.
48. Eccleston GM, Behan-Martin MK, Jones GR, Towns-Andrews E. Synchrotron X-ray investigations into the lamellar gel phase formed in pharmaceutical creams prepared with cetrimide and fatty alcohols. *Int J Pharm* 2000;**203**:127−39.
49. Shearman GC, Ugazio S, Soubiran L, Hubbard J, Ces O, Seddon JM, et al. Factors controlling the stability of a kinetically hindered lamellar−lamellar transition. *J Phys Chem B* 2009;**113**:1948−53.
50. Okuma CH, Andrade TAM, Caetano GF, Finci LI, Maciel NR, Topan JF, et al. Development of lamellar gel phase emulsion containing marigold oil (*Calendula officinalis*) as a potential modern wound dressing. *Eur J Pharm Sci* 2015;**71**:62−72.
51. Benton WJ, Miller CA, Wells RL. Phase behavior and network formation in a cationic surfactant-fatty alcohol-water system. *J Am Oil Chem Soc* 1987;**64**:424−33.
52. Kudra P, Sokolowski T, Blümich B, Wittern KP. Phase behavior of liquid−crystalline emulsion systems. *J Colloid Interface Sci* 2010;**349**:554−9.
53. Nakarapanich J, Barameesangpet T, Suksamranchit S, Sirivat A, Jamieson AM. Rheological properties and structures of cationic surfactants and fatty alcohol emulsions: effect of surfactant chain length and concentration. *Colloid Polym Sci* 2001;**279**:671−7.

CHAPTER

# 26

# Polymer–Surfactant Interactions

*B. Lindman*[1], *T. Nylander*[1,2,3]

[1]Lund University, Lund, Sweden; [2]Mid Sweden University, Sundsvall, Sweden; [3]Nanyang Technological University, Singapore, Singapore

## 26.1 INTRODUCTION

Mixed polymer–surfactant systems have broad applications, ranging from detergents, paints, pharmaceuticals, cosmetics, to biotechnologies. Formulations are typically complex multicomponent mixtures and polymers, and surfactants are ubiquitous in them. Thus in formulations like those for cosmetics and personal care products, there are always one or more macromolecular species and one or more low molecular weight amphiphiles, like a surfactant or a polar lipid. Depending on the identity of the components the macroscopic properties can vary widely. The properties have their basis in the intermolecular interactions between the different components. In this treatise, a broad overview of these interactions will be provided and, with this as a background, different aspects such as phase separation phenomena, rheological properties, and interfacial behavior will be described.

The combined action of polymer and surfactant in formulations can sometimes be complementary, with surfactant giving cleansing effects and the polymer stabilization, thickening, or prevention of redeposition. In other cases, the effect can be termed synergistic; for example, strong thickening effects or phase separation effects are used in important formulations.

In aqueous solutions there are two important attractive interactions:

- electrostatic interactions of solutes with an opposite net charge and
- hydrophobic interactions

The electrostatic interactions can be repulsive or attractive depending on whether the cosolutes have opposite or similar charges and constitute dominantly an entropic force related to the counterions; coulombic interactions have less significance in an aqueous system.

The counterion entropy effect is related to the fact that any highly charged system (macroscopic surface, polyion, surfactant aggregate, etc.) will attract counterions. There will thus be an accumulation of counterions in the vicinity of the highly charged species, which corresponds to a negative entropy contribution. If a positively charged polyelectrolyte is approaching a negatively charged surface or a negatively charged polyelectrolyte, the counterions can be released and there is an entropy gain. As we will see, this association is typically quite important and often leads to phase separation.

Approaching a positively charged polyelectrolyte to a positively charged surface or to a positively charged polyelectrolyte, on the other hand, leads to a further accumulation of counterions and a further decrease of counterion entropy; it is therefore repulsive.

The counterion entropy effect is directly related to the difference in counterion concentration at the highly charged surface/aggregate/molecule and in the bulk solution. A large difference due to attraction to the surface results in a negative entropy contribution. If an electrolyte is added to the system, the bulk counterion concentration increases, thus corresponding to an entropy increase. Therefore, electrostatic interactions are weakened by electrolyte addition; we talking about a "screening" effect.

*Cosmetic Science and Technology: Theoretical Principles and Applications*
http://dx.doi.org/10.1016/B978-0-12-802005-0.00026-4



Copyright © 2017 Elsevier Inc. All rights reserved.

For aqueous systems there is one more strongly attractive interaction, the hydrophobic interaction. This leads to an attraction between molecules, which are nonpolar or contain nonpolar groups, i.e., are amphiphilic. The hydrophobic interactions have their basis in the reduced water–water hydrogen bonding in the presence of the solute.

## 26.2 HOMOPOLYMER–IONIC SURFACTANT SYSTEMS SHOW ASSOCIATION

In a solution of a polyelectrolyte and an oppositely charged surfactant there is typically a complex formation, and the same commonly applies in mixed solutions of a nonionic polymer and an ionic surfactant. It is commonly referred to a binding of the surfactant molecules to the polymer molecules, but as we will see later an alternative picture normally gives a better rationalization.

To discuss this we need to consider the basis of surfactant self-assembly, which is driven by hydrophobic interactions. Surfactant molecules can aggregate into a large number of different structures and show very rich phase behavior in water. For a polar water-soluble surfactant, which we mainly consider here, the surfactant starts to self-assemble into micelles at a quite well-defined concentration, the critical micelle concentration (CMC). The micelles can be roughly spherical or elongated, "thread-like"; we will now focus on the spherical micelles.

For an ionic surfactant, self-assembly leads to highly charged entities; it is thus accompanied by a large decrease of counterion entropy and therefore the CMC is high. Nonionic surfactants have roughly two orders of magnitude lower CMC values. A cosolute that reduces this entropic penalty will facilitate micelle formation and lower the CMC. A simple case is that of addition of simple electrolyte. Regarding polymer addition, it is clear that an oppositely charged polyelectrolyte will have a dramatic effect because binding of the polyion releases a large number of small counterions from the micelles; the result is a large increase in entropy and a dramatic lowering of the CMC. As expected, the effect is reduced if the solution contains simple electrolyte.

In addition, a nonionic polymer will normally reduce the CMC, more so if it is has lower polarity, like poly(ethylene glycol) or poly(vinyl pyrrolidone). These molecules will be located at the micelle surface and reduce the charge density.

Rather than binding of surfactant or micelle to the polymer molecule, it is thus more correct to consider polymer-induced surfactant self-assembly: it is energetically more favorable for the surfactant to form micelles at the polymer molecule. The micelles are quite similar to those formed by the surfactant alone. For the case of spherical micelles, we will have a "pearl-necklace" structure with discrete micelles along the polymer chain (Fig. 26.1)

The surfactant–polymer association can be inferred from many physicochemical parameters, like surfactant activity, electric conductivity, solubilization, spectroscopy [nuclear magnetic resonance (NMR), etc.], calorimetry, scattering, etc. An important characteristic of a surfactant is the surface activity, and in Fig. 26.2 we compare schematically the surface tension of surfactant alone and that in the presence of a polymer. As can be seen there is a two-step lowering, rather than one such as for surfactant alone, in the presence of a polymer; the first break point indicates the onset of association and the second the saturation level after which the free surfactant concentration increases. One important feature shown in Fig. 26.2 is that in a wide range of surfactant concentration the surface tension is higher as polymer is added to a surfactant solution; thus the surfactant has lower tendency to adsorb at the air–water interface. A second feature is that at high enough surfactant concentrations the same surface tension is reached as for surfactant alone.

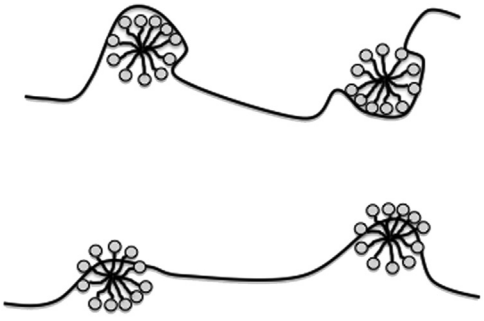


FIGURE 26.1 "Pearl-necklace model" of surfactant–polymer association. *From Kronberg B, Holmberg K, Lindman B.* Surface chemistry of surfactants and polymers. *Chichester, UK: John Wiley & Sons; 2014.*

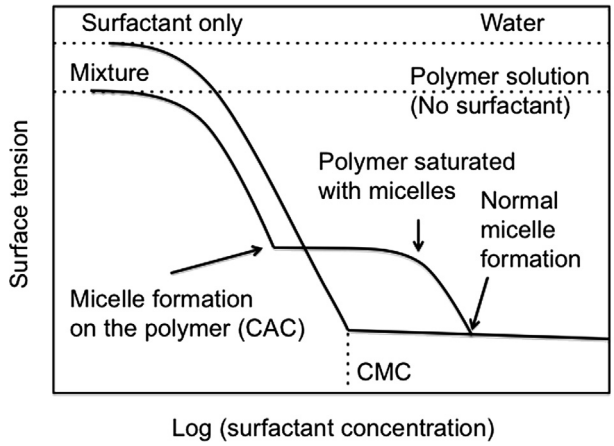



FIGURE 26.2 A schematic plot of the concentration dependence of the surface tension for mixed polymer–surfactant solutions. The corresponding curve for the system with only surfactant is also shown. For the case of surfactant alone, there is a single-step decrease before the CMC, whereas for the mixed system there is a decrease until the onset of polymer–surfactant association (an example of critical association concentration), then a plateau before a second-step decrease. *From Kronberg B, Holmberg K, Lindman B.* Surface chemistry of surfactants and polymers. *Chichester, UK: John Wiley & Sons; 2014.*

Whereas ionic surfactants broadly associate with polymers, nonionic surfactants do not associate with homopolymers; they will only associate with polymers that have hydrophobic groups, i.e., are amphiphilic.

In summary, we can distinguish between three types of polymer–surfactant systems that show association:

1. Systems of oppositely charged polymer and surfactant.
2. Systems of an ionic surfactant and a nonionic polymer.
3. Systems of an amphiphilic polymer, in which all types of surfactants show association.

## 26.3 POLYELECTROLYTE–SURFACTANT SYSTEMS MAY SHOW TWO-STEP ASSOCIATION

The association between polymer and surfactant is thus mainly determined by two interactions, electrostatic and hydrophobic. As said, an oppositely charged polymer can strongly facilitate surfactant self-assembly. If the polymer is very polar, then binding of surfactant leads to partial charge neutralization of the polymer. This is illustrated for the case of mixtures of sodium polyacrylate and cationic surfactant in Fig. 26.3. The binding is strongly cooperative,

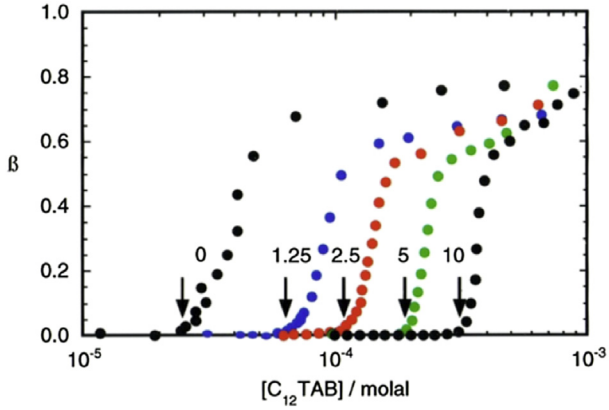



FIGURE 26.3 Binding isotherms for dodecyl trimethylammonium bromide ($C_{12}$TAB) in 0.50 mM sodium poly(acrylate) (NaPA) at indicated NaBr concentations (mM). Here, $\beta = N_s C_m / C_p$, in which $N_s$ is the aggregation number, $C_m$ is concentration of micelles and $C_p$ is the concentration of polymer charges. *Courtesy of Per Hansson.*

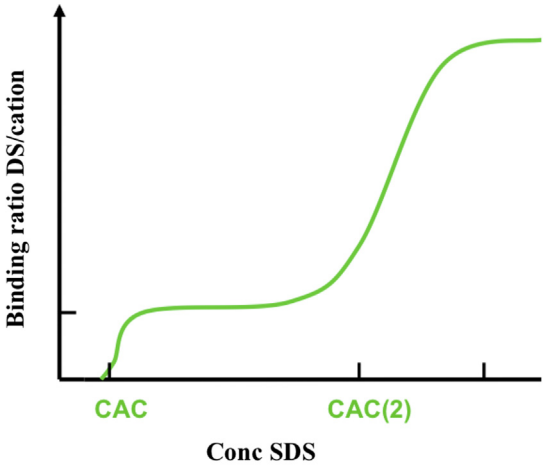



FIGURE 26.4 Typical surfactant-binding isotherm of ionic surfactant to oppositely charged polymer having some hydrophobic character. *Courtesy of Lennart Piculell.*

starting at a concentration termed the critical association concentration (CAC). The binding is best described by a micelle formation induced by the polyion, i.e., the driving force is the increased entropy of the counterions released from the polymer and the micelle. We note that it cannot be described as a binding of micelles to the polymer. The CAC is necessarily lower than the CMC, and, in the bulk solution, the free-surfactant concentration is below the CMC, and micelles do not exist.

Fig. 26.3 also illustrates that in the presence of electrolyte the association is weakened and the CAC increased, a consequence of a screened electrostatic attraction.

If the polyelectrolyte is less polar, hydrophobic interactions between surfactant and polymer can, as shown by Lennart Piculell, lead to a two-step binding isotherm as illustrated in Fig. 26.4 for the case of cationic hydroxyethyl cellulose. In a first step, the attraction between polymer and surfactant is dominated by electrostatic interaction. However, because cellulose is amphihilic, i.e., has distinct hydrophobic properties, there will also be attractive hydrophobic interactions between polymer and surfactant. At higher surfactant concentrations, there will be a second cooperative binding step, thus a second CAC. Although the first binding step leads to significant charge neutralization of the polymer, the second binding step will lead to charge reversal. As we will see, the two binding steps are often manifested in the phase behavior: The first step may lead to phase separation of an approximately charge neutral complex, whereas the second step leads to redissolution.

## 26.4 AMPHIPHILIC POLYMER SELF-ASSEMBLY

For previous case 3, in which the polymer also has distinct hydrophobic groups, both components are self-assembling individually. In combination they give mixed micelles (or other aggregates). For the case of block copolymers, the aggregates show strong resemblances to mixed aggregates of two surfactants. For the case of hydrophobically modified water-soluble polymers, the picture is different and more complex. There are two common types of hydrophobically modified water-soluble polymers, referred to as associative thickeners, end-capped, or graft copolymers; the graft copolymers, which have a hydrophilic backbone and hydrophobic grafts (for example, alkyl chains) show the largest viscosity increases and are most sensitive to surfactant addition. Such polymers have a backbone that is water soluble, like polyacrylate or a cellulose derivative; onto this have been grafted a relatively low number (typically 1–5% of the monomer units modified) of hydrophobic groups, like C12–C18 alkyl chains. In Fig. 26.5 we illustrate the self-assembly of the polymer alone. The associated hydrophobic grafts act as physical cross-links and a physical gel is formed.

Because surfactant association to hydrophobic sites is strong, there will, from low concentrations, be a binding of surfactant molecules to the hydrophobic microdomains (cross-links); these will grow and hence achieve longer lifetimes. In turn, this results in increased viscosity, typically by orders of magnitude. There is thus a dramatic synergistic effect in rheology. However, as more surfactant is added, the viscosity reaches a maximum and thereafter drops abruptly. The general behavior is schematically illustrated in Fig. 26.6.

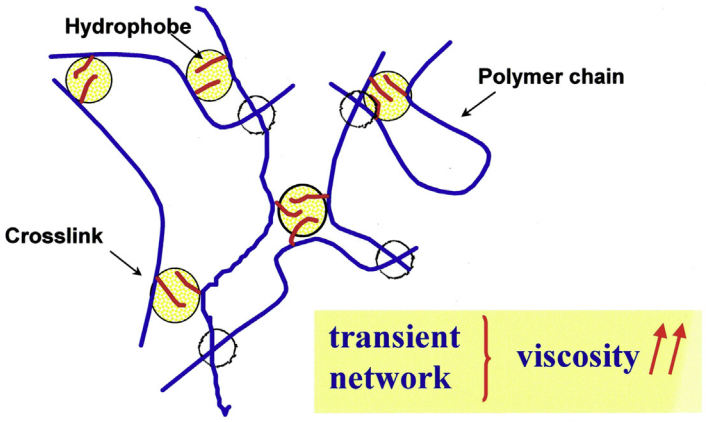



FIGURE 26.5 A hydrophobically modified water-soluble polymer associates with a three-dimensional network, giving physical gelation. *Courtesy of Leif Karlson.*

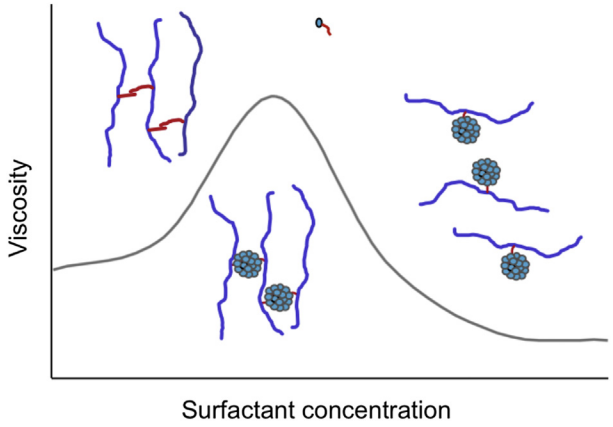



FIGURE 26.6 Association between a surfactant and a hydrophobically modified water-soluble polymer gives a strong thickening effect. Viscosity is shown as a function of surfactant concentration. *Courtesy of Leif Karlson.*

At higher surfactant concentrations there is as indicated a major loss of the thickening effect and the viscosity decreases to values well below that of the solution of the polymer alone. This occurs when the concentration of micellar aggregates reaches values similar to those of the polymer hydrophobe groups. For cross-linking at least two polymer molecules should be associated with the same micelles but at higher surfactant concentrations there is only one polymer hydrophobe in each micelle and there is a repulsion between polymer molecules.

The stoichiometric aspects are further illustrated in Fig. 26.7. Here is shown the effect of addition of sodium dodecyl sulfate (SDS) to 1 wt% solutions of a hydrophobically modified nonionic cellulose derivative (ethyl hydroxyethyl cellulose). The viscosity is related to the concentration of micelles in the solution. As can be seen, addition of SDS over a wide range of concentration does not affect the micelle concentration. SDS addition instead leads to increase of the aggregation number of the micelles. As the optimal aggregation number (ca. 60 for SDS) is reached, the micelles cannot grow further and additional micelles are created; at this point the viscosity starts to decrease abruptly.

The high sensitivity of rheology for relatively minor excesses of surfactant is a complication for several applications, because the surfactant concentration cannot always be controlled. The problem can be overcome by going away from spherical micelles, which are monodisperse and have a well-defined aggregation number. In the case of SDS, a transition from small spherical micelles to elongated thread-like micelles can be induced inter alia by addition of electrolyte or adding a long-chain alcohol or a relatively hydrophobic nonionic surfactant. Especially effective is the addition of relatively small amounts of an oppositely charged surfactant; this is illustrated in Fig. 26.8. For the case of Fig. 26.7, addition of cationic surfactant could lead to increase in viscosity by at least five orders of magnitude.

These concepts of gel formation of mixed polymer–surfactant systems have been extended to other types of surfactant aggregates, like in vesicle gels and gelled microemulsions.

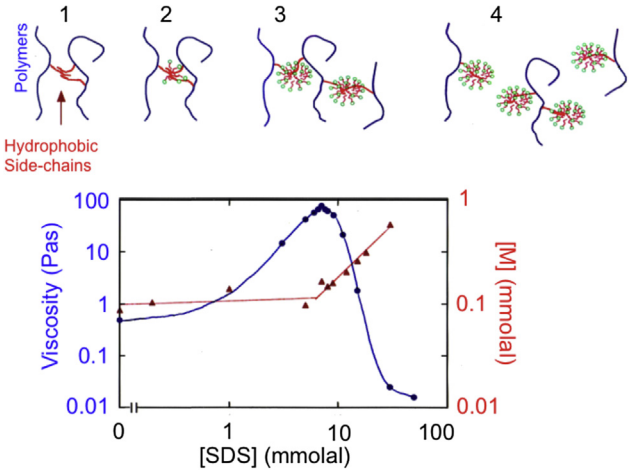



FIGURE 26.7 Viscosity of solutions of a hydrophobically modified cellulose derivative as a function of the concentration of added ionic surfactant. For comparison the concentration of micelles is shown (triangles, right axis). *Courtesy of Krister Thuresson.*

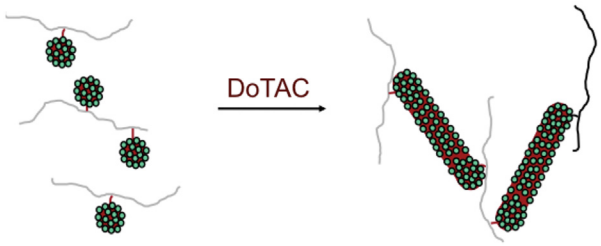



FIGURE 26.8 Micelle growth can be achieved, for example, by adding an oppositely charged surfactant. The corresponding reduction in micelle concentration can induce major increases in viscosity (see text). *Courtesy of Susanne Nilsson.*

## 26.5 PHASE SEPARATION IS COMMON FOR POLYMER–SURFACTANT MIXTURES

Polymer molecules have low translational entropy and, therefore, the solubility is typically limited. The situation is different for polyelectrolytes because of the large entropy contribution from the counterions. The general rule is that nonionic polymers have relatively low solubility whereas polyelectrolytes are highly soluble. On addition of electrolyte, however, the counterion entropy effect is lost and many polyelectrolytes lose their solubility.

In mixed systems of two nonionic polymers, there is typically a segregative phase separation; i.e., there are two solutions at equilibrium, each enriched in one of the polymers. The same applies to mixed solutions of two polyelectrolytes bearing the same charge. In mixed solutions of one nonionic and one ionic polymer there is typically miscibility, driven by the counterion entropy. Finally, if we mix two oppositely charged polyelectrolytes, there is a strong attraction that leads to associative phase separation, often denoted complex coacervation; the driving force is the release of the counterions of the two polyelectrolytes.

Because surfactant aggregates are large and have a high effective molecular weight, and then low translational entropy, the same simple principles of phase behavior apply for mixed polymer–surfactant systems as for polymer–polymer mixtures. Thus, in the absence of an attractive interaction (which for aqueous systems is either of electrostatic or hydrophobic origin) between polymer molecules and micelles, we expect a segregation. This is indeed observed when we mix in aqueous solution a nonionic polymer with a nonionic surfactant or mix a polyelectrolyte with an ionic surfactant of similar charge. An illustration is given in Fig. 26.9. This concerns an anionic surfactant (SDS) and an anionic polysaccharide (sodium hyaluronate). On salt addition, phase separation is enhanced due to micellar growth, thus reducing entropy of mixing.

An intriguing case with several important applications is that of oppositely charged systems. As mentioned, a mixture of two oppositely charged polyelectrolytes shows strongly associative behavior, as demonstrated by a strong tendency to phase separation. A mixture of a polyelectrolyte and an oppositely charged surfactant will also associate strongly. We discussed above the considerable lowering of the CMC. In addition, phase separation

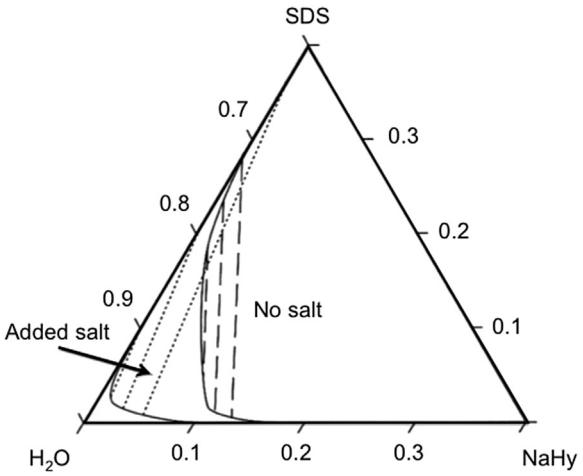



**FIGURE 26.9** Phase separation in mixtures of a polyelectrolyte and a similarly charged surfactant is typically segregative and may be enhanced on salt addition if there is an electrolyte-induced micellar growth. The example refers to mixtures of sodium dodecyl sulfate and the anionic polysaccharide sodium hyaluronate. *From Thalberg K, Lindman, B. Segregation in aqueous systems of polyelectrolyte and ionic surfactant.* Colloids Surf *1993;**76**:283–8.*

takes place in a broad range of concentrations. For example, if an ionic surfactant is progressively added to a solution of an oppositely charged polymer, turbidity is encountered for certain concentrations. As surfactant starts to bind to the polymer, at the CAC, neutral insoluble complexes come out of solution. In many cases there is as mentioned a redissolution, as seen from the solutions becoming clear at higher surfactant concentrations. This will occur if the polymer has a certain hydrophobicity and thus can bind the surfactant above charge stoichiometry; when the complexes become increasingly charged, their solubility increases. This redissolution and charge reversal will not occur for entirely hydrophilic polymers.

The strong associative phase separation of such systems can be characterized in the conventional phase diagram for three-component systems as exemplified in Fig. 26.10. As shown, an aqueous mixture of a polyelectrolyte and an oppositely charged surfactant phase separates into one dilute phase and one, typically highly viscous, phase, concentrated in both polymer and surfactant.

The extent of phase separation in the system of Fig. 26.10 increases strongly with the surfactant alkyl chain length and the polymer molecular weight. On addition of an electrolyte, the phase separation is reduced and then

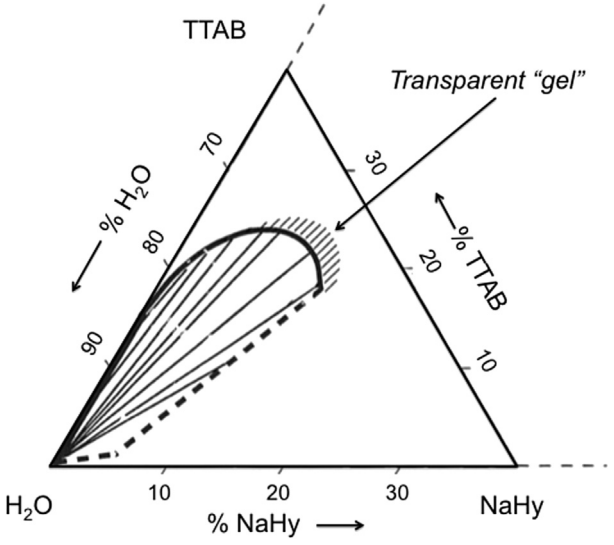



**FIGURE 26.10** A mixture of an ionic surfactant and an oppositely charged polyelectrolyte typically gives an associative phase separation, as here exemplified by tetradecyltrimethyl ammonium bromide and sodium hyaluronate. *From Thalberg K, Lindman B, Karlström G. Phase diagram of a system of cationic surfactant and anionic polyelectrolyte: tetradecyltrimethylammonium bromide–hyaluronan–water.* J Phys Chem *1990;**94**:4289–95.*

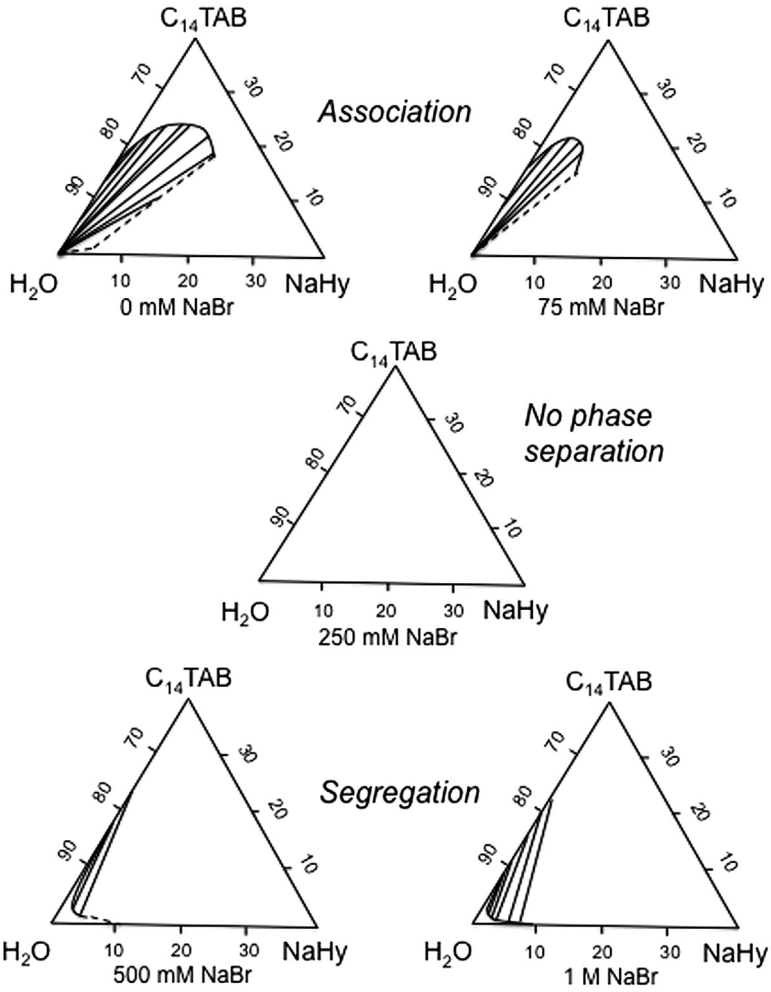



FIGURE 26.11 Phase separation in mixtures of a polyelectrolyte and an oppositely charged surfactant changes from associative, to no phase separation, and finally to segregative as electrolyte is added. The example shows mixtures of a cationic surfactant, tetradecyltrimethylammonium bromide, and an anionic polysaccharide, sodium hyaluronate. *From Thalberg K, Lindman B, Karlström G. Phase behavior of a system of cationic surfactant and anionic polyelectrolyte: the effect of salt.* J Phys Chem *1991;**95**:6004–11.*

eliminated, but at higher electrolyte content there is a phase separation again. However, as we can see in Fig. 26.11, this is of a different nature. This behavior, which is very similar to what is observed for mixtures of two oppositely charged polymers, can best be understood from a combination of polymer incompatibility and electrostatic effects. We note that the concentration of counterions is very high and, therefore, unlike for the nonionic polymers, phase separation with a polyelectrolyte in one phase leads to confinement of the counterions and a very significant entropy loss. At high electrolyte concentrations, this entropy contribution is eliminated and the phase separation will be similar to that of uncharged polymer systems. In the case of Fig. 26.11, we have an intrinsically segregating system, as can be seen from the phase diagram at high electrolyte concentrations.

The associative phase separation, occurring for mixtures of both anionic and cationic polymers with oppositely charged surfactants at low salt contents, is thus understood from the entropy of the counterion distribution. The highly charged micelles and polyelectrolyte molecules are enriched with counterions at their surface due to the coulombic attraction. On association, counterions of both cosolutes are transferred into the bulk with a concomitant entropy gain; therefore, there is a strong tendency to associative phase separation in the absence of added salt.

When the surfactant and the polymer have similar charges, the entropic loss is absent and a segregative phase separation is the rule, as illustrated earlier in Fig. 26.9.

Although the presentations of Figs. 26.10 and 26.11 are a useful starting point for considering the behavior of polyelectrolyte-oppositely charged surfactant systems, the actual phase behavior is more complex as it is for any system of two electrolytes without a common ion. Thus, we have to consider two additional electrolytes, which

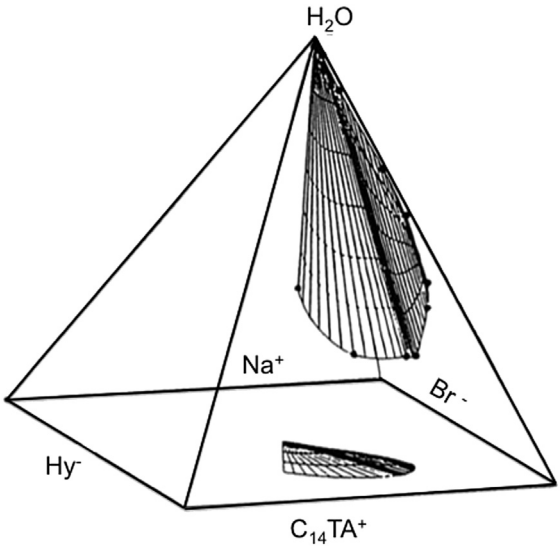



**FIGURE 26.12** Polyelectrolyte–ionic surfactant systems require a three-dimensional diagram for complete illustration of the phase behavior. *From Thalberg K, Lindman B, Karlström G. Phase diagram of a system of cationic surfactant and anionic polyelectrolyte: tetradecyltrimethylammonium bromide–hyaluronan–water.* J Phys Chem *1990;**94**:4289–95.*

are the combination of polyion and surfactant ion and the combination of the counterions. Therefore, a three-dimensional representation is needed as shown in Fig. 26.12.

Lennart Piculell in Lund has elaborated on these aspects in various ways. He has inter alia demonstrated the usefulness of basing phase diagram work on the "complex salt," i.e., the combination of polyion and surfactant ion. Aqueous mixtures of the complex salt combined with either surfactant or polymer are true three-component systems and can be accurately represented in the normal Gibbs triangle.

Piculell has also pointed out the role of the combination of the counterions, the "simple salt," as a "hidden variable." In this way, the fact that polyelectrolyte–surfactant systems may be phase separated, and concentrated on adding water, is easily illustrated. Thus, the effect of adding water leads to a dilution of the simple salt and thus to a strengthened association between polyion and surfactant and then a larger propensity to phase separation (cf. Fig. 26.11). On dilution, the attraction becomes stronger, inducing phase separation, an effect used, for example, in hair-care formulations.

The system illustrated previously concerns a rather hydrophilic polyion, hyaluronate. If the polyion is less polar, then there will be a strengthened association of surfactant and thus a larger tendency toward charge reversal of the complexes. Therefore, phase separation occurs in a more limited range, and the two-phase region is narrower.

This has consequences for using polymer–surfactant systems for rheology control. If we mix a hydrophilic polyelectrolyte with an oppositely charged surfactant, it has limited use to increase the viscosity because phase separation occurs over a wide range. Hydrophobically modified water-soluble polymers, broadly used as associative thickeners, behave differently because they easily bind surfactants in excess of charge neutrality, leading to soluble complexes. Because of the combination of electrostatic and hydrophobic association such mixed systems are very useful for thickening purposes. An even larger effect may be obtained for mixtures of two oppositely charged hydrophobically modified polyelectrolytes (cf. Fig. 26.13). Again, although two hydrophilic polyelectrolytes will phase separate over most of the mixing range, the hydrophobic modification allows for the facile formation of nonstoichiometric complexes with significant net charge.

Because of gene therapy applications, the interaction between DNA and cationic surfactants or lipids has received extensive attention. DNA is a polyelectrolyte with a particularly high linear charge density at the same time as it has strong hydrophobic groups. It is thus a distinctly amphiphilic polymer which can self-assemble driven by the hydrophobic interactions between the bases, the most well-known structure being the double helix.

The CAC values of cationic surfactant–DNA systems are quite low as expected from the high charge density. Interestingly, single-stranded DNA (ssDNA) gives stronger association than double-stranded DNA (dsDNA), showing the importance of the exposed bases promoting hydrophobic interactions. The strong interaction in DNA systems is clearly reflected in phase diagrams, showing a strongly associative behavior. This is illustrated in Fig. 26.14 on a logarithmical concentration scale for three surfactants with different chain lengths.

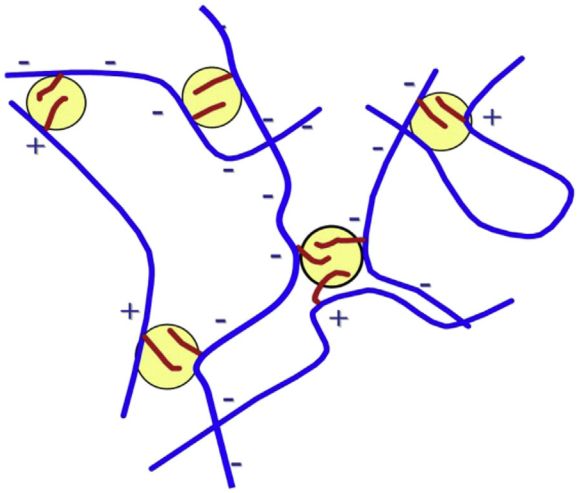


FIGURE 26.13 Illustration of the association in mixed solutions of oppositely charged hydrophobically modified polyelectrolytes. *Courtesy of Filipe Antunes.*

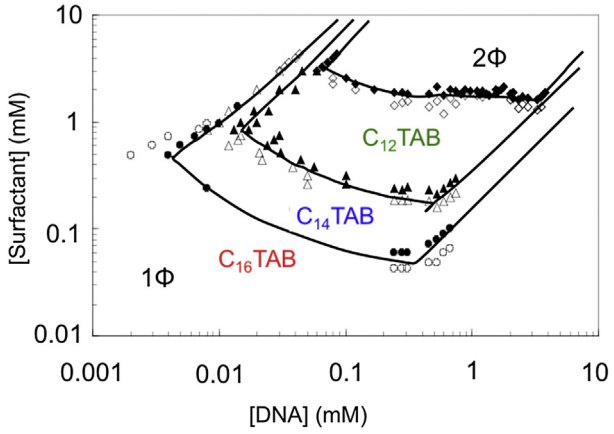



FIGURE 26.14 Phase diagrams of dsDNA–cationic surfactant systems showing a strong associative phase separation, which is strongly dependent on surfactant alkyl chain length. *Dias R, Mel'nikov SM, Lindman B, Miguel MG. DNA phase behavior in the presence of oppositely charged surfactants.* Langmuir *2000;**16**:9577–83.*

An unexpected observation in the phase diagram work on DNA was that excess surfactant was not observed to give redissolution, which would be expected for such a hydrophobic polyelectrolyte as DNA. Furthermore, unlike other systems (see earlier discussion), even high amounts of electrolyte did not lead to redissolution of the precipitate. The early work was performed in the conventional way by adding surfactant progressively to a solution of the polyelectrolyte. By introducing other mixing strategies, it could, however, be demonstrated that solutions with an excess of surfactant are indeed homogeneous solutions. This could be shown by adding DNA to concentrated surfactant solutions.

The associative phase separation occurring for systems of oppositely charged polymer and surfactant leads to one dilute and one concentrated phase. The concentrated phase can be solid or liquid in nature depending on the system but, typically, it has a liquid crystalline nature. Lamellar, hexagonal, and cubic structures have been identified. We illustrate this by structures identified for mixed systems of dsDNA, cationic surfactant, and lipid in Fig. 26.15.

## 26.6 GELS: THERMAL GELATION, CHEMICAL GELS, AND MICROGEL PARTICLES

In conjunction with gels and gelation, there are several aspects to polymer–surfactant systems. Mixed solutions can give rise to gels, and here we will illustrate with thermal gelation. Furthermore, surfactants can strongly

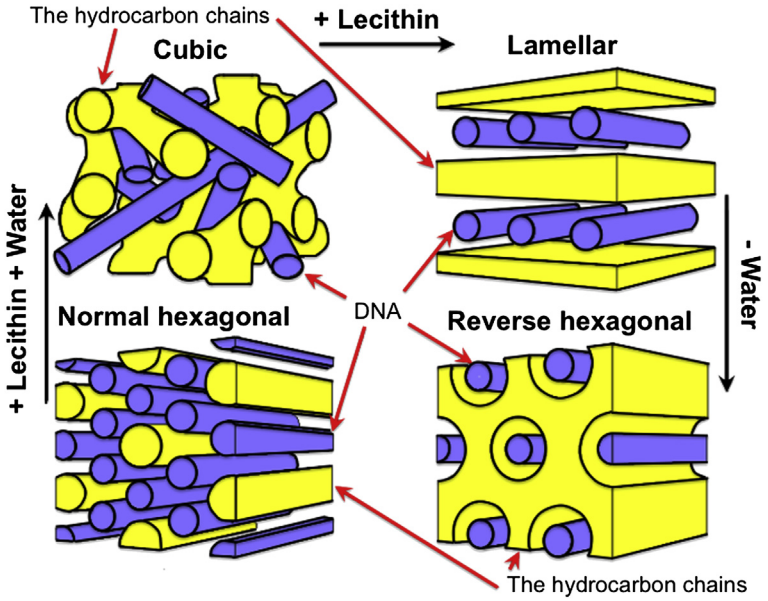



**FIGURE 26.15** The most important liquid crystalline structures occurring in mixtures of a (rigid) polyelectrolyte (in blue) and an oppositely charged surfactant (in yellow). *After Bilalov A, Olsson U, Lindman B. Complexation between DNA and surfactants and lipids: phase behavior and molecular organization.* Soft Matter *2012;8:11022–33.*

influence the swelling behavior of both macroscopic gels and microgel particles, both of which have important applications. In addition, a controlled phase separation can efficiently produce gel particles of different sizes.

The interactions of a surfactant with a polymer are as described above very much controlled by hydrophobic interactions. Several nonionic polymers like poly(ethylene glycol) and nonionic cellulose ethers change their polarity with temperature as manifested by clouding and phase separation as temperature is increased. For a mixed solution of such a polymer and an ionic surfactant the surfactant binding is induced by a temperature increase, as seen in reduced values of the CAC. This can be used to achieve a temperature-controlled gelation as illustrated in Fig. 26.16. Thus, we can design systems that are liquid solutions at room temperature and gels at body temperature, which can have pharmaceutical and other applications.

The associative phase separation just described can be the basis for formation of polymer gels by physical cross-linking. By adding small drops of a concentrated solution of a polyelectrolyte into a surfactant solution, gel particles in the size range of 100 nm to mm can be formed; based on the associative phase separation, core-shell, or homogeneous particles can be prepared.

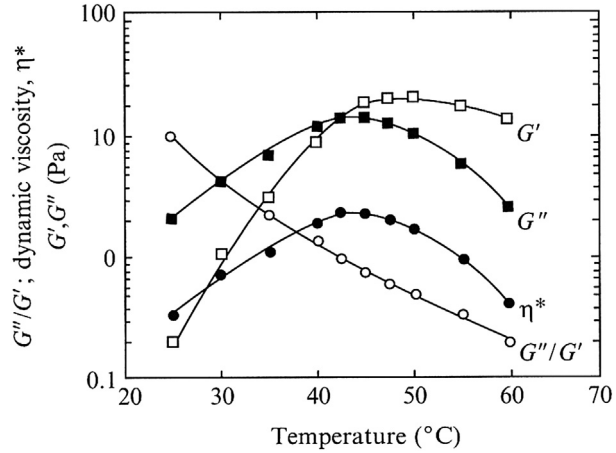



**FIGURE 26.16** For a mixed solution of a nonionic polymer and an ionic surfactant the surfactant binding is induced by a temperature increase. This can be used to achieve a temperature-controlled gelation. *Courtesy of Anders Carlsson.*

This can be illustrated with double-stranded DNA, which as described is a highly charged and stiff polyanion (Figs. 26.17 and 26.18). Because of its high charge density, DNA interacts strongly with cationic surfactants. As also noted the surfactant binding isotherms show a strongly cooperative association, and the phase diagrams display a very strong associative phase separation.

Because DNA generally has a very high molecular weight, it is possible to directly monitor the interactions on a single molecular level by using microscopy (Fig. 26.19). As a cationic surfactant is added to a dilute DNA solution, the DNA molecules change their conformation from an extended "coil" state to compact "globules." The DNA molecules are compacted individually, and, over a wide concentration range, there is a coexistence of coils and globules. DNA induces self-assembly of a cationic surfactant and DNA compaction by a surfactant can be viewed as an associative phase separation at the single molecular level.

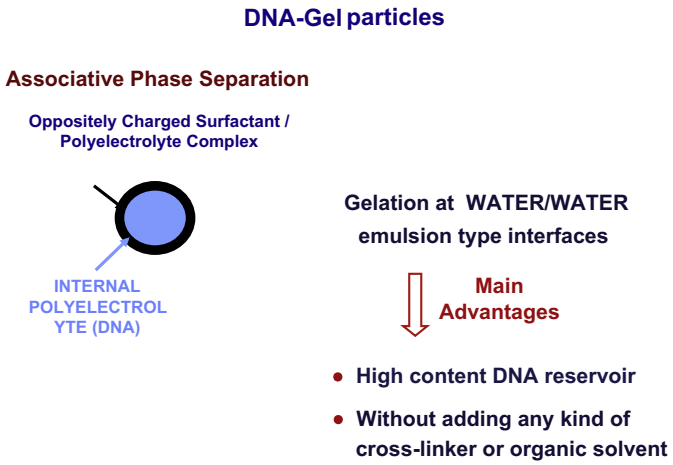



FIGURE 26.17 Scheme outlining the formulation of DNA-Gel core shell particles that utilizes the associative phase separation between the DNA and an oppositely charged surfactant. *Courtesy of Carmen Morán.*

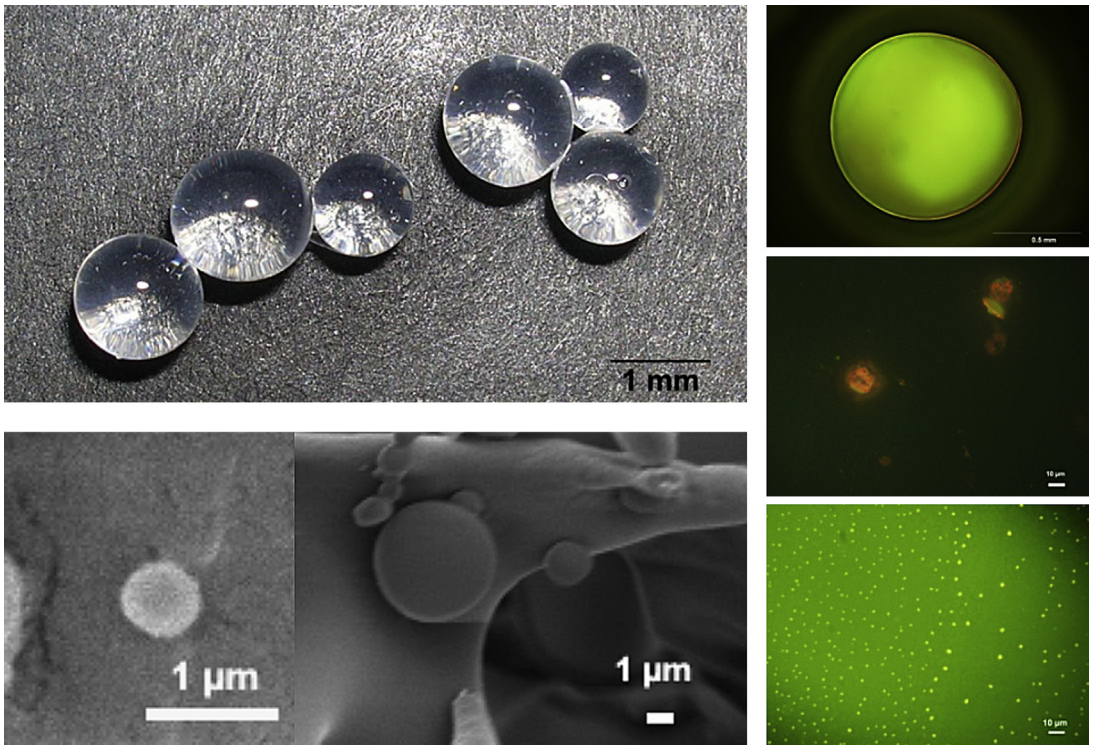



FIGURE 26.18 Gel particles can be prepared of different sizes from a few 100 nm. *Courtesy of Carmen Morán.*

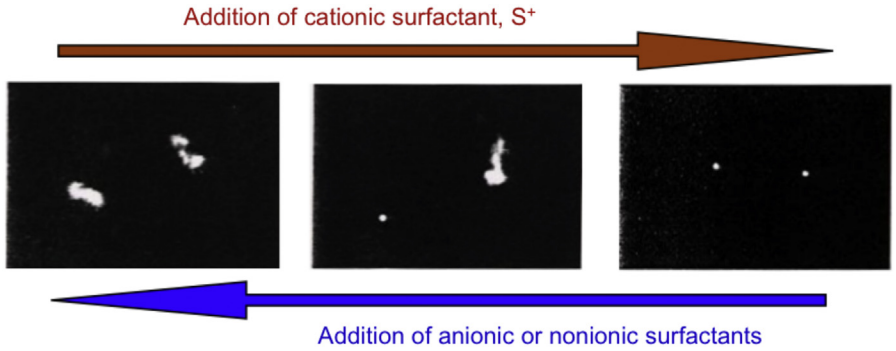



FIGURE 26.19 Adding cationic surfactant to a dilute solution of dsDNA induces compaction of DNA. This can be reversed by adding an anionic or nonionic surfactant. *Courtesy of Rita Dias.*

Many diseases have a genetic origin and may be cured by modifying the DNA sequence. However, to allow DNA to be transferred into cells, it needs to be compacted. Cationic cosolutes, such as surfactants and lipids, are efficient transfection agents of great interest for developments in gene therapy. Compaction can be used as means to regulate the transcription as well as to protect the DNA against degradation.

Addition of ionic surfactants to chemical polymer gels dramatically changes the swelling of the gels. A nonionic polymer gel has a low swelling capacity in water by itself; but when an ionic surfactant binds (from the CAC), a major increase in volume takes place. Thus, surfactant binding effectively transforms the polymer into a polyelectrolyte gel. An ionic polymer gel has, on the other hand, a large volume by itself. As an oppositely charged surfactant starts to bind (from the CAC), there is charge neutralization and shrinking to low volumes. There may be a reswelling at higher surfactant contents, which is due to surfactant binding in excess of charge neutralization (cf. earlier), leading to a charge reversal of the gel. We also note that such gel-swelling experiments provide a simple and accurate way of obtaining CAC values.

We illustrate the interactions of surfactants with polymer gels by the case of covalently cross-linked DNA and cationic surfactants (see Fig. 26.20). As seen, a surfactant has no effect on the gel volume until the CAC is reached; thereafter, there is a dramatic shrinkage with DNA concentration. The concentration for onset of shrinkage is as expected, lowered strongly as the surfactant alkyl chain length is increased. From comparison of ssDNA and dsDNA gels, a stronger interaction is inferred with ssDNA. If after shrinking, an anionic surfactant is added, there is a

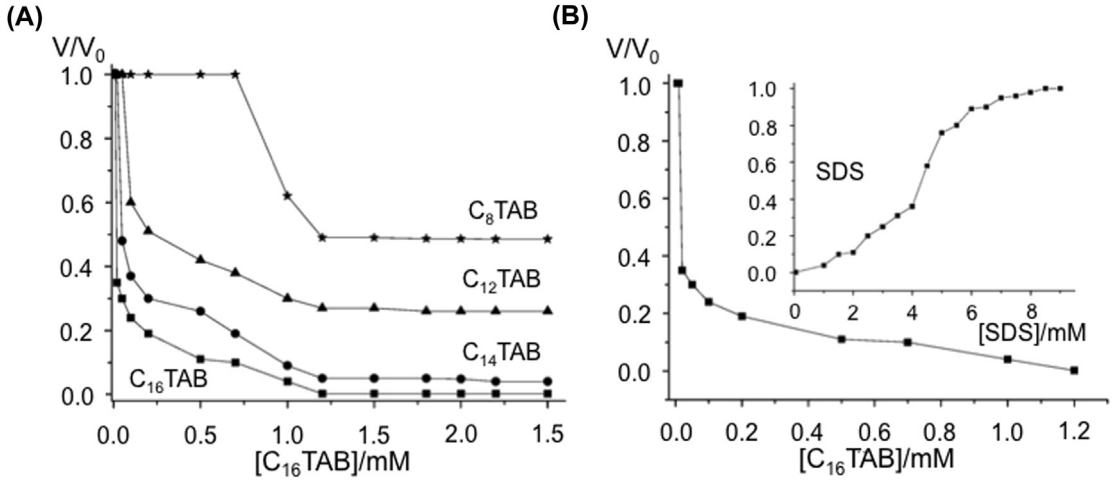



FIGURE 26.20 Cross-linked DNA gels shrink by cationic surfactant, CnTAB, (A), the efficiency being strongly dependent on alkyl chain length of the surfactant. The subsequent addition of an anionic surfactant, SDS, leads to reswelling (B). *Courtesy of Diana Costa.*

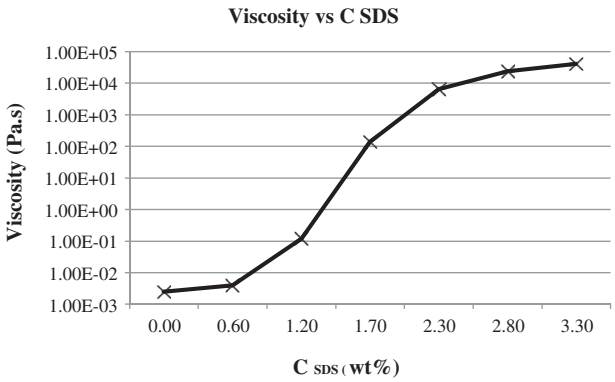



FIGURE 26.21 Ionization of microgel particles leads to swelling, which in turn produces major effects on viscosity. Ionization by deprotonation and binding of ionic surfactant (as shown here) gives similar effects. *After Antunes F, Alves L, Duarte C, Lindman B, Klotz B, Boettcher A, Haake H-M. Ionization by pH and anionic surfactant binding gives the same thickening effects of cross-linked polyacrylic acid derivatives.* J Disp Sci Technol *2012;**33**:1368–72.*

reswelling to essentially the same volume as for the initial polymer gel. The reason for this is that the association between anionic and cationic surfactant is stronger than DNA–surfactant interaction and therefore the cationic surfactant is released from the polymer gel.

A corresponding behavior is seen for small cross-linked polymer gel particles or microgels. In Fig. 26.9, we illustrated the case of segregative phase separation between an anionic polymer and an anionic surfactant. If the polymer were modified by hydrophobic groups, then the repulsive interaction can be overcome and the surfactant associates with the polymer. If the polymer, furthermore, is cross-linked, intriguing swelling effects will arise. With ionizable groups, like particles containing polyacrylate, the particle size will vary strongly with pH. This is very useful for many formulations because in a wide range of volume fractions the changes in ionization will cause major changes in viscosity due to particle overlap. Ionization by increasing the pH can induce a change in viscosity by seven orders of magnitude; this is due to particle swelling and overlap. Addition of an ionic surfactant to uncharged microgel particles gives a similar increase in viscosity (Fig. 26.21), where ionization by binding the surfactant causes a similar effect as ionization by deprotonation. In both cases, the solution clarifies on ionization because the dramatic swelling leads to very water-rich particles with negligible optical contrast to water.

## 26.7 SURFACTANT–POLYELECTROLYTE MIXTURES AT INTERFACES

Many applications, e.g., within consumer products, rest on the ability to control the deposition of active components on solid–liquid and liquid–air interfaces. Here, the associative phase separation of oppositely charged systems described earlier can be used to control the interfacial behavior. We will illustrate the interplay between bulk and surface behavior with examples for the air–water interface and for a solid surface in contact with water. Some of the typical scenarios we can expect, if we add a surfactant to a preadsorbed polymer layer at a surface, are illustrated in Fig. 26.22:

1. The polymer–surfactant interaction is so strong that the surfactant combines with the adsorbed polymer layer. This can have two consequences:
   - **a.** An increase of adsorbed amount at the interface and formation of a mixed polymer–surfactant layer.
   - **b.** Adsorption of excess surfactant and swelling of the polymer layer and eventual detachment of the formed polymer–surfactant complexes.
2. The surfactant adsorbs so strongly to the surface that it competes with the preadsorbed polymer. This leads to displacement and desorption of the polymer, which often occurs at the air–aqueous interface as well as on hydrophobic surfaces.

This points to two important aspects of the situation in which a surfactant combines with a polymer. The first is that the surfactant–polymer association changes the solubility of the polymer, which depending on the polymer–surfactant ratio either can increase or lower the solubility compared to the polymer alone. Because solvency often controls adsorption, this can in turn either decrease or increase polymer adsorption upon association with a

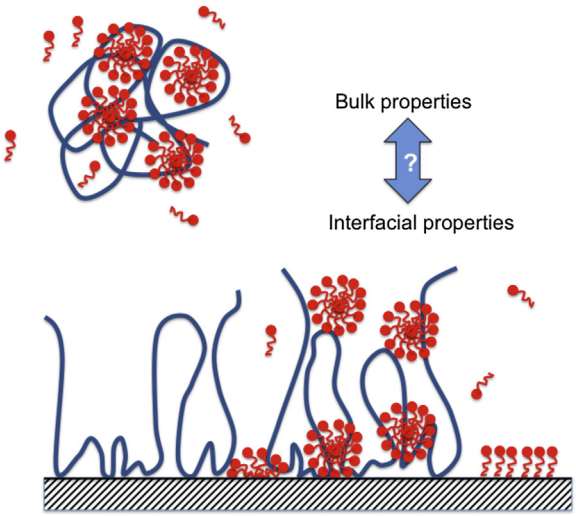



**FIGURE 26.22** Illustration of surfactant–polymer interactions at a surface and in bulk solution. *Courtesy of Fredrik Joabsson.*

surfactant. The second aspect relates to the kinetics of forming the complexes, which is very slow. Therefore, polymer desorption can take a long time, and the order of addition of the components can be crucial. In fact, the relevant timescale in application of a product containing polymer(s) and surfactant(s) is in many cases such that it rarely occurs under equilibrium conditions. This can be utilized to tune the adsorbed layer properties by accessing nonequilibrium trapped states. We will illustrate this by considering a case of the behavior of oppositely charged polyelectrolyte–surfactant systems at the air–water interface. First, we will note that one of the most significant aspects of a surfactant is its ability to lower the interfacial tension between an aqueous solution and air. In particular for an ionic surfactant, this is modified by the presence of a polymer in the solution. Equilibrium surface tension versus the surfactant concentration curve recorded in the presence of polymer (of constant concentration) usually features a decrease in surface tension far below what is observed for surfactant alone. After this decrease, more or less constant surface tension is attained. The concentration range over which this is observed is roughly proportional to the polymer concentration. Finally, at even higher surfactant concentrations there is a decrease toward the value obtained in the absence of polymer.

If we consider the time effects, a very different behavior is observed in terms of bulk and surface properties as shown in Fig. 26.23. Here, we see a dramatic increase in surface tension on further addition of surfactant (B), as observed in a number of other studies. Because of the shape of the surface tension curve, this was referred to as the "cliff-edge effect." Previously, the phenomenon was referred to a complex process involving different polymer–surfactant complexes. However, this effect is only observed after the sample has been equilibrated for some time (filled symbols in B). We also note that the corresponding behavior is observed in bulk solution, i.e., the turbidity decreases with time within the precipitation regime (A). This can in turn be related to sedimentation of formed complexes. It is, therefore, clear that this effect can be related to associative phase separation. Campbell et al. (52, 56) showed that the time effects for some common polymer–surfactant systems could be rationalized in terms of nonequilibrium effects and bulk aggregation phenomena.

Fig. 26.23C and D shows that there are almost equal amounts of polymer and surfactant at the liquid–air interface at low surfactant concentrations. Both the surface tension and the amounts are independent of the polymer concentration in this regime. This indicates the formation of a surfactant–polymer complex at the interface, which also leads to a drastic lowering of the surface tension compared to the situation with polymer alone. At higher surfactant concentrations, in the phase separation regime, the systems initially show constant surface tension because precipitation is not immediate. However, when the system is given sufficient time to undergo associative phase separation with subsequent precipitation, the solution becomes depleted of surface-active material. Therefore, a sharp increase in surface tension is observed. The surface concentrations of surfactant and polymer decrease (Fig. 26.23C and D). Above this point the surfactant dominates the liquid–air interface. The precipitation is a time-consuming process and the settling process can take several days to reach completion. This is clearly an important phenomenon, perhaps practically even more significant for oil–water interfaces.

Polyelectrolyte–surfactant adsorption at solid surfaces is of broad scientific interest as it is crucial in many different applications. Adsorption is as discussed earlier, typically controlled by solvency effects. This in turn is

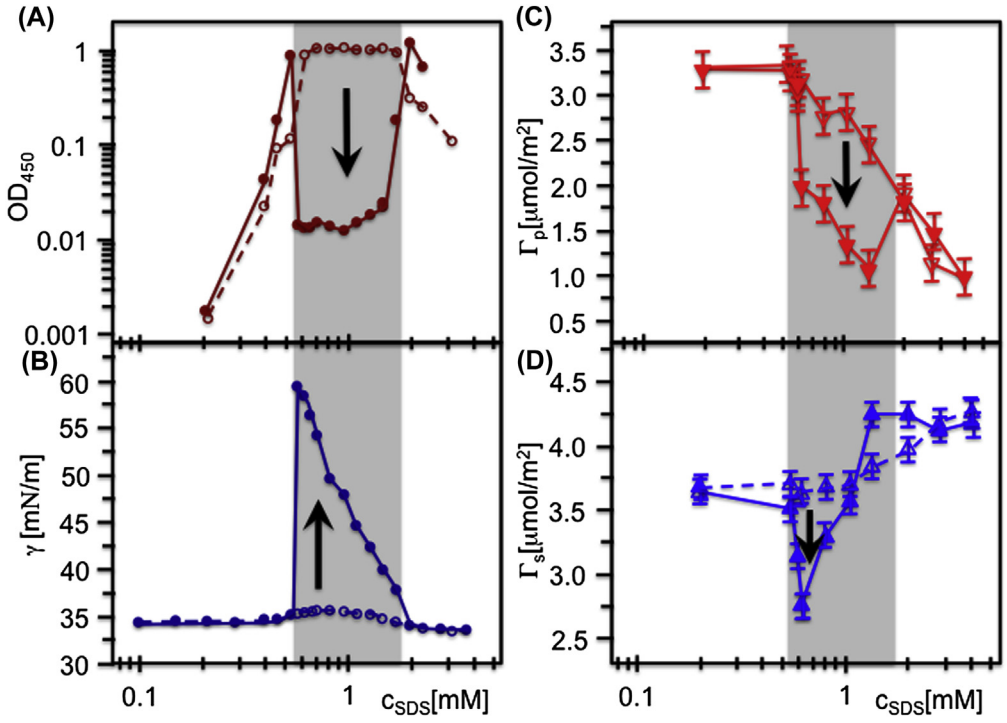



FIGURE 26.23 A comparison of the effect of time after mixing poly(diallyldimethylammonium chloride) (PDADMAC) and sodium dodecyl sulfate (SDS) on the bulk and air–aqueous interfacial behavior. Mixed just before measurements is shown as open symbols and stored and settled for 72 h is indicated as closed symbols. The gray shaded area shows the two-phase precipitation region. (A) Shows the bulk turbidity versus surfactant concentration shown as optical density at 450 nm with 100 ppm PDADMAC. (B) Surface tension of these PDADMAC/SDS solutions. (C) Shows the amount of polymer and (D) the amount of surfactant at the air–aqueous interface as determined by neutron reflectometry. *From Campbell RA, Arteta MY, Angus-Smyth A, Nylander T, Varga I. Effects of bulk colloidal stability on adsorption layers of poly(diallyldimethylammonium chloride)/sodium dodecyl sulfate at the air–water interface studied by neutron reflectometry.* J Phys Chem B *2011;**115**:15202–13.*

governed by the strength and the nature of the interaction between the surfactant and the polymer. A strong attraction between the surfactant and the polymer will lead to associative phase separation. Because of the decreased solvency, this can enhance adsorption of the surfactant–polymer complex.

In Fig. 26.24 is shown what happens when surfactant is progressively added to a hydrophilic surface with preadsorbed oppositely charged polymer in the presence of the polymer solution. No change in adsorbed amount is generally observed at low surfactant concentrations. At the CAC, i.e., at the same concentration at which

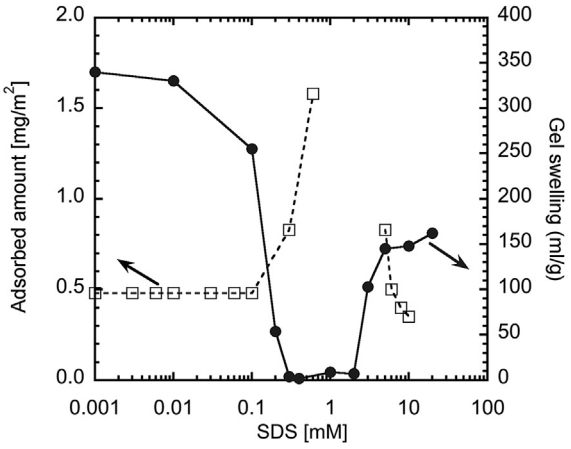



FIGURE 26.24 Adsorption on silica from a solution of cationic hydroxyethyl celluloses (JR-400) at 100 ppm with sequentially increased amount of added SDS. The data are compared with the corresponding gel-swelling data. 0.1 mM SDS corresponds to the critical aggregation concentration (cac) of JR-400/SDS. *Modified after Sjöström J, Piculell L.* Colloids Surf A: Physicochem Eng Asp *2001;**183**:429–48.*

surfactant starts to associate to the polymer in bulk solution, the adsorbed amount increases. Adsorption increases with surfactant concentration until approximate charge stoichiometry is reached. At some stage, precipitation occurs as also can be observed by turbidity measurements. It is interesting to note that data correspond to those obtained from a gel-swelling experiment, which shows that the gel formed from JR-400 contracts at the same SDS concentration as the surface deposition increases. This corroborates the strong correlation between bulk behavior and adsorption. It is clear that the surfactant alters the charge of the polymer at the interface and in the bulk phase, affecting gel properties as well as deposition. At higher surfactant concentrations, the gel, as well as the adsorbed layer, swells due to charge reversal upon additional association of surfactant. Simultaneously, the adsorbed amount decreases and, in some cases, no polymer or surfactant remains at the interface. Similar trends are observed on hydrophobic surfaces, with the difference that in this case noncooperative surfactant adsorption starts at low surfactant concentrations.

When considering the general trends just reported, the question arises to what extent we can manipulate the enhanced deposition close to the CAC by changing the polymer architecture. Here, we will discuss how we can control the deposition when we increase the hydrophobicity of the polymer and change the charge density.

The adsorption from solutions of different cationic polymers with constant content of cationic groups, but different hydrophobicity is illustrated in Fig. 26.25. As for the JR-400 system, a marked increase in both the adsorbed amount and the bulk turbidity is observed at certain SDS concentrations when the surfactant is added stepwise to the dilute polymer solution. Again, this is the result of the formation of polyion–surfactant complexes of decreasing solubility. Both the turbidity and the adsorption are maximized, which is related to the overcharging of the formed complexes that dissolve and desorb from the surface. The maxima in adsorption and turbidity occur at lower SDS concentration for a polymer with a higher hydrophobicity. This is an effect of the combined electrostatic and hydrophobic interactions, in which the SDS binding to the more hydrophobic polyions is facilitated. Consequently, the aggregates formed with the more hydrophobic polymers dissolved at a lower SDS concentration and hence the shift of the maxima.

The charge density of cationic polymer mixed with an anionic surfactant is clearly an important factor. This is illustrated in Fig. 26.26 for the interaction of sodium dodecyl sulfate (SDS) with a series of cationic copolymers of vinylpyrrolidone and quaternized vinylimidazol, with different charge density, at the silica–aqueous interface using in situ ellipsometry. The maxima in adsorption/deposition of polymer–SDS complexes scale with the SDS concentration corresponding to charge equivalence in the phase separation region. The fact that the peak position is determined by polymer charge, i.e., the amount of SDS needed to form a neutral complex, suggests that the CAC is low and the deposited amount is determined by the net charge of the polymer–surfactant complexes. That electrostatics

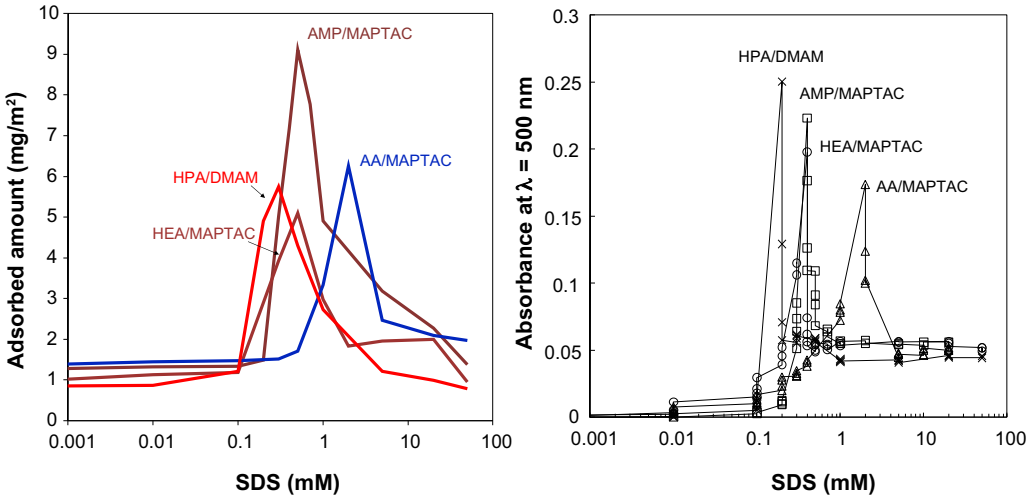



FIGURE 26.25 The effects of polyion hydrophobicity on adsorption and phase separation of oppositely charged polyion–surfactant complexes are shown. Adsorbed amount and turbidity (absorbance at 500 nm) are shown for 100 ppm solutions of acrylamide/methacrylamidopropyl trimethylammonium chloride (AA/MAPTAC), hydroxyethyl acrylate/methacrylamidopropyl trimethylammonium chloride (HEA/MAPTAC), acrylomorpholine/methacrylamidopropyl trimethylammonium chloride (AMP/MAPTAC), and hydroxypropyl acrylate/dimethylaminoethyl methacrylate (HPA/DMAM) copolymers with increasing amounts of SDS. The hydrophobicity of the polymer increases in the order AA/MAPTAC < HEA/MAPTAC ≈ AMP/MAPTAC < HPA/DMAM, but the content of cationic groups was constant at 20%. *After Santos O, Johnson ES, Nylander T, Panandiker RK, Sivik MR, Piculell L. Surface adsorption and phase separation of oppositely charged polyion-surfactant ion complexes: 3. Effects of polyion hydrophobicity. Langmuir 2010;26:9357–67.*

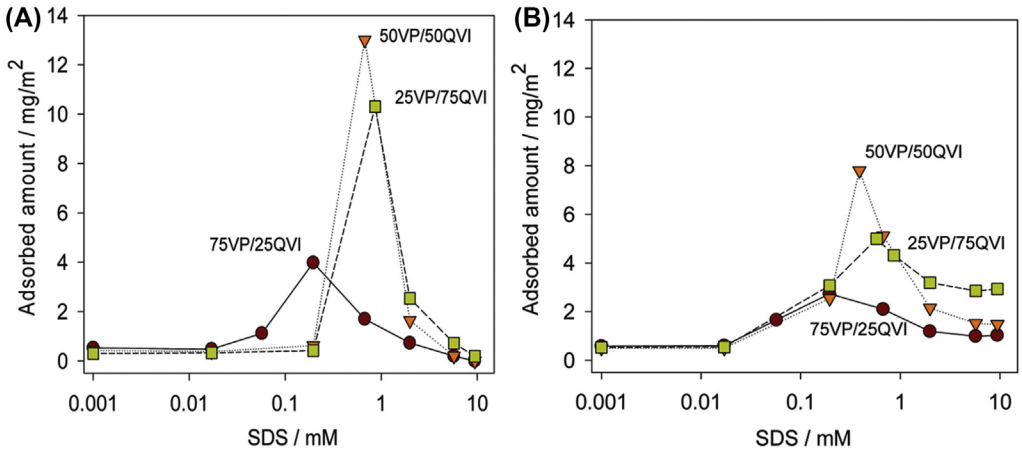



FIGURE 26.26 Effect of polymer charge density on the adsorption from mixtures of cationic polymers with SDS at the silica–aqueous interface for (A) 10 mM NaCl and (B) 100 mM NaCl solutions. The amount of the complex adsorbed from premixed solutions of 75 vinylpyrrolidone (VP)/25 quaternized vinylimidazol (QVI) (0.12 mM cationic charges), 50VP/50QVI (0.33 mM cations), and 25VP/75QVI solutions (0.42 mM cations) with SDS is shown. VP here refers to vinylpyrrolidone, QVI to quaternized vinylimidazol and the preceding number to the content in weight percent. *Mohr A, Nylander T, Piculell L, Lindman B, Boyko V, Wilko Bartels F, Liu Y, Kurkal-Siebert V.* ACS Appl Mater Interfaces *2012;**4**:1500–11.*

controls the interaction is apparent as increasing the ionic strength shifts the maxima to lower SDS concentrations, i.e., less SDS is needed to form a neutral complex. On the other hand, the maximal amount adsorbed decreases at high salt concentration.

We have so far discussed how the molecular architecture of the polymer can be used to manipulate the adsorption/deposition on a surface. Here, it should be noted that in many applications involving cleaning, not only application of the cleaning agent is important but also the rinsing step can be crucial. This is the case for, e.g., hair-care formulations, in which anionic surfactants are used for soil removal and cationic polymers are used as conditioners. This type of formulation would contain a large excess (by charge) of anionic surfactant, i.e., well above the two-phase region, thus no adsorption will occur as shown in Figs. 26.24–26.26. The action of such a formulation can be a two-step process, in which the initial step is the action of the surfactant on the soil surface leading to solubilization of the soil. In the second step, which involves dilution with water (Fig. 26.27), deposition of material will occur. The reason for this is apparent when looking at Figs. 26.24–26.26, in which, in principle, dilution means that we move to the left

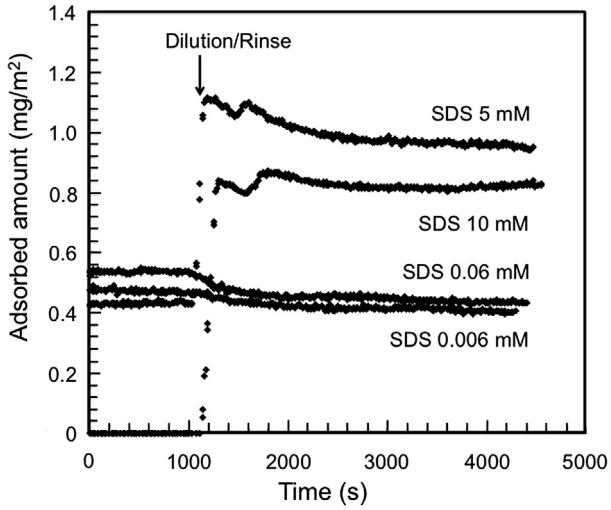



FIGURE 26.27 Dilution of solutions of anionic surfactant [sodium dodecyl sulfate (SDS) in charge excess] + cationic polymer (cationic hydroxyethyl cellulose) may lead to deposition as studied by ellipsometry. Rinsing starts at time 1000 s and is indicated with an *arrow. After Terada E, Samoshina Y, Nylander T, Lindman. B. Adsorption of cationic cellulose derivatives/anionic surfactant complexes onto solid surfaces. I. Silica surfaces.* Langmuir *2004;**20**:1753–62.*

in the graph and eventually reach the two-phase region in the phase diagram. This in turn leads to deposition of the complexes on the surface as water is added. This general phenomenon so far has received relatively little attention. Such deposition is taken advantage of in formulation of, for example, shampoos, dishwashing compounds, and detergents. Here, the deposition of polymer on rinsing is of importance for product functionality. It should be noted that it can also have negative effects, like redeposition of soil, if the formulation is imperfect. Formulation of new cleaning agents, therefore, requires knowledge of the delicate balance of interactions between the surfactant–polymer in solution and the surfactant–polymer at the surface, as well as the interaction of the individual components with the surface.

Another important aspect is that because the adsorption is mainly governed by the solubility, similar effects occur irrespectively of the surface. Here we note however that surfactants always adsorb to a hydrophobic surface, so in this respect the layer composition will be different. Hair-care formulation may also contain a silicon oil emulsion; this will affect the interfacial behavior. Thus there may be a selective deposition from mixtures of cationic polymers and SDS with silicon oil emulsion. Although the adsorption from the mixtures in most cases features co-deposition of silicone oil droplets on both hydrophilic and hydrophobic surface, the effect of dilution is quite different on the two surfaces. Here, the amount of material deposited after dilution was found to be large on the hydrophilic silica, whereas almost no significant co-deposition of silicone oil was found on the hydrophobic surface when the initial SDS concentration was high. This can be understood from the presence of similar layers on the hydrophobic silicon oil droplets as on the hydrophobic surface; thus, there is no driving force for adsorption.

Phase separation in such polyelectrolyte–ionic surfactant systems is, as discussed earlier, reduced on addition of electrolyte. We also showed in Fig. 26.26 that this is valid for the adsorption from the polyion–surfactant mixtures at or close to phase separation. Fig. 26.28 shows the strong effect on the salinity of the solution used for rinsing on the deposition.

We can conclude that deposition from polymer–surfactant mixtures is directly related to the phase behavior of the system and thus strongly dependent on the polyelectrolyte–surfactant interaction. This can be controlled by cosolutes like electrolyte, as well as polymer molecular weight and charge density, but also by polymer hydrophobicity. The functionality of the system is often limited to a narrow interval of molecular properties. For instance, if the polymer is not hydrophobic enough, the surfactant binding is too limited to ensure redissolution. On the other hand, if the polymer contains too many hydrophobic groups, surfactant binding will be too strong and the phase separation range too limited. Similarly, no phase separation might occur if the charge density is too low, but a too-high charge density will cause attractive interactions between surfactant and polymer so strong that deposition does not occur. It is important to bear in mind that during the timescale of the application of a formulation, nonequilibrium effects can be significant. This can be utilized to form a layer that is trapped in a nonequilibrium state, but gives the desired surface functionality.

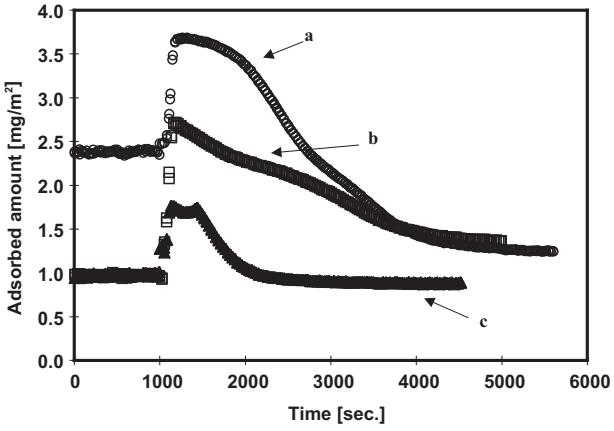



FIGURE 26.28 Effect of rinsing on adsorbed layers of cationic hydroxyethyl cellulose and SDS on hydrophobized silica. The complexes adsorbed from mixed polymer (100 ppm)/surfactant (5 mM) solutions, and rinsing was started at $t = 1000$ s. (A) Adsorption was carried out in water followed by rinsing with water; (B) adsorption was carried out in 10 mM NaCl followed by rinsing with water; (C) adsorption was carried out in 10 mM NaCl followed by rinsing with 10 mM NaCl. *Terada E, Samoshina Y, Nylander T, Lindman B. Adsorption of cationic cellulose derivatives/anionic surfactant complexes onto solid surfaces. II. Hydrophobized silica surfaces.* Langmuir *2004;**20**:6692–701.*

## Bibliography


1. Kwak JCT, editor. *Polymer-surfactant systems*. (New York): Marcel Dekker; 1998.
2. Kabalnov A, Lindman B, Olsson U, Piculell L, Thuresson K, Wennerström H. Microemulsions in amphiphilic and polymer-surfactant systems. *Colloid Polym Sci* 1996;**274**:297–308.
3. Kronberg B, Holmberg K, Lindman B. *Surface chemistry of surfactants and polymers*. (Chichester, UK): John Wiley & Sons; 2014.
4. Lindman B, Thalberg K. Polymer-surfactant interactions – recent developments. In: Goddard ED, Ananthapadmanabhan KP, editors. *Interactions of surfactants with polymers and proteins*. (Boca Raton, FL): CRC Press; 1993. p. 203–76. Chapter 5.
5. Lindman B. Surfactant-polymer systems. In: Holmberg K, editor. *Handbook of applied surface and colloid chemistry*, vol. 1. (Chichester): John Wiley & Sons, Ltd; 2002. p. 445–64. Chapter 20.
6. Piculell L, Lindman B. Association and segregation in aqueous polymer/polymer, polymer/surfactant, and surfactant/surfactant mixtures: similarities and differences. *Adv Colloid Interface Sci* 1992;**41**:149–78.
7. Piculell L, Guillemet F, Thuresson K, Shubin V, Ericsson O. Binding of surfactants to hydrophobically modified polymers. *Adv Colloid Interface Sci* 1996;**63**:1–21.
8. Piculell L, Thuresson K, Lindman B. Mixed solutions of surfactant and hydrophobically modified polymer. *Polym Adv Technol* 2001;**12**: 44–69.
9. Rubingh D, Holland PM. Interaction between polymers and cationic surfactants. In: *Cationic surfactants: physical chemistry*. (New York): Marcel Dekker; 1991. p. 189–248.
10. Bilalov A, Olsson U, Lindman B. Complexation between DNA and surfactants and lipids: phase behavior and molecular organization. *Soft Matter* 2012;**8**:11022–33.
11. Piculell L, Norrman J, Svensson AV, Lynch I, Bernandes J, Loh W. Ionic surfactants with polymeric counterions. *Adv Colloid Interface Sci* 2009; **147**–**148**:228–36.
12. Dias R, Lindman B, editors. *DNA interactions with polymers and surfactants*. (Hoboken, NJ): Wiley; 2008.
13. Goddard E, Ananthapadmanabhan K, editors. *Interactions of surfactants with polymers and proteins*. (Boca Raton): CRC Press; 1993.
14. Hansson P. Interaction between polyelectrolyte gels and surfactants of opposite charge. *Curr Opin Colloid Interface Sci* 2006;**11**:351–62.
15. Almgren M, Hansson P, Mukhtar E, van Stam J. Aggregation of alkyltrimethylammonium surfactants in aqueous poly(styrenesulfonate) solutions. *Langmuir* 1992;**8**:2405–12.
16. Kogej K. Association and structure formation in oppositely charged polyelectrolyte–surfactant mixtures. *Adv Colloid Interface Sci* 2010;**158**: 68–83.
17. Langevin D. Complexation of oppositely charged polyelectrolytes and surfactants in aqueous solutions. *A Review Adv Colloid Interface Sci* 2009; **147**–**148**:170–7.
18. Bronich TK, Cherry T, Vinogradov SV, Eisenberg A, Kabanov VA, Kabanov AV. Self-assembly in mixtures of poly(ethylene oxide)-graft-poly(ethyleneimine) and alkyl sulfates. *Langmuir* 1998;**14**:6101–6.
19. Nizri G, Makarsky A, Magdassi S, Talmon Y. Nanostructures formed by self-assembly of negatively charged polymer and cationic surfactants. *Langmuir* 2009;**25**:1980–5.
20. Bergfeldt K, Piculell L, Linse P. Segregation and association in mixed polymer solutions from Flory-Huggins model calculations. *J Phys Chem* 1996;**100**:3680–7.
21. Kizilay E, Kayitmazer AB, Dubin PL. Complexation and coacervation of polyelectrolytes with oppositely charged colloids. *Adv Colloid Interface Sci* 2011;**167**:24–37.
22. dos Santos S, Gustavsson C, Gudmundsson C, Linse P, Piculell L. When do water-insoluble polyion-surfactant ion complex salts "redissolve" by added excess surfactant? *Langmuir* 2011;**27**:592–603.
23. Thalberg K, Lindman B. Segregation in aqueous systems of polyelectrolyte and ionic surfactant. *Colloids Surf* 1993;**76**:283–8.
24. Svensson A, Piculell L, Cabane B, Ilekti P. A new approach to the phase behavior of oppositely charged polymers and surfactants. *J Phys Chem B* 2002;**106**:1013–8.
25. Ilekti P, Piculell L, Tournilhac F, Cabane B. How to concentrate an aqueous polyelectrolyte/surfactant mixture by adding water. *J Phys Chem B* 1998;**102**:344–51.
26. Thuresson K, Nilsson S, Lindman B. Effect of hydrophobic modification on phase behaviour and rheology in mixtures of oppositely charged polyelectrolytes. *Langmuir* 1996;**12**:530–7.
27. Antunes FE, Lindman B, Miguel MG. Mixed systems of hydrophobically modified polyelectrolytes: controlling rheology by charge and hydrophobe stoichiometry and interaction strength. *Langmuir* 2005;**21**(22):10188–96.
28. Lapitsky Y, Kaler EW. *Soft Matter* 2006;**2**:779–84.
29. Morán MC, Miguel MG, Lindman B. DNA gel particles. *Soft Matter* 2010;**6**:3143–56.
30. Antunes F, Alves L, Duarte C, Lindman B, Klotz B, Boettcher A, Haake HM. Ionization by pH and anionic surfactant binding gives the same thickening effects of crosslinked polyacrylic acid derivatives. *J Disp Sci Technol* 2012;**33**:1368–72.
31. Taylor DJF, Thomas RK, Penfold J. Polymer/surfactant interactions at the air/water interface. *Adv Colloid Interface* 2007;**132**:69–110.
32. Campbell RA, Angus-Smyth A, Arteta MY, Tonigold K, Nylander T, Varga I. New perspective on the cliff edge peak in the surface tension of oppositely charged polyelectrolyte/surfactant mixtures. *J Phys Chem Lett* 2010;**1**:3021–6.
33. Angus-Smyth A, Bain CD, Varga I, Campbell RA. Effects of bulk aggregation on PEI–SDS monolayers at the dynamic air–liquid interface: depletion due to precipitation versus enrichment by a convection/spreading mechanism. *Soft Matter* 2013;**23**:6017–103.
34. Aidarova S, Sharipova A, Krägel J, Miller R. Polyelectrolyte/surfactant mixtures in the bulk and at water/oil interfaces. *Adv. Colloid Interface Sci* 2014;**205**:87–93.
35. Bain CD, Claesson PM, Langevin D, Meszaros R, Nylander T, Stubenrauch C, Titmuss S, von Klitzing R. Complexes of surfactants with oppositely charged polymers at surfaces and in bulk. *Adv Colloid Interface Sci* 2010;**156**:32–49.
36. Nylander T, Samoshina Y, Lindman B. Formation of polyelectrolyte-surfactant complexes on surfaces. *Adv Colloid Interface Sci* 2006;**123**: 105–23.

37. Svensson AV, Huang L, Johnson ES, Nylander T, Piculell L. Surface deposition and phase behavior of oppositely charged polyion/surfactant ion complexes. 1. Cationic guar versus cationic hydroxyethylcellulose in mixtures with anionic surfactants. *ACS Appl Mater Interfaces* 2009;**1**: 2431−42.
38. Svensson AV, Johnson ES, Nylander T, Piculell L. Surface deposition and phase behavior of oppositely charged polyion-surfactant ion complexes. 2. A means to deliver silicone oil to hydrophilic surfaces. *ACS Appl Mater Interfaces* 2010;**2**:143−56.
39. Santos O, Johnson ES, Nylander T, Panandiker RK, Sivik MR, Piculell L. Surface adsorption and phase separation of oppositely charged polyion-surfactant ion complexes: 3. Effects of polyion hydrophobicity. *Langmuir* 2010;**26**:9357−67.
41. Clauzel M, Johnson ES, Nylander T, Panandiker RK, Sivik MR, Piculell L. Surface deposition and phase behavior of oppositely charged polyion-surfactant ion complexes. Delivery of silicone oil emulsions to hydrophobic and hydrophilic surfaces. *ACS Appl Mater Interfaces* 2011;**3**:2451−62.

CHAPTER

# 27

# Rheology of Cosmetic Formulations

*D. Gräbner, H. Hoffmann*
**University of Bayreuth, Bayreuth, Germany**

## 27.1 INTRODUCTION

Rheology is the knowledge and understanding of the flow behavior of liquids, dispersions, and stable phases with different structures. In the most simple cases, the parameter that is of interest is the zero-shear viscosity of the fluid systems, which means the viscosity under small shear stress. Cosmetic formulations usually contain surfactants, yet for different reasons and in different applications: the surfactants have to clean textiles, protect skin from the sun or from dust, and lower the surface tensions in the aqueous phase. Some cosmetic formulations contain emulsions which are formed with the help of surfactants. Formulations for a particular application should have low viscosity, sometimes an intermediate viscosity, or a gel-like behavior. Phases with these properties may contain the same amount of surfactant, and surfactants alone. It is interesting to note that many formulations contain only water, oil, and liquid nonionic surfactants. All of these compounds have low viscosity. Yet, when mixed in the right proportions, the resulting product can behave like a solid that can ring like a bell, can be a viscoelastic fluid, or a low-viscosity fluid. This statement means that it is possible in principle to prepare phases from the three simple compounds that can behave like a simple low-viscosity liquid or a solid, and the material will be a transparent single phase. On first glance, this seems difficult to comprehend. It only happens when the three components water, oil, and surfactants are mixed in a narrow range of proportions. To achieve the desired properties, it is necessary to understand phase diagrams, the solubility of one compound into the others, the formation of micellar structures, and the properties of interfacial layers. It is important to realize that a small oil droplet that is covered by a surfactant monolayer and is dispersed in water can already behave like an elastic phase and thermal energy cannot deform the droplet very much. Theoretically it behaves like a hard sphere. It is likely that if we have many such spheres in solution, and we increase the concentration until they are densely packed, then the resulting material will behave like a soft solid.

Many cosmetic formulations, however, contain other additives like polymers, cosurfactants, and solid particles. All these additives have an influence on the micellar structures that exist in the formulations and hence on the rheological properties. It is therefore important to know how the different additives interact with each other and produce a desired viscosity for a particular application. At the same time, it is of interest to know what can be learned from the viscosity of a fluid phase. Can we use this property to understand something about the structure of the phase? This is usually not possible because an aqueous phase with only 2% surfactants can have a viscosity like water, it can be viscoelastic or have gel-like properties. However, with the help of additional information that can easily be obtained from visual inspection of the fluid phase like its turbidity, its optical permanent birefringence, or flow birefringence, it is possible to make suggestions about the composition and the structure of the sample. It also will be shown that by determining not only the zero-shear viscosity but by a complete rheological characterization of a fluid, we will learn other parameters of the fluid like the loss and storage modulus, the structural relaxation time and so on, which gives an insight in the structure of the phases that control its behavior. These parameters can only be obtained with the help of an oscillating rheometer. In many research labs, it is still common practice to determine the flow behavior of a fluid with a Brookfield rheometer only. Although this method might be fine to give a viscosity that is useful for a particular application, a Brookfield rheometer cannot give a proper characterization of all possible rheological parameters. It is not even capable of distinguishing a strong viscoelastic solution from a viscoelastic phase with a yield-stress value. This difference is very important in formulations. Solid particles sink in highly viscous solutions but they are trapped and do not sediment in solutions with an adequate yield-stress value.

*Cosmetic Science and Technology: Theoretical Principles and Applications*
http://dx.doi.org/10.1016/B978-0-12-802005-0.00027-6

Copyright © 2017 Elsevier Inc. All rights reserved.

So far, we have mainly discussed and used the zero-shear viscosity to describe systems. The viscosity, however, will depend on the shear rate that is used to determine it. Surfactants can have viscosities that decrease with the shear rate. Such systems are called shear-thinning systems. In other systems, the viscosity might increase above a certain shear rate in a rheometer or on stirring of a phase. These systems are called shear-thickening systems. These properties can be very important during preparation of the phases and we have to ask the question what is causing such phenomena and can we use these properties in applications.

In the simplest case, cosmetic formulations will consist of water that contains only surfactants. We will, therefore, briefly discuss such systems, the structures that exist in such systems, and the rheological properties of the solutions or of the liquid crystalline phases that exist at higher surfactant concentrations.

## 27.2 RHEOLOGICAL PARAMETERS AND THEIR MEASUREMENTS

Many cosmetic fluids behave like Newtonian fluids. These are fluids for which the viscosity of the fluid is independent of the shear rate. In such situations, the viscosity can simply be measured by an Ubbelode Rheometer. With these instruments the viscosity can be determined from the time $\Delta t$ it takes for a volume $\Delta V$ of the fluid to flow through a capillary driven by its own weight. The viscosity $\eta$ can then be calculated by the Hagen−Poiseulle equation

$$\frac{\Delta v}{\Delta t} = \Delta p \cdot \frac{\pi R^4}{8 \eta l} \tag{27.1}$$

when $R$ is the radius of the capillary and $l$ its length. For many fluids, the viscosity in such a system would depend on the flow rate through the capillary, or in a Couette rheometer, on the shear rate $\dot{\gamma} = d\gamma/dt$ that is used for the measurements. The viscosity could increase or decrease with the shear rate. For such systems, the zero-shear viscosity $\eta^\circ$ is used as the parameter to characterize the fluids. As an introduction into rheology, see the book written by Barnes.[1]

$$\eta^\circ = \eta\left(\dot{\gamma} \to 0\right) \tag{27.2}$$

Many fluids have also elastic properties combined with the viscous properties. Such fluids are called viscoelastic liquids and can be characterized by oscillating measurements in a Couette system.[2–6] The liquid is contained in a gap between an inner and an outer cylinder. For normal viscosity measurements the outer cylinder is set in rotation and the shear stress is measured on the inner cylinder. The shear stress $p$ is then the force $F$ on the cylinder of area $A$.

$$p = \frac{F}{A} = \eta \cdot \dot{\gamma} \tag{27.3}$$

The shear rate $\dot{\gamma}$ is given by the velocity $v$ of the outer cylinder and the gap x between the cylinder. The shear rate has the dimension of a reciprocal time ($\sec^{-1}$). A viscous fluid can be represented by a mechanical model, a dashpot. The viscosity can then be determined by the volume of the liquid that is pushed through the dashpot per time. An elastic solid can be modeled as a spring. A mechanical model for a viscoelastic fluid is a spring in series with a dashpot.[7] When a force is quickly applied to the spring, which is connected to the dashpot, the spring is extended and we obtain a value for the spring constant. When a force is applied very slowly to the spring, the spring is not extended, but the dashpot is, and we measure the viscosity. For purely elastic conditions, the strain $\gamma$ (deformation) is in phase with the stress. For purely viscous conditions, the spring will not be extended.

When a sinusoidal oscillating deformation or stress

$$\gamma = \hat{\gamma} \sin(\omega t) \quad \text{or} \quad p = \hat{p} \sin(\omega t) \tag{27.4}$$

is applied to the outer cylinder of the Couette system that is filled with viscoelastic fluid, an oscillating stress is measured on the inner cylinder that is phase shifted by the angle $\delta$. The part of this total stress $p$ that is in phase with the deformation, divided by the total strain $\gamma$, is called the storage modulus $G'$, and the part that is out of phase is called the loss modulus $G''$.

$$G' = \frac{p}{\gamma} \cdot \cos\delta = G^\circ \cdot \frac{\omega^2 \tau^2}{1 + \omega^2 \tau^2} \tag{27.5a}$$

$$G'' = \frac{p}{\gamma} \cdot \sin\delta = G^\circ \cdot \frac{\omega \tau}{1 + \omega^2 \tau^2} \tag{27.5b}$$

The time constant $\tau$ is called the relaxation time of the system. It is the time constant with which the stress relaxes when the Maxwell model consisting of the dashpot and the spring is deformed.

$$p = p^{\circ} \cdot e^{-\frac{t}{\tau}} \tag{27.6}$$

This time constant $\tau$ is equal to the reciprocal of the frequency $\omega_o$ in which $G'$ and $G''$ have the same value.

$$G'(\omega_o) = G''(\omega_o); \quad \tau = \frac{1}{\omega_o} \tag{27.7}$$

It follows furthermore from the above equation that the complex viscosity is

$$|\eta^*| = \frac{\sqrt{G'^2 + G''^2}}{\omega} \tag{27.8}$$

It can be shown, furthermore, that the zero-shear viscosity $\eta^{\circ}$ is related to the modulus $G^{\circ}$ and the structural relaxation time $\tau$ by the simple Eq. (27.9).

$$\eta^{\circ} = G^{\circ} \cdot \tau \tag{27.9}$$

Rheological results from oscillating measurements are usually plotted on a double log scale of $G'$, $G''$, and $\eta^*$ against $\omega$. Oscillating rheometers usually display measured data in this fashion. Fig. 27.1 shows such a typical plot for a Maxwell fluid.

It shows that in such a plot the slope of $G'$ against $\omega$ is 2 as long as $\omega \cdot \tau << 1$. For $G''$ against $\omega$, the slope is 1. It shall be noted that the complex viscosity $\eta^*$ from oscillating measurements for a circular frequency $\omega$ is the same as the shear viscosity $\eta$ when $\omega$ and $\dot{\gamma}$ are the same. This fact is known as the Cox–Mertz rule[8] (see Fig. 27.2).

The simple equation $\eta^{\circ} = G^{\circ} \cdot \tau$ usually is the basis for the explanation for a surprising behavior of the viscosity as a function of concentration. Both parameters $G^{\circ}$ and $\tau$ are independent from each other. In general $G^{\circ}$ is increasing according to a power law with the concentration, similar to polymer solutions.[6] The time constant $\tau$ can be controlled by different mechanisms and the mechanism can depend on concentration. It is therefore possible that $\eta$ first increases with $c$, then decreases and finally increases again.[9] Micellar systems can also behave like soft solids. They do not have a zero-shear viscosity. Under a shear stress, they do not flow but are only deformed. Such systems are called Bingham systems.[10] They start to flow when the shear stress is increased to above a critical value which is called the yield stress value or simply the yield value. With a stress controlled rheometer the yield value can often be determined. Systems with a yield stress value are very interesting systems for the preparation of stable emulsions or dispersions. Particles or droplets can be dispersed in such systems and these particles cannot sediment or rise to the surface.

## 27.3 SURFACTANT SOLUTIONS, THEIR MICELLAR STRUCTURES AND RHEOLOGICAL PROPERTIES

### 27.3.1 Globular Micelles

Surfactants dissolved in water form aggregates above a critical concentration which is called the critical micellar concentration (CMC).[11–14] For nonionic and zwitterionic surfactants, the CMC decreases by a factor of 10 when the

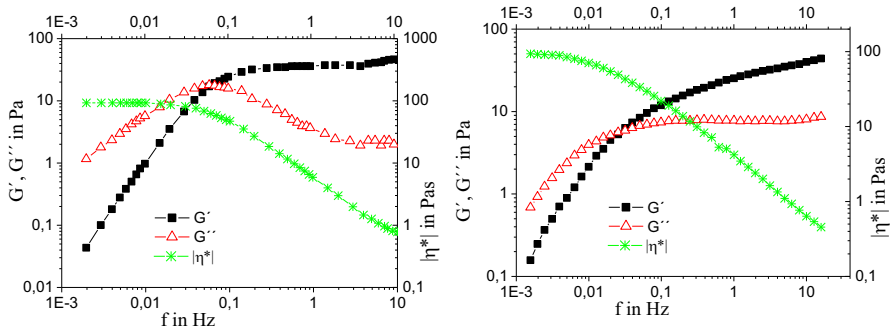



FIGURE 27.1 Moduli $G'$, $G''$, and complex viscosity $\eta^*$ against frequency $f$; $\omega = 2\ \pi\ f$ for two systems. Left: 100 mM hexadecyl pyridinium chloride with 60 mM of Na salicylate; right: 80 mM tetradecyldimethylaminoxide ($C_{14}$DMAO) + 20 mM Na dodecylsulfate (SDS) + 55 mM hexanol.

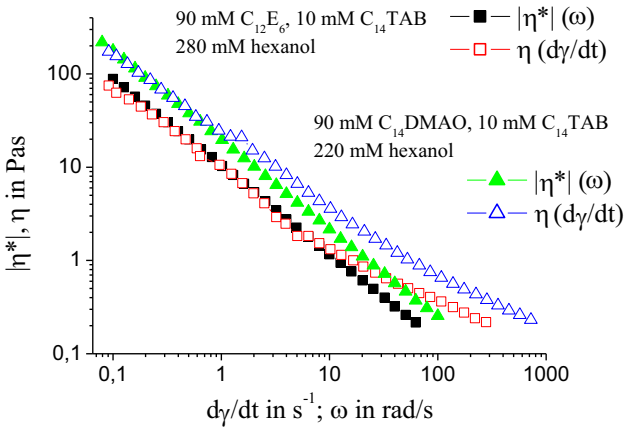



FIGURE 27.2 Cox–Merz-rule: complex viscosity from oscillating measurements compared to shear viscosity in rotating experiments for two phases with different composition. Note the deviations at high shear rates; probably continuous shear damages the structures, whereas oscillations have limited total shear and structures are preserved.

chain length of a linear surfactant is increased by two $CH_2$ groups; for ionic surfactants, it decreases by a factor of four for each two $CH_2$ groups. In the simplest case, the micelles are of globular shape and their aggregation number does not change very much with increasing concentration.

Micellar solutions of such systems have a low viscosity and the viscosity increases linearly with the concentration according to the Stokes–Einstein equation

$$\eta = \eta_o \cdot (1 + 2.5 \cdot \Phi) \tag{27.10}$$

in which $\eta_o$ is the viscosity of water and $\Phi$ is the volume fraction of the micelles. For higher concentrations, the hydrodynamic interaction becomes important and a quadratic term has to be added to the linear term and the viscosity increase like in the equation

$$\eta = \eta^\circ \cdot \left(1 + a \cdot \Phi + b \cdot \Phi^2\right) \tag{27.11}$$

The viscosity is independent of the chain length of the surfactants, the aggregation number, and size of the micelles. It only depends on the volume fraction of the globular micelles. The volume fraction includes, however, the water molecules that are bound to the surfactant head groups by the solvation forces. This water is diffusing with the micelles. A surfactant solution which contains up to 50% of surfactant ($\Phi \sim 0.5$) can thus still have a viscosity that is only a factor three to four higher than the viscosity of water. This situation continues up to the concentration of the surfactant at which the micelles reach dense packing and form a liquid crystalline (l. c.) phase,[15] the cubic phase, which can contain the same globular micelles as the solution. The solution and the l. c. phase are separated by a two-phase region in which the samples separate macroscopically in two phases; the $L_1$-phase and the cubic phase. The cubic phase actually is a solid and does not flow. The separation of the two phases may take a long time and the viscosity of the apparently single phase can then be fitted by the Krieger–Dougherty equation.[16]

$$\eta = \eta_o \left(\frac{\Phi_{max}}{\Phi_{max} - \Phi}\right)^{2.5\Phi_{max}} \tag{27.12}$$

## 27.3.2 Viscoelastic Solutions from Worm-like Micelles

Depending on the surfactant, globular micelles can grow linearly, from right above the CMC or at higher concentrations, to worm-like micelles, also called rodlike or threadlike micelles. These cylindrically shaped micelles grow unidimensionally in length with increasing concentration according to Eq. (27.13). Depending on their stiffness that is usually expressed as the persistence length $l_p$, the worm-like micelles begin to overlap at a particular concentration and the viscosity begins to increase with a power law according to Eq. (27.14)

$$\overline{L} = \varphi^{1/2} e^{\frac{E_c}{K_B T}} \tag{27.13}$$

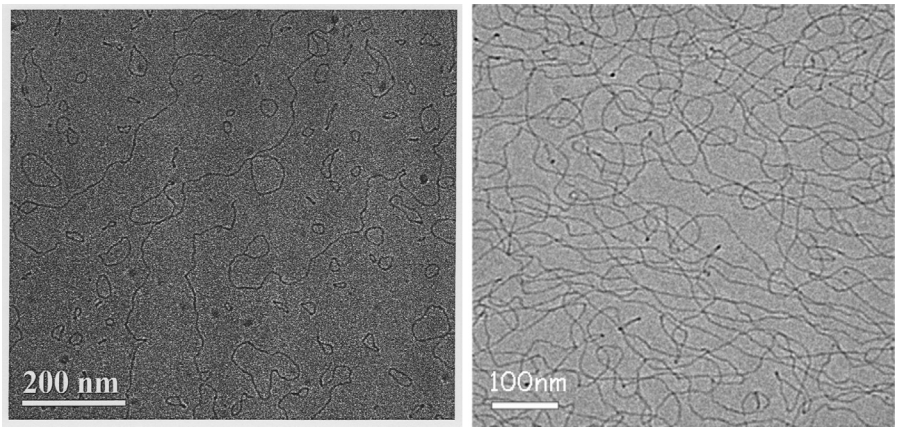



**FIGURE 27.3** Cryo-TEM from an aqueous solution of worm-like micelles of the surfactant $C_8F_{17}SO_3\ N(CH_2CH_3)_4$.[23]

$\overline{L}$ is the average contour length of the micelles, φ is the surfactant volume fraction, and $E_c$ is the end-cap energy for a micelle.

$$\eta = \eta^{\circ}\left(\frac{c}{c^*}\right)^X \tag{27.14}$$

in which the exponent $X$ can have values between 1.3 and 10, depending on the system and the physical chemistry conditions in the solution. Images of worm-like micelles can be obtained by the Cryo-transmission electron microscopy (TEM) method as is shown in Fig. 27.3 for the surfactant $C_8F_{17}SO_3\ N(CH_2CH_3)_4$

The wide variety that is experimentally found for the exponent in Eq. (27.14) is a consequence of the fact that the entanglement networks which are formed by the worm-like micelles can form real networks in which individual micelles with end-caps no longer exist. Such networks can form again after the networks are stressed till they break.[17]

For entangled worm-like micelles which do not form real networks, the situation is similar as for polymer solutions. The scaling exponent for the viscosity of polymers is 5.2. Polymers do not grow with the concentration but worm-like micelles do grow. For this reason, it is easy to realize that the scaling exponent for surfactant solutions can be larger than 5.25. The reason why some globular micelles begin to grow to worm-like micelles, whereas others keep the globular shape up to the concentration of the dense packing of the globules, is given by the area "$a$" of a surfactant molecule at the micellar interface and the dimensionless packing parameter $P$ that can be calculated from "$a$," the radius of the micelles $r_H$, and the volume $v$ of the hydrophobic chains.[18]

$$P = \frac{v}{a \cdot r_H} \tag{27.15}$$

For globular micelles, $P$ is $<1/3$, for worm-like micelles $<1/2$ and for bilayers $\sim 1$. The volume $v$ of a surfactant's hydrophobic chain cannot vary with the surfactant concentration and the radius of a globular micelles can only grow up to the chain length of the surfactant molecule, but the area "$a$" can decrease with increasing concentration because, for ionic micelles, the free counterion concentrations are increasing in solution. This increases the ionic strength and the fraction of counterions bound to the head groups increases. Both effects lead to a decrease of the repulsion between the head groups of the surfactants and a more dense packing of the surfactant results. At a critical value of "$a$" the globular micelles can begin to grow. It should be realized, however, that not all micelles begin to grow simultaneously when a certain concentration is reached. Both experimental evidence and theoretical considerations have shown that, within a small concentration region, globular micelles and worm-like micelles exist simultaneously in the solution. The worms have already a length that is several times longer than the diameter $2r$ of a globular micelle. Smaller rods cannot exist because the chemical potentials of the surfactant molecules in such micelles are higher than their chemical potential in globular micelles.[19,20]

In solutions with worm-like micelles it can be expected that the worms grow in length and the solutions become more viscous until a new phase is reached. This can be a nematic phase from worm-like micelles, a $N_c$ phase, or a hexagonal l. c. phase which is usually called an H phase.[21,22] Both phases are optically birefringent and show typical textures between crossed polarizors. Both l. c. phases are separated from the isotropic phase by a two-phase region. Like the cubic phase, the hexagonal phase is stiff and behaves like a soft solid. Exemptions can occur, however, from

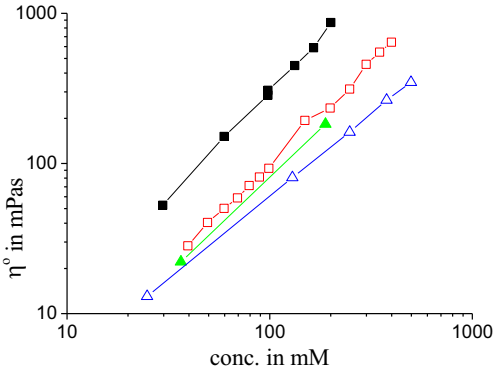



**FIGURE 27.4** Viscosity against concentration for different solutions of worm-like micelles in a log–log plot. *Filled squares*: Cetylpyridinium chloride + Na-Salicylate (T = 25°C); *open squares*: $C_{14}$DMAO: decanol = 5.1 (T = 25°C); *full triangles*: $C_{16}EO_7$ (T = 45°C); *open triangles*: Cetyltrimethylammonium bromide + Na-chlorate. The slope of the plot is 1.3.[2]

this discussed general behavior. It was shown experimentally that the viscosity in some surfactant systems passes with increasing surfactant concentration over a maximum and then through a minimum before the phase boundary is reached in the solution, a behavior that is not observed for polymers, and not expected theoretically.[9]

With increasing concentration, an increase of the viscosity would be expected (see Fig. 27.4). The unusual behavior has to do with a switch of the relaxation mechanism of worm-like micellar solutions from disentanglement-controlled reptation mechanism to a breaking-controlled mechanism. Cryo-TEM measurements show that the transition takes place when the worm-like micelles begin to show branching and are transformed from entangled worm-like micelles to real networks without end-caps.

Another peculiarity of the structures in worm-like micellar solutions can be observed around the transition of globular micelles to worm-like micelles. In this concentration region, Cryo-TEM micrographs show ring-like micelles and worm-like micelles with loops at the end of the worms. Obviously, by forming these structures, the system avoids the energetically unfavorable end-caps that have a packing different from the packing along the cylinder (see Fig. 27.3).[23]

If the micelles grow beyond the persistence length of the rods, they can close to form rings or loops at the end of longer worms. These structures have not yet been included in the theoretical treatment of the growths of worm-like micelles.

Many solutions with worm-like micelles have viscoelastic properties.[4–7] They can easily be observed when a test tube with such a solution with dispersed small bubbles is quickly turned around its main axis. The small bubbles show the recoil effect. It looks like the bubbles are connected to a spring and during the brief motion of the rotation, the spring is strained, and when the motion is stopped, the bubbles oscillate several times around their equilibrium position before they come to rest. The oscillations are the result of elastic properties. Obviously, phases with such properties have both viscous and elastic properties and their properties cannot be expressed by only measuring the viscosity. The viscoelastic properties can be measured by an oscillating rheometer with which a sinusoidal oscillating deformation at an angular frequency ω can be applied to the sample and the resulting stress is recorded. Likewise, an oscillating stress can be applied and the resulting strain can be recorded. In such measurements the stress and strain are not in phase but phase shifted by an angle $\delta$. The part of the stress that is in phase with the deformation gives us the elastic property and gives the storage modulus $G'$, whereas the part of the stress that is out of phase gives the loss modulus $G''$ (see Section 27.2).

The zero-shear viscosity $\eta^\circ$ depends on both the shear modulus and the structural relaxation time $\tau$. In viscoelastic surfactant solutions, $G^\circ$ is given by the number of entanglements per unit volume $\upsilon$ of the worm-like micelles.

$$G^\circ = \upsilon \cdot k_B T \tag{27.16}$$

In viscoelastic polymer solutions, $\tau$ is controlled by a diffusion process like the reptation process. It increases therefore with increasing concentration of the polymers. The viscosity is therefore also increasing with the polymer concentration. In surfactant solutions, the structural relaxation time can be controlled by diffusion and by breaking of the worm-like micelles. The viscosity of surfactant solutions therefore can have a complicated concentration dependence. $\eta$ can even decrease with increasing concentration. This occurs when $\tau$ and hence $\eta$ is shifted from a diffusion controlled mechanism to a kinetic controlled mechanism[9] involving rupture and fusion of micelles.

Under flow, the viscosity in worm-like micelles can also increase with shear. This phenomenon is called shear thickening. Two types of shear-thickening phenomena have to be distinguished. As mentioned, worm-like micelles are aligned in a shear flow when $\tau \cdot \dot{\gamma} > 1$. Under these conditions, the attraction between the worm-like micelles can become larger than in the random orientation state. The single-phase system can then be transformed into a two-phase system that is associated with an increase of the viscosity.[24] The other shear-thickening region can be observed in dilute solutions of worm-like micelles in which small ring-like micelles are present. Under shear of such solutions, the small objects can collide under shear and form long worm-like micelles that cause higher viscosity. These new structures that are only present under shear have been called shear-induced structures (SIS).[25]

### 27.3.3 Bilayers, Disk-like Micelles and Their Phases

Globular micelles cannot only grow unidimensionally to worm-like micelles. In special situations, they can also grow in two dimensions. Under these conditions, the disk-like structures usually grow indefinitely large and the systems forms $L_\alpha$-phases. However, with ionically charged single-chain perfluoro systems it has been observed that stable disk-like micelles are formed. These disk-like micelles can form nematic phases ($N_D$).[26] Disk-like micelles are also formed in mixed systems of ionic surfactants and cosurfactants like mixtures of SDS and *n*-alcohols.[27] The rims of the discs consist mainly of SDS, whereas the flat parts have a composition like in bilayer phases. It should also be noted that $N_D$ phases can be transformed to cholesteric phases by using optically active surfactants or optically active counterions in combination with normal surfactants.[28] Nematic phases have the interesting property of becoming aligned in magnetic fields. In special cases, the nematic phases can be transformed to lamellar phases by lowering the temperature. When this is done in a magnetic field, one obtains a completely aligned $L_\alpha$-phase.[29]

Some surfactants, particularly double-chain surfactants, can have a packing parameter that allows the formation of bilayers already at low concentrations. Such systems can form $L_\alpha$-phases at concentrations as low as one percent when strong repulsive interactions exist between the bilayers. The repulsive interactions can be due to an electrostatic interaction or due to undulation forces in nonionic systems. Like other l. c. phases, the $L_\alpha$-phases form typical textures under the polarization microscope.

### 27.3.4 Vesicle Phases

It is agreed that vesicles can form spontaneously,[30] or they are formed from ionically charged $L_\alpha$-phases by shear. These vesicles can be small unilamellar vesicles (SUV) or multilamellar vesicles (MLV).[31,32] Such systems can also have viscoelastic properties like worm-like micelles. They even can have a yield stress (see Fig. 27.6).[33]

The systems then behave as weak gels. Under these conditions other particles in these systems cannot sediment. Solutions with vesicles and worm-like micelles may look alike and may have the same zero-shear viscosity.

Vesicles are interesting structures for cosmetic formulations. They actually are small containers in which hydrophilic compounds can be trapped. Solutions with vesicles from non-ionic surfactants are low-viscosity solutions, when the vesicles are not densely packed. The situation is different when the vesicles are ionically charged. Such systems can have a yield stress value even when they are not densely packed. The reason is that the vesicles in such solutions repel each other because of the electric double layer around the vesicles. Two vesicles cannot approach each other closer than about twice the thickness of the electric double layer. This situation can already be reached when the solution contains 2.5% surfactants that form vesicles and only 10% of the surfactants are ionic surfactants. Under these conditions the vesicles are so densely packed that they cannot diffuse past each other. The vesicles are trapped in a cage. Qualitatively, it is the same situation as if the vesicles would be connected with each other. When excess salt is added to such systems, the thickness of the electric double layer becomes thinner and the yield stress of the phase disappears (see Fig. 27.5).

Without other information, vesicular and the micellar systems cannot be distinguished from each other. Both systems may show the recoil of dispersed bubbles. However, viscoelastic solutions from worm-like micelles show the Weissenberg effect, whereas solutions with vesicles do not (see Fig. 27.7).

Under flow, both types of solutions are shear thinning. In a Couette geometry (double gap) system, the shear viscosity is decreasing with increasing shear rate according to Eq. (27.17)

$$\eta = \frac{\eta_o}{1 + \left(\dot{\gamma}\tau\right)^n} \tag{27.17}$$




**FIGURE 27.5** Freeze Fracture Transmission Electron Microscopy (FF-TEM) of multilamellar vesicles (MLV's), so-called onions.

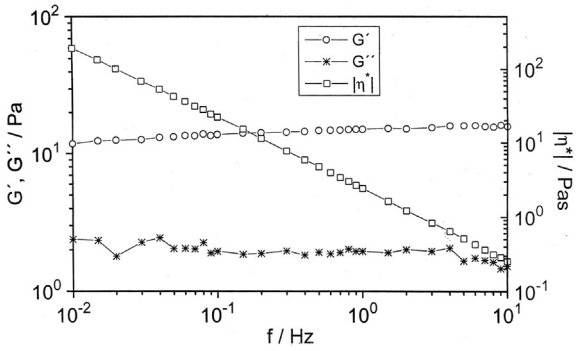



**FIGURE 27.6** Moduli and complex viscosity against frequency (log—log) from a weak vesicle gel.

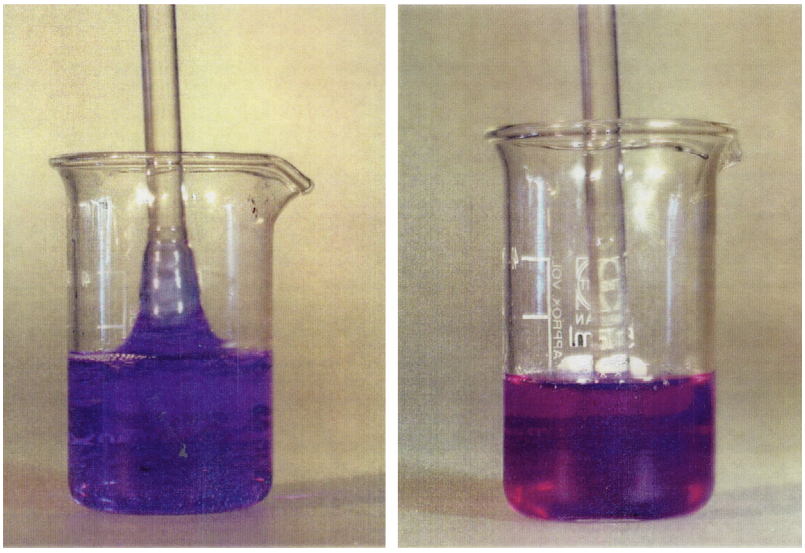


**FIGURE 27.7** Weissenberg effect: Rotating glass rod in micellar (left) and vesicular (right) solution. Both systems show viscoelastic behavior. *From Hoffmann H, Abdel-Rahem R.* Rheol Acta *2006;**45**(6):781—92. http://dx.doi.org/10.1007/s00397-006-0101-7.*

in which $\tau$ is the structural relaxation time of the fluid. The decrease of the viscosity is due to the alignment of the worm-like micelles or due to the deformation of the vesicles. Both solutions become birefringent under flow when $\tau \cdot \dot{\gamma} > 1$.

### 27.3.5 The $L_3$-phase

$L_3$-phases are bilayer phases with most unusual properties.[34–37] They can be formed from nonionic $L_\alpha$-phases by the addition of cosurfactants like *n*-alcohols. They are bicontinuous, optically isotropic phases with a low viscosity. The three-dimensional network has positive and negative curvatures, like a point on the top of a saddle (see Fig. 27.8).

We usually expect that phases with three-dimensional networks have high viscosities, but the $L_3$-phases have low viscosities. The viscosities are slightly dependent on the surfactant concentration.[38] Even though $L_3$-phases exist only in a very narrow cosurfactant/surfactant ratio, the phases can be formed over a large concentration region. Low concentrated $L_3$-phases can simply be formed by diluting a more concentrated $L_3$-phase with water. Obviously, $L_3$-phases can be formed only by surfactants that have a very well-balanced hydrophilic–hydrophobic range. It is, therefore, very unlikely that a single surfactant can form an $L_3$-phase in water on its own.

It is interesting to note that $L_3$-phases have the lowest interfacial tension that can exist for surfactants. A typical phase diagram with an $L_3$-phase is given in Fig. 27.9. It shows the typical narrow channel with a constant surfactant–cosurfactant mixing ratio.[39]

Although $L_3$-phases exist only within a narrow mixing ratio, they are important for the formation of microemulsions. $L_3$-phases are the surfactant phases that have the highest capacity for the solubilization of hydrocarbon among



FIGURE 27.8 Freeze-fracture Transmission Electron Microscopy (FF-TEM) of an $L_3$-phase (sponge phase). Smooth areas result from freeze-fracturing along the lamellar structures; coarse-grained areas show fracturing through the bulk water phase.

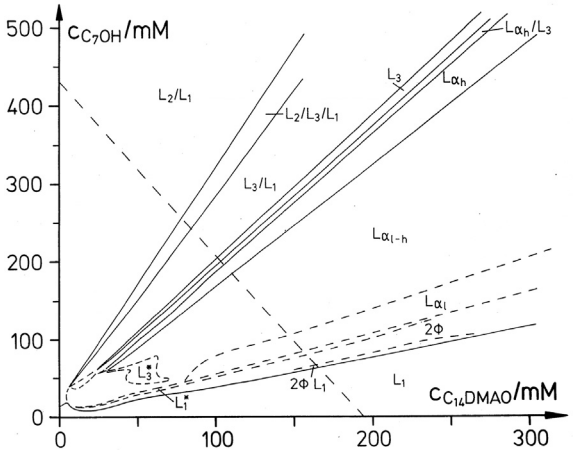



FIGURE 27.9 Phase diagram showing the long, "thin" $L_3$-phase region in aqueous mixtures of tetradecyldimethylaminoxide ($C_{14}$DMAO) and *n*-heptanol ("$C_7$OH"). Not that the extrapolation of the $L_3$ phase region hits the c($C_7$OH)-axis not at zero, but at ca. 30 mM. This is close to the solubility of individual heptanol molecules in surfactant-free water.

all surfactant phases. By solubilizing oil into the $L_3$-phase, it is possible to pass from a phase that consists mainly from water to a phase that consists mainly from oil without crossing a phase boundary (so-called single-phase channel).[40]

## 27.4 SURFACTANT SOLUTIONS AND ADDITIVES

### 27.4.1 Surfactant Solutions and Hydrocarbons

Many cosmetic formulations contain both surfactants and oil. Such phases can be single phase, transparent, and viscous. Of interest is the situation when hydrocarbons are added to viscoelastic solutions from worm-like micelles. Hydrocarbons can be solubilized in micelles. The amount of hydrocarbon that can be solubilized depends on the chain length of the hydrocarbon and the interfacial tension $\sigma$ between the micellar solutions and the oil phase. This is because on transfer of a hydrocarbon molecule from the oil phase to the interior of the micelles, the work $\Pi \cdot v$ has to be delivered by thermal energy $kT$, in which $\Pi$ is the Laplace pressure ($\Pi = 2\ \sigma/r$) in the micelles and $v$ is the volume of a single hydrocarbon molecule in which $v = m \cdot a$ with m the chain length and "$a$" the cross-section of the chain. The solubility of the hydrocarbon is therefore

$$S = \exp -\frac{\Pi v}{kT} = \exp -\frac{2\sigma v}{rkT} \tag{27.18}$$

The equation shows that the hydrocarbon is more soluble in the micellar phase the lower the surface tension and the smaller the volume of the hydrocarbon. This equation is also valid for worm-like micelles. With increasing solubilization the radius of the worms increase and the packing of the head group becomes denser. When the worm-like micelles reach the packing for spheres, they will switch from worms to microemulsion droplets and therefore to low-viscosity solutions. The droplets can then continue to grow until the saturation limit for the hydrocarbon is reached. If $v$ is too large, not enough oil can be solubilized to make the cylinder−sphere transition.[41]

### 27.4.2 Surfactant Solutions and Cosurfactants

Cosurfactants can be considered as surfactant molecules with small head groups. They are surface active, but they do not form micelles. When the concentration is raised above their solubility limit, they form a new phase because the head group is so small it cannot stop the aggregation process at a particular aggregation number. The solubility limit of the co-surfactant can therefore be considered as the CMC of the cosurfactants. Typical co-surfactants are $n$-alcohols and alkyl carboxylic acids.

Cosurfactants are miscible with surfactants and form mixed micelles. Because their head groups are small, the average head group area between the surfactant and the cosurfactant at the micellar surface is decreased and the packing parameter for the mixed system is increased. Addition of cosurfactants to surfactants therefore makes the combination:

- more surface active
- increase the packing parameter
- change the micelles from globules to worm-like micelles to bilayer phases (see Fig. 27.9)
- decrease the interfacial tension

Addition of cosurfactants to a surfactant solution with globular micelles can therefore transform the globular micelles to worm-like micelles to lamellar phases and vesicles, and to $L_3$-phases with a positive and negative curvature.[42]

Such a situation is shown in Fig. 27.10 for alkyldimethylaminoxide surfactant. As for hydrocarbons, the solubility of cosurfactants decreases continuously with increasing length of alkyl group.

### 27.4.3 Surfactant Solutions and Polymers

Many polymers are water soluble, and solutions of such polymers are used in cosmetic formulations. Typical water-soluble polymers are polyethylenoxide (PEO), Polyvinylalcohol (PVA), polyvinylpyrrolidone (PVP), Polyacrylamide (PAM), Protein, Hydroxycellulose (HEC), and polyelectrolytes. Solutions of these compounds are used in different cosmetic products like hair sprays, superabsorbers, shampoos, emulsions, and lotions. Most of the water-soluble polymers are surface active and lower the surface tension of water. Surfactants in general bind

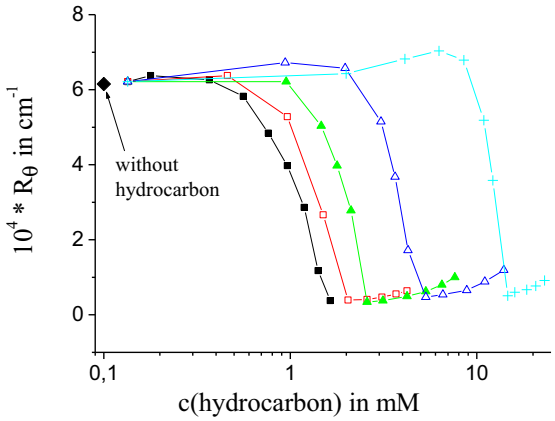



FIGURE 27.10 Light-scattering intensity proportional to particle size when different hydrocarbons are added to aqueous surfactant mixturesof alkyldimethylaminoxide. Filled squares: Tetradecane; open squares: Dodecane; filled triangles: Decane; open triangles: Octane; " +": Hexane. The diamond close to y-axis shows scattering intensity for c(hydrocarbon) = 0; note that x-axis is logarithmic.

to the polymers and thereby change the properties of the dissolved polymers. Some polymers are used as thickeners in various formulations. The thickening effect can be markedly increased by attaching hydrophobic groups to the polymers. The compounds are then called hydrophobically modified polymers. These compounds have excellent properties as thickeners and they are called associative thickeners. The thickening effect is due to the binding of the hydrophobic groups of the polymers to each other. The polymers thereby form a three-dimensional network in the solution. Surfactants can also bind to the hydrophobic groups and the cross-links between the hydrophobic groups are thereby strengthened which further increases the viscosity of the solutions. Very surfactant-sensitive systems for the control of the viscosity are obtained when the hydrophobic group is connected to an ionic charge. Ionic surfactants of opposite charge then bind, even at low surfactant concentrations, on the hydrophobically modified polymer and can thereby change the viscosity of the solution by many orders of magnitude. The solution can actually develop a yield stress value. Fig. 27.11 shows that for a 1% solution of a cationically modified cationic hydroxyethyl (HM-cat-HEC) cellulose system, the elastic modulus is greater than the loss modulus, therefore this viscoelastic system exhibits more solid-like behavior than liquid-like behavior. The complex viscosity is reduced by increasing shear frequency.

The addition of a few mM SDS increases the viscosity by several orders of magnitude and finally to a yield stress before the viscosity collapses. The collapse of the viscosity is due to the charge neutralization of the ionic polymer by the oppositely charged surfactant ions. In the neutral state, the system phase separates as a dense coacervate of the system which is dispersed in water. With excess of the surfactant the precipitate dissolves again into a viscous fluid. When the hydrophobic groups are saturated with the micellar surfactant, cross-links between the molecules are no longer possible and the systems transform into low-viscosity solutions.

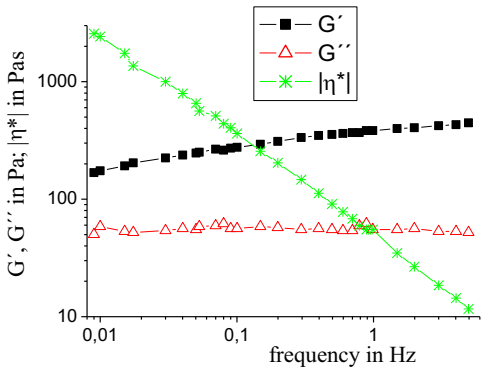



FIGURE 27.11 Moduli and viscosity against frequency for a solution of 1 wt-% hydrophobically modified cellulose with cationic groups and 2 mM anionic surfactant.

The example shows that such hydrophobically modified (HM)-ionic polymers are ideal systems for the thickening of aqueous formulations. The systems can be prepared from most of the water-soluble polymers. The systems with a yield-stress value behave like weak gels as is shown in Fig. 27.11. The systems are of particular interest for the preparation of stable dispersions, emulsions, and even foams because the thickener molecules do not only cross-link their own molecules, they also bind to small particles, droplets, and small bubbles.

## 27.5 MICROEMULSIONS

Microemulsions are thermodynamically stable phases from water, oil, and surfactants. Typically, they can contain 45% water, 45% oil, and 10% surfactant (for details see Ref. 43). They can be formed most easily by establishing the $L_3$-phase in a surfactant–water system. As mentioned before in the chapter on the $L_3$-phase in which the $L_3$-phase was formed by the addition of a cosurfactant to a surfactant, the $L_3$-phase can also be formed when the temperature is varied in solutions with nonionic surfactants.[43] The hydrophilic–lipophilic character of these surfactants can be tuned by variation of the temperature. A compound like $C_{12}E_5$ is water soluble and forms globular micelles. With increasing temperature, the globular micelles turn to worm-like micelles, then to $L_\alpha$-phases and within a narrow temperature range to an $L_3$-phase and finally into a multiphase region with an $L_2$-phase. Oil can be dissolved into the $L_3$-phase without loss of the bicontinuous structure of the $L_3$-phase. With more and more oil in the microemulsion, the temperature has to be adjusted to remain in this phase.

Microemulsions are, like the $L_3$-phase, low-viscosity phases. The viscosity changes only little across the whole existence region from the water-side to the oil side of the single phase channel.[44] The range of temperatures in which nonionic microemulsions exist is given by the temperatures at which the $L_3$-phase is formed. The situation changes when some of the nonionic surfactants in the system are replaced by an ionic surfactant. The $L_3$-phase can then be formed at any temperature starting with the ionic surfactant and adding more and more of a lipophilic surfactant while keeping the temperature constant.[45] The mixed surfactant solutions then become more lipophilic and pass through the $L_\alpha$ and $L_3$-phase in the same way as the pure nonionic solution with increasing temperature. Microemulsions can now be formed again by dissolving oil into the $L_3$-phase. In contrast to the microemulsions from pure nonionic surfactants, the structure in the single-phase channel changes with increasing oil content. With as little as 5% oil, the bicontinuous $L_3$-phase is transformed into a high internal phase microemulsion (HIPME) structure in which the water is trapped inside the foam-like structure that is formed from the surfactant and the oil.[46] The typical dimension of the cells is in the range of 30 nm (see Fig. 27.12). In spite of the fact that the microphase comprises 80% of water and the remaining 20% is surfactant and oil, the microemulsion is not a bicontinuous phase but the water is encapsulated by the surfactant bilayer.

As can be imagined, the physicochemical properties like the conductivity and the viscosity change strongly at the transition of the structure. The viscosity passes over a maximum and the conductivity decreases several orders of magnitude from the bicontinuous $L_3$-phase to the high internal phase emulsion (HIPE) structure (see Fig. 27.13).[46]

It is thus not only possible to prepare low-viscosity microemulsions but also viscous microemulsions.

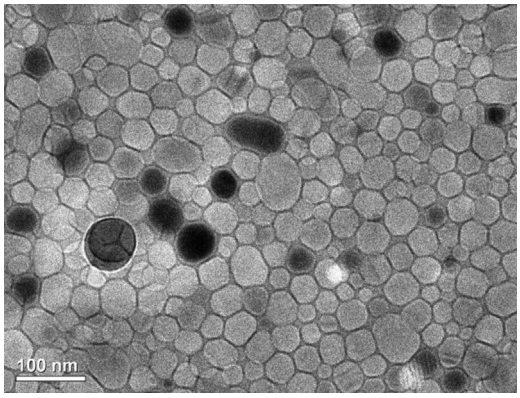



FIGURE 27.12 Cryo-TEM of high internal phase microemulsion (HIPME) structures (Cryo-TEM micrograph of a microemulsion with 15% of the anionic/nonionic surfactant mixture Mg (DS) 2/IT 3, x IT 3 0.7, x iso-octane 0.3 (water:oil = 7:3), quenched from 25°C).

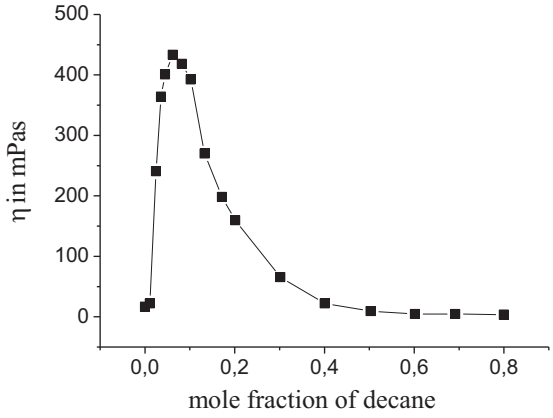



FIGURE 27.13 Viscosity of a microemulsion as a function of the oil content.

Microemulsions are interesting phases for cosmetic formulations because both hydrophilic and hydrophobic compounds can be dissolved in these phases. In contrast to the microemulsions formed from nonionic surfactants that have a narrow existence region in a small temperature range, microemulsions from mixed ionic and nonionic surfactants are stable within a large temperature range.

## 27.6 EMULSIONS

In contrast to microemulsions, normal emulsions are thermodynamically unstable systems which also consist of water, oil, and surfactants.[47–49] Two types of emulsions can be distinguished on the basis of what is the continuous and what is the dispersed phase. Emulsions with oil droplets dispersed in water are called oil–water (o/w) emulsions. When water is dispersed in oil, they are called water–oil (w/o) emulsions.

The phases are prepared by dispersing oil in an aqueous surfactant solution to reach an o/w phase. Depending on the shear rate in the dispersing machine, the droplets usually have a diameter in the range of μm. However, for special applications, small droplets in the nm range (nanoemulsions) and large droplets can be prepared.[50] Emulsions are unstable and separate by various mechanisms. Oil in the emulsion droplets usually has a lower density than water. As a consequence, the drops rise to the surface, make contact with each other, and with time the drops coalesce to a macroscopic oil phase. When the oil has the same density as water, the drops can also coalesce in the bulk phase. Finally, the drops can change their size by Ostwald ripening,[51] which means that some of the droplets become larger, whereas other ones become smaller. The transfer of the oil molecules from the smaller into the larger droplets is a result of the higher Laplace pressure in the smaller droplets.

Emulsions are usually prepared so they can have a long shelf life. They should be stable for long periods. This can be accomplished by charging the droplets with ionic surfactants or by adding hydrophobically modified (HM) polyelectrolytes to shield direct contact between the droplets, or by making the volume fraction of the droplets small enough to avoid dense packing. The viscosity of such emulsions is mainly given by the viscosity of the continuous water phase.

It should be mentioned, however, that emulsions can also be prepared with gel-like properties. When emulsions are prepared with proteins as emulsifiers, the resulting protein-covered droplets have sticky properties, even when the droplets are ionically charged.[52] Obviously, the adhesion energy between the droplets is larger than the repulsive energy. This property is a result of the multipolar character of the proteins. Parts of the surface of the proteins are hydrophobic and other parts are hydrophilic. Even though the emulsion droplets with such proteins are in direct contact, the drops do not coalesce. Such emulsions no longer flow spontaneously, and they typically have properties like mayonnaise. A picture of such an emulsion is shown in Fig. 27.14. The shear modulus in such systems can be as high as 1000 Pa.

Other emulsions with gel-like properties are HIPE emulsions.[53] The surfactants in these systems form a foam-like structure with little water, and the interior of the cells is filled with oil. The structure in HIPE-systems is the same as that of HIPME-systems (see Fig. 27.12), but the emulsion droplets are several orders of magnitude larger than the microemulsion droplets, typically 2–5 μm for emulsions, but only 5–20 nm for microemulsions.




FIGURE 27.14 Protein-stabilized emulsion with gel-like properties.

## 27.7 HYDROGELS AND ORGANOGELS

Hydrogels and organogels are systems that consist of water or an organic solvent with a few percent of another compound. They have special features which other systems like viscoelastic solutions do not have. They behave like soft solids. One of the best-known gels is gelatin in water.[54] These systems no longer flow when a small shear stress is applied to the system. A typical feature of a gel is the fact that a rough surface of a gel does become a smooth surface with time. A gel longer has a zero-shear viscosity on a timescale that is relevant for the shelf life of the system. It can be compared with a viscoelastic system for which the structural relaxation time is indefinitely long, or for practical systems as long as the samples are sitting in a storeroom. Particles or bubbles which are dispersed in a gel cannot settle down or rise. Gels can therefore be used to produce stable dispersions or emulsions. Gels have a yield-stress value. This is the shear stress below which the system cannot flow. It can be determined by a stress-controlled rheometer. As long as the applied shear stress is lower than the yield stress, the system does not flow. The sample is only elastically deformed by the stress. When the applied stress becomes larger than the yield stress, the system begins to flow. A typical situation for such a system is shown in Fig. 27.15.

The yield stress is an important parameter for a gel. A yield stress can vary between a few mPa and several kPa for typical gels.

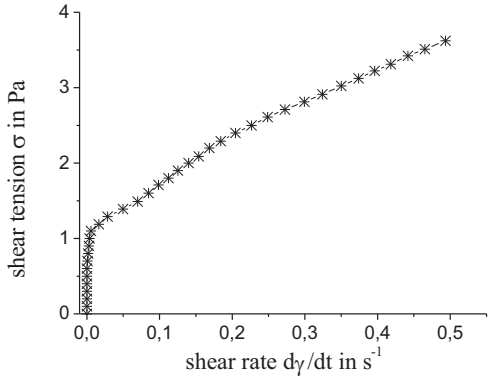



FIGURE 27.15 Stress against shear rate for a system with a yield stress. The value of the yield stress is easily seen where the shear rate rises abruptly.

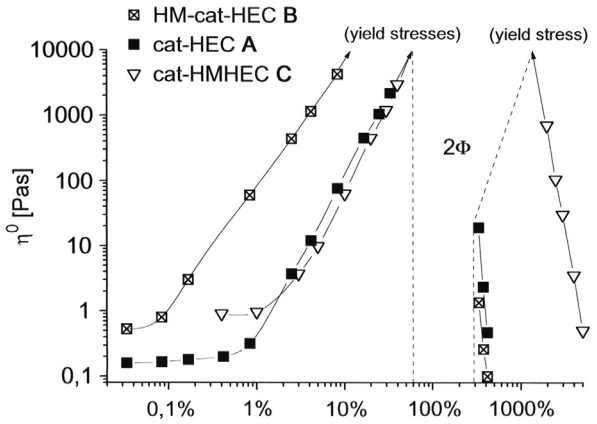



FIGURE 27.16 Cationically modified cellulose in water with increasing amounts of anionic surfactant.

The yield stress of a system is often of the order of 10 times smaller than the shear modulus of the system. This means that the system begins to flow when the existing structure in the system is deformed by more than 10%. Gels usually contain networks that are suspended in a liquid. They also can contain particles which are not directly connected. Isotropic gels become birefringent when the systems are deformed.

When oscillating measurements are made on gels, the storage modulus usually is an order of magnitude larger than the loss modulus and independent of frequency.

The additives in gels usually form different structures which in general cannot be distinguished by rheological measurements. The structures can be formed by self-aggregation processes. Gels can be formed from surfactants and functionalized polymers, cross-linked micelles, ionically charged vesicles, gelatin, tubuli in water, or HIPE systems.[55–59]

Many hydrophobically-modified hydrophilic polymers are known that consist of a long chain to which hydrophobic groups are attached. In aqueous solutions the hydrophobic groups bind to each other and a three-dimensional network is formed. The bonds between the hydrophilic groups open and close again with time, and the system is viscous but has not yet a yield stress. When surfactants are added, they bind to the cross-links and strengthen the bonds. The viscosity increases therefore, and the system can reach a yield stress at a particular surfactant concentration. When more surfactants are added, they form micelles around the hydrophobic groups, the cross-links disappear, and the viscosity breaks down (see Fig. 27.16).[55]

## 27.8 FOAMS

Some cosmetic formulations like shaving cream contain foams. Foams consist of small bubbles that are so densely packed that the bubbles are strongly deformed and of polyhedral shape.[60] All surfactants, and amphiphilic polymer solutions like proteins, foam. The thickness of the bilayers in foams like in soap bubbles depends on the physicochemical conditions of the solution from which the bubbles and the foam are prepared. All foams have a yield stress, and their shear modulus depends on the radius of the bubbles, the surface tension of the aqueous solution, and the volume fraction of air in the foam. The modulus can be given by an equation that was developed by Princen.[61] With time, the bilayer of the foam becomes thinner because of drainage of the liquid in the bilayers and in the plateau regions.

One parameter which varies very much for different foams is stability. Some foams break in a few minutes and other foams are stable for days. The stability of foam depends very much on the viscosity of the solution because the drainage, that is the flow of the solution through the capillary systems, depends on the viscosity.

$$G^{\circ} = a \cdot \frac{\sigma}{r_{32}} \cdot \Phi \cdot (\Phi - \Phi_C) \tag{27.19}$$

The modulus $G^{o}$ is calculated from the surface tension $\sigma$, the specially averaged bubble radius $r_{32}$, the actual volume fraction of the bubbles $\Phi$, and their maximum volume fraction $\Phi_C$, including another parameter "$a$" to be obtained from a fit.

## 27.9 LIQUID CRYSTALS

When in micellar solutions with globular micelles, the concentration is increased up to the concentration of dense packing, and the globular micelles form a lattice like in a crystal. These phases are called discontinuous cubic phases.[62–64] These cubic phases are separated from the micellar solution by a narrow two-phase region. Obviously, the spherical micelles are so monodisperse that they form a lattice that gives the sharp reflexes typical of crystals in small-angle X-ray scattering (SAXS) and small-angle neutron scattering (SANS) measurements. Studies have shown that several cubic phases can be distinguished on the basis of the scattering reflexes.[65]

The properties of the phases can be understood on the basis of a "hard sphere model" for the micelles.

Cubic phases essentially behave like soft solids with a yield-stress value. The micelles cannot move around in the crystalline phase by thermal motion. The particles have to be deformed to move to another lattice point which requires energy. To understand the elastic properties of this cubic phase, we can assume that each micelle is a gas molecule and the compressibility of the phase is then given by the compression modulus $K$ with

$$K = \frac{v \cdot kT}{S(0)} \tag{27.20}$$

in which $v$ is the number density of the micelles in the cubic phase and $S(0)$ is the structure factor at zero angle.

The shear modulus $G'$ is then given by

$$G = K\frac{3 \cdot (1 - 2\mu)}{2 \cdot (1 + \mu)} \tag{27.21}$$

in which $\mu$ is the Poisson number.[66]

Experimental values for $G'$ and theoretical values show good agreement and are in the range of 100 kPa for globular micelles.

The hard-sphere model can also be used for microemulsion droplets that can be formed from worm-like micelles by solubilization of hydrocarbon into the worms. It is interesting to mention that cubic phases with shear moduli in the range of 100 kPa show the 'ringing phenomenon'.[67] Glass containers filled with a cubic phase ring like a bell when they are tapped with a soft object. These phases have therefore been called ringing gels. To have this property, the $G''$ values must be several orders lower than the $G'$ values. The damping of shear waves in the cubic phases is then low.

It is noteworthy to mention that the crystallization of globular micelles to cubic phases can take quite a long time (sometimes days). The systems then have no long-range order and can theoretically be treated as glasses.[68] It should be realized that the micelles can be considered as hard spheres because the Laplace pressure $\Pi$ inside the micelles is in the range of the compressibility $K$ with $\Pi = 2\sigma/r$ when $\sigma$ is the interfacial tension between the micellar phase and the hydrocarbon phase.

If the micellar solution already contains worm-like micelles, cubic phases can no longer be formed. In this case, hexagonal phases are formed when the dense packing of the worms is reached. These phases have $G^{\circ}$ values in the same range as the cubic phase.

When the concentration in the micellar solution is increased to above the existence region of the hexagonal phase, these phases can no longer be formed.

Bilayer phases can now be formed until the bilayers fill the entire space available. These $L_\alpha$-phases should be distinguished from the $L_\alpha$-phases which form at low concentration. They are formed because the packing parameter of the surfactant molecules is around unity in dilute solution. These $L_\alpha$-phases can be diluted until the bilayers are separated so much from each other that they form iridescent phases.[69] The $L_\alpha$-phases at high concentration cannot be diluted to low concentration.

For surfactant concentrations which are higher than the existence region of the hexagonal phase, worm-like micelles can no longer be packed. In this region, the surfactants have to form lamellar phases which can be packed up to high volume fractions close to one. The properties of these $L_\alpha$-phases have to be distinguished from the properties of $L_\alpha$-phases which are formed at small surfactant concentrations because their packing parameter is close to one. It should be realized that $L_\alpha$-phases which are formed above the hexagonal phases can still be sheared because the bilayers can slide past each other. It should be noted, however, that it is difficult to dilute these phases into the $L_1$-phases because on dilution one has to pass the hexagonal phase which behaves like a soft solid.

## References


1. Barnes HA, Hutton JF, Walters K. *An Introduction to Rheology, Rheology Ser*. New York: Elsevier; 1989.
2. Hoffmann H. In: Herb CA, Prud'homme RK, editors. *Viscoelastic surfactant solutions***578**. ACS-Symposium Series; 1994. p. 1–31.
3. Clansen TM, Vinson PK, Minter JR, Davis HT, Talmon Y, Miller WG. *J Phys Chem* 1992;**16**(1):474–84.
4. Shikata T, Hirata H, Kotaka T. Micelle formation of detergent molecules in aqueous media: viscoelastic properties of aqueous cetyltrimethylammonium bromide solutions. *Langmuir* 1987;**3**:1081–6.
5. Cates ME. Flow behaviour of entangled surfactant micelles. *J Phys Condens Matter* 1996;**8**:9167–76.
6. Kern F, Lequeux F, Zana R, Candau SJ. Dynamical properties of salt-free visoelastic micellar solutions. *Langmuir* 1994;**10**:1714–23.
7. Rehage H, Hoffmann H. Viscoelastic surfactant solutions: model systems for rheological research. *Mol Phys* 1991;**74**(5):933–73.
8. Cox WP, Merz EH. *J Polym Chem* 1958;**28**(118):619–22.
9. Hoffmann H, Löbl M, Rehage H, Wunderlich I. Rheology of surfactant solutions. *Tenside Deter* 1985;**22**:290.
10. Kostas H, Avramidis S, Turian RM. Yield stress of laterite suspensions. *J Colloid Interface Sci* 1991;**143**(1):54–68. http://dx.doi.org/10.1016/0021-9797(91)90436-C.
11. Tanford C. *The hydrophobic effect*. New York: Wiley-Interscience; 1973.
12. Shah DO. *Micelles, Microemulsions and monolayers: Science and Technology*. CRC Press; 1998. ISBN: 9780824799908.
13 Mukerjee P, Mysels K. Critical micelle concentration of aqueous surfactant systems. *J Pharm Sci* 1972;**61**(2):319. http://dx.doi.org/10.1002/jps.2600610254.
14 Rosen MJ, Kunjappu JT. *Surfactants and interfacial phenomena*. Wiley & Sons, Hoboken, NJ; 2012. ISBN: 1-118-22902-9.
15 Laughlin RG. *The aqueous phase behaviour of surfactants*. Academic Press; 1994.
16. Krieger IM, Dougherty TJ. A mechanism for non-Newtonian flow in suspensions of rigid spheres. *T Soc Rheol* 1959;**3**:137–52. http://dx.doi.org/10.1122/1.548848).
17. Candau SJ, Khatory H, Lequeux F, Kern FJ. Rheological behaviour of wormlike micelles: Effect of salt content. *Phys IV France* 1993;**03**(C1).
18. Israelachvili JN, Mitchell DJ, Ninham BW. *J Chem Soc Faraday Trans II* 1976;**72**:1525–68.
19. Mackintosh FC, Safran SA, Pincas PA. *Europhys Lett* 1990;**12**:697–702.
20. Danino D, Talmon Y, Levy H, Beinert G, Zana R. *Branched threadlike micelles*. a. Vensen GV, Lund R, Gummel J, Narayanan T, Pedersen JS. Monitoring the transition from spherical to polymer-like surfactant micelles using small angle X-ray scattering. *Angew Chem Int Ed* 2014;**53**:11524–8. http://dx.doi.org/10.1002/anie.201406489.
21. Hertel G, Hoffmann H. New lyotropic nematics of double chain surfactants. *Liq Cryst* 1989;**6**:1883–98.
22. Rodenas E, Valiente M, Montalvo G. Rheological properties of the L phase and the hexagonal, lamellar, and cubic liquid crystals of the CTAB/benzyl alcohol/water system. *Langmuir* 1996;**12**:5202–8.
23. Ionita-Abutbul I, Abezgauz L, Danino D, Hoffmann H. Rings and loops in perfluorosurfactants viscoelastic solutions. *Colloids Surf A Eng Asp* 2015;**483**:150–4. http://dx.doi.org/10.1016/j.colsurfa.2015.07.026.
24. Schubert BA, Wagner HJ, Kaler EW, Raghavan SR. Shear-induced phase separation in solutions of wormlike micelles. *Langmuir* 2004;**20**:3564–73.
25. Wunderlich I, Hoffmann H, Rehage H. Flow birefringence and rheological measurements on shear induced micellar structures. *Rheol Acta* 1987;**26**:532–42.
26. Hertel G, Hoffmann H. Lyotropic nematic phases of double chain surfactants. *Prog Colloid Polym Sci* 1988;**76**:123–31.
27. Fromherz P, Röcker C, Rüppel D. From discoid micelles to spherical vesicles. *Faraday Discuss Chem Soc* 1986;**81**:39–48.
28. Bartusch G, Dörfler H-D, Hoffmann H. Behavior and properties of lyotropic-nematic and lyotropic-cholesteric phases. *Prog Colloid Polym Sci* 1992;**89**:307–14.
29. Fischer A, Hoffmann H, Medick P, Rössler E. A novel method for the alignment of lyotropic $L_\alpha$ phases in magnetic fields. *J Phys Chem B* 2002;**106**:6821–6. http://dx.doi.org/10.1021/jp020699q.
30. Kaler EW. Spontaneous vesicles and other solution structures in catanionic mixtures. *Mat Res Soc Symp Proc* 1992;**248**.
31. Oberdisse J, Couve C, Appell J, Berret JF, Ligoure C, Porte G. Vesicles and onions from charged surfactant bilayers: a neutron scattering study. *Langmuir* 1996;**12**(5):1212–8.
32. Laughlin RG. Equilibrium vesicles: fact or fiction? *Colloids Surf A Physicochem Eng Asp* 1997;**128**:27–38.
33. Hoffmann H, Thunig C, Schmiedel P, Munkert U. Surfactant systems with multilamellar vesicles and their rheological properties. *Langmuir* 1994;**10**:3972–81.
34. Daicic J, Olsson U, Wennerström H, Jerke G, Schurtenberger P. Thermodynamics of the $L_3$ (sponge) phase in the flexible surface model. *J Phys II France* 1995;**5**:199–215.
35. Vinches C, Coulon C, Roux D. Viscosity of sponge phase in porous medium. *J Phys II France* 1992;**2**:453–69.
36. Wennerström H, Olsson U. On the flexible surface model of sponge phases and microemulsions. *Langmuir* 1993;**9**(2):365–8.
37. Jonströmer M, Strey R. Nonionic bilayers in dilute solutions: effect of additives. *J Phys Chem* 1992:96.
38. Miller CA, Gradzielski M, Hoffmann H, Krämer U, Thunig C. $L_3$-Phases: their structure and dynamic properties. *Prog Colloid A. Polym Sci* 1991;**84**:243.
39. Lichterfeld F, Schmeling T, Strey R. Microstructure of microemulsions of the system $H_2O$-n-tetradecane-$C_{12}E_5$. *J Phys Chem* 1986;**90**:5762–6.
40. Shinoda K, Lindman B. Organized surfactant systems: microemulsions. *Langmuir* 1987;**3**:135.
41. Bayer O, Hoffmann H, Thurn H, Ulbricht W. The influence of solubilized additives on surfactant solutions with rodlike micelles. *Adv Colloid Interface Sci* 1986;**26**:177–203.
42. Hoffmann H, Thunig C, Valiente M. *Colloids Surf* 1992;**67**:223–37.
43. Strey R. Microemulsion microstructure and interfacial curvature. *Colloid Polym Sci* 1994;**272**(8):1005–19.
44 Fanun M. *Microemulsions: properties and applications*. CRC Press; 2008. p. 560. ISBN: 9781420089592.
45. Hoffmann H, Richter W, Teshigawara T, Okamoto T. Dynamic properties of microemulsions in the single-phase channels Lukas Wolf. *J Phys Chem B* 2011;**115**:11081–91.

46. Wolf L, Hoffmann H, Teshigawara T, Okamoto T, Talmon Y. Microemulsions with a HIPME (High Internal Phase Microemulsion) structure. *J Phys Chem B* 2012;**116**(7):2131–7.
47. Mason TG, Bibette J, Weitz DA. Yielding and flow of monodisperse emulsions. *J Colloid Interface Sci* 1996;**179**:439–48, 0235.
48. Binks BP, Dong J. Emulsions and equilibrium phase behaviour in silicone oil + water + non-ionic surfactant mixtures. *Colloids Surf A: Physicochem Eng Asp* 1998;**132**:289–301.
49. Ivanov IB, Kralchevsky PA. Stability of emulsions under equilibrium and dynamic conditions. *Colloids Surf A: Physicochem Eng Asp* 1997;**128**: 155–75.
50. Dimitrova, et al. *Adv Colloid Interface Sci* 2004;**108–109**:49–61.
51 Taylor P. Ostwald ripening in emulsions. *Adv Colloid Interface Sci* 1998;**75**(2):107–63. http://dx.doi.org/10.1016/S0001-8686(98)00035-9.
52. Reger M, Sekine T, Hoffmann H. Boosting the stability of protein emulsions by the synergistic use of proteins and clays. *Colloid Polym Sci* 2012; **290**(7):631–40.
53. Kronberg B, Kizling J. On the formation and stability of concentrated water-in-oil emulsions, aphrons. *Colloids Surf* 1990;**50**:131–40.
54. Wu C, Schrof W, Lilge D, Lüddecke E, Horn D. Study of structure and dynamics of gelation gels by temperature ramped holographic relaxation spectroscopy. *Makromol Chem Macromol Symp* 1990;**40**:153–66.
55. Tanaka F, Stockmayer WH. Thermoreversible gelation with junctions of variable multiplicity. *Macromolecules* 1994;**27**(14):3943–54.
56. Ross-Murphy SB, Shatwell KP. Polysaccharide strong and weak gels. *Biorheology* 1993;**30**(3–4):217–27.
57. Dickinson E. On gelation kinetics in a system of particles with both weak and strong interactions. *J Chem Soc Faraday Trans* 1997;**93**(1):111–4.
58. Terech P, Weiss RG. Low molecular mass gelators of organic liquids and the properties of their gels. *Chem Rev* 1997;**97**(8):3133–59.
59. Kawasaki H, Mitou T, Sasaki S, Maeda H. Partition of salts between N-isopropylacrylamide gels and aqueous solutions. *Langmuir* 2000;**16**(3): 1444–6.
60. Weaire D, Hutzler S. *The physics of foams*. Clarendon Press Oxford; 1999. p. 2001.
61. Princen HM. Rheology of foams and highly concentrated emulsions, I. Elastic properties and yield stress of a cylindrical model system. *J Colloid Interface Sci* January 1983;**91**(1):160.
62. Fontell K. Cubic phases in surfactant and surfactant-like lipid systems. *Colloid Polym Sci* 1990;**268**:264–85.
63. Johansson LB-A, Söderman O. The cubic phase ($I_1$) in the dodecyltrimethylammonium chloride/water system. A fluorescence quenching study. *J Phys Chem* 1987;**91**:5275.
64. Barois P, Hyde S, Ninham B, Dowling T. Observation of two phases within the cubic phase region of a ternary surfactant solution. *Langmuir* 1990;**6**:1136.
65 Ström P, Anderson DM. The cubic phase region in the system didodecyldimethylammonium bromide – water – styrene. *Langmuir* 1992;**8**(2): 691–709. http://dx.doi.org/10.1021/la00038a065.
66. Gradzielski M, Hoffmann H, Oetter G. Ringing gels: their structure and macroscopic properties. *Colloid Polym Sci* 1990;**268**:167–79.
67. Gradzielski M, Hoffmann H, Panitz J-C, Wokaun A. Investigations on $L_2$ phase and cubic phase in the system AOT/1-octanol/water. *J Colloid Interface Sci* 1995;**169**:103–18.
68. Mallamace F, Corsaro C, Mallamace D, Chen S–H. The fragile-to-strong dynamical crossover and the system viscoelasticity in attractive glass forming colloids. *Colloid Polym Sci* 2015;**293**:3337–49.
69. Platz G, Thunig C, Hoffmann H. Iridescent phases in amineoxide surfactant solutions. *Colloid Polym Sci* 1990;**83**:167.

CHAPTER

# 28

# Emulsion and Emulsification Technology

*Y. Yamashita*[1], *R. Miyahara*[2], *K. Sakamoto*[3]

[1]Chiba Institute of Science, Choshi, Japan; [2]Shiseido Global Innovation Center, Yokohama, Japan; [3]Tokyo University of Science, Chiba, Japan

## 28.1 INTRODUCTION

An emulsion is a dispersion of one liquid in another liquid of which both are obviously immiscible, and emulsification is preparation of such a dispersion. Namely, emulsification is a "process" of making a metastable mixture like water and oil, which eventually separates into two phases in equilibrium. A number of the emulsion systems are found in nature and our bodies; bile acid acts as an emulsifier to help digestion and absorption of fat by the formation of finely dispersed emulsion droplets, and lipoprotein forms an emulsion to deliver and metabolize fat in the body. Thus, it is conceivable that emulsions have unique properties relating to biological functions and metabolism, whereas the intrinsic biological system maintaining and controlling the dynamic, nonequilibrium state called "homeostasis," could be attributed to the steady exertion of the emulsion's function. For food science, emulsions can be functionalized with respect to the sense of taste by manipulating the stable or unstable state of the emulsion. Likewise, utilizing the nonequilibrium state of the emulsion could create sophisticated tactile sensations which are one of important properties of the cosmetic products. On the other hand, this nonequilibrium state is unfavorable from the quality assurance viewpoint, and foreseeable long-term stability is required in an emulsion product. Contrary to the solubilized system, the emulsion under a nonequilibrium state eventually separates into two phases driven by destabilization processes such as creaming, coagulation, coalescence, and Ostwald ripening. To obtain a practically stable emulsion, preparation process and stabilizing factors should be understood; in particular, the emulsification process should be a key factor because the objective is to confer tailored stability on a nonequilibrium system.

This chapter explains and reviews the following points:

1. Definition and classification of the emulsions
2. Factors that determine the type of emulsion
3. Stabilizing strategies for emulsions (strategies to stabilize emulsion)
4. Development of chemical and physical aspects of emulsification technology

## 28.2 DEFINITION AND CLASSIFICATION OF EMULSION

Typical emulsion droplet sizes range from 0.1 to 10 μm, which covers the wavelengths of visible light, and hence emulsions often appears cloudy or pale white (bluish) (Fig. 28.1). Some specific emulsions in the size of 20–100 nm can be prepared and they appear translucent despite of their dispersed nature. Such translucent emulsions are called "nanoemulsions" or "ultrafine emulsions" and they are distinguished from thermodynamically stable microemulsions. Emulsions are roughly divided into two categories, oil-in-water (O/W) and water-in-oil (W/O) types, in which water or oil is the continuous phase, respectively. As shown in Fig. 28.2, in addition, multiple emulsions can be prepared by dispersing the O/W (or W/O) emulsion in oil (or water) using the specific surfactants and procedures.

*Cosmetic Science and Technology: Theoretical Principles and Applications*
http://dx.doi.org/10.1016/B978-0-12-802005-0.00028-8



Copyright © 2017 Elsevier Inc. All rights reserved.

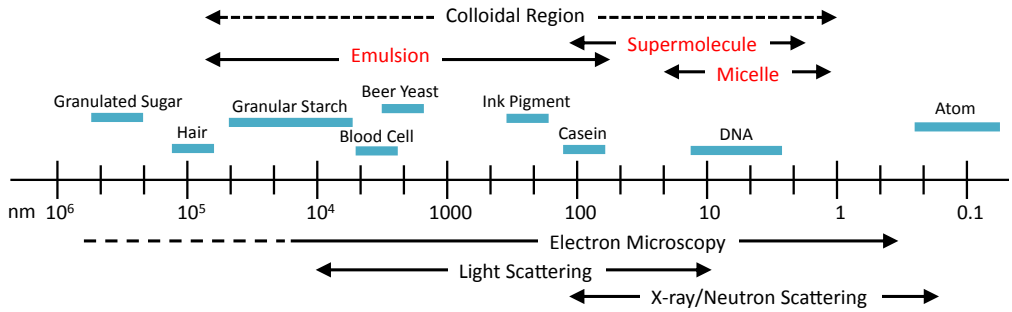



**FIGURE 28.1** Comparison of "size" among a variety of colloidal objects.

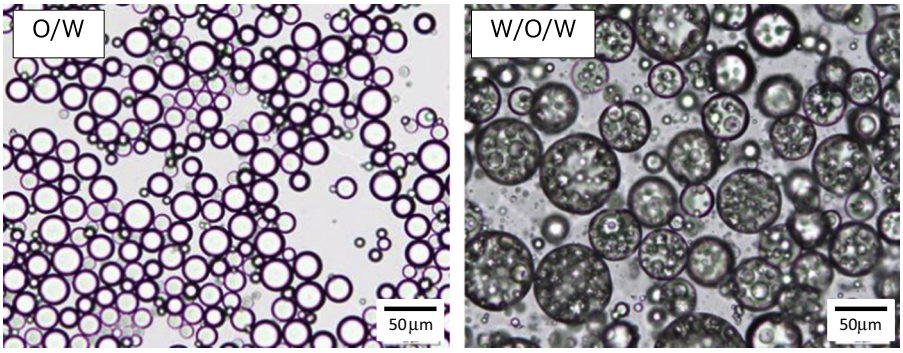



**FIGURE 28.2** Optical microscope images of emulsions: oil-in-water emulsion (O/W, left) and water-in-oil-in-water (W/O/W) emulsion right.

## 28.3 PROPERTIES OF SURFACTANT ON EMULSIFICATION

A surfactant is a chemical substance that alters interfacial properties by absorbing to the boundary between two immiscible phases. The chemical structure of surfactant consists of hydrophilic and lipophilic groups. The lipophilic group of surfactant molecule tends to move away from the water molecules by so-called "hydrophobic interaction."[1] Surfactant molecules spontaneously absorb to the interface when dissolved in an aqueous or emulsion system in which an air–water surface or oil–water interface is always present. Furthermore, surfactant molecules will self-assemble in water, typically forming of micelles, beyond a critical concentration. This is also due to the hydrophobic interaction; the unfavorable contact of the hydrophobic groups with water leads to the formation of a hydrophobic compartment surrounded by the hydrophilic shell (Fig. 28.3). It should be noted that a certain concentration of surfactant molecules are dissolved in the monomeric form in the micellar solution and there is a kinetic exchange between monomer and multimer (micelles) at equilibrium. For some surfactants the order of the exchange rate is $10^{-5}$ to $\sim 10^{-3}$ s,[2] and micellization may be referred to as a dynamic equilibrium. These fundamental properties of surfactant, absorption and micellization, are important parameters in emulsion formulation.

Another notable property of surfactant is the lowering of interfacial tension. Surfactant absorbed to the interface is able to reduce excess free energy at the water–oil interface. This excess energy is called "interfacial energy" ($G_{Intef}$), arising from a gap between the intermolecular interactions at the immiscible liquid–liquid interface and in each bulk phase. Table 28.1[3–9] shows interfacial tensions of various oils against water. The interfacial tension, proportional to $G_{Intef}$, tends to decrease with lowering polarity of oil. Emulsions with smaller droplet size, or larger interface area, have larger oil/water interfacial area, and a higher concentration of surfactant is required to maintain the droplet size. If there is insufficient surfactant to cover the large interfacial area, the system will undergo a change to minimize the interfacial area, i.e., and in the limit, this could lead to phase separation.

## 28.4 SELECTION OF EMULSIFIER SUITABLE FOR APPLICATIONS: HYDROPHILE–LIPOPHILE BALANCE NUMBER

As described previously, surfactants are used to stabilize emulsions. For this purpose, various types of compounds can be used, such as amphiphilic polymers, proteins, particles, etc., which may be good at stabilizing the

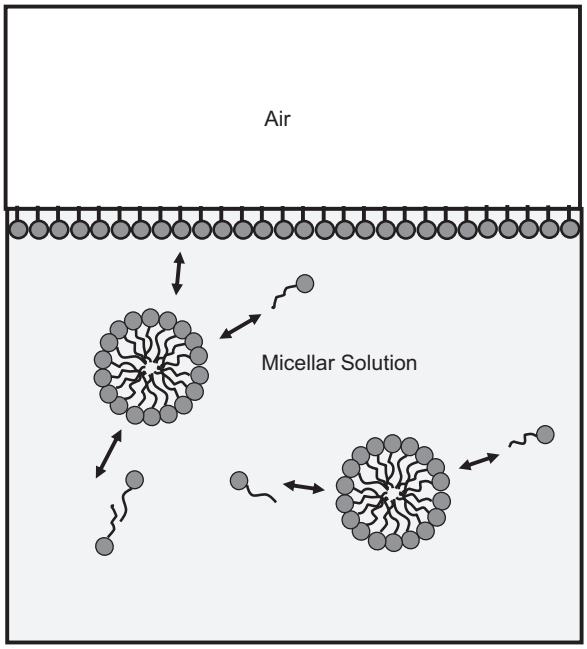



**FIGURE 28.3** Schematic representation of surface adsorption of surfactant molecules at the air–water interface and surfactant micelle.

**TABLE 28.1** Surface Tensions of a Variety of Liquids and Their Interfacial Tensions Against Water

| | Surface Tension (mN/m) | Interfacial Tension (Water, mN/m) |
|---|---|---|
| Water | 72.8 (20°C) [3] | – |
| Ethanol | 22.4 (20°C) [4] | – |
| 1-Butanol | 25.4 (20°C) [4] | 1.8 (20°C) [4] |
| 1-Hexanol | 26.2 (20°C) [4] | 6.8 (20°C) [4] |
| 1-Octanol | 27.5 (20°C) [4] | 8.5 (20°C) [4] |
| Hexane | 18.4 (20°C) [4] | 50.8 (20°C) [4] |
| Octane | 21.6 (20°C) [4] | 51.7 (20°C) [4] |
| Dodecane | 25.4 (20°C) [4] | 52.8 (20°C) [4] |
| Hexadecane | 27.5 (20°C) [4] | 53.8 (20°C) [4] |
| Squalane | 28.2 (20°C) [5] | 52.3 (22.5°C) [6] |
| Isopropyl myristate | 27.8 (20°C) [7] | 28.6 (20°C) [7] |
| Olive oil | 35.8 (20°C) [8] | 31.0 (20°C) [9] |
| Polydimethylsiloxane | 21.3 (20°C) [7] | 38.0 (20°C) [7] |

oil–water interface, but most of them are large species that diffuse slowly to the newly created interface. The rapid absorption on the interface is crucial for the nonequilibrium emulsion system and therefore low molecular weight surfactants are often suitable for this requirement.

On handling emulsions especially in industrial fields, a surfactant used for the sake of forming emulsion is referred to as an "emulsifier" and the characteristics of an emulsifier is often expressed by the Hydrophile–Lipophile Balance (HLB) number. The HLB number is an index of the affinity of a surfactant toward a solvent; for example, a high HLB number indicates that the surfactant is more compatible with water (water soluble). It is well known, that the HLB number can be used to select an appropriate surfactant to emulsify a particular oil-in-water (O/W) solution. Table 28.2 lists applications corresponding to the HLB number range, and thus a suitable surfactant can be chosen by reference to the HLB number. In addition, Bancroft's rule[10] states that oil-soluble surfactants preferably form W/O

TABLE 28.2 HLB Numbers and Corresponding Applications

| HLB Number Range | Corresponding Application |
|---|---|
| 1.5–3 | Antifoaming agent |
| 1–4 | Emulsifier for W/O emulsions |
| 6–8 | Wetting agent |
| 10–13 | Emulsifier for O/W emulsions |
| 13–15 | Detergent |
| 15–18 | Solubilizer |

emulsions, and water-soluble ones O/W emulsions. The HLB number also practically correlates to solution properties such as cloud point or critical micellar concentration (CMC), and has provided significant benefit to the development of advanced emulsification technology.

Various equations to calculate the HLB number have been proposed over the past 50 years. The HLB number scale, introduced by Griffin,[11,12] was the first successful attempt at quantitative characterization of polyoxyethylene (POE) surfactants. After that, many versatile calculation methods such as Davies'[13] and Kawakami's[14] equations have been proposed.

## 28.4.1 Griffin's Equation[11,12]

The equation proposed by Griffin is still commonly used. This equation expresses the structural balance between hydrophilic and lipophilic groups in a surfactant molecule as numeric index from 0 to 20 on the basis of empirical emulsification with POE emulsifiers. Specifically, the HLB numbers of the POE alkyl ethers ($C_mEO_n$) are given by the following equation, in which the HLB number equals the weight fraction of POE moiety in the molecule:

$$\mathrm{HLB} = \frac{\mathrm{POE\ (wt\%)}}{5} \tag{28.1}$$

The Griffin's HLB number was established empirically from emulsification testing, and thus this equation can be utilized as a convenient tool for industrial applications. On the other hand, Griffin also obtained another equation to calculate the HLB number for fatty-acid esters chemically bonded with polyols as follows:

$$\mathrm{HLB} = 20 \times \left(1 - \frac{S}{A}\right) \tag{28.2}$$

in which $S$ and $A$ are the saponification and acid numbers of the ester, respectively. These equations can be also expressed by the following general equation, in which $M$ is the molecular weight of a surfactant and $M_w$ is the molecular weight of the hydrophilic group.

$$\mathrm{HLB} = 20 \times \frac{M_W}{M} \tag{28.3}$$

## 28.4.2 Davies' Equation[13]

Davies's method, which is one of the traditional methods used to calculate the HLB number, is based on the unit value given to the each functional group as either a hydrophilic or a hydrophobic element, and the HLB number of the molecule can be calculated as a summation of whole unit values:

$$\mathrm{HLB} = 7 + \sum(\text{unit value of hydrophilic group}) + \sum(\text{unit value of lipophilic group}) \tag{28.4}$$

The representative unit values are shown in Table 28.3, in which the positive and negative values are assigned to the hydrophilic and lipophilic species. This versatile equation is able to calculate the HLB number even for ionic surfactants, although the resulting HLB value may not absolutely predict the properties of the surfactant solution.

**TABLE 28.3** Representative Unit Values Used in Davies Equation

| Hydrophilic Group | Unit Value | Lipophilic Group | Unit Value |
|---|---|---|---|
| $-SO_4Na$ | 38.7 | $CH_3-$ | −0.475 |
| −COONa | 19.1 | $-CH_2-$ | −0.475 |
| $-(CH_2-CH_2-O)-$ | 0.33 | | |
| −OH | 1.9 | | |

### 28.4.3 Kawakami's Equation[14]

The calculation method reported by Kawakami, which is obtained from a similar hypothesis to Davies', defines the HLB number to be seven when hydrophilicity and lipophilicity of the surfactant are equivalent, and can be given by the following equation using two molecular weights of the hydrophilic ($M_W$) and lipophilic groups ($M_O$):

$$\mathrm{HLB} = 7 + 11.7 \times \log \frac{M_W}{M_O} \tag{28.5}$$

### 28.4.4 Organic Conceptual Diagram[15]

Another important equation commonly used for the HLB number calculation is based on the *organic conceptual diagram*. Initially, the primary objective of this method was to identify the complex properties of organic compounds via intermolecular interactions. The conceptual diagram consists mainly of an *organic value* (OV) and an *inorganic value* (IV), which respectively relate to the intermolecular force generated by van der Waals and electrostatic interactions, and the combination of the two values corresponds to the HLB number:

$$\mathrm{HLB} = \frac{\sum \mathrm{IV}}{\sum \mathrm{OV}} \times 10 \tag{28.6}$$

The representative organic and inorganic values are shown in Table 28.4. The OV and IV values are assumed to have relation with respectively lipophilicity and hydrophilicity of surfactant and the ratio, IOB (=IV/OV), is approximately equivalent to the HLB number.

## 28.5 HYDROPHILE–LIPOPHILE BALANCE NUMBER OF OIL (REQUIRED HLB NUMBER)

It is no doubt that a suitable surfactant must be chosen to formulate a stable emulsion, whereas the HLB number of the surfactant is not a universal factor to control emulsion type and stability. Practically, complex multicomponent emulsions often fail to be stabilized, because a suitable HLB number for the system can be influenced by the coexisting components such as electrolytes, polyols and their concentrations in water, oil polarity, water-to-oil ratio, as well as temperature.

As for the oil polarity, HLB numbers have been assigned to various oils that are frequently used for common formulations, such as vegetable oils, paraffin oils, etc., and determined on the basis of emulsifying experiments. In

**TABLE 28.4** Representative IV and OV Used in Organic Conceptual Diagram

| Functional Group | IV | OV |
|---|---|---|
| C | 0 | 20 |
| $-(CH_2-CH_2-O)-$ | 60 | −10 |
| −OH | 100 | 0 |
| −O− | 20 | 0 |
| −COOH | 150 | 0 |
| $-NH_2$ | 70 | 0 |

**TABLE 28.5** Required HLB Numbers of Various Oils Used for Cosmetics

| Oil | Required HLB |
|---|---|
| Lauric acid | 16 |
| Cetyl alcohol | 15–16 |
| Isostearic acid | 15–16 |
| Polyethylene wax | 15 |
| Isopropyl myristate | 11–12 |
| Mineral oil | 11–12 |
| Paraffine | 10 |
| Bees wax | 9 |
| Dimethyl silicone | 9 |
| Lanolin oil | 9 |
| Vaseline | 9 |
| Cyclic silicone | 7–8 |
| Jojoba oil | 6 |

general, the more polar the oil phase, the more hydrophilic the emulsifier should be. Namely, selection of suitable emulsifier strongly depends on the kind of oil used in the system. The HLB number of oil is sometimes referred to as the required HLB number, and these numbers for various oils are listed in Table 28.5.[16]

It has been found empirically that a combination of emulsifiers, one of which is more hydrophilic whereas the other is more hydrophobic, produce a better emulsion rather than a single emulsifier with the intermediate HLB number. This could be attributed to the combination of two emulsifiers with very different critical packing parameters (CPP, see Chapter 24) which gives better packing at the interface. Besides molecular packing, the advantage of mixed emulsifier may also relate to the rapid supply of emulsifier during the emulsification process. For these reasons, a combination of a low-HLB and a high-HLB surfactant is frequently used in practice. If a surfactant mixture is used to prepare an emulsion, the HLB number of the mixture corresponds to the weight average of the individual HLB numbers. The average HLB number is expressed by Eq. (28.7), in which $HLB_i$ is the HLB number of emulsifier $i$, and $x_i$ is the weight fraction of emulsifier $i$ in the total emulsifiers.

$$\text{Average HLB} = \sum_{i=1}^{n} (HLB_i \cdot x_i) \tag{28.7}$$

On the other hand, the effect of water-soluble additives on the HLB number is not systematized yet. As can be understood from the phase behavior, for example, a change in the cloud point upon addition of such substance reflects the HLB number of the entire solution in the nonionic surfactant system (Fig. 28.4).[17] However, it should be noted that the effects of these additives on the surfactant properties are not uniform, depending on the types of additive and surfactant in the system as shown in Fig. 28.4. For nonionic surfactants, one additive causes a continuous decrease in the cloud point that indicates a decrease in the HLB number. The effect of salts on the water solubility of organic compounds can be ranked according to the *Hofmeister series*.[18] For ionic surfactants, on the other hand, the HLB number of the surfactant decreases upon addition of small amounts of ionic water-soluble additives because of depression of the electrical interaction between surfactant head groups, and electric permittivity.

As mentioned previously, a major disadvantage of the HLB number for the selection of surfactants as emulsifying agents is that the HLB number does not comply with the change in the chemical and physical conditions for emulsification: temperature, nature of oil phase, presence of cosurfactants or other additives. In relation to such an HLB issue, Shinoda and Kunieda[19] introduced a new index, "HLB temperature" or "Phase Inversion Temperature (PIT)", instead of the HLB number. When temperature is raised, the degree of hydration of POE nonionic surfactant decreases and then the surfactant becomes less hydrophilic. Consequently, an O/W emulsion may invert to a W/O emulsion at the PIT with increasing temperature. Thus, PIT is defined as the specific temperature at which hydrophilic and lipophilic natures of a surfactant are balanced, and it is intrinsic to the molecule but variable depending on the components present in the system. Therefore, PIT provide more accurate information on surfactant properties and behavior in an emulsion. Recently, a new method using PIT, PIT slope method, has been proposed by Aubry's

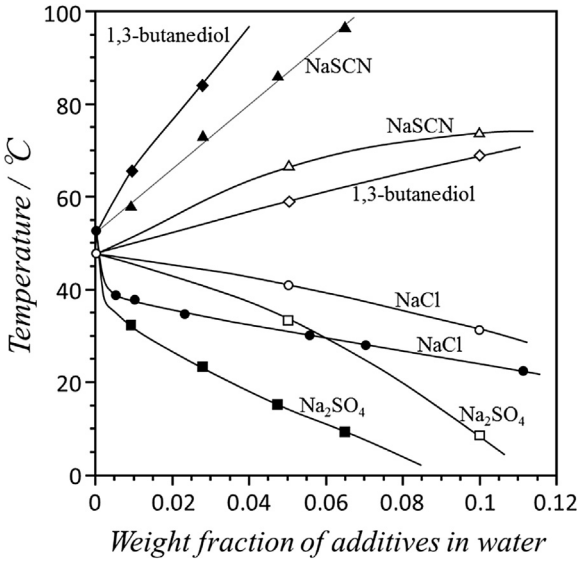



**FIGURE 28.4** Effects of added water-soluble additives on the clouding temperature in the hexaoxyethylene dodecyl ether ($C_{12}EO_6$)/water (filled symbols) and polyglycerin dodecanoic acid ester (($(C_{11})_2G_n$)/water (open symbols) systems.[17] The surfactant concentration is kept at 3 wt%.

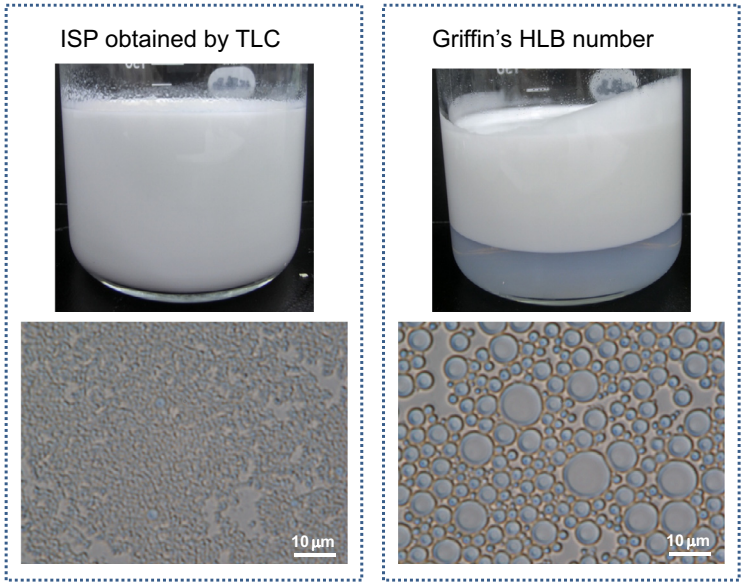



**FIGURE 28.5** Stability of the oil-in-water (O/W) emulsions prepared using integrated surfactant property (ISP) and Griffin's hydrophilic–lipophilic balance (HLB) number. The compositions were fixed at surfactants/liquid paraffin/water=4/40/56. Two surfactants, glycerol surfactant and polyoxyethylene surfactant, were used to adjust an optimal HLB number by their mixing ratio. The HLB number of the glycerol surfactant calculated by the Griffin's equation provides the unstable emulsion with larger droplet sizes, while the emulsion becomes much stable when prepared using the ISP value of the glycerol surfactant. The scale bar in the micrographs corresponds to 10 μm.

group,[20] and specifies the polar head hydrophilicity for various ionic and nonionic surfactants. We have also developed a new empirical parameter (ISP: integrated surfactant property) to characterize hydrophilic–hydrophobic properties of emulsifiers by utilizing thin-layer chromatography (TLC) measurement. We found ISP to correlate better with the physicochemical properties for both ethylene oxide (EO)-type and glycerin-type emulsifiers. With ISP, we could prepare a stable emulsion better than with the HLB (Fig. 28.5).[21]

## 28.6 DESTABILIZING FACTORS OF EMULSIONS AND THEIR HANDLING METHODS

Although a change in the free energy on forming emulsions can be calculated, the rate of emulsion breakdown and the changes in physical aspects with time may be unpredictable. Therefore, it is important to understand the

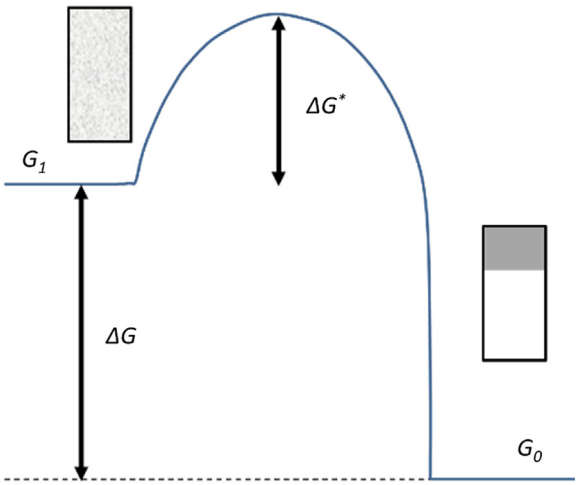



FIGURE 28.6 Metastable state of emulsion. $G_0$, $G_1$, and $\Delta G^*$ represent the free energies of the separated two-phase state and the emulsion state, and the activation energy, respectively.

kinetic stability of an emulsion. Droplets dispersed in emulsions always move around due to the thermal and gravitational effects, and repeatedly collide with one another. Factors involved in the kinetic emulsion stability can be attributed to a kinetic state of a dispersed droplet and interactions operative between the droplets, suggesting that emulsions can be stabilized by controlling their interface and bulk properties.

Fig. 28.6 represents the concept of kinetic emulsion stability using the activation energy. Energy input through an emulsification process changes from an equilibrium state, in which oil and water are separated, assigned to a low free energy ($G_0$), to an emulsion state ($G_1$). Then, the emulsion system can be stable when the activation energy ($\Delta G^*$) is sufficiently larger than the thermal energy $\sim kT$; typically, the emulsion may be stabilized for a couple of years if $\Delta G^* \sim 20\ kT$.[22]

Emulsion disruption can occur via various fundamental steps. These steps are known to be creaming, coagulation, coalescence, and Ostwald ripening (Fig. 28.7), and may not occur independently, but some or all of them may simultaneously progress with time. In addition, a new process called contact ripening has recently been

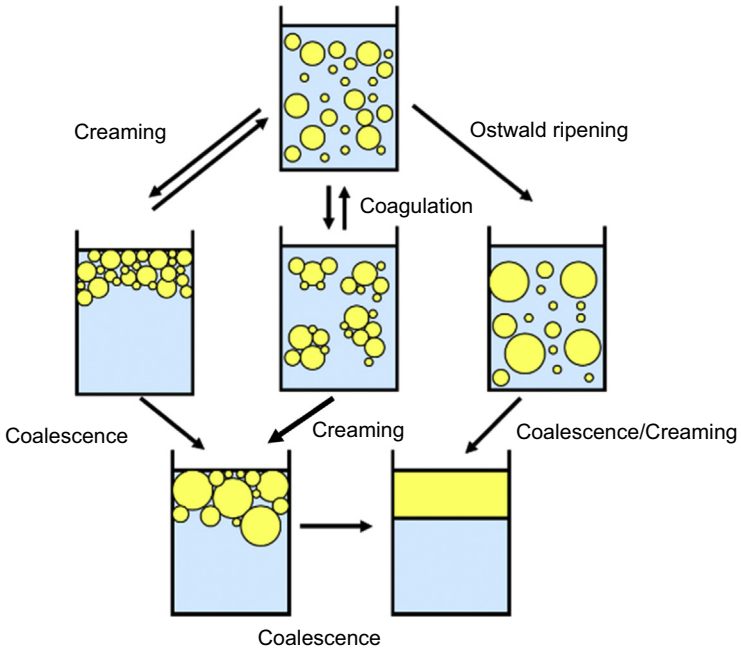



FIGURE 28.7 Processes of emulsion disruption.

proposed.[23] Although the emulsion stability should be improved if either process can be inhibited or delayed, any systematic mechanisms such as interplay between these processes have not yet been established, and the processes of emulsion disruption are indefinite among different emulsion systems.[24–26] Difficulties of individually evaluating these processes prevents comprehensive answers as to how to stabilize emulsions, whereas recent emulsion studies on the disruption processes have been performed utilizing a microgravity environment[27,28] and clarification is expected.

The mechanisms and handling methods of the four processes on emulsion disruption, creaming, coagulation, coalescence, and Ostwald ripening, are described in the following sections.

### 28.6.1 Creaming

Creaming is a phenomenon that the dispersed phase of an emulsion floats over the continuous phase under the influence of buoyancy. The density difference between the two phases ($\Delta\rho$) plays a key role in the creaming phenomenon, referring to the Stokes equation:

$$v = \frac{2gr^2\Delta\rho}{9\eta} \tag{28.8}$$

in which $v$ is the creaming velocity, $g$ is the acceleration due to gravity, $r$ is the droplet radius, and $\eta$ is the viscosity of the medium (continuous phase). Although Brownian motion is predominant when the droplet size becomes smaller, creaming takes place when flotation of the droplet is faster than its thermal motion, i.e., the droplet size becomes larger beyond a threshold value. It is evident from Eq. (28.8) that creaming can be suppressed by increase in $\eta$ and decreases in $\Delta\rho$ and $r$, among which $r$ is the most effective factor.

### 28.6.2 Coagulation

A very useful tool for understanding the stability of colloids is provided by the Derjaguin–Landau–Verwey–Overbeek (DLVO) theory. The DLVO theory allows for both the forces between electrical double layers and the long-range van der Waals force that are usually attractive. In this theory, the total potential energy, $V(H)$, is expressed by Eq. (28.9)

$$V(H) = V_R + V_A \tag{28.9}$$

in which $V_R$ is the repulsive potential energy due to the overlap of electrical layers on colloid particles and $V_A$ is the attractive van der Waals energy.

Fig. 28.8 exhibits a potential energy curve of the interparticle interaction as a function of the distance between the particle surfaces (H). The potential energy curve has a smaller secondary minimum separated from a deeper primary minimum by a barrier ($V_{max}$), and the repulsive contribution becomes larger when the two particles approach to a short distance. Sometimes the particle distance stays in the vicinity of the secondary minimum, and this

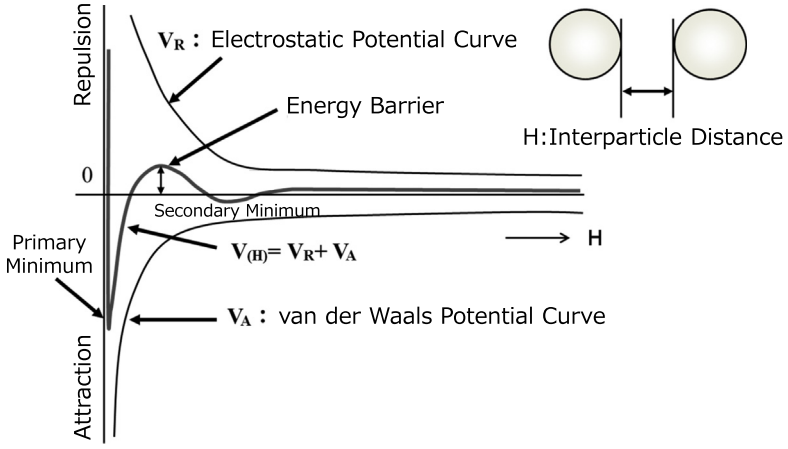



FIGURE 28.8 Changes in the attractive potential ($V_A$), repulsive potential ($V_R$), and summation of these interaction potentials [V(H)] as a function of the interparticle distance (H).

phenomenon can be called flocculation. If this barrier is large compared to $kT$ but secondary minimum is comparable to $kT$, then reversible flocculation can occur. On the other hand, as the electrostatic potential energy ($V_R$) decreases, for example, by adding an electrolyte, the particles can come close to the distance at the primary minimum and irreversible coagulation occurs because of the very low potential energy between the two particles.

The repulsive force between the dispersed droplets in emulsions arises from the overlapped diffuse electric double layer for ionic surfactants and the steric stabilization conferred by long hydrophilic groups for nonionic surfactants. Such overlaps cause a difference in osmotic pressure, resulting in entropically driven repulsion. Thus, effective methods to inhibit coagulation are to form thicker diffuse double layers around the droplet surfaces of an emulsion or to select nonionic surfactants having bulky (long) POE chains. In addition, hydrophilic colloids are often used for cosmetics and foods because of inhibition of coagulation, coalescence, and creaming.

### 28.6.3 Coalescence

Coalescence of emulsions is an irreversible process by which two or more droplets merge during contact to form a single daughter droplet. The driving force for emulsion coalescence is the thinning and disruption of the liquid film between the droplets (Fig. 28.9). This can happen if the emulsion droplets closely approach each other in a cream layer, in a floc, or during Brownian diffusion. When the droplets approach each other very closely, the liquid film between them undergoes some thermal fluctuation, and when the film thickness approaches a critical value, film collapse occurs resulting in its rupture. The lower interfacial tension is one of the important properties for surfactants to prepare emulsions, but leads to fluctuation of the film. The surfactant not only influences the intermolecular interaction across the film, but also creates gradients in the interfacial tension (Marangoni effect). These gradients oppose film drainage and distribution of the interfacial tension on the film, whereas the temporal inhomogeneity of the surfactant molecules perforates the thin film. In addition, surfactant molecules adsorbing on an oil−water interface always wander back and forth in the oil and water phases (see Section 28.3 in this chapter), and may dip into the oil phase when the two droplets contact which can contribute to coalescence.

Accordingly, effective methods to inhibit coalescence are (1) to use surfactants having hydrophilic groups with higher lipophobicity (e.g., OH group) which can be sparingly soluble in an oil phase, (2) to apply self-assemblies such as liquid crystal and α(alpha)-gel to strengthen an interfacial film, and (3) to utilize polymeric emulsifiers and powder materials which effectively inhibit coalescence.

### 28.6.4 Ostwald Ripening

Ostwald ripening is an observed phenomenon in solid or liquid solutions that describes the change of an inhomogeneous structure over time, i.e., small crystals dissolve, and redeposit onto larger crystals. It can be also observed in liquid−liquid systems, for example, in an oil-in-water emulsion. In this case, Ostwald ripening results from the diffusion of monomers (i.e., individual molecules or atoms) from smaller droplets to larger droplets due to greater solubility of the single monomer molecules in the larger monomer droplets resulting from difference in Laplace pressure. The solubility, $S(r)$, of a dispersed droplet with a radius $r$ is expressed by the following equation:

$$S(r) = S(\infty) \cdot \exp\left(\frac{2\gamma V_m}{rRT}\right) \tag{28.10}$$

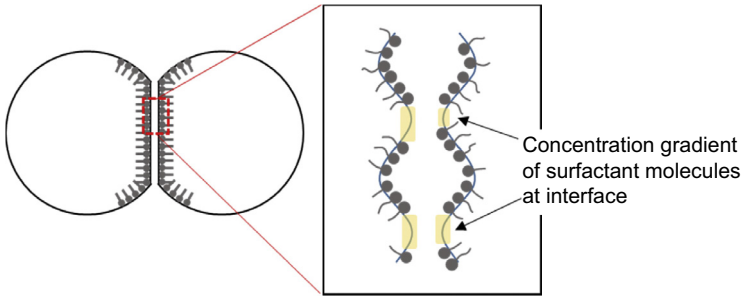



FIGURE 28.9 Lamellar film formation and interfacial state when two dispersed droplets contact.

in which $S(\infty)$ is the solubility of the droplet with the infinite radius (flat plane, curvature = 0), $\gamma$ is the interfacial tension, $V_m$ is the molecular volume of a solute, $R$ is the gas constant, and $T$ is the temperature. The rate of this diffusion process is linked to the solubility of the monomer in the continuous (water) phase of the emulsion. This can lead to the destabilization of emulsions (for example, by creaming and sedimentation).

From this mechanism, Ostwald ripening can be inhibited by homogenization of emulsion droplet sizes and selection of a suitable oil phase less soluble in water. In the case of polar oils, a small amount of nonpolar oil may improve the influence of Ostwald ripening because of lowering the solubility of the polar oil in water. Contrarily, presence of alcohols and polyols helps the solubility of oils to increase, resulting in promotion of Ostwald ripening.

## 28.7 EMULSIFICATION METHODS

It sounds like common sense that fine dispersion should be essential to maintain stable emulsions as long as possible, whereas it should also be noted that emulsions have no uniform size of the dispersed droplets the distribution of droplet sizes always depends on the emulsification process and conditions and duration of storage, since emulsions are a thermodynamically nonequilibrium systems.

The interfacial tension ($\gamma$) indicates the amount of work ($\omega$) required to extend unit interfacial area, thereby a newly extended interface area ($\Delta S$) can be expressed by Eq. (28.11):

$$\Delta S = \omega/\gamma \tag{28.11}$$

Because $\Delta S$ enlarges when the droplet size becomes finer, application of a very large energy (large $\omega$) to a system or a very low interfacial energy (low $\gamma$) at the oil−water interface must be achieved to obtain a stable emulsion. The large $\omega$ can be generated by mechanical forces using a microfluidizer and high-pressure equipment, and the low $\gamma$ can be manipulated by various emulsification techniques. Here, the representative emulsification methods reported so far are interpreted as follows.

### 28.7.1 Oil-in-Water Emulsion

Surfactant acts to reduce the excess energy at the oil−water interface and enables emulsification to be easier as understood from Eq. (28.11). Namely, such emulsification methods consider of interface science to manipulate the physicochemical properties of surfactants and entire systems. For example, the PIT emulsification method takes into account the most effective adsorption of a surfactant molecule on the interface and the minimum interfacial tension at PIT leads to formation of a very fine emulsion or self-emulsification (Fig. 28.10). In this temperature region close to PIT, however, the emulsion undergoes coalescence of emulsion droplets once agitation stops, and will be separated into two phases within a short period. To prevent this, an emulsion made at PIT should be quenched to the O/W region in which the surfactant is dissolved in a micellar solution.

A number of emulsification methods have been reported and seem complicated, but a factors common to every method provide guidance. These are: (1) high probability of surfactant molecules present at the oil−water interface to sufficiently reduce the interfacial tension, (2) a two-step procedure that immediately transfers from PIT to O/W state by changing the physical condition.

Fig. 28.11 illustrates the processes of *inversion emulsification method*, *PIT emulsification*, and *quenching method* (using microemulsion) in the phase diagram as functions of oil−water ratio and temperature in the nonionic surfactant−water−oil system.[29] The surfactant concentration is held constant at 7 wt%. The dotted lines indicate solutions with lower interfacial tension, which then are immediately transferred to the O/W region to form fine emulsions. With reference to the *D-phase emulsification method*[30] and *liquid crystal emulsification*,[31] emulsification starts from a more-hydrophilic state of the solution and the finally obtained emulsion will be in a state containing a larger amount of oil compared to the water phase. It can be considered that these emulsification methods would result in the highest rate of surfactant molecules accumulating at the oil−water interface.

In summary, the essential points in the course of emulsification are (1) to utilize a region (or phase) having a low interfacial tension, (2) to encourage surfactant molecules to effectively adsorb onto the interface, and (3) to transfer the solution state immediately from one region to the O/W region in which a surfactant will be dissolved in water. By manipulating these emulsification procedures on the basis of individual destabilizing factors, we can obtain O/W emulsions with a finely dispersed phase.

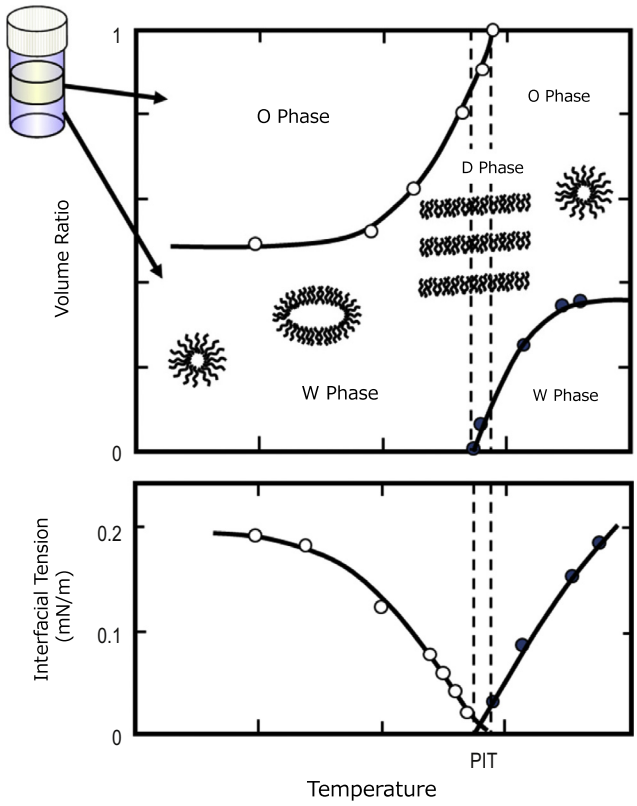



**FIGURE 28.10** Basic physicochemical phenomena in a surfactant system on PIT emulsification: changes in the volume ratio of the dissolved phases, oil (O) and water (W) phases, of a surfactant (top) and the interfacial tension (bottom) as a function of temperature.

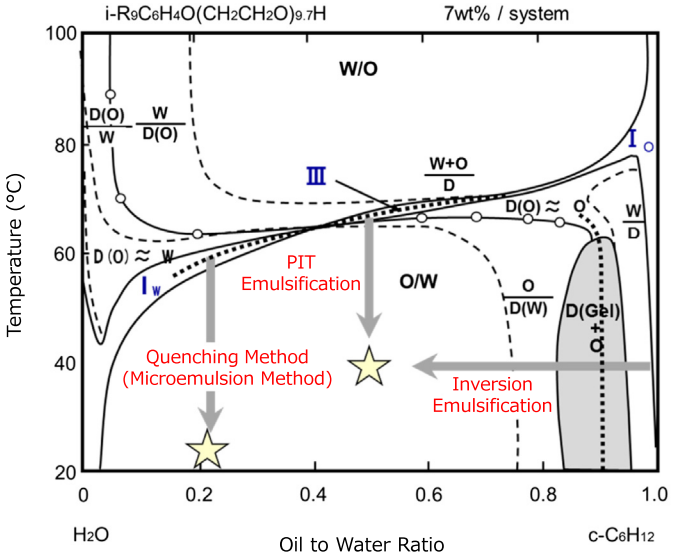



**FIGURE 28.11** Various emulsification processes, inversion emulsification method, PIT emulsification, and quenching (microemulsion) method illustrated in the phase diagram of the nonionic surfactant–water–oil system.[29] Basic physicochemical phenomena in a surfactant system on PIT emulsification: changes in the volume ratio of the dissolved phases, oil (O) and water (W) phases, of a surfactant (top) and the interfacial tension (bottom) as a function of temperature.

### 28.7.2 Water-in-Oil Emulsion

The concepts of preparation methods of W/O emulsions are similar to those of O/W emulsions, except that great repulsive forces cannot be achieved in the W/O emulsion systems because of the continuous oil phase. In addition, it is difficult to effectively stabilize W/O emulsions by adsorption of surfactants at the oil−water interface, because the quantity of dissolved surfactant molecules in the oil phase of the W/O emulsion can become much larger than that of O/W emulsion. Stabilization of W/O emulsions could be attained by increasing viscosity by addition of amino acids[32] and clay minerals,[33] and also a reverse hexagonal liquid crystal[34] may be available to stabilize the dispersed water phase. As for W/O emulsion consisting mainly of silicone oils, polyether-modified silicone emulsifiers are useful, and furthermore silicone emulsifiers with glyceryl groups show higher emulsifying capacity and can improve the stability of a low viscous W/O emulsions by combined usage with the polyether-modified silicone.[35]

### 28.7.3 High Internal Phase Ratio Emulsions (HIPRE)

High Internal Phase Ratio Emulsions (HIPREs) have been known for many years[36] and find applications in areas such as food preparation, fuels, oil recovery, and cosmetics. Their defining feature is an internal phase volume ratio ($\phi$) of 0.74 or greater (i.e., at least 74% of the volume of the emulsion comprises droplets). This value of $\phi$ represents the maximum volume ratio of uniform nondeformable spheres when packed in the most efficient manner. Because HIPREs can be formed with much higher values of $\phi$, in fact up to 0.99, it is obvious that either the droplets are nonuniform in size or are deformed into polyhedral structures (Fig. 28.12).

Viscous cubic liquid crystals have been used to form a stable O/W emulsion with a high internal phase ratio.[37,38] In recent years, the HIPRE using a bicontinuous microemulsion ($W/L_3$) has been discovered.[39]

### 28.7.4 Multiple Emulsion

During the past several years, there has been considerable interest in multiple emulsions, in part because of their potential as a means of (1) delivering drugs to specified targets in the body without the possible deleterious effects of these drugs on other organs, (2) prolonging the release of drugs that have a short biological half-life, and (3) creating novel texture on breaking the multiple structure. Both W/O/W and O/W/O emulsions exist (see Fig. 28.2).

The preparation methods of multiple emulsions can be divided into one-step and two-step procedures. Multiple emulsions of the W/O/W type are generally prepared by a two-step procedure: a preformed W/O emulsion is added slowly, with stirring, to an aqueous solution containing a hydrophilic emulsifying agent. The two-step procedure has been in widespread use because ingredient composition in each phase can be controlled.[40] On the other hand, a one-step procedure is possible and this often uses the phase inversion method.[41] The one-step procedure has disadvantages that the same compositions exist between the internal and external phases, and an undefined amount of an active encapsulated in the emulsion droplets: the advantage being simple handling and a high production rate.

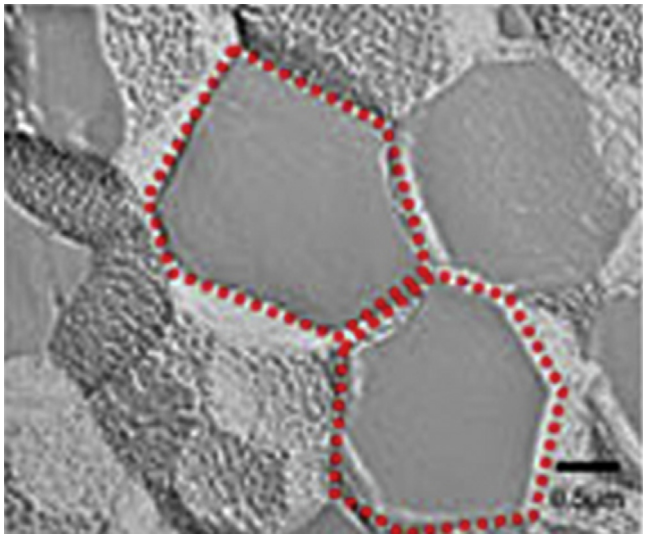


FIGURE 28.12 Electron microscope image of a high internal phase ratio emulsion (HIPRE).[39]

As other methods, membrane emulsification[42] and microchannel[43,44] have been attempted to apply to formation of multiple emulsions with a homogeneous droplet size.

The most important issue to utilize multiple emulsions in industry is long-term stability. In particular, disruption processes in a multiple emulsion are quite complicated; not only coalescence among the dispersed droplets in the internal phase but fusion between the internal and outermost phases occurs. To prevent them, many methods have been reported; for example, (1) using a mixture of several surfactants with different HLB,[45] (2) utilizing D-phase emulsification and a high-pressure homogenizer,[46,47] and (3) formulating with a gelation agent.[48]

## 28.7.5 Surfactant-Free Emulsion (sf-Emulsion)

Surfactant-free emulsions (sf-emulsions) would be broadly defined as an emulsion stabilized without any surfactants, but here emulsions without all emulsifiers including surfactants are explained as a topic of interest.

sf-Emulsions can be prepared by ultrasonic irradiation ranging from tens to thousands kHz to the mixture of water and a little amount of oil.[49–54] Ultrasonication at a high frequency generates active oxygen species such as OH radical and hydrogen peroxide, and these active species or their reacted products (e.g., nitrate ion) may alter the charge state on the oil–water interface. As demonstrated in Fig. 28.13, the sf-emulsion prepared by ultrasonication has negative zeta potentials, which is one of the stabilization mechanisms of sf-emulsions.[55]

The stability of sf-emulsions remarkably depends on the kind of oil and the irradiation way of ultrasonic wave. In the case of nonpolar oils, the stability of sf-emulsions is improved with increasing the number of hydrocarbons, especially alkanes more than C10 that form smaller oil droplets with sizes less than 100 nm, and suppressing the growth of droplet size.[52,56] The disruption processes of sf-emulsions are also dependent on the molecular weight of alkane, that is, short-chain alkanes (C6 ~ C8) lead to coagulation and coalescence, but Ostwald ripening predominantly occurs in the long-chain oil (C10 ~ C16) systems. Unstable sf-emulsions consisting of low molecular weight oils such as benzene can be effectively stabilized by adding a small amount of a long-chain alkane (hexadecane and squalane). This would be due to the balance of Kelvin's and Raoult's laws; it is concluded that when a concentration distribution between oil droplets is present, progression of Ostwald ripening (Kelvin's law) is repressed by the depressive effect of the molecular diffusion that occurs causing the chemical potential to be equivalent.[57,58] For polar oils with a long chain such as ester oils, sf-emulsions demonstrate better stability.[50,56] Furthermore, the stability of sf-emulsions can be influenced by the process of irradiation with ultrasonication and interestingly improved by the stepwise irradiation of low- and high-frequency waves. This may be the reason why the low- and high-frequency waves are responsible for increase in the amount of dispersion and reduction of the oil droplet size, respectively.[56]

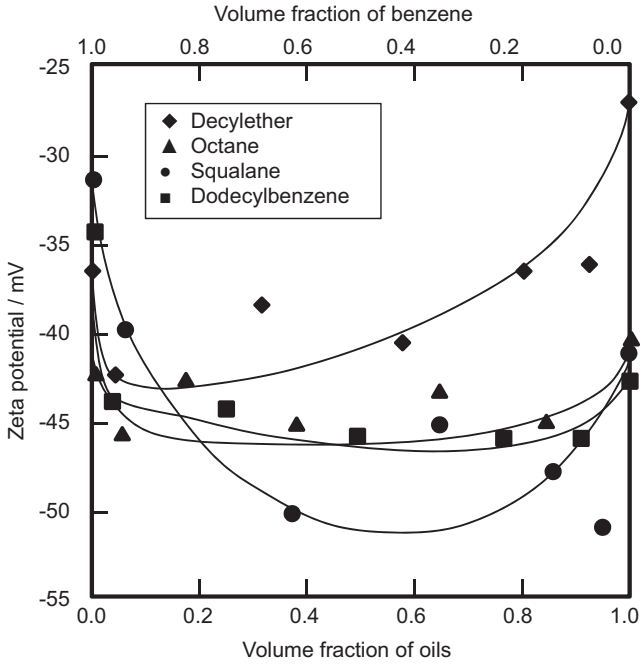



FIGURE 28.13 Zeta potentials of sf-emulsions using various mixed oils: benzene/decyl ether (◆), benzene/octane (▲), benzene/squalane (●), and benzene/dodecylbenzene (■).[55]

### 28.7.6 Bottom–Up Emulsification

Emulsions are usually prepared by top–down processes. Unlike the top–down process, the bottom–up process starts with homogeneous solutions and solutes are allowed to assemble to form nanoparticles. PIT and Phase Inversion Composition (PIC) are good examples of this bottom–up emulsification utilizing the microemulsion phase as homogeneous solution. In a novel bottom–up process, so-called "*bottom-up emulsification*," performed under high temperature and high pressure (Fig. 28.14), fine nanoemulsions are formed when homogeneous solutions of supercritical water and oil are rapidly quenched to room temperature.[59] The oil droplet size depends on the quenching rate and surfactant concentration; for example, fine monodispersed nanoemulsions can be produced when the quenching rate is more than 200°C/sec.

### 28.7.7 Control of Interfacial Phase

Destabilization of emulsions is a consequence of interfacial destabilization, which typically contributes to the molecular solubility for a number of surfactants with low molecular weight. To avoid destabilization, a larger amount of surfactant than anticipated must be added to a system, which is certainly not efficient interfacial control. Therefore, it is essential that a surface active agent will be partitioned at the interface alone to form stable emulsions, in particular to inhibit coalescence. Such materials have been utilized for a long time, and the representatives are proteins, solid particles, and so on. The essence of emulsification here is that a material insoluble in both water and oil phases is specifically localized at the interface; as a result, it can spread over the interfacial area in small amounts. We have found such a material in hybrid amphiphilic polymer composed of hydrophobic alkyl-silicone backbone with peptide as hydrophile and named it "*Active Interfacial Modifier* (AIM)."[60,61] Then, we extended the AIM concept to a novel unified concept including polymers and fine particles.[62] Examples of emulsions with AIM are *Three-Phase Emulsions*, *Pickering Emulsions*, *Liquid Crystal Emulsions*, and so on, as interpreted later on.

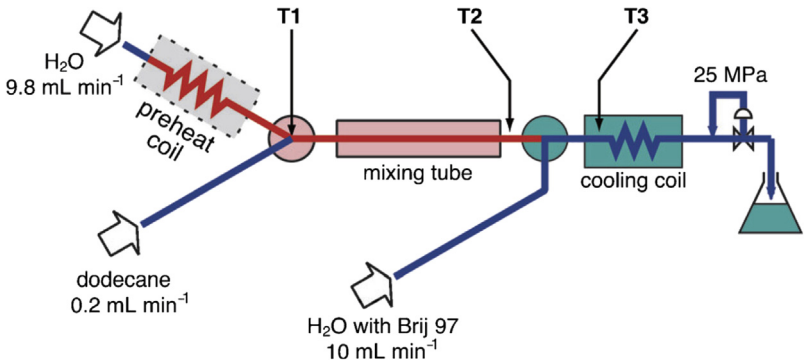



FIGURE 28.14 Schematic representation of a flow-type instrument for the bottom–up emulsification.[59] T1, T2, and T3 represent thermocouples.

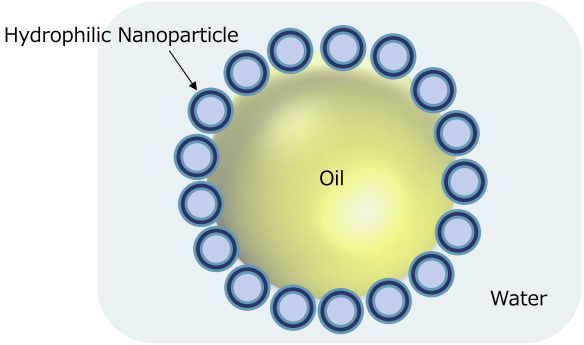



FIGURE 28.15 Adhesion of hydrophilic nanoparticles to the surface of an oil droplet.

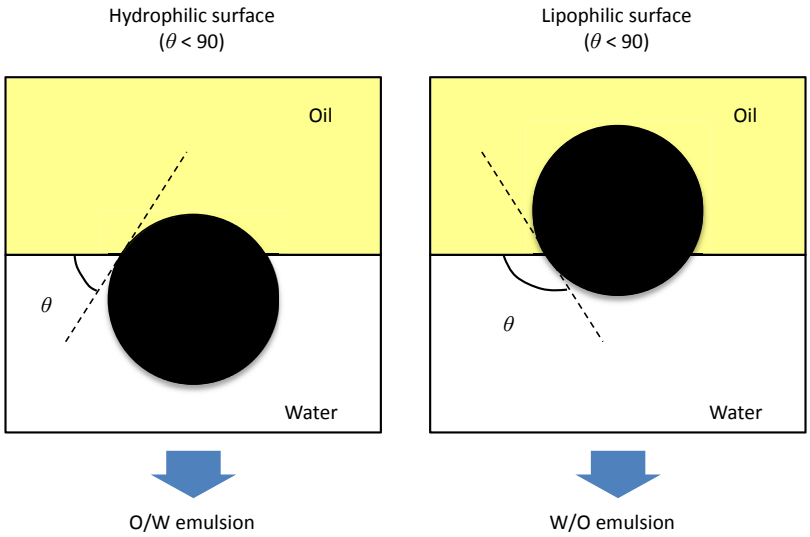



FIGURE 28.16 Wettability of particles and emulsion type.

### 28.7.7.1 *Emulsification Prepared by Hybrid-Type Polymer*

Recently, it was found that an amphiphilic polymer such as AIM can stabilize the oil–water interfaces.[60–64] This polymer consists of a silicone backbone modified with hydrocarbon chains and hydrolyzed silk peptides, being molecularly soluble in neither water nor most organic solvents. This property causes preferential localization of the polymer at the oil–water interface (Fig. 28.17), leading to high stability of the interfacial phase. Addition of AIM to a mixture of water and silicone oil gives stable monodispersed W/O emulsion in a wide range of compositions by small energy input such as gentle agitation by a Vortex mixer. Unlike general emulsification, there are no significant reductions of oil–water interfacial tension, but AIM's preferential localization at water–oil interface prevents coalescence to maintain stable emulsions for a long period.[63]

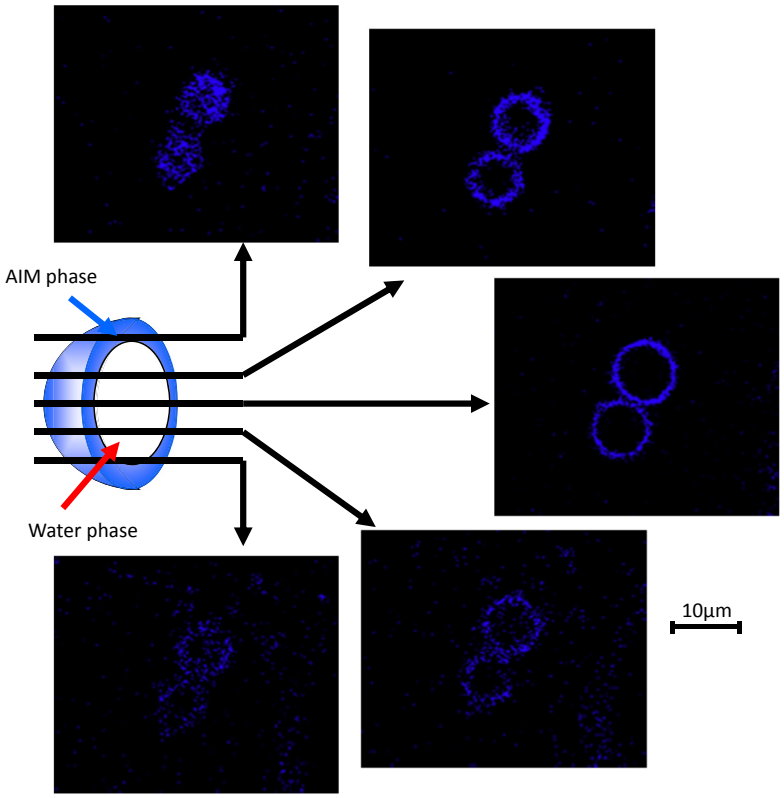



FIGURE 28.17 Confocal laser scanning microscope (CLSM) images of W/O emulsion droplets with fluorescence-labeled polymer.[62]

Take a conceptual figure of kinetic emulsion stability using activation energy, as in Fig. 28.6. An energy input $\Delta G$ is much smaller than normal emulsification and the activation energy ($\Delta G^*$) to coalesce water particles is significantly larger than the thermal energy $\sim kT$. This is the reason why AIM emulsion is so stable. Such surface-active materials as AIM will be expected to become widely used in industry because of their efficient interfacial adsorption, which may accept reduction of the consumed amount of surfactants.

#### 28.7.7.2 Three-Phase Emulsions

Soft, hydrophilic nanoparticles adhere firmly to the interface of oil droplets through van der Waals interaction between the nanoparticle and oil droplet (Fig. 28.15), resulting in formation of stable emulsions. This emulsion is called "*Three-Phase Emulsion*" and often uses self-assembly (vesicle, etc.) or polycondensation polymer as the soft nanoparticle. Stability of this emulsion can be independent of the kind of oil, in contrast to the general surfactant-based emulsion.

#### 28.7.7.3 Pickering Emulsions

The ability of solid particles to adhere to soft deformable interfaces, for example to the surface of emulsion droplets or bubbles, is currently the subject of renewed interest in material science. The phenomenon that solid particles can reside at the interface of droplets, thereby providing them with resistance against coalescence or fusion, and Ostwald ripening, is known as "Pickering emulsification." When solid particles are used as an emulsifier, the contact angle ($\theta$), which correlates to the wettability of particles against oil or water, is a key factor to determine the stability and type of emulsions. Namely, hydrophilic particles are wetted by water and $\theta < 90$ degree, whereas hydrophobic particles display a preference for oil and $\theta > 90$ degree, as shown in Fig. 28.16. The type of emulsions, i.e., O/W or W/O, could be predicted on the basis of this wettability, that is, the contact angle of the interface with the solid.

To describe the behavior of a single particle at the liquid−liquid interface, the adhesion energy ($\Delta G_a$) can be expressed as a function of $\theta$ as follows[65]:

$$\Delta G_a = -\gamma_{OW}\pi R^2(1 \pm \cos\theta)^2 \tag{28.12}$$

in which $\gamma_{OW}$ and $R$ are the interfacial tension and the radius of the particle, respectively. The signs in bracket, "−" and "+", represent adsorption of the particle from the water phase to the interface and adsorption from the oil phase to the interface. This equation indicates that $\Delta G_a$ becomes larger when the particle size and oil−water interfacial tension increase and $\theta$ approaches 90 degrees. With $R \sim$ several tens of nanometers and $\theta = 90$ degrees, $\Delta G_a$ reaches several thousands of kJ. Because the adsorption energy of a general surfactant is on the order of several tens of kJ,[66] it can be realized that Pickering emulsions have a very large adsorption energy and stabilize the oil−water interface.

There are a variety of particles used for Pickering emulsion, for example, hydrophobic silica, resin powders such as polystyrene, metal oxide, clay minerals, biologically relevant materials, and so on.[67] In addition, the stability of emulsions are influenced by the configuration of particles such as sphere, plate, and needle-like configurations, and non-spherical Janus particles, dumbbell- and acorn-like particles, are developing further.

## 28.8 CONCLUSION

Emulsions can be made simply by mixing immiscible liquids with force and stabilizing it by adding surfactants or emulsifiers, but to make an emulsion that is comfortable, safe, and stable is not something that can be easily achieved. In this chapter, we have explored the fundamental nature of emulsions and techniques of creating better products that overcome these challenges of emulsion. Tips to improve emulsion stability from the viewpoint of HLB, physical property of bulk phase, and controlling the interfacial phase are explained. Further development to control interfacial properties will help formulators to solve problems and create better emulsion products.

## References

1. Tanford C. *The hydrophobic effect*. New York: Wiley; 1980.
2. Israelachvili JN. *Intermolecular and surface forces*. London: Academic Press; 1992.
3. Vargaftik NB, et al. *J Phys Chem Ref Data* 1983;**12**:817.
4. Jasper JJ. *J Phys Chem Ref Data* 1972;**1**:841.
5. Korosi G, et al. *J Chem Eng Data* 1981;**26**(3):323.

6. Riddle FL, et al. *J Am Chem Soc* 1990;**112**(9):3259.
7. Binks BP, et al. *Langmuir* 2002;**18**(4):1270.
8. Halpern A. *J Phys Chem* 1949;**53**(6):895.
9. Gaonkar AG. *J Am Oil Chem Soc* 1989;**66**(8):1090.
10. Bnacroft WD. *J Phys Chem* 1913;**17**:514.
11. Griffin WC. *J Soc Cosmet Chem* 1949;**1**:311.
12. Griffin WC. *J Soc Cosmet Chem* 1954;**5**:249.
13. Davies JT, Rideal EK. *Interfacial phenomena*. Academic Press; 1961. p. 371.
14. Kawakami Y. *Kagaku* 1953;**23**:546.
15. Nihon Emulsion Co. Ltd. https://www.nihon-emulsion.co.jp/en/tech/organic.html; [cited on April 7, 2016].
16. *The HLB system: a time-saving guide to emulsifier selection*. ICI Americas Inc.; 1984.
17. Kunieda H, Kaneko M, Fujiyama R, Ishitobi M. *J Oleo Sci* 2002;**51**(6):379.
18. Hofmeister F. *Arch Exp Pathol Pharmakol* 1888;**24**:247.
19. Shinoda K. *Solution and solubility*. 3rd ed. Maruzen; 1991.
20. Ontiveros JF, Pierlot C, Catte M, et al. *J Colloid Interface Sci* 2015;**448**:222.
21. Yamashita Y, et al. *Bull Chiba Inst Sci* 2013;**6**:89.
22. Friberg E. In: Friberg E, Larrson K, editors. *Food emulsions*. 3rd ed. New York: Marcel Dekker; 1997. p. 1−55. 11.
23. Roger K, et al. *Angew Chem* 2015;**54**(5):1452.
24. Porras M, et al. *Colloids Surf A* 2008;**324**:181.
25. Wang L, et al. *Langmuir* 2008;**24**:6092.
26. Pons R, et al. *Colloid Interface Sci* 2003;**106**:129.
27. Miller R, et al. *Microgravity − Sci Technol* 2006;**18**:104.
28. Yamashita Y, et al. *30th ISTS (Web Paper)*, 2015. http://archive.ists.or.jp/.
29. Shinoda K, et al. *J Colloid Interface Sci* 1968;**26**:70.
30. Sagitani H. *J Dispersion Sci Technol* 1988;**9**:115.
31. Suzuki T, et al. *J Colloid Interface Sci* 1989;**129**:491.
32. Kumano Y, et al. *J Soc Cosmet Chem* 1977;**28**:285.
33. Yamaguchi M, et al. *Yukagaku* 1991;**40**:491.
34. Nakama Y, et al. *Yukagaku* 1998;**47**:585.
35. Nagatani N, et al. *J Colloid Interface Sci* 2001;**234**:337.
36. Lissant KJ, editor. *Emulsions and emulsion technology part 1*. New York: Marcel Dekker Inc.; 1974.
37. Kunieda H, et al. *Langmuir* 2000;**16**:6438.
38. Rodrigues C, et al. *J Colloid Interface Sci* 2000;**223**:197.
39. Watanabe K, et al. In: *Proceedings of 25th IFSCC Congress, MC-95, Barcelona*; 2008.
40. Imamura H. *Shikizai* 2010;**83**(1):33.
41. Matsumoto S. *J Colloid Interface Sci* 1983;**94**(2):362.
42. Mine Y, et al. *Colloid Surf B* 1996;**6**(4−5):261.
43. Kawakatsu T, et al. *J Am Oil Chem Soc* 1997;**74**(3):317.
44. Kobayashi I, et al. *J Am Oil Chem Soc* 2005;**82**(1):65.
45. Sekine T, et al. *J Surf Deterg* 1999;**2**:309.
46. Takahashi Y. *Sci Cook* 1990;**23**:12.
47. Hirai Y. *Fragr J* 1993;**4**:34.
48. Sekine T. *Oleo Sci* 2001;**1**:229.
49. Kamogawa K, et al. *J Jpn Oil Chem Soc* 1988;**47**:159.
50. Kamogawa K, et al. *Colloids Surf A Physicochem Eng Asp* 2001;**80**:41.
51. Sakai T, et al. *Langmuir* 2001;**17**:255.
52. Sakai T, et al. *Langmuir* 2002;**18**:1985.
53. Sakai T, et al. *Colloid Polym Sci* 2002;**280**:99.
54. Sakai T, et al. *J Phys Chem B* 2002;**106**:5017.
55. Sakai H, et al. *Hyomen* 2003;**41**:37.
56. Sakai T, et al. *Oleo Sci* 2001;**1**:33.
57. Davis SS, et al. *J Colloid Interface Sci* 1979;**80**:636.
58. Buscall R, et al. *Colloid Polym Sci* 1981;**257**:508.
59. Deguchi S, et al. *Angew Chem Int Ed* 2013;**52**:6409.
60. Sakamoto K, Otani N, Koyanagi A, Morita K, Ueda Y, Yoshioka M. In: *7th World Surfactants Congress (CESIO-2008) in Paris (No-O-A08)*; June 2008.
61. Otani N, et al. *J Soc Cosmet Chem Jpn* 2009;**43**(4):247−53.
62. Sakai K, et al. *Langmuir* 2010;**26**(8):5349.
63. Sakai K, et al. *J Oleo Sci* 2013;**62**(7):505.
64. Agari Y, et al. *J Soc Cosmet Chem Jpn* 2014;**48**(4):287−95.
65. Levine S, et al. *Colloids Surf* 1989;**38**:325.
66. Aveyard R, et al. *Phys Chem Chem Phys* 2003;**5**:2398.
67. Ngai T, Bon SAF, editors. *Particle-stabilized emulsions and colloids*. Cambridge: Royal Society of Chemistry; 2015.

CHAPTER

# 29

# Microemulsions and Nano-emulsions for Cosmetic Applications

*C. Solans*[1], *M.J. García-Celma*[2]

[1]Institute of Advanced Chemistry of Catalonia, Spanish Council for Scientific Research (IQAC-CSIC) and Biomedical Research Networking Center: Bioengineering, Biomaterials and Nanomedicine (CIBER-BBN), Barcelona, Spain; [2]Faculty of Pharmacy and Food Sciences, University of Barcelona (UB) and Biomedical Research Networking Center: Bioengineering, Biomaterials and Nanomedicine (CIBER-BBN), Barcelona, Spain

## 29.1 INTRODUCTION

Microemulsions and nano-emulsions (nanosize emulsions) are colloidal systems with great impact/potential in cosmetic applications.[1,2] Although they show certain similarities (e.g., transparent/translucent aspect, large interfacial area, low viscosity), they are different in nature—microemulsions are thermodynamically stable while nano-emulsions are thermodynamically unstable and can only be kinetically stabilized. This implies that microemulsions form spontaneously (i.e., their properties do not depend on the method of preparation) whereas nano-emulsions need an energy input for their formation (i.e., their properties depend on the method of preparation). Another important difference is the greater structural variability of microemulsions, which can be composed of spherical droplets or bicontinuous structures, while nano-emulsions are composed only of spherical droplets. These characteristic properties are summarized in Fig. 29.1. Both colloidal systems are appealing for their use in cosmetics due to, among others, the previously mentioned properties. For some applications either microemulsions or nano-emulsions can be appropriate, but, for certain applications, as it is described in more detail in Sections 29.5 and 29.6, choosing the right colloidal system is a key factor to achieve a successful/optimum formulation (e.g., if seeking a high-solubilizing power, microemulsions are the best option). There has been, and there still is, confusion in the literature with regard to the correct use of the terms *microemulsion* and *nano-emulsion*. The misuse of these terms has its origins in their similarities and also in the inadequacy of the term microemulsion. The characteristic size of microemulsions lies not in the micrometer but in the nanometer scale, and being thermodynamically stable, obviously, they are not emulsions. Although the term microemulsion is a misnomer, it is well established in the scientific community since it was coined by Schulman in 1959,[3] and to avoid further misunderstandings it should not be changed.

In this chapter the characteristic properties of microemulsions and nano-emulsions will be first summarized (Sections 29.2 and 29.3, respectively). A description of interest in them in the cosmetic field will follow (Section 29.4), and then components to formulate them (Section 29.5). Finally, examples of percutaneous absorption of actives from microemulsions and nano-emulsions will be given in Section 29.6.

## 29.2 MICROEMULSIONS

Microemulsions are thermodynamically stable isotropic colloidal solutions of two immiscible liquids (i.e., water and oil) stabilized by surfactant molecules with appropriate hydrophilic-lipophilic properties.[4] They are macroscopically homogeneous but heterogeneous on a microscopic level since a surfactant monolayer separates water and oil domains.

*Cosmetic Science and Technology: Theoretical Principles and Applications*
http://dx.doi.org/10.1016/B978-0-12-802005-0.00029-X



Copyright © 2017 Elsevier Inc. All rights reserved.

| Properties | Nano-emulsions | Microemulsions |
|---|---|---|
| Visual aspect |  |  |
| Typical characteristic size | 20-200 nm | 5-100 nm |
| Stability | Kinetic | Thermodynamic |
| Formation | Energy input | Spontaneous |
| Surfactant concentration | Low | High |

**FIGURE 29.1** Differences and similarities between nano-emulsions and microemulsions.

Microemulsions have attracted a great deal of attention both from scientific and technological viewpoints due to their characteristic properties, namely, ultralow interfacial tensions, large interfacial area, and solubilization capacity for both water and oil soluble compounds.[5,6]

As it occurred with other colloidal systems, the use of microemulsions in practical applications preceded their scientific recognition. The history of the development of microemulsions of industrial interest can be found in the book by Prince.[7] Microemulsions were introduced in the scientific field by Schulman in 1943,[8] who reported the spontaneous formation of a transparent or translucent solution when coarse emulsions composed of water, oil, and a soap (i.e., ionic surfactant) were titrated with a medium-chain alcohol. Schulman and collaborators studied this phenomenon in detail, viewing the transparent solutions, as a natural consequence of their experimental approach, as two-phase kinetically stable emulsions[8] that were termed with different names, among them, microemulsions,[3] the one that prevailed. The spontaneous formation of small droplets from the bigger ones was attributed to a reduction of the oil/water interfacial tension by three to four orders of magnitude and to temporary negative interfacial tension values.[3,8] However, phase behavior studies in water/ionic surfactant/cosurfactant/oil, and water/nonionic surfactant/oil systems by Shinoda et al.[9,10] and Friberg et al.[11,12] showed that Schulman's microemulsions fell in one (liquid)-phase regions of the corresponding four- or three-component phase diagrams and pointed out that these colloidal solutions should be related to micellar solutions, not to emulsions. These studies evidenced that microemulsions could be prepared by adding oil to micellar solutions without causing phase transitions. The thermodynamic stability of microemulsions was the object of intensive research in this area. The basis to clarify this issue were provided by Ruckenstein and Chi[13] who calculated the free energy of formation of microemulsions considering enthalpic (van der Waals attractive potential, electrical double-layer repulsive potential and interfacial free energy) and entropic (dispersion) contributions. Analysis of these thermodynamic factors revealed that the contribution of the interaction energy between droplets is negligible and that a negative free energy of formation can be achieved if the interfacial tension is extremely low (of the order of $10^{-2}$–$10^{-3}$ mN/m) but not necessarily negative. Other studies confirmed that microemulsions are thermodynamically stable because the oil/water interfacial tension is low enough to be compensated by the entropy of dispersion.[14] The recognition of microemulsion thermodynamic stability (i.e., directly related to micellar solutions rather than to emulsions) was a key step in their development. Another important issue was that of microemulsion structure. The picture that had emerged initially was that of a globular structure consisting of oil-in-water (O/W) and water-in-oil (W/O) droplets with diameter of the order of 100 nm. However, from phase behavior studies[9–12] and without structural characterization, it was pointed out that a structure consisting of O/W and W/O droplets was an oversimplification and was not consistent with the wide range of compositions in which microemulsions were formed (namely, those containing similar concentrations of water and oil). An enormous research effort was devoted to elucidate microemulsion structure from the beginning using a great variety of techniques (scattering, viscometry, conductivity, nuclear magnetic resonance, electron microscopy, etc.); the diversity and intensity of those studies is an indication of the complexity of microemulsions. The progress on this issue was facilitated by both theoretical treatments and accessibility to new and powerful characterization techniques. Scriven[15] proposed minimal surfaces of zero or low mean curvature,

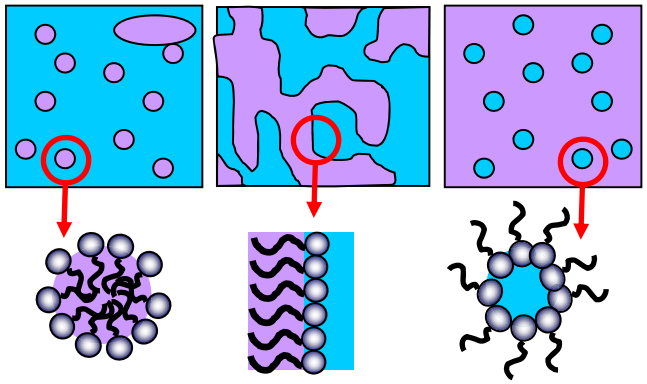


**FIGURE 29.2** Schematic representation of microemulsion structures: O/W (left), bicontinuous (middle), and W/O (right).

saddle shaped, (i.e., bicontinuous structures), a model consistent with most of the experimental observations on microemulsion systems. Bicontinuous structures were described as disordered, connected surfactant films separating water and oil domains. Fig. 29.2 shows a schematic representation of the globular and bicontinuous structures of microemulsions. The existence of bicontinuous microemulsions was first proved by NMR self-diffusion studies[16,17] and later by freeze-fracture electron microscopy.[18] There is now general agreement to consider that the spontaneous curvature,[19] $H_o$, of the surfactant monolayer at the oil-water interface dictates phase behavior and microstructure. Thus, hydrophilic surfactants produce O/W microemulsions ($H_o > 0$) and lipophilic surfactants produce W/O microemulsions ($H_o < 0$). Bicontinuous microemulsions are formed when the hydrophilic-lipophilic properties of the surfactant monolayer at the water−oil interface are balanced ($H_o \approx 0$), and under these balanced conditions, extremely low values of oil/water interfacial tension are attained and maximum solubilization of water and oil with the minimum amount of surfactant is achieved. Phase behavior studies have been and are essential to understand the conditions under which the different microemulsion structures are formed. The main features of microemulsion phase behavior were described by Winsor in the 1950s[20] in systems composed of water, ionic surfactant, oil, cosurfactant, and inorganic electrolyte. By increasing the electrolyte and/or cosurfactant concentration in mixtures with comparable amounts of water and oil and suitable concentrations of surfactant, the following phase equilibria were observed: an O/W microemulsion coexisting with excess oil phase (Winsor I equilibrium), a bicontinuous microemulsion coexisting with excess water and oil phases (Winsor III equilibrium), and a W/O microemulsion coexisting with excess water phase (Winsor II equilibrium). This phase sequence was attributed to a change in the curvature of the surfactant interfacial film. It was difficult to rationalize microemulsion phase behavior in such complex systems. In this context, Shinoda's studies[9,10] on phase behavior of water/polyoxyethylene-type nonionic surfactant/oil systems represented a significant contribution. It was shown that in these systems, the temperature is the parameter that controls the hydrophilic-lipophilic properties of the surfactant film. Shinoda[10] introduced the concept of hydrophilic-lipophilic balance (HLB) temperature ($T_{HLB}$) or phase inversion temperature (PIT) as the temperature at which the hydrophilic-lipophilic properties are balanced and, consequently, maximum solubilization of water in oil (or oil in water) and ultralow interfacial tensions are achieved (i.e., bicontinuous microemulsions are formed). At low temperatures, the so-called Winsor I equilibrium exists, at high temperatures Winsor II equilibrium, while at intermediate temperatures, at the $T_{HLB}$, the bicontinuous microemulsion phase coexists with excess oil and water phases (Winsor III equilibrium). Therefore, the same phase transitions are encountered in polyoxyethylene-type nonionic surfactant systems (triggered by temperature) and in ionic surfactant systems (triggered by electrolyte and/or cosurfactant concentration) as illustrated in Fig. 29.3.

Microemulsion formation in most of the basic investigations has been studied using three- or four-component systems. Although this is an oversimplification considering the number of components of microemulsion formulations used in cosmetics and in other applications, the study of relatively simple systems has allowed an understanding of the trends of microemulsion phase behavior. In practice, when investigating the formation of microemulsions in complex systems composed by several surfactants, oils, and additives, the study can be simplified by grouping the components by categories (polar, nonpolar, and amphiphilic), which allows working with pseudo-ternary systems and better rationalizing the whole phase behavior. A drawback of the systems used in early basic investigations was the fact that most of them hardly met industrial, environmental, and biological needs, and therefore were not suitable for practical applications. Another drawback was the occurrence of microemulsions over a narrow range of temperature (especially in polyoxyethylene-type nonionic surfactant systems). The need to overcome these

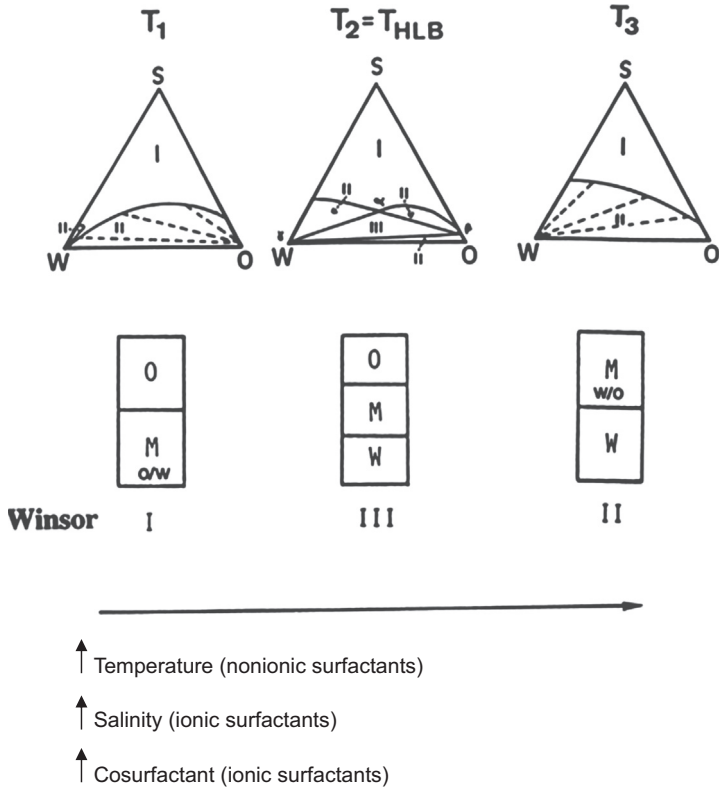



**FIGURE 29.3** Schematic representation of the phase behavior of a water/nonionic surfactant/oil system at the hydrophilic-lipophilic balance (HLB) Temperature ($T_2 = T_{HLB}$), at temperatures below it ($T_1$) and above it ($T_3$) with the corresponding microemulsion phase equilibria Winsor III, Winsor I, and Winsor II. The same phase transitions occur in ionic surfactant systems with electrolyte and/or cosurfactant concentration.

drawbacks has been a strong motivation for research in recent years. An account of this research effort in the cosmetic field is described in Sections 29.4–29.6.

## 29.3 NANO-EMULSIONS

Nano-emulsions, are emulsions with droplet size in the nanometer range that are the focus of an enormous amount of interest due to their wide range of applications (in the cosmetic, pharmaceutical, food, etc., fields).[2,21] The advantages of using nano-emulsions over conventional emulsions (micrometer-size droplets) are a consequence of the small droplet size, which confers high kinetic stability, high interfacial area, and optical transparency. Nano-emulsions also have advantages over microemulsions, namely the lower surfactant concentration required for their formation. The terminology to designate these colloidal systems in the literature is quite vast. "Nano-emulsion" is being increasingly adopted over other terms such as miniemulsion, submicron emulsion, or ultrafine emulsion. The authors prefer using "nano-emulsion" to emphasize the emulsion nature of these systems. The different size ranges for nano-emulsions found in the literature, which may vary from 20 nm up to 500 nm, are established generally on criteria based on optical properties as there is not a drastic change in the physicochemical properties when the emulsion droplet size is decreased from micrometer to nanometer range.

Although nano-emulsions are stable to sedimentation or creaming (Brownian motion overcomes gravity due to the small size), they may undergo flocculation, coalescence, and/or Ostwald ripening; the latter is the main breakdown process for nano-emulsions.[22,23] Ostwald ripening consists of the diffusion of molecules of the disperse phase from small to big droplets, through the continuous phase, as a consequence of their different Laplace pressures. However, with appropriate selection of system components, composition, and preparation method, nano-emulsions with high kinetic stability can be achieved. Nano-emulsions, being emulsions (thermodynamically unstable systems), require an energy input for their formation, which can be external (dispersion or high-energy methods) or internal (condensation or low-energy methods). Nano-emulsion formation by high-energy methods is quite straightforward as the higher the energy input the smaller the droplet size. However, to generate small droplets requires application of very high levels of energy, which may be achieved only by specific equipment such as high-

pressure homogenizers or ultrasound sonicators. Moreover, the process of emulsification is generally inefficient as about 99% of the energy applied is dissipated as heat.[2] That is why low-energy methods, where the energy for emulsification arises from the intrinsic energy of the emulsion components that is released during the emulsification process, are receiving an enormous research and industrial interest.[24,25] In, general smaller droplet sizes and narrower size distributions than with high-energy methods are achieved. Moreover, no complex equipment is required and the process can be performed under mild experimental conditions.

In low-energy emulsification, inversion of the spontaneous curvature of the surfactant film from negative to positive or vice versa (to obtain O/W or W/O emulsions, respectively) may or may not be produced. When changes in the spontaneous curvature of the surfactant film are produced during the emulsification process, they are designated as "phase inversion" methods. Phase inversion can be triggered by temperature, the well-known PIT method,[26] or by a change in composition at constant temperature, the so-called phase inversion composition (PIC) method.[21,25] Emulsification can also be produced without phase inversion at constant temperature, referred to as "self-emulsification."[27,28] Nano-emulsion formation by self-emulsification is triggered by the rapid diffusion of surfactant and/or solvent molecules from the dispersed phase to the continuous phase. In free-surfactant systems this emulsification mechanism is known as "Ouzo effect."[29] Although the "self-emulsification" method is used in industry, namely, to obtain O/W nano-emulsions as carriers for lipophilic active molecules, the low fraction of disperse phase that can be achieved is a major drawback.

Knowledge of surfactant phase behavior is important in low-energy methods, since the phases involved in the emulsification process play a key role in obtaining nano-emulsions with minimum droplet size and low polydispersity. In phase inversion methods, transitions through structures having a surfactant film with an average zero curvature (e.g., bicontinuous microemulsions or lamellar liquid crystalline phases) are those determining nano-emulsion droplet size.[21,30,31] However, it should be noted that the kinetics of the emulsification process also may play a role in the properties of the resulting nano-emulsions, especially when hexagonal or cubic liquid crystalline phases (of high viscosity) are present at some stage of the emulsification process.

The PIT method, introduced by Shinoda,[26] has been used in industry for a long time. It makes use of the changes in the hydrophilic-lipophilic properties of polyoxyethylene-type nonionic surfactants as a function of temperature. Therefore, it can only be used when these types of nonionic surfactants are present in the system. As described in the previous section, these surfactants are hydrophilic at low temperatures—the surfactant film has a large positive spontaneous curvature, forming O/W-type structures. At high temperatures, dehydration of the polyoxyethylene chains occurs and become lipophilic giving rise to W/O structures. At an intermediate temperature, the $T_{HLB}$ or PIT, the surfactant affinity for water and oil phases is balanced and structures with zero mean curvature such as bicontinuous microemulsions or lamellar liquid crystals may form depending on the concentration of surfactant and the system.[20,30–32] At the $T_{HLB}$, the formation of very small droplets are favored because of the extremely low interfacial tensions achieved[33] (around $10^{-2}$–$10^{-4}$ mN/m). However, the barriers that oppose coalescence processes are low and coalescence rate is extremely high resulting in very unstable emulsions.[34–36] To produce kinetically stable nano-emulsions the temperature has to be moved away from the $T_{HLB}$ by rapid cooling or heating (obtaining O/W or W/O emulsions, respectively). If the cooling or heating process is not fast, coalescence predominates and polydisperse coarse emulsions are formed. Depending on the composition of the system, a bicontinuous microemulsion or a lamellar liquid crystal is generally present around the $T_{HLB}$. Once this temperature is reached, the components are intimately dispersed in a single phase. Then, to obtain O/W nano-emulsions, the system is rapidly cooled, inducing a sudden change in the spontaneous curvature of surfactant monolayers. The formation of W/O nano-emulsions is analogous, but they form at temperatures higher than $T_{HLB}$. A schematic representation of the phase transitions encountered during emulsification by the PIT method is depicted in Fig. 29.4.

The PIC method involves the progressive addition of water to the oil phase which contains a surfactant or a surfactant mixture at constant temperature.[37–40] When water is progressively added to the oil phase, the initial system is, generally, a W/O microemulsion (Om). As the volume fraction of water increases, the hydration degree of the surfactant progressively increases, changing the spontaneous curvature from inverse (negative) to a planar (zero) curvature.[21,30] The mechanism is analogous to that of the PIT method. Around the transition composition, surfactant affinity for water and oil phases is balanced. Consequently, bicontinuous or lamellar structures are formed. With further addition of water, structures with zero curvature separate into metastable small O/W droplets, which implies a very high positive curvature of the surfactant layer. This process is schematically illustrated in Fig. 29.5.

The conditions for obtaining O/W nano-emulsions with a minimum droplet size and consequently low polydispersity by phase inversion emulsification methods (PIT and PIC) can be summarized as follows: A bicontinuous microemulsion or a lamellar liquid crystalline phase with all the oil dissolved must be formed immediately before reaching the two-phase region where the nano-emulsions form. In order to obtain small droplets with low

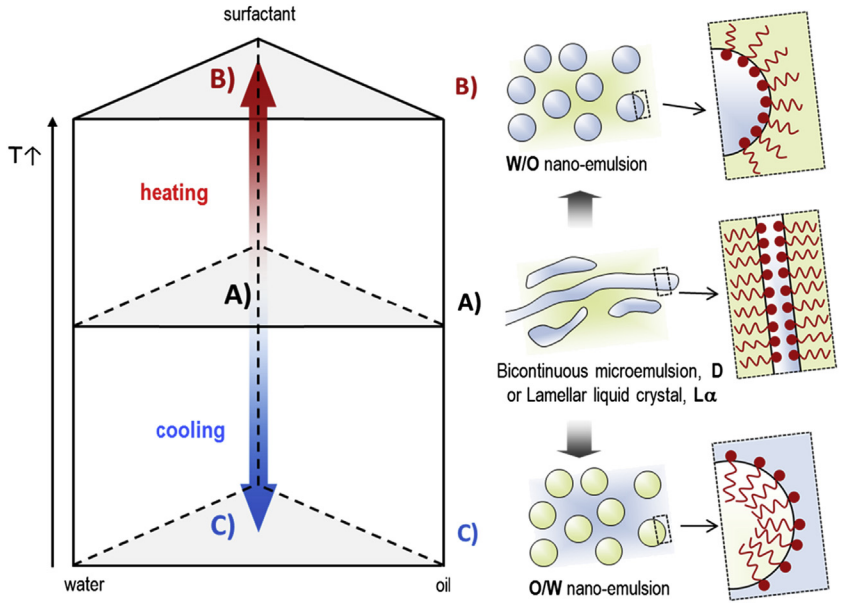



FIGURE 29.4 Schematic representation of the formation of nano-emulsions by the phase inversion temperature, PIT, method. *From Solans C, Solè I.* Curr Opin Colloid Interface Sci *2012;**17**:246.*

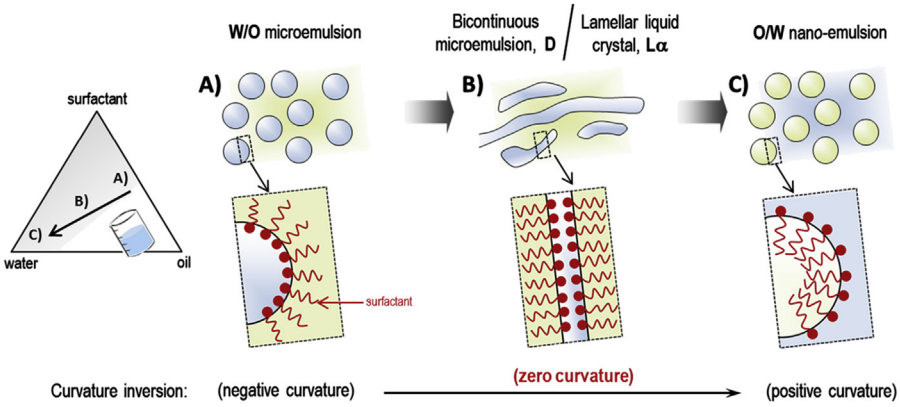



FIGURE 29.5 Schematic representation of the formation of nano-emulsions by the phase inversion composition, PIC, method. *From Solans C, Solè I.* Curr Opin Colloid Interface Sci *2012;**17**:246.*

polydispersity, at the inversion point all of the oil must be incorporated into the bicontinuous or lamellar liquid crystal structure.[21,31] If at the phase inversion composition some oil remains out of the bicontinuous or lamellar structure, this fraction of oil will be emulsified only by mechanical energy, producing big and polydisperse droplets, the more free oil fraction present, the higher mean size and polydispersity.

## 29.4 COSMETIC APPLICATIONS OF MICROEMULSIONS AND NANO-EMULSIONS

Microemulsions and nano-emulsions have been developed as suitable vehicles for cosmetic active ingredients due to their numerous advantages over the existing conventional formulations. Microemulsion and nano-emulsion technology, as claimed by different patents, can bring unique products with great commercial prospects in a very competitive and lucrative global cosmetic market.[41]

Since microemulsions were discovered approximately seven decades ago, their applications in cosmetics have increased recently due to their good appearance, thermodynamic stability, high-solubilizing power and ease of preparation.[42] As described earlier, microemulsions are capable of solubilizing both hydrophilic and lipophilic

ingredients with relatively higher incorporation for many skin care applications, where they provide very good cosmetic attributes and outstanding stability. Microemulsions have been proposed for moisturizing and soothing agents and for body cleansing, sunscreen and antiperspirant products due to their ability to solubilize relative large amounts of water-insoluble ingredients, i.e., emollients and fragrances, and also hydrophilic actives, with long-term stability.[43] They are also valuable for use in hair care preparations, which ensure good conditioning of hair as well as good hair feel and hair gloss. They have also found application in aftershave formulations, which upon application to the skin provide reduced stinging, less irritation, a comforting effect without tackiness, with high-hydration properties and rapid cutaneous penetration. Microemulsions are also suitable for perfuming purposes where minimum amount of organic solvents is required, such as perfuming skin or hair.[41]

Nano-emulsions are attractive systems for use in the cosmetics, pharmaceutical, food, and other industries due to the properties described previously, such as their low amount of surfactant, stability against sedimentation/creaming, lack of toxicity or irritant characteristics, low viscosity, good appearance, and versatility of formulation as foams, creams, liquids, and sprays. In the cosmetic field, the O/W nano-emulsion type has been studied more than the W/O, and high-energy methods of preparation were the most reported recently in the literature.[44] Nano-emulsions are particularly useful systems for cosmetics because the small droplet size ensures a closer contact with the stratum corneum, increasing the amount of active compound reaching the desired site of action. Besides, nano-emulsions can carry actives into the skin, improving the skin layer penetration and thus enhancing efficacy.[45] Moisturizers are one of the most important classes of cosmetic products due to their preventive action against xerosis and delaying of premature aging and for their use in helping dermatological therapies in a wide variety of skin disorders. Several studies have been carried out to demonstrate a higher hydration power of nano-emulsions in comparison with conventional formulations. An O/W nano-emulsion containing *Opuntia ficus-indica* (L.), a mill hydroglycolic extract, demonstrated high-moisturizing efficacy.[46] A comparative study of the hydration power of a nano-emulsion, a body milk and a body water, has also been reported.[47] Although higher hydration power was obtained for the nano-emulsion than for the other formulations, the influence of other effects, such as formulation components, that may also be responsible for the higher hydration power was not taken into account.

Nano-emulsions have been compared to solid lipid nanoparticles as colloidal carriers for bioactive compounds such as ceramides. Ceramides are main components of the stratum corneum and are essential for the efficient barrier function, but their very high lipophilicity renders them difficult to incorporate in an acceptable formulation. The results showed that the nano-emulsions can incorporate a high percentage of ceramides giving more homogeneous particle distributions of spherical-shaped nanoparticles and maintaining their characteristics over time.[48]

Fullerene-loaded nano-emulsions were applied transdermally to seek their effects in regulating the human skin structure and amelioration of collagen within the skin. Safety evaluation was conducted based on cytotoxicity and dermal irritation testing. The fullerene nano-emulsions developed were demonstrated to be effective and safe skin care products in protecting collagen and delaying the skin-aging process. The biophysical impacts of fullerene nano-emulsions on human skin hydration were significantly increased and the transepidermal water loss was reduced during the span of 28 days of treatment.[49]

Nano-emulsions are being increasingly exploited in the development of advanced skin care products, specifically targeting the hair follicle and shaft.[50] Silicone oil, as a major component in hair conditioners, is beneficial in the moisture preservation and lubrication of hair. However, it is difficult for silicone oil to directly adsorb on the hair surface because of its hydrophobicity. Silicone O/W nano-emulsions containing nonionic surfactants were developed as a promising solution to improve the silicone oil deposition on the hair surface for hair care applications.[51]

## 29.5 MICROEMULSION AND NANO-EMULSION COMPONENTS

A variety of surfactants, cosurfactants, and oils have been proposed to obtain microemulsions and nano-emulsions for cosmetic use. Selection of components have to take into account skin sensitization and toxicity as well as the influence on formulation properties and stability. The favorable active delivery properties of microemulsions appear to be attributed mainly to the excellent solubility properties. However, the microemulsion components may also act as penetration enhancers depending on the oil/surfactant constituents, which involve a risk of inducing local irritancy. The correlation between microemulsion structure/composition and active delivery potential is not yet fully elucidated. However, a few studies have indicated that the internal structure of microemulsions should allow free diffusion of the drug to optimize cutaneous delivery from these vehicles.[52]

O/W microemulsions were reported as vehicles for the sunscreens 4-methylbenzilidene camphor or octyl methoxycinnamate. Some of the components of the microemulsions were soya lecithin, decyl polyglucose,

cyclomethicone, menthol, allantoin, and stearyl methicone, which provided good skin feel, waterproof effect, nonstickiness, and easy spreadability.[53] Microemulsion formulations not only improve product efficiency but also enhance stability of the active ingredients. For instance, the photostability to ultraviolet B irradiation of the whitening agents arbutin and kojic acid was higher in O/W microemulsions comprising lecithin and an alkyl glucoside as amphiphiles than in aqueous solutions.[54]

To formulate an optimal microemulsion for an active ingredient, the factors that influence the stability of the product have to be considered. The type of microemulsions contributes to the stability of the active ingredients. For example, ascorbyl palmitate was more stable in W/O than in O/W microemulsions because the cyclic ring of the active ingredient that was sensitive to oxidation if located in the water phase, was shielded in microemulsion droplets. In contrast to ascorbyl palmitate, sodium ascorbyl phosphate was stable in both types of microemulsions. The location of the actives in the microemulsion nanostructure significantly influenced their release profiles.[55]

Nonionic surfactants used to form both micro- and nano-emulsions include polyoxyethylene surfactants or sugar esters such as sorbitan esters. Among ionic surfactants, the anionic sodium bis-2-ethylhexylsulphosuccinate has been widely used because of its ability to stabilize W/O microemulsions. As cationic surfactants, quaternary ammonium alkyl salts such as hexadecyltrimethyl-ammonium bromide, and didodecylammonium bromide have been largely investigated to form microemulsions. Due to their high biocompatibility, biodegradability, and safety, phospholipids are the main class of zwitterionic surfactants used to form colloidal systems based on nanodroplets for drug or cosmetic delivery.[56] Generally, microemulsions need high concentrations of surfactant and cosurfactant to reduce the interfacial tension and increase the flexibility of the interfacial film, respectively. Therefore, the probability of skin irritation or toxicity is also high depending on the properties of the surfactant and/or cosurfactant. Consequently, the choice of components is challenging and, besides their ability to form microemulsions, the formulator should carefully take into account their biological and cosmetic acceptability.[57] Here, there is a growing interest in using nonionic surfactants, which are reportedly less toxic and irritant than other types of surfactants. New raw materials have been developed to be used in microemulsion formulations in order to give the cosmetic products more efficiency with less toxicity.[42] Some examples of cosmetic acceptable excipients are pentyl rhamnoside and cetyl rhamnoside that could be used as biocompatible cosurfactants.[58] Biologically mild surfactants, such as the mixtures of ethoxylated glycerides, PEG8 caprylic/capric glyceride, and poly(glyceryl-6-dioleate), could be used to obtain microemulsions.[59] Sucrose esters are meant to be nontoxic surfactants obtained from a naturally occurring carbohydrate, with features of low skin sensitization and enhancing skin penetration, as well as with a high environmental compatibility.[60] Sucrose esters and lecithin-based microemulsions showed excellent eudermic properties.[61] Polyoxyethylene/polyoxypropylene dimethyl ether, a random copolymer of ethylene oxide and propylene oxide, was developed to use for skin care due to its humectant property and can be used to form microemulsions with water, liquid paraffin, and POE(7).[62] Different oils have been used to obtain microemulsions and nano-emulsions for pharmaceutical and cosmetic use. The most widely used are medium-chain triglycerides and fatty esters (isopropyl myristate, isopropyl palmitate, ethyl or methyl esters of lauric, myristic, and oleic acid).[56]

The nanostructure of microemulsions has been reported to influence dermal compatibility. Skin irritation and phototoxicity potentials of several microemulsions were studied. All microemulsions comprised approximately the same percentage of surfactant mixture, but varying oil/water content and consequently the inner structure; being either droplet-like (O/W microemulsion, O/W microemulsion with carbomer, W/O microemulsion, and W/O microemulsion with white wax) or lamellar (gel-like microemulsion). The gel-like microemulsion was more irritant compared to other tested formulations and the results of the phototoxicity test again indicated the increased potential of gel-like microemulsion to cause adverse effects on skin. Then, when comparing microemulsions consisting of the same amount of identical surfactants but having different structures, the latter represent a crucial factor that determines their dermal toxicity.[63]

Preconcentrated microemulsions, also known as self-microemulsifying drug delivery systems, are mixtures consisting of drugs, oils, and surfactants. Upon dilution with aqueous media and accompanied by gentle agitation, the preconcentrate spontaneously forms clear isotropic solutions, or microemulsions. The combined use of surfactants in preconcentrate microemulsions showed the formation of microemulsions with small particle size, increased drug loading, and improved physical stability, with significant implications in the development of poorly water-soluble actives formulations. The effect of different surfactants, when used either alone or in combination, on microemulsion formation from preconcentrates was studied. Cremophor EL (polyoxyl 35 castor oil) and Tween 20 (polysorbate 20) were used as surfactants, and Capmul PG8 (propylene glycol monocaprylate) as oil. Both Tween 20 and Cremophor EL are nonionic and generally-recognized-as-safe excipients and are widely used in pharmaceutical preparations. With Tween 20 being more hydrophilic than Cremophor EL, this surfactant combination (1/1 ratio, w/w) was found to be effective in drug emulsification in a number of compounds.[64]

## 29.6 PERCUTANEOUS ABSORPTION OF ACTIVES FROM MICROEMULSIONS AND NANO-EMULSIONS

The percutaneous absorption of cosmetic ingredients, such as moisturizers, whitening agents, or antioxidant agents, is low due to the barrier function of the stratum corneum of the skin. Several strategies have been proposed to overcome the barrier function of the stratum corneum for the purpose of increasing the skin permeation of cosmetic actives.[42] Microemulsions are one of the useful formulation approaches that have been shown to be able to deliver cosmetic actives and drugs through the skin better than simple solutions or conventional dosage forms.[65,66] The mechanisms proposed to explain the skin permeation enhancement properties of microemulsions[67–69] are the following: (1) a large amount of active can be included in the formulation due to the high-solubilization capacity, (2) the thermodynamic activity of the active can be modified to favor partitioning into the stratum corneum, (3) the surfactants may reduce the diffusional barrier of the stratum corneum, (4) microemulsions can act as active ingredients reservoirs where loaded active is released from the inner pseudophase to the outer pseudophase and then to the skin, (5) microemulsion droplets might break down on the surface of the stratum corneum and then release their contents to the skin, (6) the nanosized droplets can move easily through the stratum corneum and carry the active through the skin barrier, and (7) percutaneous absorption can increase due to the hydration effect of the stratum corneum if the water content in the microemulsion is high enough. However, the nature of microemulsions was found to be a crucial parameter for permeation of an active ingredient through heat-separated human epidermis.[70] Formulation viscosity also has been considered in transdermal permeation—microemulsions containing sugar-based surfactants (laurate and myristate) increased delivery of an antiinflammatory active through stratum corneum by increasing its fluidity and showing overall more satisfying safety profiles.[71]

The influence of emulsion droplet size on the delivery rate of active ingredients through the skin is also a subject of fundamental and applied interest but still a matter of controversy.[72] Most authors have believed that the delivery of active ingredients can be influenced by droplet size, but other researchers have shown no significant effect. Some studies indicated that skin penetration is dependent on the droplet size of the emulsion, as skin penetration was higher from emulsions with smaller droplets.[73,74] However, some problems with most of these comparison studies are the low number of replicates and also that the formulations differ in their composition, and, therefore, it is difficult to subtract the pure effect of the droplet size. For example, percutaneous absorption from a microemulsion might not only be enhanced because of smaller droplet sizes but also because of a higher amount of surfactants and a larger concentration gradient provided by the higher solubilization capacity of the microemulsion.[52] A more systematic study has been performed[75] to investigate the effect of droplet size on dermal and transdermal delivery of tetracaine. Two sets of emulsions were incorporated into this study: one set of emulsions with identical composition but different droplet sizes, and another set of emulsions with constant surfactant concentration in the aqueous phase but different overall surfactant concentration and droplet size. Fig. 29.6 shows the results of transdermal permeation of the active from macroemulsions and nano-emulsions with identical composition as a function

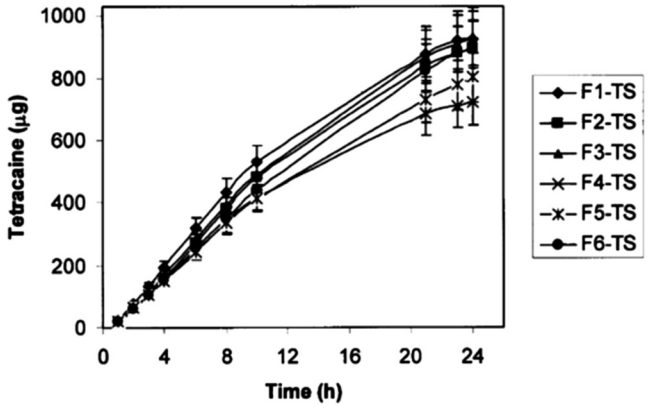



FIGURE 29.6 Tetracaine permeation as a function of time for emulsions with constant surfactant concentration in the aqueous phase (3.97 wt%) in the system: water/$C_{12-15}E_7$/hexadecane/tetracaine, at 20 wt% hexadecane and 0.5 wt% tetracaine concentrations. Average droplet size of emulsions: F1-TS: 3.5 µm, F2-TS: 1.8 µm, F3-TS: 1.0 µm, F4-TS: 88 nm, F5-TS: 68 nm, and F6-TS: 48 nm. *From Izquierdo P, Wiechers JW, Escribano E, García-Celma MJ, Tadros TF, Esquena J, Dederen JC, Solans C.* Skin Pharmacol Appl Skin Physiol *2007;**20**:263.*

of droplet size. Interestingly, no correlation could be found between the droplet size and dermal as well as transdermal delivery. Similar results were obtained recently with transdermal absorption of forskolin from O/W macroemulsions, O/W nano-emulsions, and oil solutions—no correlation between emulsion droplet size and active penetration through excised human skin could be found. Forskolin penetration through skin was considered mainly governed by the partition of the active between the skin and the vehicle.[76]

The combination of unsaturated phospholipids and amphiphilic block copolymers such as polyethylene oxide-block-poly(-caprolactone) resulted in an effective means of enhancing the skin delivery capability of nano-emulsions while maintaining their long-term dispersion stability. Tocopheryl acetate was used as the oil component delivered, and large variations were found in the emulsion droplet size, microviscosity, and the skin absorption efficiency as a function of lipid−polymer ratio.[77]

Charged delivery systems are interesting candidates for the delivery of actives through skin. Cationic compounds can also have a positive effect on skin permeation, since the skin carries a negative surface charge due to the negatively charged residues of proteins. Positively charged oil/water nano-emulsions were created by using the skin-friendly mild surfactant sucrose laurate and polysorbate 80 as nonionic surfactants. The positively charged nano-emulsions were generated by adding cationic phytosphingosine (PS). PS nano-emulsions showed an enhancement effect on skin permeation that can be attributed to their hydrating and antiinflammatory power.[78]

A variety of W/O nano-emulsions were prepared using sorbitan monooleate, polyoxyethylene 20 sorbitan monooleate, olive oil, and water. The nano-emulsions were tested for their ability to facilitate transport of a model hydrophilic solute, inulin, following topical in vitro application. The transport of inulin incorporated in W/O nano-emulsions was found to be significantly higher than that obtained with micellar dispersions or aqueous controls. The combined results suggest that W/O nano-emulsions that are compatible with the lipophilic sebum environment of the hair follicle facilitate efficient transport of incorporated hydrophilic solutes and imply that such transport is predominantly transfollicular in nature.[79]

## 29.7 CONCLUSIONS

Microemulsions and nano-emulsions, although different in nature have properties, such as large interfacial area, solubilizing capacity, transparent/translucent aspect, and low viscosity, of special interest in the cosmetic field. Microemulsions, being thermodynamically stable, form spontaneously and their properties are independent of the method of preparation. They can be formulated with globular (direct/reverse) as well as bicontinuous structures and among colloidal systems are those with higher solubilization capacity for both lipophilic and hydrophilic compounds. In contrast, nano-emulsions (emulsions with submicron-size droplets) are thermodynamically unstable systems. Consequently, an energy input (external or internal) is required for their formation and their properties (droplet size, stability, etc.) depend on the preparation method.

Conveniently formulated, microemulsions and nano-emulsions are suitable vehicles for, among others, skin care and hair care products and for perfuming purposes. It has been shown that they present advantages over other conventional formulations in terms of high-hydration power, ability to solubilize both water- and oil-soluble ingredients, and enhanced skin penetration of actives. Moreover, they show versatility to be formulated as foams, creams, and sprays. Another advantage is the ease of preparation as they can be formed under mild experimental conditions.

Most of the early fundamental investigations on microemulsions and nano-emulsions were based on model systems that hardly met industrial, environmental, and toxicological requirements. Although considerable research effort has been made in the last years to use components suitable for cosmetic applications, more fundamental work is needed, especially with newly developed raw materials, to produce more efficient and biocompatible cosmetic products.

An important issue that has not been fully elucidated is the correlation between structure/composition and active delivery potential. This aspect is of utmost interest to optimize cutaneous delivery from these vehicles and for the development of advanced skin care and hair care products. The influence of emulsion droplet size on the delivery rate of the active ingredients through the skin is also a subject of fundamental and applied interest but still a matter of controversy. Research on these topics will certainly allow to expand the future prospects of microemulsions and nano-emulsions in cosmetic science and technology.

## References


1. von Rybinski W, Hloucha M, Johansson I. In: Stubenrauch C, editor. *Microemulsions: background, new concepts, applications, perspectives*. Oxford: Wiley-Blackwell; 2009. p. 230.
2. Tadros T, Izquierdo P, Esquena J, Solans C. *Adv Colloid Interface Sci* 2004;**108**–**109**.
3. Schulman JH, Stoekenius W, Prince LM. *J Phys Chem* 1959;**63**:1677.
4. Danielsson I, Lindman B. *Colloids Surf* 1891;**3**:391.
5. Solans C, Kunieda H, editors. *Industrial applications of micoremulsions*, **66**. New York: Marcel Dekker; 1997.
6. Kummar P, Mittal KL, editors. *Handbook of microemulsion science and technology*. New York: Marcel Dekker; 1999.
7. Prince LM. In: Prince LM, editor. *Microemulsions. Theory and practice*, **21**. New York: Academic Press; 1977.
8. Hoar TP, Schulman JH. *Nature* 1943;**152**:102.
9. Saito H, Shinoda K. *J Colloid Interface Sci* 1967;**24**:10.
10. Shinoda K, Saito H. *J Colloid Interface Sci* 1968;**26**:70.
11. Gillberg G, Lehtinen H, Friberg SE. *J Colloid Interface Sci* 1970;**32**:40.
12. Rance DG, Friberg SE. *J Colloid Interface Sci* 1977;**60**:207.
13. Ruckenstein E, Chi JC. *J Chem Soc Faraday Trans II* 1975;**71**:1690.
14. Miller CA, Neogi P. *AIChE* 1980;**26**:212.
15. Scriven LE. *Nature* 1976;**263**:123.
16. Lindman B, Kamenka N, Kathopoulis T-M, Brun B, Nilsson P-G. *J Phys Chem* 1980;**84**:2485.
17. Lindman B, Olsson U, Söderman O. In: Kummar P, Mittal KL, editors. *Handbook of microemulsion science and technology*. New York: Marcel Dekker; 1999. p. 309.
18. Jahn W, Strey R. *J Phys Chem* 1988;**92**:2294.
19. Helfrich W. *Naturforsch* 1973;**28c**:693.
20. Winsor PA. *Solvent properties of amphiphilic compounds*. London: Butterworth; 1954.
21. Solans C, Solè I. *Curr Opin Colloid Interface Sci* 2012;**17**:246.
22. Taylor P, Ottewill RH. *Colloids Surf A* 1994;**88**(2–3):303.
23. Taylor P. *Adv Colloid Interface Sci* 1998;**75**:107.
24. Nakajima H. In: Solans C, Kunieda H, editors. *Industrial applications of microemulsions*. New York: Marcel Dekker; 1997. p. 175.
25. Solans C, Izquierdo P, Nolla J, Azemar N, García-Celma MJ. *Curr Opin Colloid Interface Sci* 2005;**10**:102.
26. Shinoda K, Saito H. *J Colloid Interface Sci* 1969;**30**:258.
27. Miller CA. *Colloids Surf* 1988;**29**:89.
28. Bouchemal K, Briançon S, Perrier E, Fessi H. *Int J Pharm* 2004;**280**:241–51.
29. Vitale SA, Katz JL. *Langmuir* 2003;**19**:4105.
30. Forgiarini A, Esquena J, González C, Solans C. *Langmuir* 2001;**17**:2076.
31. Morales D, Gutiérrez JM, García-Celma MJ, Solans C. *Langmuir* 2003;**19**:7196.
32. Sonneville-Aubrun O, Babayan D, Bordeaux D, Lindner P, Rata G, Cabane B. *Phys Chem Chem Phys* 2009;**11**(101).
33. Kunieda H, Friberg SE. *B Chem Soc Jpn* 1981;**54**:1010.
34. Taisne L, Cabane B. *Langmuir* 1998;**14**:4744.
35. Kabalnov A, Wennerström H. *Langmuir* 1996;**12**:276.
36. Roger K, Olsson U, Zackrisson-Oskolkova M, Lindner P, Cabane B. *Langmuir* 2011;**27**:10447.
37. Solè I, Pey CM, Maestro A, González C, Porras M, Solans C, Gutiérrez JM. *J Colloid Interface Sci* 2010;**344**:417.
38. Solé I, Pey CM, Maestro A, González C, Porras M, Solans C. *J Colloid Interface Sci* 2010;**344**:417.
39. Roger K, Cabane B, Olsson U. *Langmuir* 2011;**27**:604.
40. Heunemann P, Prévost S, Grillo I, Marino CM, Meyer J, Gradzielski M. *Soft Matter* 2011;**7**:5697.
41. Azeem A, Rizwan M, Ahmad FJ, Khan ZI, Khar RK, Aqil M, Talegaonkar S. *Recent Pat Drug Deliv Formul* 2008;**2**(3):275.
42. Boonme P. *J Cosmet Dermatology* 2007;**6**:223.
43. Tsolis P, Heisig C. *Cosmet Toiletries* 2011;**126**(10):608.
44. Yukuyama MN, Ghisleni DDM, Pinto TJA, Bou-Chacra NA. *Int J Cosmet Sci* 2016;**38**:13.
45. Morganti P. *Clin Cosmet Investig Dermatology* 2010;**3**:5.
46. de Azevedo Ribeiro RC, Gomes Barreto SMA, Arantes Ostrosky E, Alves da Rocha Filho P, Mafra Veríssimo L, Ferrari M. *Molecules* 2015;**20**: 2492.
47. Sonneville-Aubrun O, Simonnet JT, L'Alloret F. *Adv Colloid Interface Sci* 2004;**145**:108–9.
48. Deli G, Hatziantoniou S, Nikas Y, Demetzos C. *J Liposome Res* 2009;**19**(3):180.
49. Ngan CL, Basri M, Tripathy M, Karjiban RA, Abdul-Malek E. *Eur J Pharm Sci* 2015;**70**:22.
50. Rosen J, Landriscina A, Friedman AJ. *Cosmetics* 2015;**2**:211.
51. Hu Z, Liao M, Chen Y, Cai Y, Meng L, Liu Y, Lv N, Liu Z, Yuan W. *Int J Nanomed* 2012;**7**:5719.
52. Kreilgaard M. *Adv Drug Deliv Rev* 2002;**54**(Suppl. 1):S77.
53. Carlotti ME, Gallarate M, Rossatto V. *J Cosmet Sci* 2003;**54**:451.
54. Gallarate M, Carlotti ME, Trotta M, Grande AE, Talarico C. *J Cosmet Sci* 2004;**55**:139.
55. Spiclin P, Homar M, Zupancic-Valant A, Gasperlin M. *Int J Pharm* 2003;**256**:65.
56. Montenegro L, Lai F, Offerta A, Sarpietro MG, Micicch L, Maccioni AM, Valenti D, Fadda AM. *J Drug Deliv Sci Technol* 2016;**32**:100.
57. Das A, Mitra RK. *Colloid Polym Sci* 2014;**292**:635.
58. Houlmont J, Vercruysse K, Perez E, Rico-Lattes I, Bordat P, Treihou M. *Int J Cosmet Sci* 2001;**23**:363.
59. Gloukhova TV, Kienskaya KI, Myakon'kii AG, Kim V. *Colloid J* 2005;**67**:291.
60. Száts A, Szabó-Révész P. *Int J Pharm* 2012;**433**:1.
61. Schwarz JC, Klang V, Hoppel M, Mahrhauser D, Valenta C. *Eur J Pharm Biopharm* 2012;**81**:557.

62. Miyahara R, Nakanishi Y, Maruyama K, Chandra Sharma S, Abe M. *J Oleo Sci* 2009;**58**(2):65.
63. Rozman B, Gosenca M, Falson F, Gasperlin M. *Int J Pharm* 2016;**499**:228.
64. Lia P, Ghosha A, Wagnera RF, Krillb S, Joshia YM, Serajuddina ATM. *Int J Pharm* 2005;**288**:27.
65. Sintov AC, Shapiro L. *J Controlled Release* 2004;**95**:173.
66. Rangarajan M, Zatz JL. *J Cosmet Sci* 2003;**54**:161.
67. Delgado-Charro MB, Iglesias-Vilas G, Blanco-Méndez J, López-Quintela J, Marty MA, Guy RH. *Eur J Pharm Biopharm* 1997;**43**:37.
68. Peltola S, Saarinen-Savolainen P, Kliesvaara J, Suhonen TM, Urtti A. *Int J Pharm* 2003;**254**:99.
69. Sintov AC. *Int J Pharm* 2015;**481**:97.
70. Junyaprasert VB, Boonme P, Songkro S, Krauel K, Rades T. *J Pharm Pharm* 2007;**10**:288.
71. Todosijevi MN, Savi MM, Batini BB, Markovi BD, Gasperlind M, Ranpelovi DV, Luki MZ, Savi SD. *Int J Pharm* 2015;**496**:931.
72. Otto A, du Plessis J, Wiechers JW. *Int J Cosmet Sci* 2009;**31**:1.
73. Kotyla T, Kuo F, Moolchandani V, Wilson T, Nicolosi R. *Int J Pharm* 2008;**347**(1−2):144.
74. Ktistis G, Niopas I. *J Pharm Pharmacol* 1998;**50**:413.
75. Izquierdo P, Wiechers JW, Escribano E, García-Celma MJ, Tadros TF, Esquena J, Dederen JC, Solans C. *Skin Pharmacol Appl Skin Physiol* 2007; **20**:263.
76. Sikora E, Llinàs M, García-Celma MJ, Escribano E, Solans C. *Colloids Surf B: Biointerfaces* 2015;**126**:541.
77. Nam YS, Kim JW, Park JY, Shim J, Lee JS, Han SH. *Colloids Surf B: Biointerfaces* 2012;**94**:51.
78. Hoeller S, Sperger A, Valenta C. *Int J Pharm* 2009;**370**:181.
79. Wu H, Ramachandran C, Weiner ND, Roessler BJ. *Int J Pharm* 2001;**220**:63.

CHAPTER

# 30

# Effect of Molecular Assembly for Emulsion and Gel Formulations

*T. Suzuki*

**Cosmos Technical Center Co., Ltd., Tokyo, Japan**

## 30.1 INTRODUCTION

Amphiphilic molecules like surfactants and polar lipids form self-assembling molecular aggregates such as micelles and lyotropic liquid crystals.[1] They are used in the preparation of emulsions, solubilization systems, and gel systems. In particular, liquid crystals, which are infinite aggregates of molecules, markedly enhance the ability to emulsify and solubilize. When liquid crystals are cooled down to a temperature below the Krafft point (Kp) corresponding to the gel-liquid crystal transition temperature (Tc), alpha-gels (α-gels) often appear. An α-gel is a crystal retaining a large amount of water within the hydrophilic groups. The formation of a liquid crystalline phase or a gel phase is often observed in cosmetic emulsions. When a liquid crystalline phase or a gel phase appears in an emulsion, the physical properties like rheology and stability of the emulsion change significantly.[2,3]

A liquid crystal and an α-gel also contribute to the supplementation and maintenance of the physiological functions of the stratum corneum by forming a layer structure composed of amphiphilic lipids and water.[4,5] These characteristic behaviors of molecular assemblies are closely related to the affinity, delivery, and sustainability of cosmetic bases applied to the skin. In this chapter, the basics of molecular assemblies, the mechanism of liquid crystal emulsification and the application of molecular assemblies, liquid crystals and α-gels, to the functional cosmetics are reviewed.

## 30.2 FORMATION AND THE CHARACTERIZATION OF LYOTROPIC LIQUID CRYSTALS AND α-GELS

### 30.2.1 Formation of Molecular Assemblies

Amphiphilic molecules possessing a hydrophilic group and a lipophilic group within a molecule show a self-organizing property induced by hydrophobic interactions with water addition. Fig. 30.1 shows the dissolution behavior of a surfactant/water system with temperature and concentration as the state variables. The line gradually extending from the lower left to the upper right is the solubility curve of a monomeric dispersing surfactant molecule. At temperatures lower than the Kp, monomeric molecules coexist with the hydrated crystals in a high-concentration region from the solubility curve. When the temperature reaches Kp, the solubility curve of the surfactant extends upward substantially parallel to the vertical axis, where the hydrophobic chains of the surfactant molecules change from solid to liquid.

When a hydrophilic amphiphile is added to water, the state of the system changes to micellar solution, liquid crystal, and finally the hydrate of amphiphile from monomeric dispersion, with increasing concentration. A micelle is a spherical molecular aggregate having a limited association number of around 80 to 100. In the lower concentration region, only the number of micelles increases without changing the association number when increasing the concentration. However, when the concentration of the amphiphile continues to rise, the association number

*Cosmetic Science and Technology: Theoretical Principles and Applications*
http://dx.doi.org/10.1016/B978-0-12-802005-0.00030-6



Copyright © 2017 Elsevier Inc. All rights reserved.

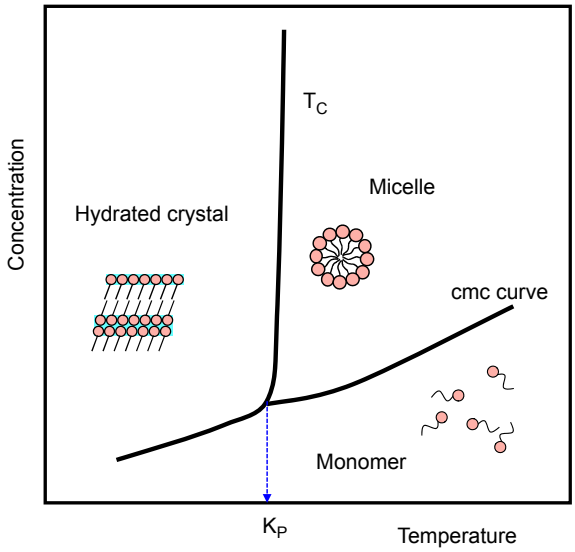



**FIGURE 30.1** Dissolution behavior of surfactant/water system.

increases gradually and the aggregate becomes a rod-shaped micelle. Further addition results in the formation of infinite aggregates of lyotropic liquid crystal.[1,6]

Micelles or liquid crystals are formed only when the hydrophobic portion is in a liquid state. Surfactants possessing solid hydrophobic chains cannot form molecular assemblies like micelles and liquid crystals without heating above the gel-liquid crystal transition point (Tc). Fig. 30.2 shows the appearance of a surfactant/water system observed above and below Tc. The upper photographs were observed under ordinary light, whereas the lower photographs were observed under crossed polarizers. Under crossed polarizers the optical anisotropic substances like crystals, liquid crystals, and gels appear to be glowing brightly, and the isotropic substances such as water and micellar solutions remain dark. The hydrated crystals, called "coagel," appear as precipitate and coexist with water and are seen in the left-hand side of Fig. 30.2.

When the coagel is heated above Tc, it changes to a liquid crystal, slightly viscous transparent phase retaining a large amount of water within the hydrophilic moiety, and shows optical anisotropy. In the transition of coagel to liquid crystal, a relatively large endothermal peak induced by the melting of hydrophobic chains is observed by differential scanning calorimetry (DSC) measurement. The gel-liquid crystal transition is reversible and the water held in the liquid crystal is released and separated into two phases of hydrated crystalline and water at below Tc. On the other hand, a translucent gel state may remain without releasing the interlayer water when it is cooled below Tc in case of some compounds (Fig. 30.2 the right-hand side). This state is called "α-gel." Since an α-gel is generally a

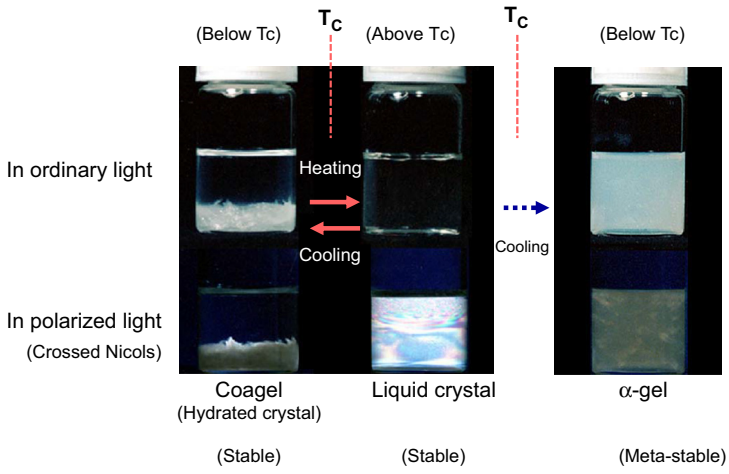


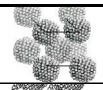
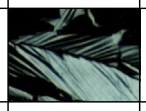
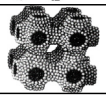
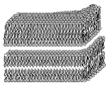
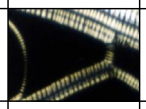
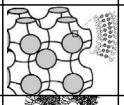
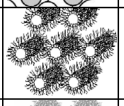
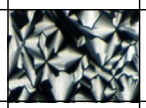
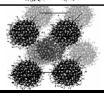

**FIGURE 30.2** Appearances of surfactant/water system observed at above and below the phase transition temperature (Tc).

thermodynamically metastable system, it changes to a coagel by releasing interlayer water with the passage of time. However, the gel state might be maintained for a long time depending on the storage conditions.

### 30.2.2 Characterization of Liquid Crystal and α-Gel

The relationship between molecular shapes and their association structures is summarized in Table 30.1. Association structures reflect the molecular shapes of the constituent molecule and they are predicted by the numerical value of the critical packing parameter ($CPP = v/al$), where $a$ indicates the cross-section area of the hydrophilic group, $l$ is the extended length of the hydrophobic chain, and $v$ *is* the volume of the hydrophobic group.[7,8] CPP is a nondimensional parameter and is useful for the estimation of association structures. An amphiphilic molecule having a CPP around 1 forms plate-like molecular aggregates of zero curvature. If the CPP is smaller than 1, then molecular aggregates having a convex curvature toward the water phase are formed. Spherical aggregates are formed at CPP values smaller than 1/3, whereas rod-shaped aggregates are formed at CPP values between 1/2 and 1/3. On the other hand, reversed aggregates orienting their hydrophobic chains toward the outside are formed at CPP values larger than 1. Although CPP is not a perfect guarantee for the formation of a certain association structure, it is useful for understanding the relationship between the geometrical character of an amphiphilic molecule and the association structure.

**TABLE 30.1** Relationship Between Molecular Shapes and Their Association Structures of Amphiphiles

| | Solution state | Critical packing parameter | | Association structure | | Symbol | Optical texture | Bragg spacing ratio |
|---|---|---|---|---|---|---|---|---|
| Hydrophilic ↑ Curvature ↓ Lipophilic | Micelle |  | $v/al \le 1/3$ |  | Sphere | $L_1$ | Isotropic | — |
| | |  | $1/3 < v/la \le 1/2$ |  | Rod | $L_1$ | Isotropic | |
| | Liquid crystal | | $v/al \le 1/3$ |  | Cubic | $I_1$ | Isotropic | $1:\sqrt{3/4}:\sqrt{3/8}:\sqrt{3/11}$ (BCC)<br>$1:\sqrt{1/2}:\sqrt{1/3}:1/2$ (FCC) |
| | |  | $1/3 < v/la \le 1/2$ |  | Hexagonal | $H_1$ |  | $1:1/\sqrt{3}:1/\sqrt{4}:1/\sqrt{7}$ |
| | | | $1/2 < v/al \le 1$ |  | Cubic | $V_1$ | Isotropic | $1:\sqrt{3/4}:\sqrt{3/8}:\sqrt{3/11}$ |
| | |  | $v/al \approx 1$ |  | Lamellar | $L\alpha$ |  | $1:1/2:1/3:1/4$ |
| | | | $1 \le v/al$ |  | Cubic | $V_2$ | Isotropic | $1:\sqrt{3/4}:\sqrt{3/8}:\sqrt{3/11}$ |
| | |  | $1 < v/al$ |  | Reversed hexagonal | $H_2$ |  | $1:1/\sqrt{3}:1/\sqrt{4}:1/\sqrt{7}$ |
| | | | $1 < v/al$ |  | Cubic | $I_2$ | Isotropic | $1:\sqrt{3/4}:\sqrt{3/8}:\sqrt{3/11}$ (BCC)<br>$1:\sqrt{1/2}:\sqrt{1/3}:1/2$ (FCC) |
| | Reversed micelle |  | $1 < v/al$ |  | Sphere | $L_2$ | Isotropic | — |

The formation and structure of a liquid crystal relate to the hydrophilic-lipophilic balance and concentration besides the geometrical factor of an amphiphilic molecule. As shown in Table 30.1, four typical liquid crystalline structures (hexagonal, lamellar, cubic, and reverse hexagonal structures) can be identified. A hydrophilic molecule with a large head group and a tail of small cross-section tends to form a hexagonal liquid crystal in which rod-shaped micelles are packed hexagonally. A balanced molecule in which the cross-sectional area of the polar head group and its tail are almost equal forms a lamellar liquid crystal, whereas a hydrophobic molecule with a small head and large tail tends to form a reversed hexagonal liquid crystal in which rod-shaped reversed micelles are packed hexagonally. Lamellar liquid crystals of slightly hydrophobic molecules tend to form dispersions of concentric lamellae in dilute conditions.

These liquid crystalline structures are estimated from optical textures using microscopy under crossed polarized light (Fig. 30.3). An α-gel is a hydrated crystal and shows a unique optical texture reflecting the layer structure, which is different from liquid crystal in which hydrophobic chains are in a liquid state. A cubic liquid crystal does not show optical anisotropy due to its symmetric configuration. Two types of cubic liquid crystalline structures are known. One is the discontinuous cubic liquid crystal composed of a cubic packing of spherical micelles or reversed micelles ($I_1$, $I_2$ in Table 30.1). The other is the bicontinuous cubic liquid crystal forming an infinite periodic minimal surface (IPMS)[1,9] ($V_1$, $V_2$ in Table 30.1).

The state and structure of liquid crystals and α-gels are determined by X-ray scattering measurements.[10–12] Fig. 30.4 shows the typical X-ray scattering patterns and schematic models of liquid crystal and α-gel. The diffuse halo at around $2\theta = 20$ degree ($d = 4.5$ Å) in wide-angle X-ray diffraction indicates that the lipophilic group is in liquid state owing to the thermal motion (Fig. 30.4A). The sharp peaks in a small angle X-ray scattering curve indicate the formation of a long-range structure. Therefore, "long-range order and short-range disorder" is the strict definition of a lyotropic liquid crystal. The structure is determined from the ratio of the Bragg spacing corresponding to the peaks in the small-angle X-ray scattering spectra. Bragg spacing in a ratio of $1{:}1/2{:}1/3{:}1/4\cdots$ corresponds to the lamellar structure, whereas a ratio $1 : 1/\sqrt{3} : 1/\sqrt{4} : 1/\sqrt{7}\cdots$ indicates the hexagonal or reverse-hexagonal structure (Table 30.1).

When a liquid crystal is cooled to a temperature below Tc, it often changes to an α-gel. Fig. 30.4B shows X-ray scattering patterns and a schematic model of an α-gel. The sharp single peak at 21.5 degree ($d = 4.1$ Å) in wide-

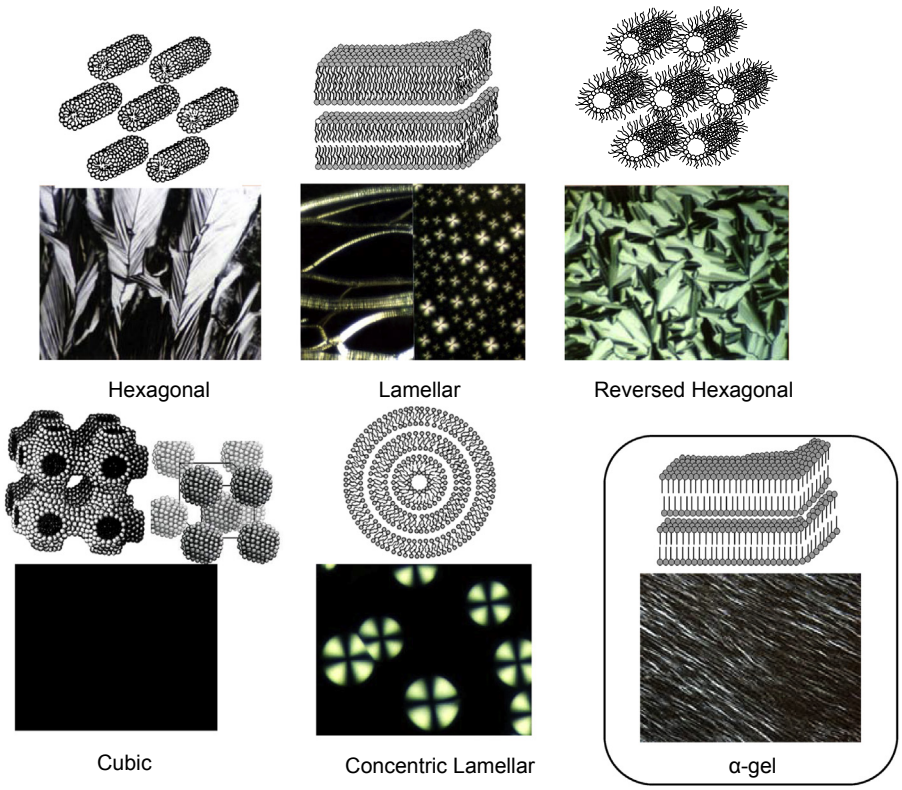



FIGURE 30.3 Typical optical texture of liquid crystals and an α-gel.

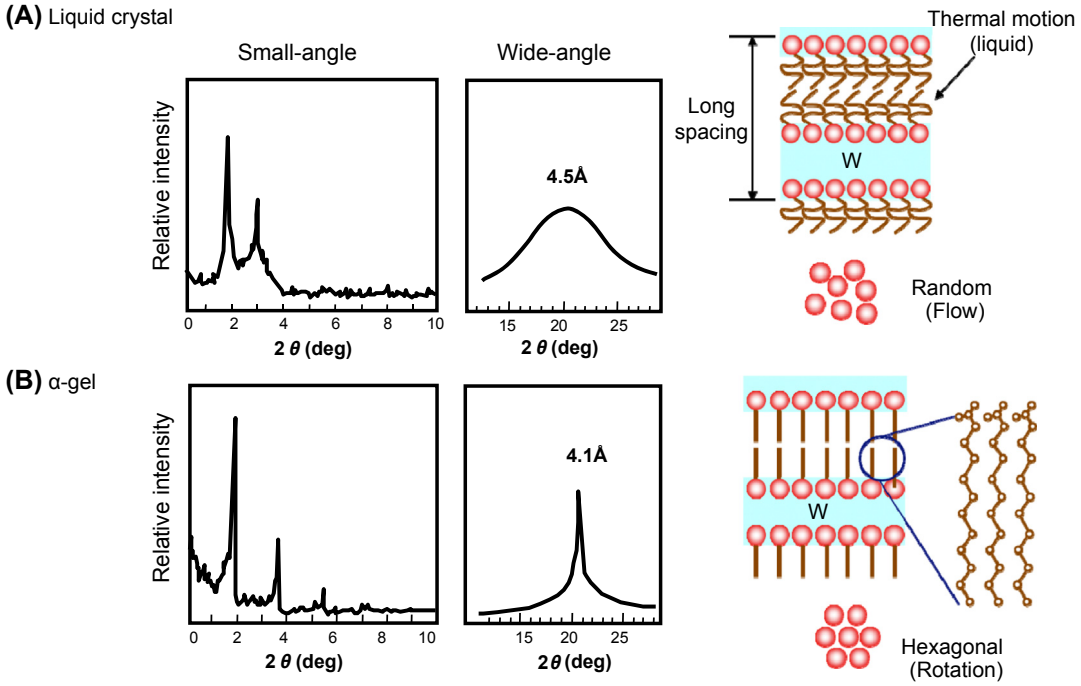



FIGURE 30.4 X-ray diffraction pattern and schematic model of a liquid crystal and an α-gel.

angle X-ray diffraction indicates that the hydrophobic chains in solid state are arranged hexagonally. An α-gel comprises a crystal retaining a large amount of water in the hydrophilic moiety, and it shows free molecular rotation in each layer.[13] However, it does not show a variety of association structures such as liquid crystals.

## 30.3 MOLECULAR ASSEMBLY AND EMULSION

### 30.3.1 Recognition of Liquid Crystal and α-Gel in Cosmetic Emulsions

Fatty alcohols like cetyl and stearyl alcohol are often used for cosmetic emulsions (oil-in-water; O/W type) as the bodying agents, which improve the stability and enhance the viscosity and the consistency. This is due to a physical protection effect of the liquid crystal or gel phase formed in an emulsion.[14–16] Fig. 30.5 shows the state of emulsions composed of nonionic surfactant/fatty alcohol/liquid paraffin/water in the weight ratio of 4/0–4/24/72–68. They are prepared by varying the fatty alcohol content and HLB number of mixed surfactant. O/W emulsions are obtained within the region surrounded by solid lines. Emulsions formed in the region ① are semisolid (cream) whereas fluid emulsions are formed in the region ②. Though the appearance and the microscopic image of these emulsions are identical, emulsions obtained in region ① form secondary droplets, aggregates of emulsion droplets.[17] They are observed by microscopy of the diluted emulsion with water as shown in the picture of Fig. 30.5.

Fig. 30.6 shows the changes in the rheological properties of emulsions owing to the formation of the secondary droplets. Typical flow curves of emulsions formed in the regions ① and ② of Fig. 30.5 are indicated in Fig. 30.6A, and the yield value and viscosity (apparent viscosity at shear rate 400 $s^{-1}$) corresponding to emulsions E1∽E7 are plotted as a function of fatty alcohol content in Fig. 30.6B. It is obvious that the yield value and the viscosity increases remarkably by the formation of secondary droplet emulsion containing more than a certain amount of fatty alcohol. The secondary droplet emulsion enhances the stability against creaming. Though a coarse emulsion is formed in the region ③ where the HLB is not optimum, it shows relatively high-yield value and good stability. As shown in Fig. 30.7, the emulsion possesses a double structure in which oil droplets are surrounded by a translucent optically anisotropic substance.

When an emulsion of region ① was treated by ultracentrifugation at 20,000 G, it separated into three layers of condensed emulsion, water, and lamellar liquid crystal. Based on this fact, the model shown in Fig. 30.8 could be considered.[17] The self-bodying property of the secondary droplet emulsion exhibiting excellent stability against

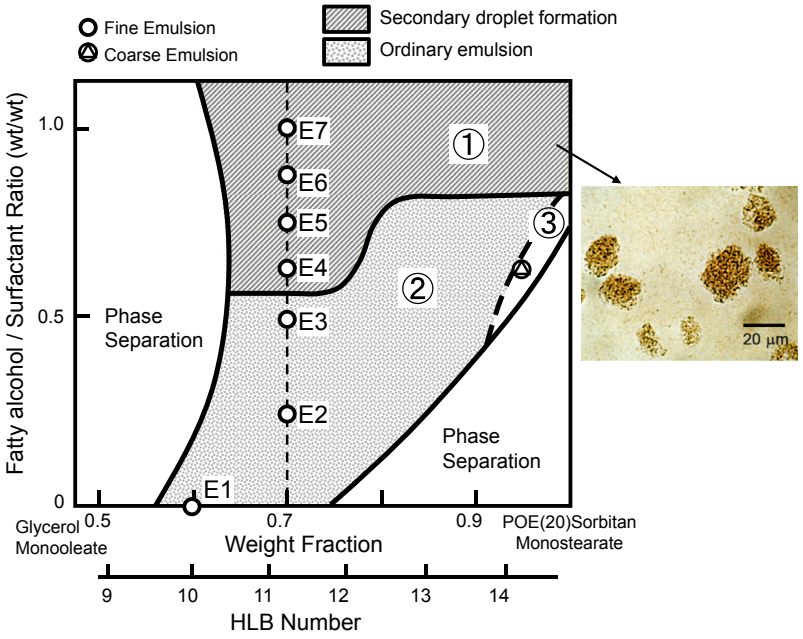



FIGURE 30.5 State of emulsions composed of nonionic surfactant/fatty alcohol/liquid paraffin/water.

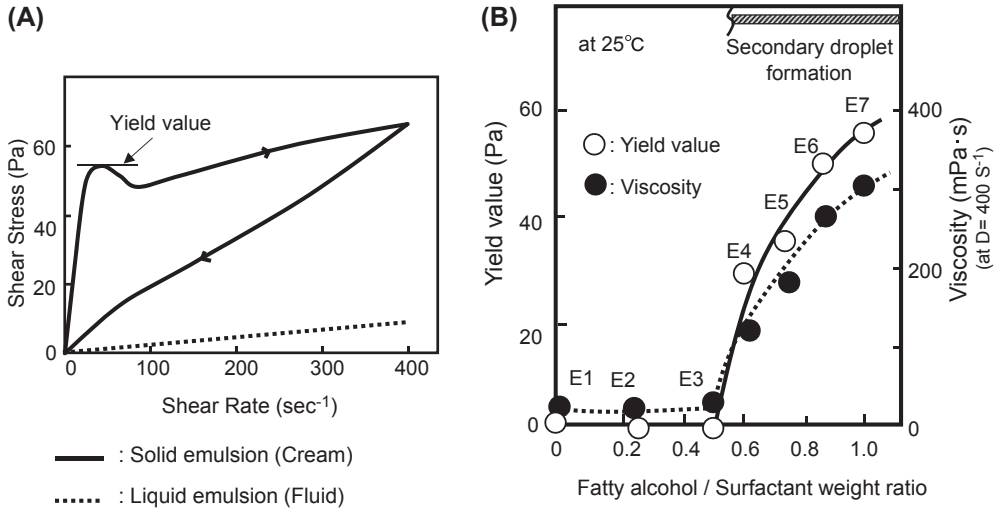



FIGURE 30.6 Flow curve and change in rheology properties of emulsions with secondary droplet formation.

coalescence and creaming is attributed to the formation of a molecular assembly surrounding the emulsion droplets as well as in the continuous phase. The molecular assembly formed in an emulsion was confirmed to be a liquid crystal or an α-gel depending upon the character of the surfactant and the fatty alcohol/surfactant ratio.

## 30.3.2 Significance of Liquid Crystal Formation in Emulsification

Since an emulsion is a thermodynamically unstable system, the state and stability are greatly influenced by the preparation process. In Fig. 30.9, four different preparation processes of an O/W emulsion are indicated by the arrows in the phase diagram of the nonionic surfactant (POE·POP dimethylpolysiloxane)/oil (methyl phenyl polysiloxane)/ethanol/water system. The point marked with a star (☆) corresponds to the composition of the low-viscosity emulsion composed of silicone oil (2 wt%), surfactant (1 wt%), ethanol (12 wt%), and water (85 wt%). In spite of having the same composition, the state of these emulsions is very different. Of these four emulsification

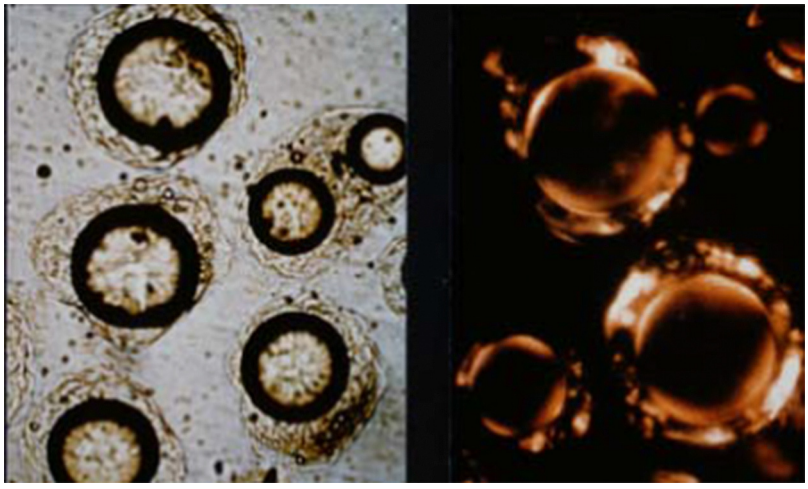



FIGURE 30.7 Emulsion droplets surrounded by optically anisotropic substance.

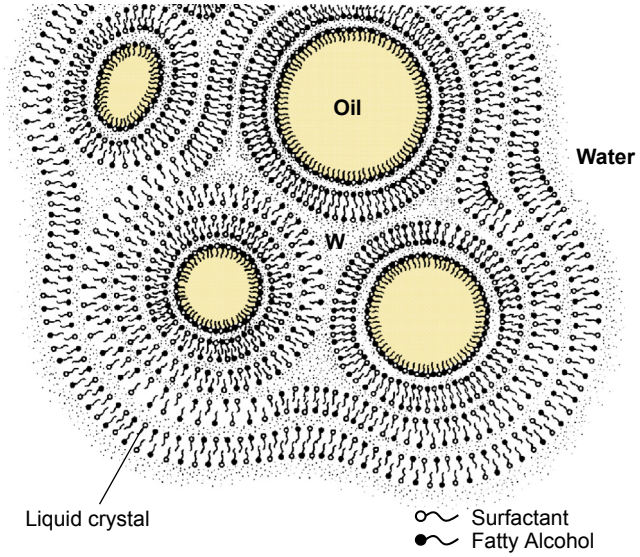



FIGURE 30.8 Schematic model of an O/W emulsion stabilized with a lamellar liquid crystalline phase.

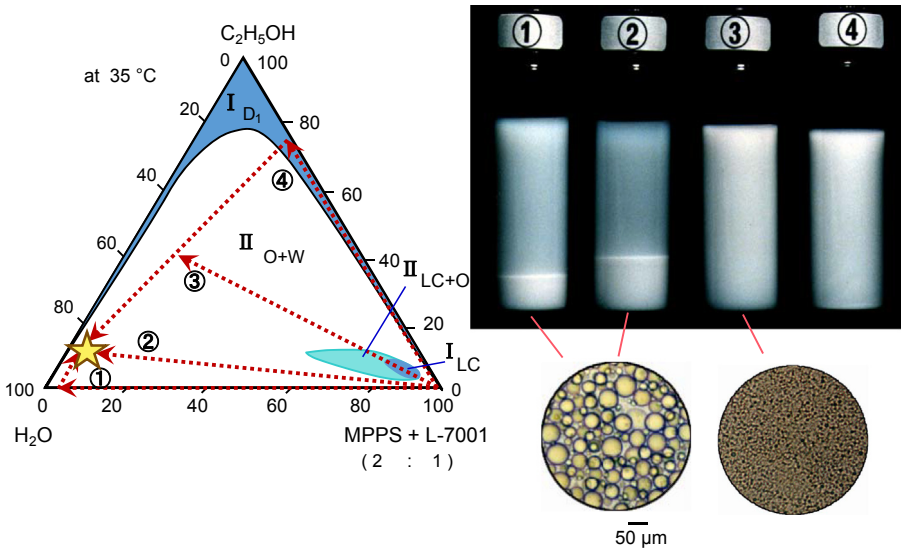



FIGURE 30.9 Emulsification processes indicated in a phase diagram, and state of emulsions after storage at room temperature for one month.

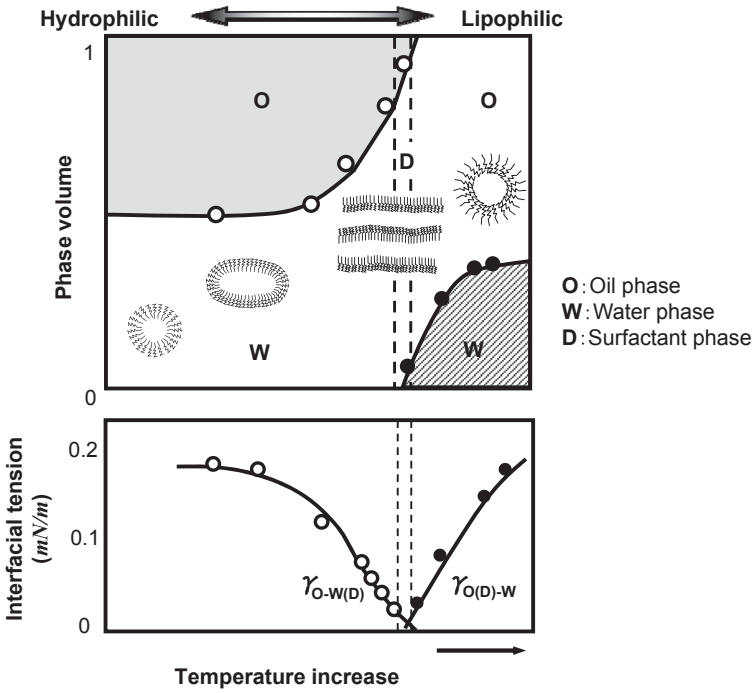



FIGURE 30.10 Changes in the phase state and interfacial tension of surfactant/oil/water system.[19]

processes, only method ③, which passes through the liquid crystal region and the two-phase region of the liquid crystal + oil in the phase diagram, produces a fine emulsion of excellent stability.[18]

The significance of the formation of molecular assemblies like liquid crystal and D-phase during emulsification is supported by Fig. 30.10, which was reported by Shinoda et al., and shows the changes in the phase state and interfacial tension of the water-surfactant-oil system.[19] The hydrophilic-lipophilic balance of a nonionic surfactant is shifted from hydrophilic to lipophilic with increasing temperature. The oil-water interfacial tension decreases dramatically with the formation of infinite aggregates of surfactant molecules under hydrophilic-lipophilic balanced conditions.[19,20] It is possible to prepare a fine emulsion easily by stirring under these conditions. An effective emulsification is accomplished by selecting such optimal conditions.

## 30.4 LIQUID CRYSTAL EMULSIFICATION

### 30.4.1 Preparation of Oil-in-Liquid Crystal Gel Emulsion Using Lamellar Liquid Crystal

Finding the optimum conditions for liquid crystal formation in the emulsification pathway by investigating different variables such as temperature, concentration, and combination of each component is time consuming. To avoid these complicated processes, an emulsification method using a liquid crystal phase was developed.[21,22] In this method, an oil phase is added directly to a lamellar liquid crystalline phase, which is prepared from a surfactant and a portion of the water phase, and is then dispersed by agitation to produce an emulsion.

The key to this emulsification is selecting a surfactant that easily forms a liquid crystalline phase. In general, it is known that hydrophilic-lipophilic balanced, dialkyl-type surfactants tend to form lamellar liquid crystals. Fig. 30.11 shows the phase diagram of β-branched L-arginine hexyldecyl phosphate ($R_6R_{10}$MP-Arg)/water system. Since the phase transition temperature is quite low due to the branched alkyl chain, the major portion of the phase diagram is occupied by lamellar liquid crystalline phase. The lamellar liquid crystal is maintained as a dispersion of concentric lamella even in the diluted system. Based on this result, liquid crystals of L-arginine monoalkyl phosphate were selected as the media for the continuous phase in which oil droplets are dispersed and retained.

As indicated by the flow chart in Fig. 30.12, an oil phase is added directly to a liquid crystalline phase in the initial stage of liquid crystal emulsification. When the major portion of water in the liquid crystal is replaced by a polyol such as glycerol, the oil phase is easily retained in the liquid crystalline phase. Emulsification is achieved in two steps

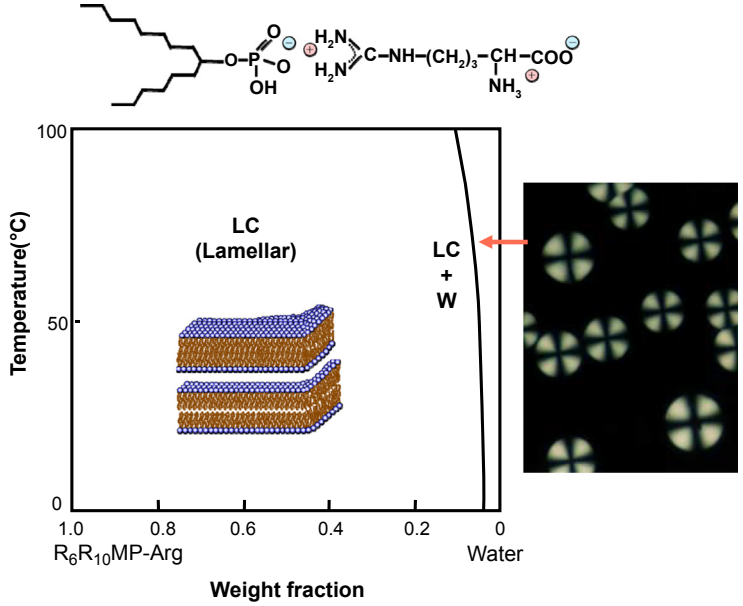



FIGURE 30.11 Phase diagram of β-branched L-arginine hexyldecyl phosphate ($R_6R_{10}$MP-Arg)/water system.

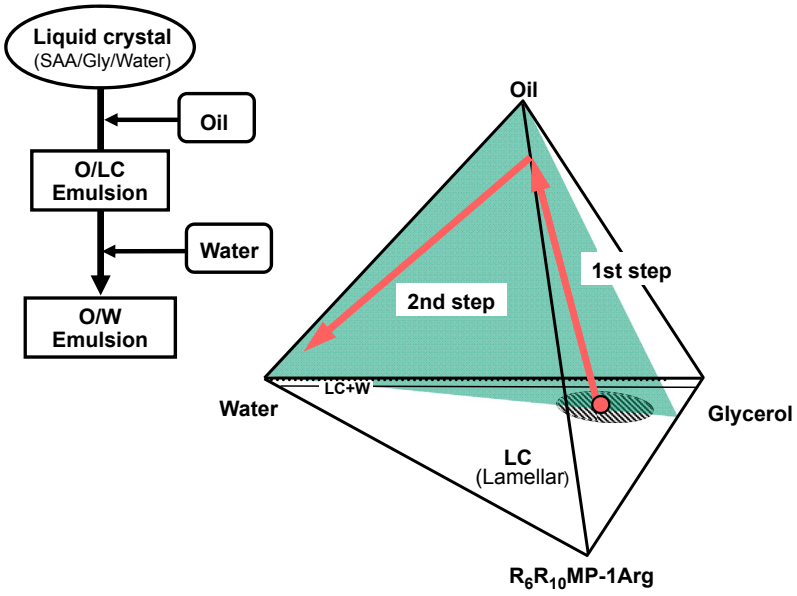



FIGURE 30.12 Process of liquid crystal emulsification.

corresponding to the arrows in Fig. 30.12. In the first step, the oil phase is added and dispersed into the liquid crystalline phase composed of surfactant/glycerol/water to form the gel-like phase. In the second step, water is poured into the gel-like phase to generate an emulsion. The changes in phase state during emulsification are analyzed with a phase diagram (Fig. 30.13) corresponding to the shaded plane in Fig. 30.12 where two arrows exist.

The emulsification starts from a point in the one-phase liquid crystal region in the first step. The composition moves toward the oil apex to form a clear gel. Since the one-phase liquid crystal region is so small, the arrow representing the emulsification process enters into the two-phase region of liquid crystal and oil with addition of a small amount of oil in the initial stage. The pictures in the upper right of Fig. 30.13 show the appearance and the cryo-SEM image of the gel formed in the first step. Though the appearance is transparent and looks homogeneous, closely packed oil droplets are observed in the electron microphotograph. Therefore it is concluded that the gel-like phase is an oil-in-liquid crystal (O/LC) emulsion in which oil droplets are dispersed and retained within

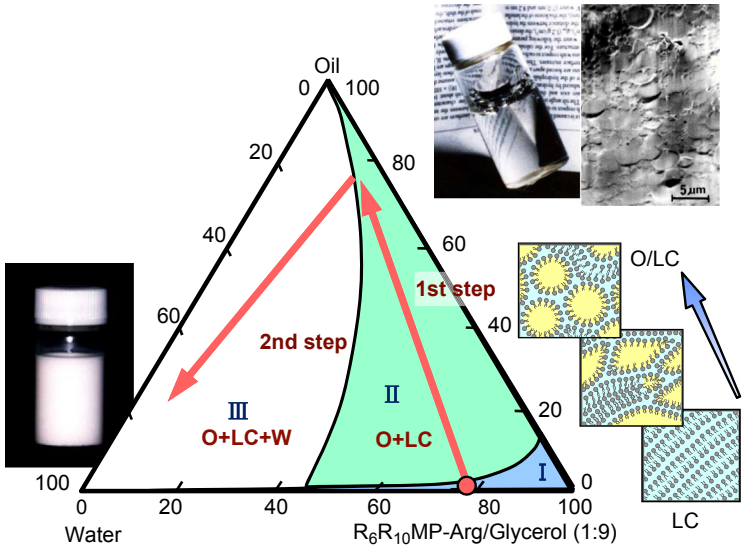



FIGURE 30.13 Process of liquid crystal emulsification indicated in phase diagram.

the liquid crystal, as shown in the schematic model in Fig. 30.13. The transparent appearance of the gel is due to the close refractive indexes of the oil and the continuous liquid crystalline phase composed of water, glycerol, and surfactant. The small one-phase solubilization area suggests that there is little interaction between the oil and the liquid crystalline phase.

### 30.4.2 Formation of Fine Three-Phase Emulsions by Liquid Crystal Emulsification

After preparing a gel-like O/LC emulsion, an O/W emulsion is formed by adding water to the O/LC emulsion in the second step. In this step, gentle stirring with rapid water addition is available as compared with the first step. When the state change of the emulsion is seen along with the arrow of the second step in Fig. 30.13, it changes from the two-phase system of O + LC to the three-phase system of O + LC + W. Therefore it is considered to have generated a three-phase emulsion, in which emulsion droplets are surrounded by liquid crystal and dispersed in the water phase.[21] Since the emulsion droplets are protected by a liquid crystalline shell, the three-phase emulsion shows excellent stability against coalescence.

Emulsification processes, mean droplet diameters, and appearances of emulsions with various oil content are indicated in (A), (B), and (C) of Fig. 30.14, respectively. Numerical values shown in the cap of the sample bottle in the photograph (C) indicate the oil/surfactant weight ratio. Since surfactant molecules effectively orient at the oil/water interface in liquid crystal emulsification, the droplet diameters of emulsions depend mainly on the oil/surfactant ratio and the efficiency of stirring during the formation of O/LC emulsions. Nanoemulsions with a translucent appearance as well as ordinary macroemulsions can be obtained in an identical manner with this type of emulsification.

### 30.4.3 Analysis of the Emulsification Mechanism From the Dynamic Behavior of the Liquid Crystal Membrane

Liquid crystal emulsification is suitable for a wide variety of oils including hydrocarbons, ester oils, triglycerides, and even silicone oils and fluorocarbons.[23,24] This fact suggests that this emulsification is independent of the hydrophilic-lipophilic balance required of oils, and this knowledge saves a lot of the time needed for adjustment to seek the optimal conditions for emulsification. Fig. 30.15 shows the oil retention capacity of 1.0 ml of lamellar liquid crystal composed of $R_6R_{10}$MP-Arg (10 wt%)/aqueous solution of glycerol systems. Gel-like O/LC emulsions are formed with oils of different atomic species, squalane as hydrocarbon, dimethylpolysiloxane as silicone oil, and perfluoropolyether as fluorine oil. Since the specific gravities of the oils are significantly different, the vertical axis is shown with the volume of oils being retained in the O/LC emulsions. The appearances of gels vary from transparent to turbid white according to the differences in the refractive index, but they are all O/LC emulsions. Though the oil retention capacity also varies with oil type, the liquid crystal containing about 60 wt% glycerol exhibits the

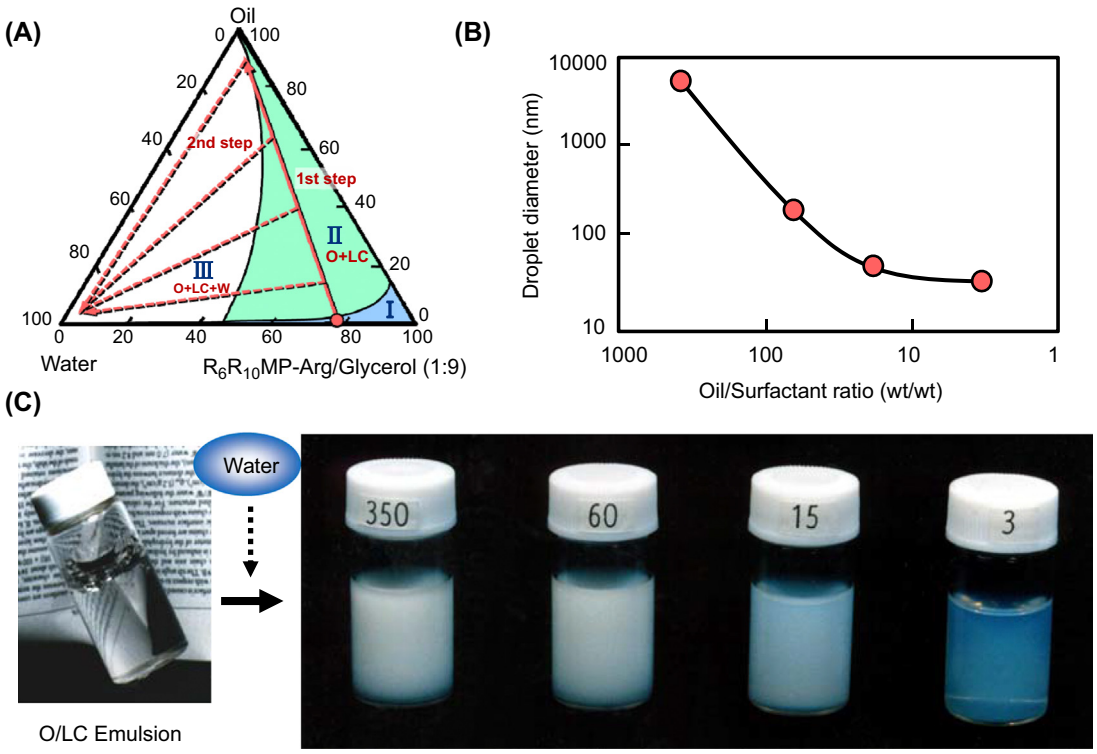



FIGURE 30.14 Mean diameters and appearances of emulsions produced in the second step of the liquid crystal emulsification. (A) Emulsification process of different oil content systems. (B) Relation between oil/surfactant ratio and mean droplet diameter of emulsion. (C) Appearance of emulsions.

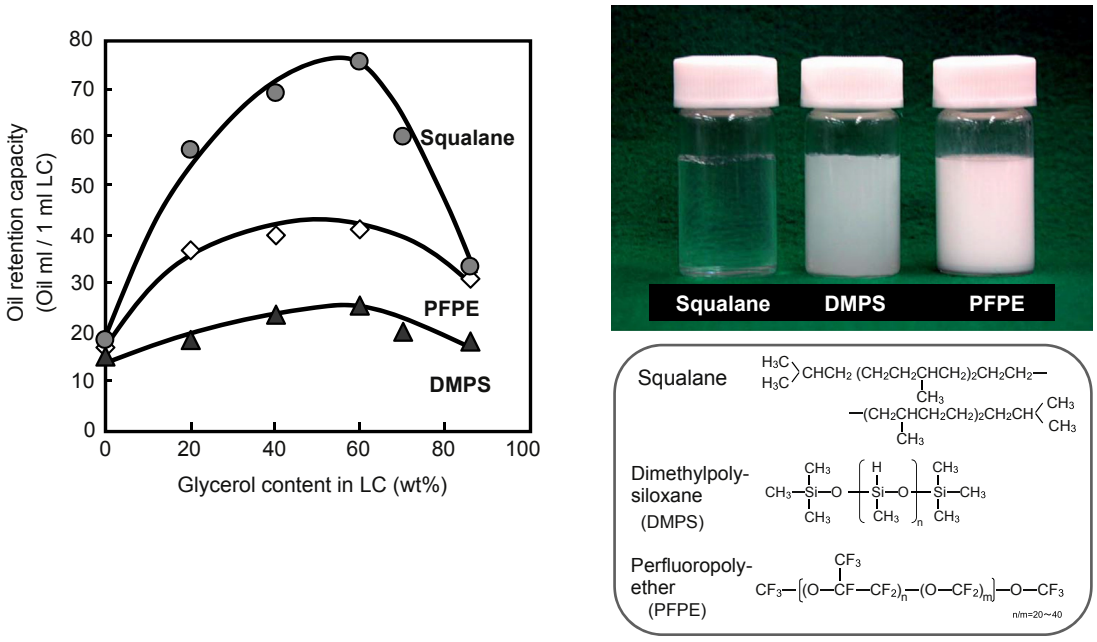



FIGURE 30.15 Oil retention ability of liquid crystal and the appearance of O/LC emulsions for various oils (LC: $R_6R_{10}$MP-Arg 10 wt%).

maximum oil retention ability against all the oils and produces high internal phase emulsions retaining over 95 vol% oils as the dispersed phase.

To clarify the reason for these unique properties of liquid crystal emulsification, the dynamic behavior of the liquid crystalline membrane was analyzed by the spin probe method of electron spin resonance (ESR). Local

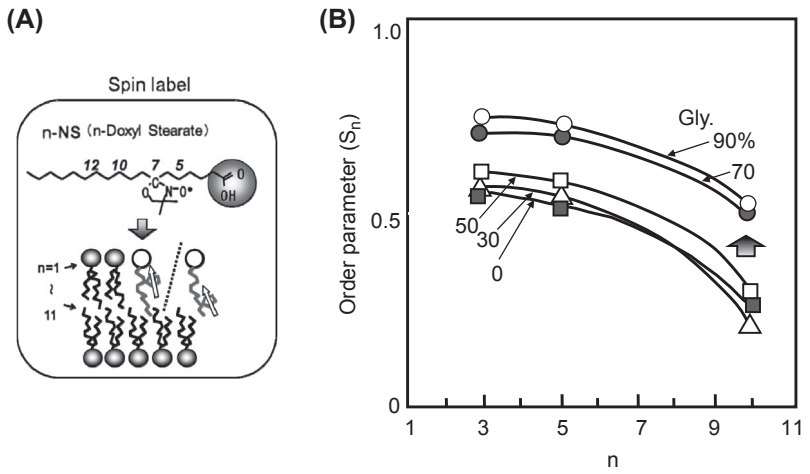



FIGURE 30.16 Electron spin resonance (ESR) analysis of liquid crystals of various glycerol content using fatty acid spin labels. (A) Fatty acid spin label located in liquid crystal membrane. (B) Changes in order parameter as a function of n, position of radical in spin labels, for liquid crystals of different glycerol content.

environment around probes with unpaired electron spins, such as a nitroxide radical, is examined by ESR spectra of the spin probe method. Using a series of fatty acid−type spin labels of different radical position as shown in Fig. 30.16a, the local motility of the alkyl chains in liquid crystal membrane can be analyzed.[25–28] In Fig. 30.16B, the order parameter Sn, which shows the rigidity of the membrane, was plotted as a function of "n" indicating the position of the nitroxide radical away from the hydrophilic end. Sn has a value from 0 to 1, and the closer to 1 means the motility around the probe is suppressed. Sn values decrease with increasing "n" for all the liquid crystals of different glycerol content. This is due to the promotion of molecular mobility of the hydrophobic chains with increasing distance from the polar group. Glycerol does not affect the Sn value of liquid crystals until it is present at 50 wt% in concentration, but the Sn value remarkably increased when the glycerol content exceeds 50 wt%. That is, high-concentrations of glycerol enhance the intermolecular interactions of surfactant molecules by hydrogen bonding, thus stabilizing the gel structure retaining a high amount of oil.

Fig. 30.17 shows the effect of oil addition to the liquid crystal membrane from the viewpoint of changes in Sn values. Interestingly, the Sn curve of O/LC emulsion systems obtained by adding various oils to a liquid crystal are exactly the same as the Sn curve in the liquid crystal system. This means that the state of the liquid crystal membrane is maintained intact in spite of the addition of a variety of oils, and suggests that the liquid crystal membrane

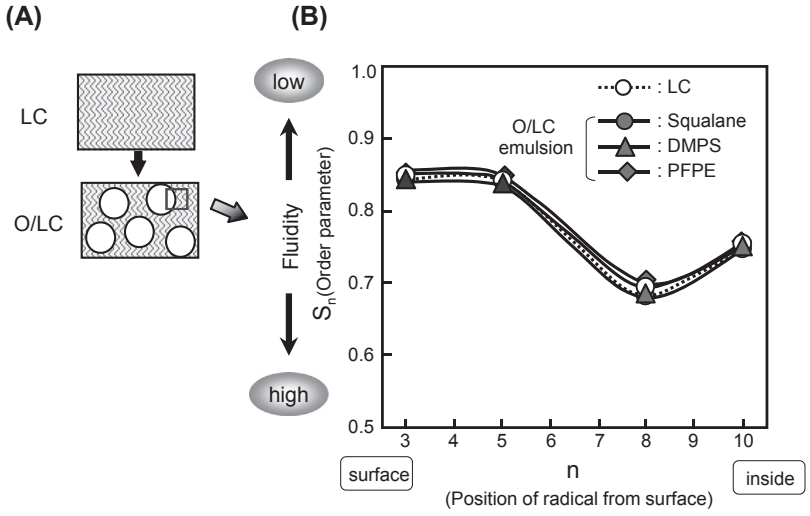



FIGURE 30.17 Analysis of changes in dynamic behavior of liquid crystal membrane with the addition of various oils. (A) Schematic model of O/LC emulsion. (B) Changes in order parameter, Sn, in O/LC emulsions.

exists as an independent phase against oil and water. The unique property of liquid crystal emulsification, which is available for a wide variety of oils, is derived from the independency of liquid crystal membrane as a phase.

## 30.5 APPLICATION OF MOLECULAR ASSEMBLIES TO FUNCTIONAL COSMETICS

### 30.5.1 Stabilization of α-Gel and its Possibility as a New-Type Cosmetic Base

An α-gel retaining a large amount of water between the hydrophilic groups of the crystal forms a layered association structure similar to lamellar liquid crystal. However, since the molecular mobility of α-gel constituent molecules is low as compared with that of liquid crystal component molecules, α-gel cannot be used in the preparation of fine emulsions such as a liquid crystal. On the other hand, α-gel formation in an emulsion is effective for stabilization, control of rheological properties, and water retention of the emulsion. It has also been reported that an α-gel formulation obtained in combination with the pseudo-ceramide and amphiphilic lipids exhibits excellent barrier function as well as high skin moisturizing effect, the same as liquid crystal formulations.[29]

Generally, it is difficult to prepare a stable α-gel system at the application scene, owing to the thermodynamic instability. Under these circumstances, L-arginine hexadecyl phosphate, which forms stable α-gel at below the phase Tc, has been developed and has been attempted to be applied to the emulsions and α-gel formulations.[30,31] The presence of thermodynamically stable α-gel has already been reported for the quaternary ammonium salt−type cationic surfactant/water system. However, it exists only in a very narrow temperature range below Tc.[32]

Fig. 30.18A shows the phase diagram of the $R_{16}$MP-Arg/water system. It exhibits a unique property that forms stable α-gel in all of the regions below the Tc of about 53°C[33]. The preparation of an α-gel is generally performed by heating the mixture of amphiphilic material and water above Tc to form the liquid crystal phase, followed by cooling it below the Tc to produce the so-called supercooled liquid crystal. The α-gel of $R_{16}$MP−Ar/water system is also obtained by an identical process. It is noteworthy that the α-gel of $R_{16}$MP-Arg is formed spontaneously in the condition below the Tc by swelling water without heating it above Tc. This self-swelling behavior has been observed in the temperature range from 0°C to Tc, and the α-gel state was maintained stably even after repeated of freezing and thawing. From this point of view, the α-gel of $R_{16}$MP-Arg/water system is concluded to be thermodynamically stable. The α-gel occupies the whole system until the water content is about 3−4 wt%. In the more dilute system, water phase separates and it coexists with the α-gel phase.

The unique behavior of $R_{16}$MP-Arg to form thermodynamically stable α gel is also maintained in the mixed system with polar lipid-like fatty alcohol. Fig. 30.18B shows the state of $R_{16}$MP-Arg/hexadecanol/water (3/3/94 weight ratio) and $R_{16}$MP-Arg/hexadecanol/monohexadecyl glyceryl ether/water (3/3/1/93 weight ratio) systems prepared at above the melting point of solid polar lipids followed by standing at room temperature for two years. Precipitation of crystals does not occur in both systems, and the α-gel state, which holds a large amount

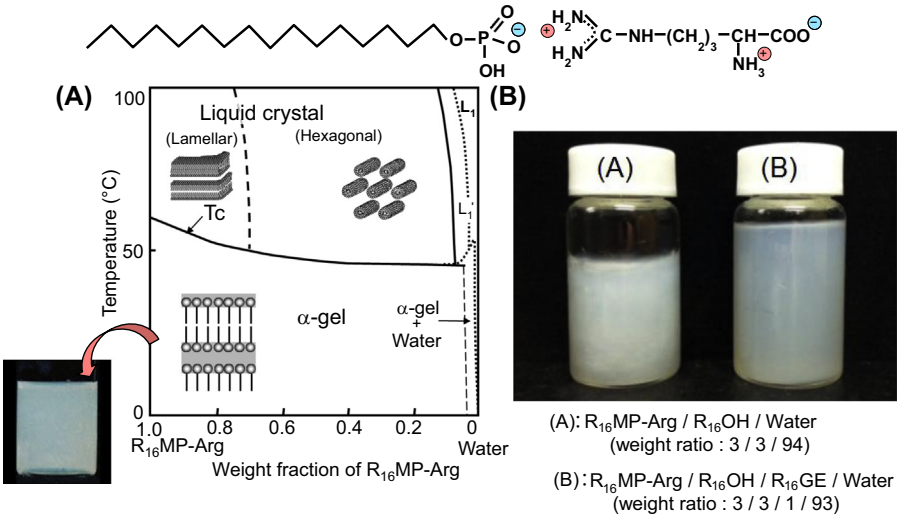



FIGURE 30.18 Phase diagram of L-arginine hexadecyl phosphate/water system and α-gels formed with $R_{16}$MP-Arg/polar lipid/water systems. $R_{16}$OH: Hexadecanol, $R_{16}$GE: Monohexadecyl glyceryl ether.

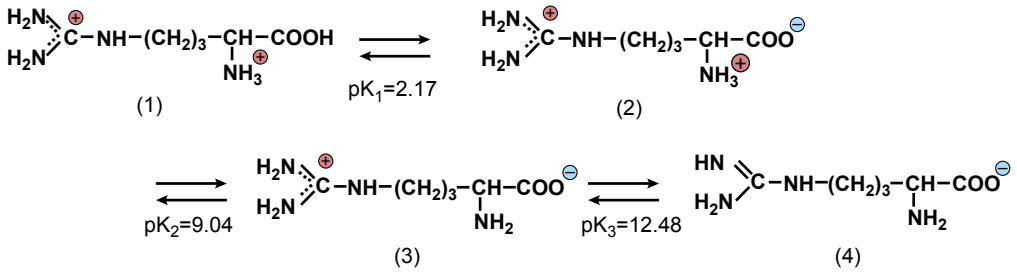



FIGURE 30.19 Dissociation of L-arginine.

of water, is maintained. Fatty alcohol is the optimal polar lipid, which maintains α-gel in combination with R16MP-Arg. For example, hexadecanol/$R_{16}$MP-Arg mixed system maintains stable α-gel at any ratio within the molar ratio from 6/1 to 0/1.

When considering the reason that $R_{16}$MP-Arg forms stable α-gel at the temperature below Tc, the bulkiness and dissociation state of the L-arginine molecule as counterion is thought to exert a big influence. As shown in Fig. 30.19, L-arginine has four different dissociation states. Since the pH value of R16MP-Arg aqueous solution is around 6, three functional groups of L-arginine are dissociating as shown in state (2) of this figure. Of these three dissociation groups, the guanidyl group at the ω-position is the strongest base, and therefore it is attracted close to the phosphate group as a direct counterion of $R_{16}$MP. On the other hand, the amino and carboxyl groups of the amino acid residue in the α position dissociate to form zwitterions. Therefore, it is considered that the strong intermolecular interaction between neighboring molecules enhances the formation and maintenance of infinite molecular assemblies, like liquid crystal or α-gel, while the bulkiness of L-arginine as the counterion suppresses the crystallization of $R_{16}$MP-Arg.

An α-gel, paste-like crystal retaining water exhibits pseudoplastic flow with a yield value in its rheological properties as a consequence of the layered association structure. It exhibits the fresh feeling of solid fat as well as excellent spreadability when applied onto the skin. Furthermore, excellent skin moisturizing effect and barrier function of an α-gel arising from the close packing of the constituent molecules will be expected from its application as a base of skin care cosmetics.

### 30.5.2 Multilamellar Emulsions of Pseudo-Stratum Corneum Lipids

Molecular assemblies are also formed in biological systems such as cell membranes and the intercellular stratum corneum lipids of the human epidermis. Intercellular stratum corneum lipids help to maintain healthy skin by regulating its water-retaining capacity and barrier function.[34,35] Fig. 30.20 shows the composition, transmission electron microscopic (TEM) image, and schematic model of the intercellular stratum corneum lipids. As indicated in the illustration, the amphiphilic stratum corneum lipids retain water within the structure by forming a layered association structure.[11] It was found that the water-holding ability of stratum corneum could be recovered by applying intercellular lipids isolated from healthy stratum corneum by solvent extraction.[36] The use of these lipids as the oil component of cosmetic emulsions is of interest. Currently 11 types of ceramides are known.[37] All of them are rare materials in nature, and therefore substitute lipids such as pseudo-ceramide and similar polar lipids are used as key components of cosmetics. However a lipid possessing a saturated long-chain that includes pseudo-ceramide tends to crystallize without forming a molecular assembly, due to its high crystallinity and high melting point. It is necessary to promote self-organizing ability with inhibition of crystallinity when applied to a formulation. To achieve this, polar lipids of other intercellular lipid components have been introduced to the pseudo-ceramide to enhance the self-organizing ability and stabilize the layered association structure by intermolecular interaction.[4,38]

The state of the lipid mixture can be indicated by a triangle phase diagram with pseudo-ceramide, stearic acid, and cholesterol as the key components, in combination with the X-ray diffraction patterns (Fig. 30.21). The optical texture of a hydrated lipid mixture observed by polarizing microscopy is also shown. It can be seen that the addition of an appropriate amount of fatty acid stabilizes the lamellar structure. When cholesterol is introduced into the mixture of pseudo-ceramide and fatty acid, the melting entropy of the lipid mixture declines markedly with the mixing ratio of cholesterol, and therefore a diffuse halo appears and coexists with a sharp single peak of α-crystal in the wide-angle region of the X-ray diffraction curve. This means that the cholesterol molecule promotes molecular motion of the lipid mixture. As shown in Fig. 30.21, the optical texture of hydrated lipid mixture of pseudo-ceramide/stearic acid/cholesterol indicates the typical Maltese cross mosaic texture, which suggests a lamellar structure. This lipid mixture was applied as an artificial stratum corneum lipid to a formulation of emulsion.

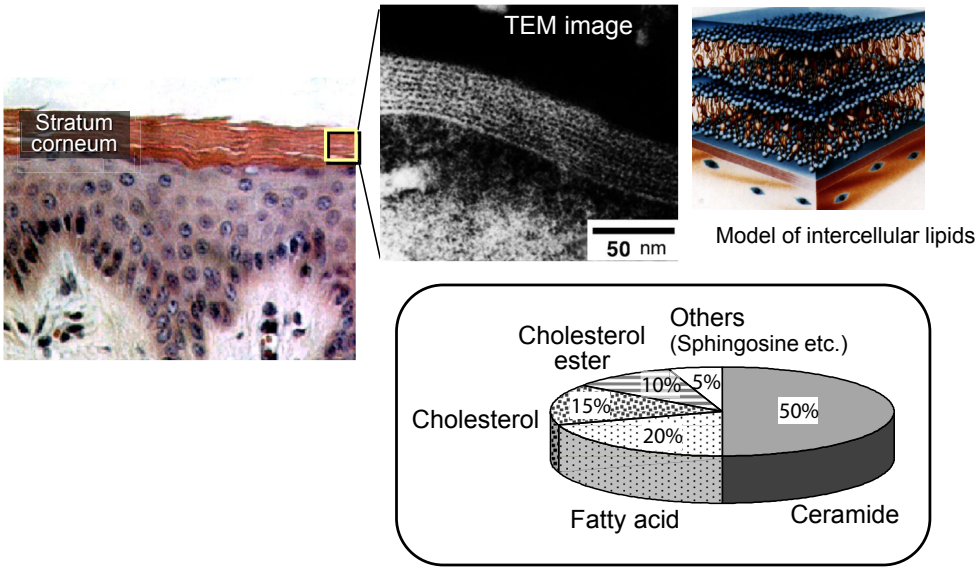



FIGURE 30.20 Composition, TEM image and schematic model of intercellular stratum corneum lipids.

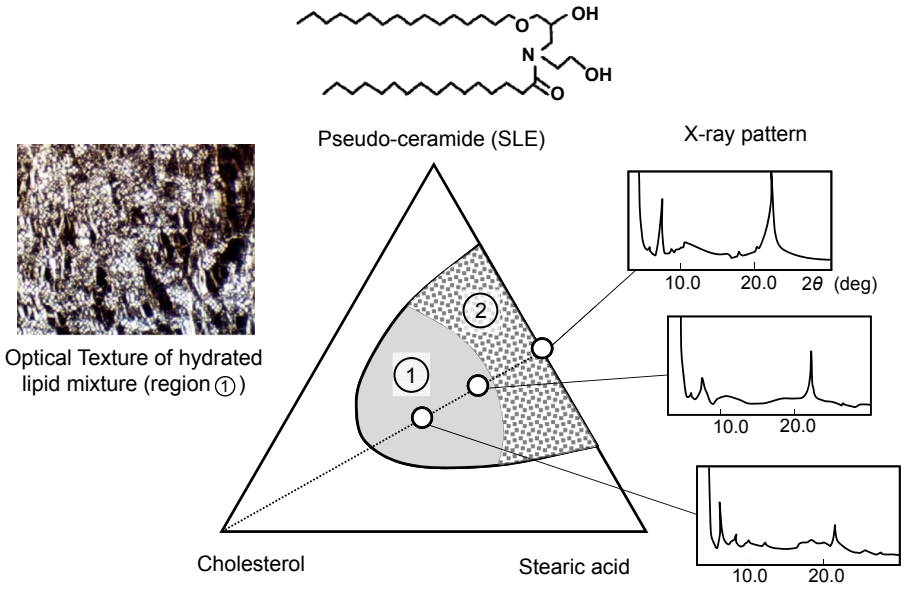



FIGURE 30.21 State of the lipid mixture indicated in a triangle phase diagram composed of pseudo-ceramide, stearic acid, and cholesterol, in combination with the X-ray scattering patterns. Also, optical texture of hydrated lipid mixture in region ①.

A lipid emulsion and a petrolatum emulsion as placebo were prepared by liquid crystal emulsification according to the formulations shown in Table 30.2. Though the appearance of the lipid emulsion containing pseudo-ceramide and polar lipids as the main component is the same as that of an ordinary emulsion, each emulsion droplet possesses optical anisotropy (Fig. 30.22). Fig. 30.23 shows the cryo-SEM image of the lipid emulsion. The formation of a multilamellar structure can be recognized.[38]

When the lipid emulsion was applied to dry and scaly skin, the skin surface conductance, which is the index of water retention capacity of stratum corneum, recovered to the level of healthy skin and the surface texture of skin was improved. Furthermore, the bound water content of stratum corneum was examined by means of DSC measurement using biopsy stratum corneum sheets isolated directly from human forearm skin (Fig. 30.24). Bound water content of the stratum corneum is obtained from the extrapolation of the melting enthalpy (ΔH) plotted against the water content of the stratum corneum sheets stored for one day under different humidity conditions. Fig. 30.25 shows the changes in the amount of bound water of stratum corneum by application of emulsions. Although it is known that the stratum

**TABLE 30.2** Compositions of Multilamellar Lipid Emulsion and Placebo Emulsion

| | **Lipid Emulsion** | **Placebo Emulsion** |
|---|---|---|
| Pseudo-ceramide (SLE) | 10.0 wt% | – |
| Stearic acid | 6.0 | – |
| Cholesterol | 3.0 | – |
| Cholesteryl isostearate | 1.0 | – |
| Petrolatum | – | 20.0 |
| Squalane | 10.0 | 10.0 |
| $R_6R_{10}$MP-Arg | 0.5 | 0.5 |
| Glycerol | 3.0 | 3.0 |
| Water | 66.5 | 66.5 |
| | 100.0 | 100.0 |

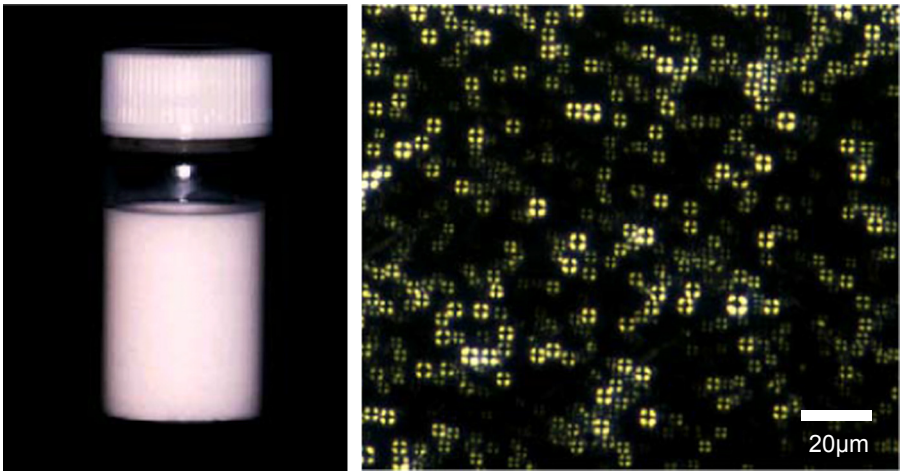



**FIGURE 30.22** Appearance and polarizing microscopic image of lipid emulsion.

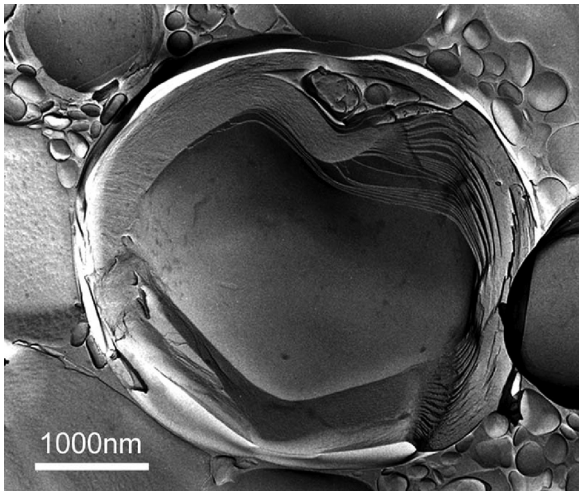



**FIGURE 30.23** Scanning electron microscopic image of lipid emulsion.

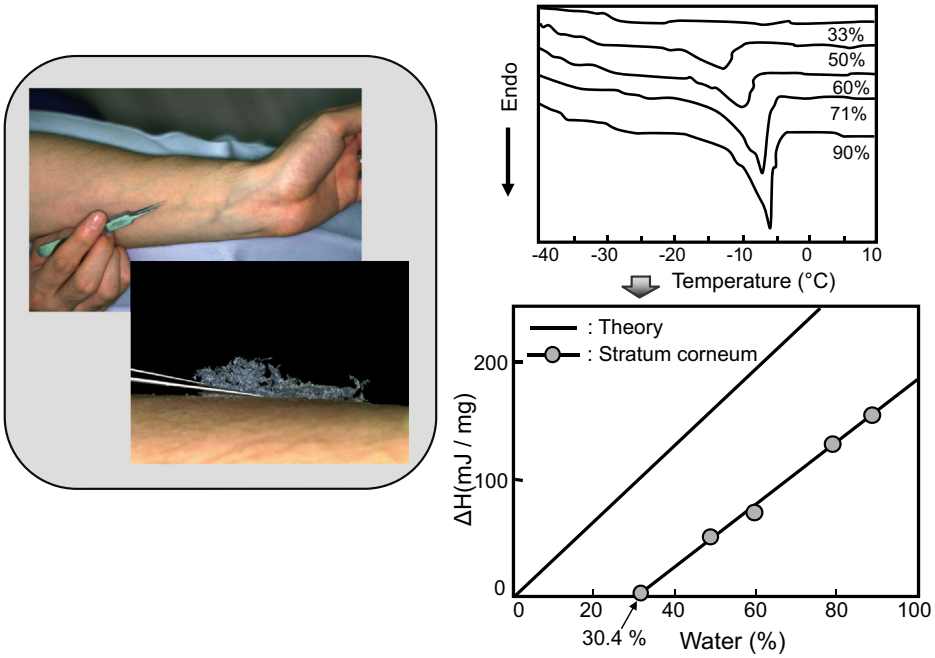



FIGURE 30.24 Isolation of stratum corneum sheet and the measurement of bound water in stratum corneum by DSC.

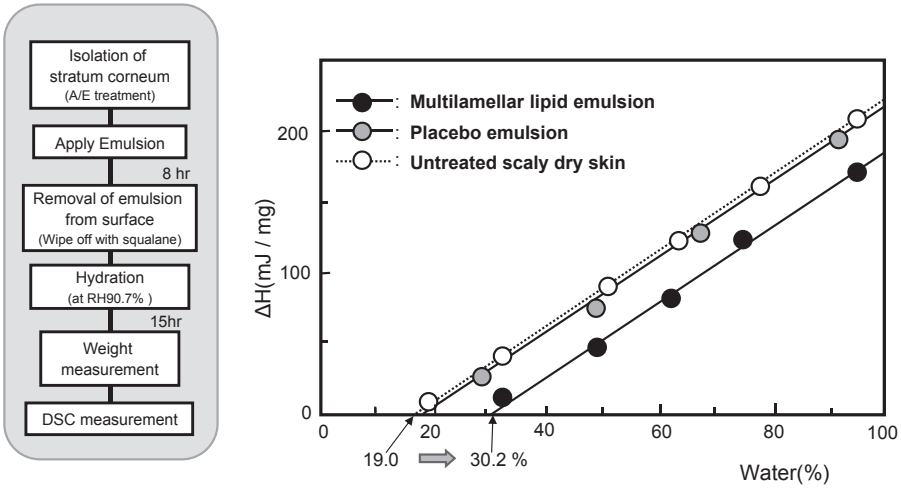



FIGURE 30.25 Changes in the amount of bound water of stratum corneum by application of emulsions.

corneum of healthy skin retains around 30 wt% of water as the bound water, it decreases to about 19 wt% in the dry rough skin prepared by removing the intercellular lipids.[39] The bound water recovered up to the level of healthy skin when dry and scaly skin was treated with a multilamellar lipid emulsion, whereas no remarkable change was recognized when it was treated with the placebo emulsion. This is manifested by the self-organization ability of the oil phase of lipid emulsion, which penetrates into the stratum corneum and retains water within the structure.

Though a vacant space was observed in the TEM image of the intercellular moiety of stratum corneum of rough skin, the reconstruction of the lamellar structure could be recognized after treatment with the lipid emulsion (Fig. 30.26). The multilamellar emulsion supplements the physiological function of the stratum corneum by the same mechanism as the natural intercellular lipids.

## 30.6 CONCLUSIONS

Gel-like O/LC emulsions are formed by dispersing oil phase into a lamellar liquid crystalline phase composed of double-chain-type surfactant/glycerol/water under stirring. When the O/LC emulsions are diluted with water with

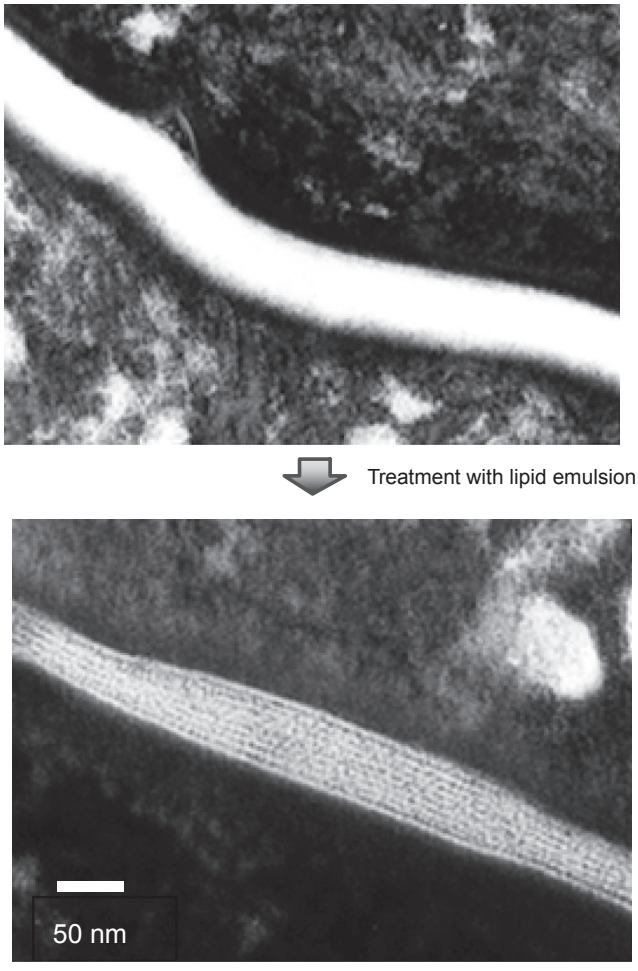



**FIGURE 30.26** Reconstruction of lamellar structure by the treatment of lipid emulsion.

gentle stirring, fine O/W emulsions can be generated easily. From the phase study and analysis of dynamic local molecular motion of the liquid crystal membrane, the characteristic behavior is concluded to be attributed to the independency of the liquid crystalline phase, which scarcely interacts with either oil or water phases.

An α-gel cannot be used in the preparation of fine emulsions because of the low molecular mobility of its constituent molecules, whereas it contributes to the stabilization of emulsions and to gel formation identically to a liquid crystal. It also exhibits excellent barrier function when applied to the skin by providing close molecular packing.

Liquid crystals and α-gels, infinite aggregates of amphiphilic molecules, are effective for the enhancement of moisturizing function as well as for the formation and stabilization of emulsions.

## References

1. Hassn S, Rowe E, Tiddy GJT. Surfactant liquid crystals. In: Holmberg K, Shah DO, Schwuger MJ, editors. *Handbook of applied surface and colloid chem.* John Wiley & Sons Ltd.; 2002. p. 465–508 [Chapter 21].
2. Friberg S, Jansson PO, Cederberg E. Surfactant association structure and emulsion stability. *J Colloid Interface Sci* 1976;**55**:614–23.
3. Friberg S, Solans C. Surfactant association structures and the stability of emulsions and forms. *Langmuir* 1986;**2**:121–6.
4. Suzuki T, Fukasawa J, Iwai H, Sugai I, Yamashita O, Kawamata A. Multilamellar emulsion of stratum corneum lipid; formation mechanism and its skin care effects. In: *Proc. 17th IFSCC Congress Yokohama*, vol. 1; 1992. p. 3–28.
5. Iwai H, Fukasawa J, Suzuki T. A liquid crystal application in skin care cosmetics. *Int J Cosmet Sci* 1998;**20**(2):87–102.
6. Hyde ST. Identification of lyotropic liquid crystalline mesophases. In: Hormberg K, editor. *Handbook of applied surface and colloid chemistry*, vol. 2. Chichester: John Wiley & Sons; 2002. p. 299–332 [Chapter 16].
7. Israelachvili JN, Mitchell DJ, Ninham B. Theory of self-assembly of hydrocarbon amphiphiles into micelles and bilayers. *J Chem Soc Faraday Trans* 1976;**2**(72):1525–68.
8. Israelachvili JN. The science and applications of emulsions – an overview. *Colloids Surf A Physicochem Eng Asp* 1994;**91**:1–8.
9. Jonsson B, Lindman B, Holmberg K, Kronberg B. *Surfactants and polymers in aqueous solution*. New York: Wiley; 1998 [Chapter 3].

10. Luzzati V. In: Chapman D, editor. *Biological membranes*. London and New York: Academic Press; 1968. p. 71–123 [Chapter 3].
11. Fontell K. X-ray diffraction by liquid crystals and amphiphilic systems. In: Gray GW, Winsor PA, editors. *Liquid crystals and plastic crystals*, vol. 2. Ellis Horwood; 1974. p. 80–109 [Chapter 4].
12. Bouwstra JA, Gooris GS, van der Spek JA, Bras W. The structure of human stratum corneum as determined by small angle X-ray scattering. *J Invest Dermatol* 1991;**96**:1006–14.
13. Larsson K, Krog N. Structural properties of the lipid—water gel phase. *Chem Phys Lipids* 1973;**10**(2):177–80. North-Holland Publ. Co.
14. Barry BW. Rheology of emulsions stabilized by sodium dodecyl sulfate/long-chain alcohols. *J Colloid Interface Sci* 1970;**32**:551–60.
15. Fukushima S, Takahashi M, Yamaguchi M. Effect of cetostearyl alcohol on stabilization of oil-in-water emulsion I., Difference in the effect by mixing cetyl alcohol with stearyl alcohol. *J Colloid Interface Sci* 1976;**57**:201–5.
16. Fukushima S, Yamaguchi M, Harusawa F. Effect of cetostearyl alcohol on stabilization of oil-in-water emulsion II., Relation between crystal form of the alcohol and stability of the emulsion. *J Colloid Interface Sci* 1977;**59**:159–65.
17. Suzuki T, Tsutsumi H, Ishida A. Secondary droplets formed in 0/W emulsion; formation mechanism and effects of their formation on the properties of emulsion. *J Chem Soc Jpn* 1983;(3):337–44. Suzuki T, Tsutsumi H, Ishida A. Secondary droplet emulsion; effects of liquid crystal formation in O/W emulsion. *J Dispersion Sci Technol* 1984;**5**:119–41.
18. Suzuki T, Kai M, Ishida A. Formation mechanism of stable low viscous O/W emulsions containing ethanol; influence of ethanol concentration during emulsification. *Yukagaku* 1985;**34**(11):938–45. Suzuki T. Emulsions and gels. In: Ohshima H, Furusawa K, editors. *Electrical phenomena at interfaces*. New York: Marcel Dekker Inc.; 1998. p. 553–68 [Chapter 29].
19. Saito H, Shinoda K. The stability of W/O type emulsions as a function of temperature and of the hydrophilic chain length of the emulsifier. *J Colloid Interface Sci* 1970;**32**:647–51.
20. Solans C, Pons R, Kunieda H. Overview of basic aspects of microemulsions. In: Solans C, Kunieda H, editors. *Industrial application of microemulsions*. New York: Marcel Dekker; 1997. p. 1–19.
21. Suzuki T, Takei H, Yamazaki S. Formation of fine three-phase emulsions by liquid crystal emulsification method with arginine β-branched monoalkyl phosphate. *J Colloid Interface Sci* 1989;**129**:491–500.
22. Suzuki T, Iwai H. Formation of lipid emulsions and clear gels by liquid crystal emulsification. *IFSCC Mag* 2006;**9**(3):183–94.
23. Suzuki T, Yoda K, Iwai H, Fukuda K, Hotta H. Multiphase emulsions by liquid crystal emulsification and their application. *Stud Surf Sci Catal* 2001;**132**:1025–30 (Proc. International Conference on Colloid and Surface Science, 25th Anniversary of the Division of Colloid and Surface Chemistry, The Chemical Society of Japan Tokyo, Japan).
24. Yoda K, Shibata M, Suzuki T. Multiphase emulsions by liquid crystal emulsification and Their Application. *J Jpn Soc Color Mater* 2004;**77**(7): 309–13.
25. Berliner LJ. *Spin labeling: theory and applications*, vol. 1. New York and London: Academic Press; 1976.
26. Hubbell WL, McConnell HM. Molecular motion in spin-labeled phospholipids and membranes. *J Am Chem Soc* 1971;**93**(2):314–26.
27. Tajima K, Imai Y, Horiuchi T, Koshinuma M, Nakamura A. ESR study on DMPC and DMPG bilayers in the ($L_\alpha + H_2O$) phase. *Langmuir* 1996; **12**:6651.
28. Shioya Y, Suzuki Y, Tsutsumi H. Electron spin resonance study on the orientation of 5-doxyl stearic acid in water-in-oil emulsion. *J Jpn Oil Chem Soc (Yukagaku)* 1995;**44**:16–22.
29. Orita M, Uchiyama M, Hanamoto T, Yamashita O, Naitou S, Takeuchi K, et al. Formation of pseudo-intercellular lipids membrane on the skin surface by the alpha-gel holding a large amount of water. *J SCCJ* 2012;**46**(1):25–32.
30. Suzuki T. Progress in emulsion technology, particularly gel-emulsions. *Fragr J* 2014;(10):12–20. No. 412.
31. Tanaka K, Suzuki T. The unique self-assembling behavior of highly purified long chain mono alkyl phosphate salt. *Oleo Sci* 2015;**15**(1):5–10.
32. Kodama M, Seki S. Thermoanalytical investigation on the *coagel-gel*-liquid crystal transition in some water-amphiphile systems. *Prog Colloid Polym Sci* 1983;**68**:158–62.
33. Suzuki T, Takei H. Solution behavior and the association structures of long-chain monoalkyl phosphates. *J Chem Soc Jpn* 1986;(5):633–40.
34. Elias PM. Lipids and the epidermal permeability barrier. *Arch Dermatol Res* 1981;**270**:95–117.
35. Lampe MA, Burlingame AL, Whitney J, Williams MI, Brown BE, Roitman E, et al. Human stratum corneum lipids; characterization and regional variations. *J Lipid Res* 1983;**24**:120–30.
36. Imokawa G, Hattori M. A possible function of structural lipids in the water-holding properties of the stratum corneum. *J Invest Dermatol* 1985; **84**:282–4.
37. Masukawa Y, et al. Characterization of overall ceramide species in human stratum corneum. *J Lipid Res* 2008;**49**(7):1466–76.
38. Suzuki T, Imokawa G, Kawamata A. Development of synthetic ceramide-based biomimetic skin care products. *J Chem Soc Jpn* 1993;(10): 1107–17.
39. Imokawa G, Kuno H, Kawai M. Stratum corneum lipids serve as a bound-water modulator. *J Invest Dermatol* 1991;**96**:845–51.

CHAPTER

# 31

# Liposomes for Cosmetics

*T. Himeno, Y. Konno, N. Naito*
**KOSÉ Corporation, Tokyo, Japan**

## 31.1 INTRODUCTION

Phospholipids are biologically derived substances that have high affinity to the skin and are safe to use; they have high functionality and thus are widely used in cosmetics. When phospholipids are dispersed in aqueous solutions, they create liposomes, which are microcapsule-like closed vesicles that encapsulate the water phase. Liposomes are believed to be highly effective percutaneous absorbents because they have high permeability and storability on the outermost layer of the skin, or the stratum corneum, and have many effects such as improving the low affinity of slightly soluble active components or chemical agents to the skin. Further, liposomes can be designed to encapsulate a wide variety of substances depending on the specific purpose, and there are many studies on such use of liposomes. The number of published reports on liposomes is increasing yearly; some examples of prominent research areas are for use as biomembrane models, application as microcapsules, applications to genetic engineering, and applications for artificial red blood cells. One of the most active studies on liposomes involves their application as drug-delivery systems (DDSs) in the medical field. There are also many studies on liposomes in the world of cosmetics, including research for application as topical agents[1,2] or for safety evaluation research as artificial biomembranes such as ocular–mucus membrane models.[3]

In this chapter, we discuss the physiochemical properties of phospholipids that are the precursor of liposomes and we study liposomes in cosmetics through examples of pharmaceutical formulation methods and research on their effectiveness.

## 31.2 PROPERTY OF PHOSPHOLIPIDS

Phospholipids are commonly found in the natural world as a component of biomembranes. For ingredients that are used for application, soybeans are commonly used as a botanical base material and egg yolk is used as an animal-derived base material. Soy phospholipids are cost efficient and can be acquired in large quantities, and egg yolk phospholipids have a relatively large content of phosphatidylcholine (PC) that shows emulsification effects. Natural phospholipids have unsaturated fatty acid groups and can lead to problems with storage stability due to oxidation and other reasons. However, cosmetics must have a long shelf life in a wide temperature range (based on room temperature) to maintain their stability in various situations such as the use environment of consumers or in-store shelf storage conditions. Thus, it is vital to maintain the stability of phospholipids when applied to cosmetics; they must have oxidation stability and inhibit both physical change (i.e., condensation, sedimentation) and chemical change (i.e., color change, smell change, lipid decomposition) in aqueous solutions.

Let's take a look at the oxidation stability of phospholipids. The pH decrease of phospholipid-dispersed solutions is mainly induced by oxidation of the phospholipid. The stability against oxidation must be maintained by using highly hydrogenated and unsaturated fatty acids with a low peroxide value (Fig. 31.1). In other words, highly hydrogenated phospholipids are chemically stable against oxygen, heat, or light, and they should be chosen when using natural phospholipids for cosmetics. Although the stability differs among phospholipids, they should be carefully chosen because they are strongly affected by various factors, such as electrically charged substances that influence their hydrolysis or surfactants that break the membrane by desorption and adsorption.

*Cosmetic Science and Technology: Theoretical Principles and Applications*
http://dx.doi.org/10.1016/B978-0-12-802005-0.00031-8

Copyright © 2017 Elsevier Inc. All rights reserved.

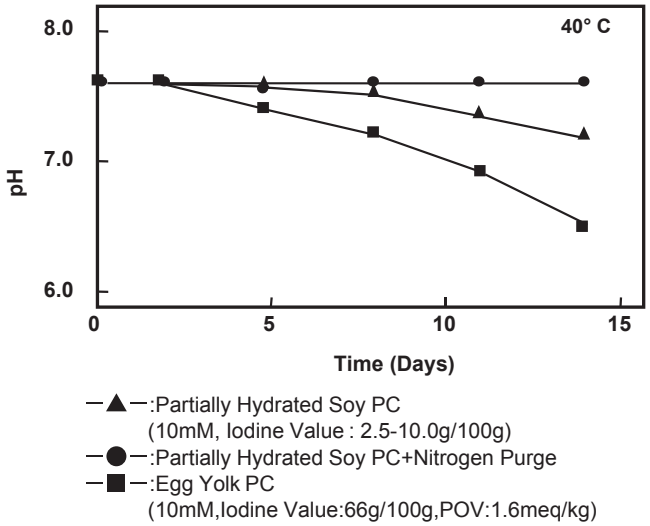



**FIGURE 31.1** pH change of liposome solutions.

An important characteristic that makes liposomes preferable in cosmetics is that liposome-composing phospholipids independently have moisture-retaining properties. One of the main components of phospholipids, PC, can hydrate 10 water molecules per PC molecule and create lamellar liquid crystals. Reports on the effect of the caloric value against the water content in distearoyl phosphatidylcholine using differential scanning calorimetry showed that with phospholipids, 20% bound water (w/w) was found,[4] indicating that phospholipids themselves are effective as moisturizing materials. Further, studies on the skin softening effect of the moisture-retaining property of phospholipids[5] showed that phospholipid-added systems had higher skin-softening effects and that these effects were sustained compared with the use of glycerin.

## 31.3 LIPOSOMES

In the mid-1960s, Alec Bangham of the United Kingdom isolated biomembrane-composing phospholipids and found that they create closed vesicles when dispersed in water.[6,7] These vesicles made from phospholipids were named liposomes, derived from the terms *lipo* for "fats" and *soma* for "cellular bodies." Bimolecular membrane capsules are called "vesicles" in general, and other than phospholipids, nonionic surfactants and unsaturated fatty acids are also known as molecules that form vesicles. These composing molecules usually have a cylindrical structure with balanced lipophilic and hydrophilic groups and often form liquid crystals or gel structures in water.

In the 1980s, liposome-like cosmetics came into production in European and American markets. It is likely that these products were developed because liposome formulas are made of biologically derived phospholipids and had many potential advantages in cosmetics. However, most of these products merely added liposome-like suspensions to generic cosmetics; the phospholipids were roughly refined, and few maintained liposome structures.

Under similar circumstances in Japan, the possibility of inducting cutaneous absorption was reported, and a regulatory standard became necessary to ensure the safety and stability of liposome products. To meet these demands, the Ministry of Health and Welfare of Japan set an approval standard for liposome products.[8] Kose launched the Cosme Decorde skin toner in 1992, which was the first product to clear these standards.

## 31.4 LIPOSOME FORMATION CONDITIONS

Liposome formation conditions are based on general vesicle formation theory. Surfactants are one of vesicles' component substances; when they dissolve in aqueous solutions, the molecules align at the oil—water interface with the hydrophilic groups facing toward the water phase and the lipophilic groups facing toward the oil phase. They can disperse as single molecules, or monomers, in the water phase, but due to their amphiphilic property, the solubility in aqueous solutions as monomers is extremely low compared with that of other hydrophilic substances.

When the surface excess concentration saturates, the surfactant molecules do not disperse with concentration increases like other molecules but instead form molecular associations called "micelles." Micelles are self-organized aggregations of surfactant molecules in which the hydrophilic group faces the water (outward) and the hydrophobic group faces inward. The concentration at which this micelle formation occurs is called critical micelle concentration. When the concentration increases even higher, surfactants form various self-organizing structures.

The critical packing parameter (CPP) is an important parameter that shows the relationship of the molecular structure and self-organizing structures of surfactants. CPP can be calculated from the following formula, which was first proposed by Israelachvili et al.[9]

$$\mathrm{CPP} = \frac{V_L}{a_s \cdot l} \tag{31.1}$$

where $V_L$ is the exclusive area of the molecule in self-organization, $l$ is the length of the hydrophobic group in self-organization, and $a_s$ is the effective cross-sectional area of the hydrophobic group−hydrophilic group interface. CPP shows a higher value when the hydrophobic property is higher. CPP is a parameter that shows the curvature of the self-organization, where the curvature is negative at $\mathrm{CPP} > 1$, the curvature is positive at $\mathrm{CPP} < 1$, and the surfactant forms a bimolecular membrane lamellar structure at $\mathrm{CPP} = 1$. As the bimolecular sheet grows larger, the interface tension leads to a larger loss of energy. The linear energy of edge of the bimolecular membrane disk is calculated by

$$E_{disk} = 2\pi R_D \gamma \tag{31.2}$$

where $R_D$ is the disk radius and $\gamma$ is the line tension. To supply the lost energy, the bilayer molecule sheet closes into a shell and forms a vesicle. When the vesicle is formed, elastic energy

$$E_{bend} = 8\pi\kappa \tag{31.3}$$

is generated, where $\kappa$ is the elastic modulus. When the elastic energy $E_{bend}$ is smaller than the linear energy $E_{disk}$, the disk bends to form a vesicle. The minimum radius of this formation is

$$R_D = \frac{4\kappa}{\gamma} \tag{31.4}$$

If the disk area and vesicle surface area are the same, the radius of the vesicle $R_V$ is

$$R_V = \frac{2\kappa}{\gamma} \tag{31.5}$$

As such, vesicles are easily formed when the elastic modulus of the bimolecular membrane is low and the interface tension is high. This is how unilamellar vesicles formed from a single bimolecular membrane or multilamellar vesicles with multiple concentric vesicles are formed.

## 31.5 MORPHOLOGY OF LIPOSOMES

Phospholipids are used for applications other than liposomes, such as DDS formulations like fat emulsions (lipid microspheres). Fat emulsions are oil-in-water emulsions, and phospholipids are used to finely disperse the lipids in an aqueous solvent. These formulations preserve lipids and lipid agents in droplets and do not encapsulate water-soluble substances or moisturizers like liposomes.

On the contrary, liposomes can encapsulate water-soluble substances and can hold lipophilic or slightly soluble substances on their bimolecular membrane or surface membrane. Further, functions such as pH, ion, or enzyme-reacting functions can be added to by adding sugars or electrically charged substances to the membrane. The morphological classification of liposomes is shown in Table 36.1. When liposomes are used for base materials in cosmetics, they must have a certain capacity for holding chemical agents in the inner water phase and have long shelf life stability in a wide range of temperatures based on room temperature. Large unilamellar vesicles and giant unilamellar vesicles have an inclusion rate of 35−65% and are effective to hold high concentrated soluble active ingredients.[10] On the contrary, small unilamellar vesicles have an inclusion rate of only 0.5−1.0%. Unilamellar liposomes are more appropriate when using liposomes for medical topical agents because all of the encapsulated substances are released when the membrane breaks, but multilamellar liposomes are more appropriate in cosmetics due to their structural stability. As such, liposomes should be chosen based on their structure depending on the application; for cosmetic use, relatively small multilamellar liposomes are presumably the most appropriate because they do not

**TABLE 36.1** Classification of Liposomes by Morphology

| | |
|---|---|
| Multilammellar Liposome [Size: 0.1-several μm] | Multilammellar Liposome (multilamellar vesicle; MLV) |
| | Oligolamellar Liposomes (oligolamellar vesicle; OLV) |
| | Multivesicular Liposomes (multivesicular liposome) |
| Unilamellar Liposomes | Small Unilamellar Liposomes [Size: 0.02 - 0.1μm] (small unilamellar vesicle; SUV) |
| | Large Unilamellar Liposomes [Size: 0.1 - 1.0μm] (large unilamellar vesicle; LUV) |
| | Giant Unilamellar Liposomes [Size: At Least Several μm] (giant unilamellar vesicle; GUV) |

easily cause condensation or sedimentation, they can hold a certain amount of active ingredients, and they permeate the stratum corneum. Also, they have production advantages because the formulation methods are simple and do not require special operations in large-scale production.

## 31.6 STABILITY OF LIPOSOMES

### 31.6.1 Factors That Influence the Stability of Liposomes

As stated here earlier, the phospholipids (mainly PC) that compose liposomes must have physical and chemical stability. These following methods are commonly used to enhance long-term storage stability of liposomes in aqueous dispersed systems: (1) use phospholipids with low peroxide value and oxidation value, (2) thoroughly purge with nitrogen, (3) set the initial pH to 6–7, and (4) use polyols or sugars as osmotic pressure mediators. In addition to the chemical stability of the phospholipids, the physical stability of the liposome membrane is important to maintain the stability of liposomes. High PC purity is a necessary condition to maintain the chemical stability of phospholipids,[11] but studies indicate that it is also important to diminish even the slightest amount of unsaturated groups in the fatty acids that compose the phospholipids.[12] Even if a small amount of unsaturated groups are found in the fatty acids, the pH decreases over time can lead to degeneration such as condensation of the dispersed materials or a change in the smell. Because the gel–liquid crystal phase transition temperatures (Tc) of saturated fatty acids that compose phospholipids are in normal temperature ranges, the phase condition of the lipid bimolecular membranes also changes in this temperature range and can cause leakage of the encapsulated substances or condensation of the liposomes. Adding cholesterol is an effective method to inhibit this phenomenon. Cholesterols are known to inhibit the interaction of hydrophobic groups in the phospholipids when the temperature is lower than Tc, and when higher than Tc, they enhance the interaction, stabilizing the membrane and inhibiting the membrane permeability of the encapsulated substances. The stability reaches its maximum when the composition ratio of phospholipids to cholesterols is 0.2 mol of cholesterol to 1 mol of phospholipid. It has been reported that Tc is diminished with phytosterol-added liposomes when 0.25 mol or more of phytosterol are added for each 1 mol of phospholipid.[13] As such, adding cholesterols to liposomes can inhibit the membrane fluidity of liposomes and prevent hydrolysis of the phospholipids; this is an effective method to obtain long-term stability.[12] However, saturated fatty acid–composed liposomes that encapsulate lower-molecular-weight water-soluble substances such as glucose show different properties, whereas the membrane permeability contrarily increases when the molar ratio of cholesterol is near 0.2. Because the property differs depending on different substances, it is important to understand the physiochemical properties of the encapsulated substances such as their molecular weight or dissociation condition when deciding the additive concentration (Fig. 31.2).[11] There are also studies on liposome stabilization with cholesterol that evaluate the storage property of encapsulated chemical agents. Naito et al.[14] evaluated the stabilization of cholesterol against liposomes by evaluating the storage property of the encapsulated chemical magnesium ascorbyl phosphate (VC-PMG). Figs. 31.3 and 31.4 show the storage property and average particle diameter change of VC-

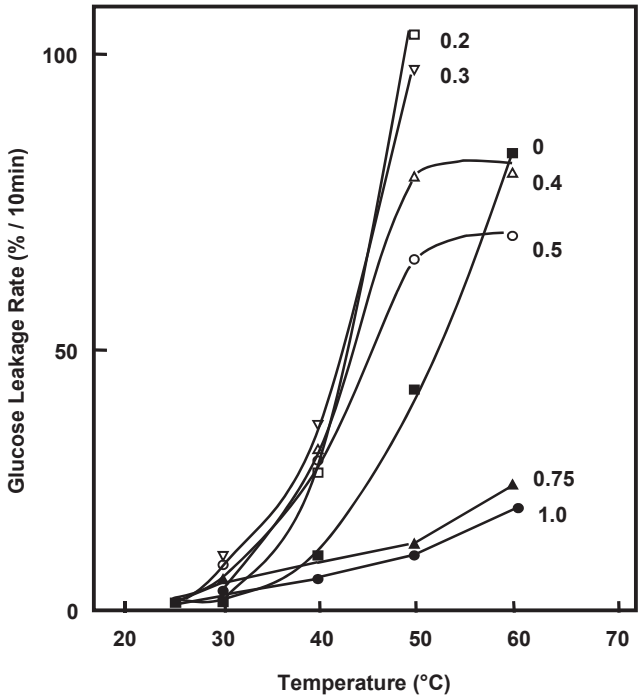



FIGURE 31.2 Effect of cholesterols on glucose leakage.

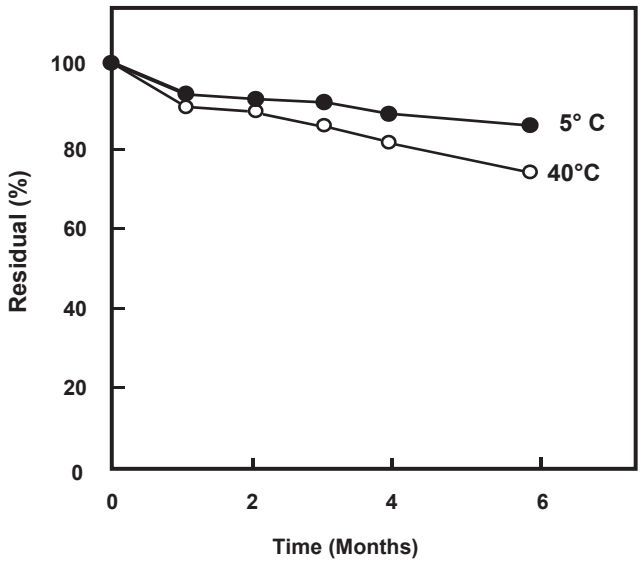



FIGURE 31.3 Chronological change of magnesium ascorbyl phosphate storage property.

PMG—encapsulated liposomes stored at 40°C for 6 months. Eighty percent of the encapsulated chemical agents were stored compared with the initial value, and the particle diameter showed no change. Additionally, a sample of a lamellar structure with multiple layers was observed under a transmission electron microscope (TEM), and it was found that the morphological stability was also maintained (Image 1). As such, adding cholesterol is vital when formulating stable liposome formulations. Further, there are studies on using substances other than sterols as membrane-stabilizing agents. Egawa et al.[13] examined the dispersed system of phospholipids and ceramide 3, along with a dispersed system of phospholipids, cholesterols, and ceramide 3, under differential scanning calorimetry (Fig. 31.5). The liposome system with only ceramide 3 added showed that the peak area of Tc decreased and shifted to a higher temperature. Further, the liposome system with both ceramide 3 and cholesterol added showed

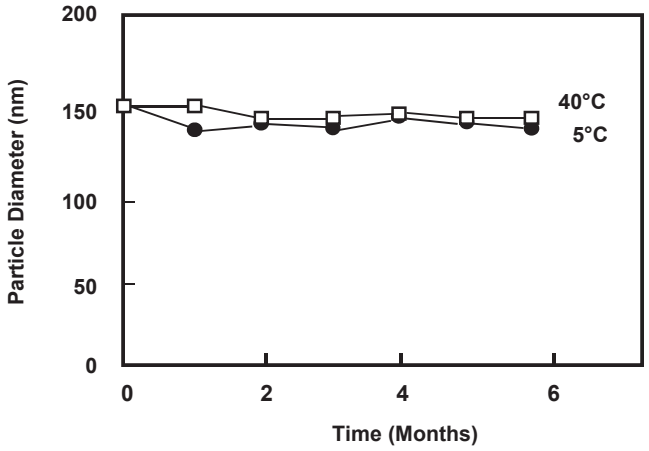



FIGURE 31.4 Average particle diameter change of liposome formulations.

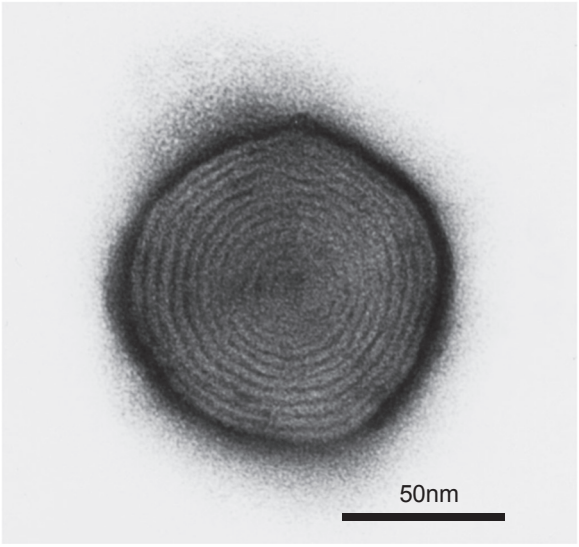



IMAGE 1 Transmission electron microscopic image of a multilamellar liposome.

that the peak area of Tc was eliminated. These results indicate that lipid structures of phospholipids, ceramides, and cholesterols are effective when creating a liposome with a stable lipid membrane. Abe et al.[15] also examined the interaction of phospholipids and ceramide 3 on the lipid membrane with ceramide 3–added liposomes. This research reports that when ceramide 3 is added to liposomes, the membrane of the liposome becomes stronger. This result suggests that this method is effective for preventing leakage of the encapsulated chemical agents. Other substances used in cosmetics can also influence the stability of liposomes, and there are reports on the influence with electrically charged substances,[16] surfactants, polyols such as glycerin, electrolytes, and water-soluble polymers such as hyaluronate. Although the character differs with different phospholipids, their stability can be strongly influenced by these materials. For example, electrically charged substances are known to influence the hydrolysis of phospholipids, and surfactants can break the membrane with desorption and adsorption, indicating that other ingredients must be chosen carefully when liposomes are applied to cosmetics.[14]

### 31.6.2 Stabilizing Dispersion of Liposomes

Like emulsions, phenomena such as creaming, condensation, and coalescence must be prevented to stabilize the dispersion of liposomes in water. Creaming is a phenomenon where the density differences of the liposome particles (dispersion phase) and outer phase (continuous phase) cause the particles to float or sediment and the liquid

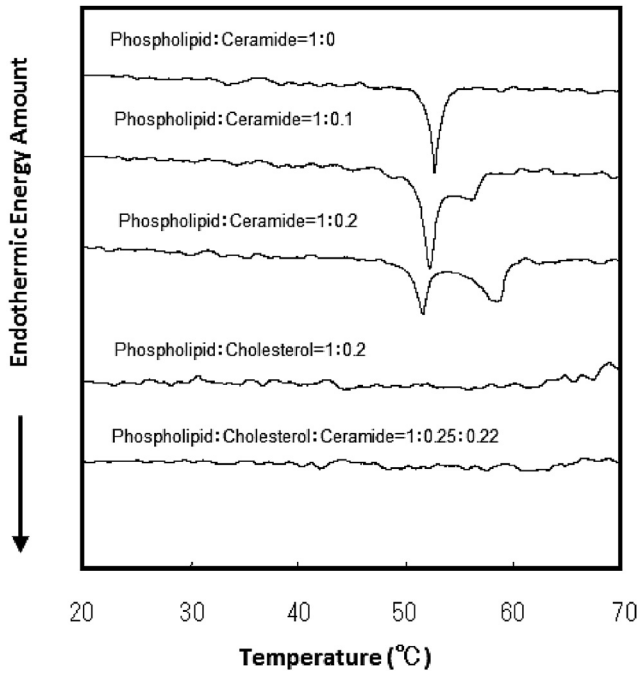



FIGURE 31.5 Effect of various lipids on gel−liquid crystal phase transition temperatures of liposome.

becomes partially condensed. Condensation is caused by the London−van der Waals attraction between the particles, causing them to contact and condensate, and this can induce creaming. Condensation or creaming can break the membranes through coalescence if the interfacial membrane of the contacting droplets is weak.

### 31.6.3 Creaming of Liposomes and Controlling Creaming

The floating (or sedimentation) velocity of the particles, caused by the density difference between the particles and medium, is an indicator of creaming and can be calculated by the Stoke law of sedimentation.

$$V = \frac{2r^2(\rho - \rho_0)g}{9\eta}$$

where $V$ is the sedimentation velocity, $r$ is the particle radius, $g$ is gravitational acceleration, $\eta$ is the viscosity of the continuous phase, and $\rho$, $\rho_0$ is the viscosity of the continuous phase and dispersion phase, respectively. In other words, the sedimentation or floating velocity of the particle $V$ is proportional to the particle radius $r$ squared and is in reverse proportion with the viscosity of the outer phase $\eta$. Reducing the particle radius is effective to inhibit creaming, and both chemical and physical methods can be used to reduce the particle radius. For chemical methods, hydrophilic surfactants are commonly used, but they also reduces the inner water phase volume so the vesicles would not be able to show their full effects. Matsuo et al.[17] reported that small liposomes with a large inner water phase volume can be formulated by adding polyoxyethylene (25) phytosterol ether and phytosterol as surfactants to the phospholipid. Machines are also often used for physical methods to make microparticles. After preparing the average particle diameter to 1 μm to several micrometers with the use of mixers and others, high-energy−generating instruments such as high-pressure homogenizers can be used to make liposomes.

### 31.6.4 Stabilization of Liposomes With Electrostatic Repulsive Force

The Derjaguin, Landau, Vervey, and Overbeek (DLVO) theory of colloidal stability is a theory developed to explain the colloidal stability of solid particles, and it can be applied to determine the stability against condensation. The main forces that respectively destabilize and stabilize colloid particles are London−van der Waals force and electrostatic repulsive force caused by the electrical charge of the particle surface and its associated counterions. DLVO theory explains the stability of dispersed systems through the balance of these forces. We will omit the details

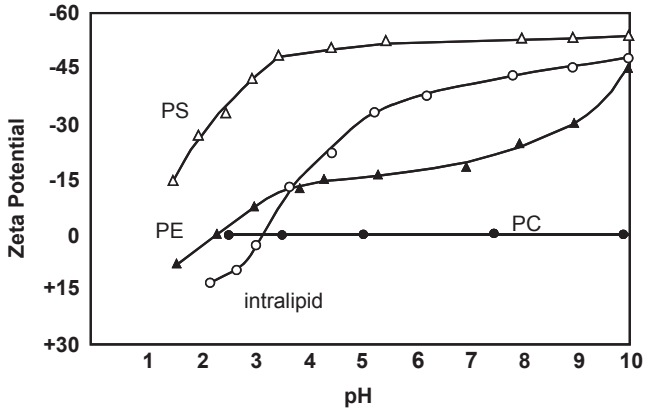



FIGURE 31.6 Zeta potential of phospholipid components.

of the DLVO theory, but it shows that using ionic surfactants to raise the surface charge is effective to prevent condensation. In opposition, increasing the concentration of electrolytes induces condensation. Fig. 31.6 shows the zeta potential of PC, phosphatidyl ethanolamine (PE), phosphatidyl serine (PS), and intralipid (PC:PE:PS = 72:15:12).[18] Encapsulation of active components is an important characteristic of vesicles, and the encapsulating property can be stabilized when the PC concentration of the liposome-composing phospholipids is higher. However, this brings the zeta potential close to zero, which is not appropriate in terms of dispersion stability and can easily cause condensation. Thus the lipids must be electrically charged to improve the dispersion stability by adjusting the phospholipid composition such as with the intralipid shown in Fig. 31.6. Additionally, it has been reported that formulating liposomes by combining phospholipids and cholesterols further increases the zeta potential and improves the dispersion stability. Electrically charging the liposome surface to control the electrostatic interaction of the particles is another method to stabilize the electrostatic interaction of particles. The electrical charge of the membranes changes when charged substances are added to the components, so the membrane can be positively charged by adding stearylamine and can be negatively charged by adding substances such as phosphatidyl inositol, PS, or phosphatidic acid. By adding electrical charge to the surface of liposomes, the interparticle electrostatic repulsive force increases and improves the dispersion.

## 31.7 EFFECTIVENESS OF LIPOSOME FORMULATIONS

Liposomes are effective ingredients for cosmetic formulation due to their properties of (1) encapsulating both hydrophilic and lipophilic chemical agents into their membranes, (2) being biologically derived and having high biocompatibility and low toxicity, (3) having high storability in the skin, and (4) having high moisture-retaining properties.

For example, by encapsulating polymers such as collagen, elastin, or hyaluronate, botanical extract with various medicinal effects, water-soluble whitening agents, or antioxidative agents, liposomes can improve the affinity to the skin or increase the duration of water-soluble chemical agents. Further, lipophilic or slightly soluble chemical agents can be added onto the bilayer membrane and can improve the diffusion efficacy of these effective agents. Fig. 31.7 shows the results of tape stripping evaluation of the storability of several biotin-added formulations when a fixed amount was applied to the inner forearm.[19] The biotin-encapsulated liposome showed higher storability in the stratum corneum compared with biotin aqueous solutions or solubilized biotin, especially with storability near the surface of the stratum corneum. Liposomes are known to show such effectiveness and are expected to be a very effective ingredient for skin care cosmetics. Further, it is widely known that phospholipids and other lamellar structured substances have high moisture-retaining properties and are especially effective in preventing moisture evaporation of the skin. For example, Suzuki et al.[20] used intercellular lipids to formulate lamellar structured emulsions and reported that they show high moisture-retaining properties compared with normal reference emulsions. In addition, dispersed systems of lamellar-structured liquid crystals made from selachyl alcohol are reported to show high moisture-retaining properties, so liposomes, which are closed vesicles with lamellar structures, are also expected to have effective moisture-retaining properties. To prove that lamellar structures are effective for moisture retention, the moisture-retaining properties of 10% lipid concentration liposome formulations were tested, as well as a

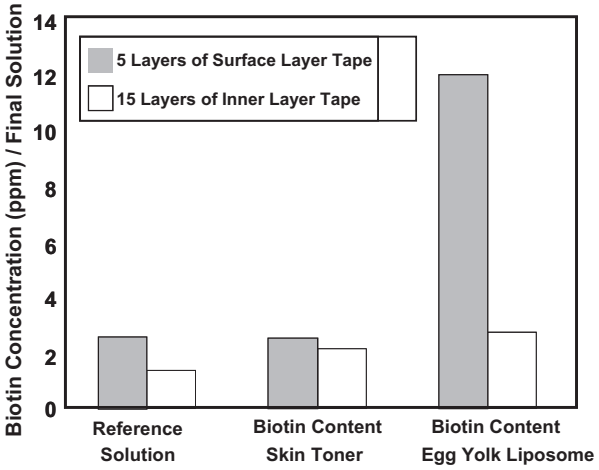



FIGURE 31.7 Stratum corneum storability of formulations with biotin.

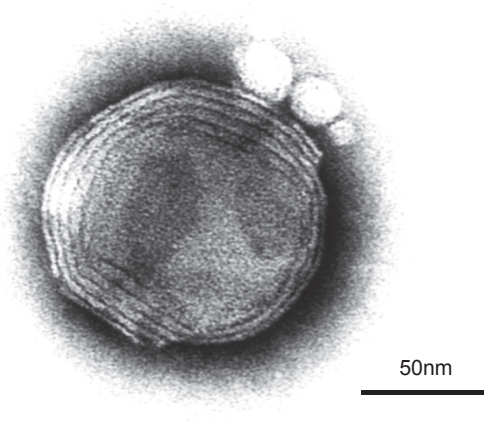



IMAGE 2 Transmission electron microscopic image of water-evaporated liposome.

reference formulation with surfactants added to break the lamellar structure. Liposome formulations showed significantly higher moisture retention compared with a reference sample with lamellar structures broken with 1% concentration octylphenyl ether.[21] As such, liposomes are thought to have a high moisture-retaining property from their structure of closed lamellar vesicles. When liposomes are applied to the skin as topical agents, the moisture can evaporate or the liposomes can be subjected to a high shear rate, so a simple model was used to examine how much of the liposome structures were maintained on the skin. Two samples were observed under TEM examinations—with one sample stored at room temperature for a fixed period and another sheared sample to break the structure (Image 2 and 3). The results suggested that the membrane structures of the liposomes was preserved even if strong shearing was applied or, in other words, if they are applied like normal cosmetics. From these results, it can be concluded that the high moisture-retaining property of liposomes is due not only to the function of the phospholipids composing liposomes but also to the preserved lipid bimolecular membrane structure.

Many studies have been conducted to evaluate these effects of liposomes as moisturizers. Noguchi et al.[22] tested the effect of amino acids on the moisture-holding property of bilayer lipid membranes. An increase in the bound water content was found when a highly hydrophilic amino acid, proline, was added to a bimolecular membrane of soy phospholipid, and when amino acids with lower water solubility such as isoleucine or leucine were added, the bound water was reported to increase and the water transmission amount was reported to decrease. The bound water content of the bilayer lipid membrane increased significantly when amino acids are mixed and added, and long-term moisture retention has also been observed.

Further, there are reports on liposome formulations and their effect on small wrinkles near the corner of the eyes.[23] After the application of liposome formulations for 2 months, microscopic observations showed that the condition of

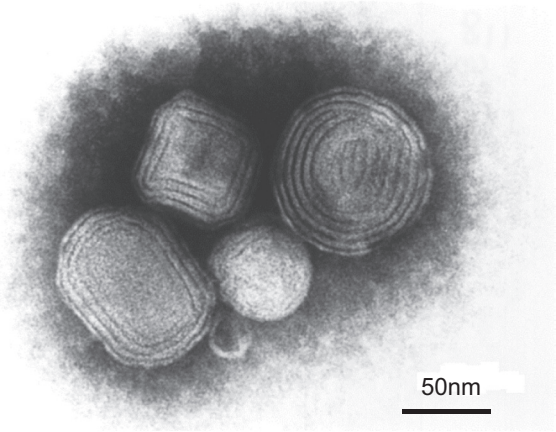



IMAGE 3 Transmission electron microscopic image of sheared liposome.

the small wrinkles improved significantly. Further, questionnaire surveys were conducted on liposome use in cosmetics and showed that the feel of the application of liposome formulations was positively accepted. This shows that liposome formulations are not only effective but also comfortable to use, which is an important factor in cosmetic formulations for everyday use.

In addition to these reports, phospholipids are also known to function as antioxidative substances.[24,25] Nath et al.[26] reported that the oxidation stability of unsaturated fatty acids improved when milk-derived phospholipids were added to milk fat triacylglycerol. Chen et al.[27] conducted similar research and reported that the antioxidative effect of PE against milk fat is influenced by the amino group ($NH_2$) in PE. In the field of cosmetics, issues of lipid peroxidation and aging remain important topics, and active research in these areas is expected to continue.

## 31.8 CUTANEOUS ABSORPTION OF LIPOSOME FORMULATIONS

To show moisture-retaining, whitening, or antiaging properties, active components must be sent to the skin's stratum corneum, stratum granulosum, stratum spinosum, basal membrane, or dermis depending on the purpose of the effect. Liposome formulations have the potential to greatly improve the permeability of these substances. Here, we will look at some research that reported the cutaneous absorption effect of liposome formulations with whitening and hair-growing agents. There are many reports on the cutaneous absorption of agents that are encapsulated in liposomes and the cutaneous permeability of liposomes,[1,28] and these studies report both induction and inhibition of agent absorption, but the results may have varied because the experimental conditions and other conditions were not unified. Although liposomes can be used to effectively deliver the encapsulated active ingredients to the blood or urine, when using liposomes in cosmetics, it is more important to improve the effects at skin level, such as improving restoration of the encapsulated materials. Iwanaga et al.[29] studied the application of liposomes as topical agents for local effectiveness and reported in their detailed studies that when labeled soluble agents are encapsulated into liposomes, the percutaneous penetration significantly decreases, suggesting that liposomes can inhibit skin permeability. They also reported that the decreasing rate of the accumulating amount and percutaneous permeability of mannitol were smaller compared with that of the epidermis and dermis layers under the stratum corneum, while the systemic clearance, which indicates the transfer from the skin to the metabolic system, was significantly inhibited. Imanaka et al.[30] validated that when the melanogenesis inhibitor linolic acid was encapsulated into liposomes, the agent showed stability in aqueous solutions and time-dependently penetrated substratum corneum layers. Further, the liposome formulations with encapsulated linolic acids were clinically tested on patients with chloasma and showed high whitening effects. Tamura et al.[31] encapsulated the hair growth–promoting agent minoxidil into liposomes as a DDS formulation and tested their effectiveness, and they found that more liposome-encapsulated minoxidil was incorporated into hair follicles in vivo and more was incorporated into cultivated fibril-derived cells in vitro compared with free minoxidil.

These results show that liposomes can be used in cosmetic formulations to promote penetration or to keep the encapsulated agents on the skin and suggest that liposomes have the potential as effective DDS formulations to improve the efficacy of active ingredients.

## 31.9 CLOSING REMARKS

In this chapter, we have studied the basics of liposomes regarding their stability and effectiveness in cosmetics. As long as liposome formulations clear a specific quality standard, they can be applied to cosmetic formulations to improve permeability or restoration on epidermal levels of the skin, and they even have strong potential as high moisturizing agents. Safety and effectiveness will become increasingly important in cosmetics, and we hope formulation studies on liposomes will evolve to meet these demands.

## References


1. Mezei M, Glasekharam V. *Life Sci* 1980;**26**:1473.
2. Wohlrab W, Lasch J. *Dermatological* 1987;**174**:18.
3. Nagata M, et al. *J Pharm Pharmacol* 1988;**40**:85.
4. Chapman D, et al., editors. *Foam and function of phospholipids*. Elsevier Scientific; 1973. p. 117.
5. Kakoki H, et al. *Fragr J* 1991;**19**(3):49.
6. Bangham AD, Horne RW. *J Mol Biol* 1964;**8**:660–8.
7. Bangham AD, Standish MM, Watkins JC. *J Mol Biol* 1965;**13**:238.
8. No 26 *Notification issued by Ministry of Health and Welfare of Japan*. September 13, 1990.
9. Singer SJ, Nicolson GL. *Science* 1972;**175**:710.
10. Pozansky MJ, et al. *Pharmacol Rev* 1984;**36**:277.
11. Arakane K, et al. *J Soc Cosmet Chem Jpn* 1991;**25**:171.
12. Arakane K, Hayashi K, Naito N, nagano T, Hirobe M. *Chem Pharm Bull* 1995;**43**(10):1755.
13. Egawa J, et al. *Fragr J* 2000;**28**(12):32.
14. Arakane K, Hayashi K, Naito N, Iwanaga K, Yamashita S, Oku N. *J Soc Cosmet Chem Jpn* 1993;**27**(3):216.
15. Abe M, et al. *Fragr J* 1999;**27**(10):58.
16. Hayashi K, et al. *Chem Pharm Bull* 1995;**43**(10):1751.
17. Matsuo M, et al. *J Soc Cosmet Chem Jpn* 2003;**41**(3):167.
18. Bangham AD. *Prog Biophys J Mol Biol* 1968;**18**:29.
19. Tokubuchi S, Hamamatsu K, Fujishiro H, Egawa J. In: *24th IFSCC Congress, PC-137*; 2006.
20. Suzuki T, et al. *J Soc Cosmet Chem Jpn* 1993;**27**(3):167.
21. Takano A, Murata Y, Tabata Y. *J Soc Cosmet Chem Jpn* 1995;**29**(3):221.
22. Noguchi C, et al. *J Soc Cosmet Chem Jpn* 1995;**29**:49.
23. Sasaki I, et al. *Fragr J* 1995;**23**(1):56.
24. Hildebrand D, Terao J, Koto M. *J Am Oil Chem Soc* 1984;**61**:552.
25. Husain S, Terao J, Matsushita S. *J Am Oil Chem Soc* 1986;**63**:1457.
26. Nath B, Murthy M. *Indian J Daily Sci* 1983;**36**:151.
27. Chen Z, Nawar W. *J Am Oil Chem Soc* 1991;**68**:938.
28. Komatsu H. *Pharm Tech Jpn* 1989;**5**(12):1363.
29. Iwanaga K, et al. In: *The 111nd Annual Meeting abstract of the Pharmaceutical Society of Japan*, vol. 4; 1990 (111).
30. Imanaka H, et al. *J Soc Cosmet Chem Jpn* 1999;**33**:277.
31. Tamura K, et al. *J Soc Cosmet Chem Jpn* 1998;**32**:345.

CHAPTER

# 32

# Skin Care Cosmetics

*K. Watanabe*

**Shiseido Global Innovation Center, Yokohama, Japan**

## 32.1 INTRODUCTION

By definition, *skin care* is literally the practice of taking care of the skin's wellness by cleansing, protecting, maintaining, and improving skin conditions over its homeostatic balance. Many types of cosmetics are developed and used to provide these functional tasks of skin care. For cleansing skin care cosmetics, there are traditional and well-established product types such as bar soap, liquid or gel facial cleansers, and cream-type cleansers, which are water-based formulations with surfactants to remove unnecessary materials deposited or secreted on the skin surface. Dirty oil, which consists of sebum and some remaining excessive materials from cosmetics, can be removed by oil-based cosmetics formulated as emulsions or microemulsions such as cleansing oils, gels, milks, or lotions. Skin toners, emulsion products, and skin creams are common types of skin care cosmetics used to protect, maintain, and improve skin conditions. Active or functional materials are often incorporated into these skin care cosmetics and can sometimes cause difficulties for formulation stability.

Based on the product's application, skin care cosmetics can be divided into skin, hair, and oral products. Although the skin covers the entire body surface, skin care cosmetics generally refer to facial skin care products, and in this book, body care cosmetics are distinguished by their specific body part other than the face. The scalp is the skin around the hair and is discussed in the chapter on hair care cosmetics. In this chapter, we mainly discuss the scientific and technological basics of formulation. The physiological aspects of skin care cosmetics are discussed in the chapters "New Aspects of Cosmetics and Cosmetic Science," "Bioactive Ingredients," "Structure and Function of Skin From a Cosmetic Aspect," "Skin Lipids," "Skin Aging," and "Melanogenesis."

## 32.2 FUNCTIONS OF SKIN CARE COSMETICS

The most important role of skin care cosmetics is to use "the skin's self-preserving function to restore health, or in other words enhance the body's homeostasis," and such function helps the skin approach its most ideal condition. Although the ideal condition for the skin depends on many factors, an example of an ideal condition is soft, smooth, firm, and evenly colored skin.

The uppermost layer of the skin, the stratum corneum, is mainly composed of water, sebum, and substances that are collectively called natural moisturizing factor (NMF). NMF is a moisture-retaining substance that is naturally derived from the epidermis, with amino acid as its main component. An effective way to help the body's homeostasis, when the stratum corneum's moisture-retaining functions do not work properly, is to choose and apply oils or humectants that meet the skin's condition. This concept is called *moisture balance* and is an extremely important factor when choosing the ingredients in skin care cosmetics.[1–3]

Specifically, water, oils, and humectants are used as the basic ingredients of skin care cosmetics to imitate the components of the stratum corneum. When skin care cosmetics spread onto the skin, a layer that can be called an artificial stratum corneum is formed, and from this layer, water and moisturizing substances such as glycerin penetrate the stratum corneum, while semisolid oils such as Vaseline or liquid oils prevent moisture

*Cosmetic Science and Technology: Theoretical Principles and Applications*
http://dx.doi.org/10.1016/B978-0-12-802005-0.00032-X



Copyright © 2017 Elsevier Inc. All rights reserved.

from evaporating from the stratum corneum (an effect known as occlusion), helping the skin reach its ideal condition.

In skin care cosmetic formulation, the basic ingredients of moisture balance, namely water, oil, and humectants do not always mix stably from a physiochemical aspect, so the key is to formulate the target formula to stabilize the formula while making the product comfortable to use. Traditionally, formulating cosmetics was an art that was passed down from engineer to engineer, but technology today uses interface science to understand and analyze phenomena to create various technologies for formulation.

## 32.3 STRUCTURING COMPONENTS AND TECHNOLOGY OF SKIN CARE COSMETICS

The key technologies that support skin care cosmetics formulations are stabilizing and homogenizing water and oil, which is achieved through emulsification and solubilization technologies. Because most humectants are soluble in water, the actual key technology in formulation is in homogenization and stabilization of the water-humectant solution and oil. Emulsions are products formulated by emulsification, and microemulsions are products formulated by solubilization.

Skin toners, emulsion products, and skin creams are common types of skin care cosmetics. The amount of oils and humectants differs depending on the kind of product.

Very little oil is formulated with skin toners; the main ingredients are the humectant−water solution, surfactant, stabilizers, and fragrances. Oil-soluble ingredients and fragrances are added to these products by using solubilizing methods in the micelles of water-soluble surfactants. The concentration of surfactants is approximately 5−10 times the total amount of the oil-soluble ingredients and fragrances. The concentration of humectants is approximately 5−20%. When a small amount of oil (0.1−1%) is added to the skin toner for an occlusion effect, a method called *ultrafine emulsification* is used to create oil particles with a diameter size of approximately 100 nm, such that they are stably dispersed in the water system.

Emulsion products have an approximately 2−25% oil content and 5−20% humectant content. Surfactant and stabilizers are also used in their formulation. Due to their high oil content, it is difficult to stabilize the formulation by the use of ultrafine emulsification, so surfactants are used to create emulsions to increase the viscosity and stabilize the product. Thickeners are also used to increase the viscosity. The surfactant content of emulsion products is 1−5%, and the thickener content is 0.1−1%. In recent years, thickeners with an added surfactant-like amphiphilic property have been frequently used to give the thickeners an emulsification function in addition to their thickening effect.

Skin creams have an approximately 10−50% oil content and 5−30% humectant content. In addition to oil-in-water (O/W) products, there are also water-in-oil (W/O) products. Because skin creams have an extremely high oil content, elastic properties are added to stabilize the product.

For O/W products, alpha-type crystals (also known as alpha gels) are frequently used to add elasticity. The alpha-type crystals used in creams are often composed of surfactants, higher alcohols, and water (Fig. 32.1). Alpha-type crystals have a bimolecular membrane with a stacked structure of surfactants and higher alcohols; water is solubilized between the hydrophilic groups and spreads between the surfaces. Further, the alpha-type crystals with solubilized water create a network throughout the system, and because this network has a continuous structure, the water particles can be seen as particles preserved throughout the network, resembling a gel structure. Thus they are called alpha gels, but the system is actually a two-phase system of alpha-type hydrate crystals and an excess water phase that does not dissolve between the hydrophilic groups but is preserved in the network structure. Such a two-phase system is capable of storing a large amount of oil particles. O/W emulsions that are stabilized via this mechanism are called alpha-gel emulsions.

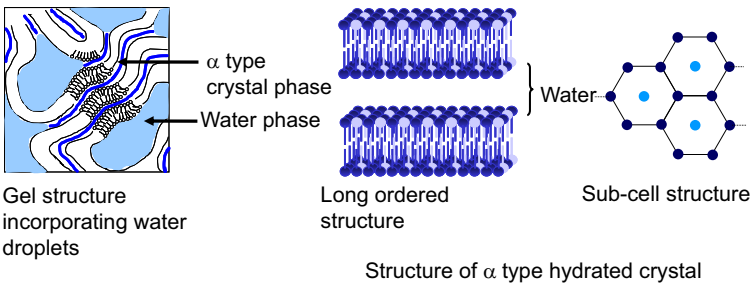



**FIGURE 32.1** Structure of an alpha-type hydrated crystal and gel structure incorporating water droplets.

Elasticity is occasionally added to W/O emulsions by using oil gels from organic modified clay minerals and by adding water particles.

Among creams, there are facial creams that are used for the entire face, eye creams that are used around the eyes, and creams that are used around the mouth. Polymers and waxes are used to add physical firmness, and elastomers with leveling effects are used in eye creams to hide wrinkles.

## 32.4 SOLUBILIZATION

Solubilization is a phenomenon in which aggregations such as micelles, which form in surfactant solvents, are used to solubilize substances that otherwise do not solubilize into these solvents.[4] Micelles in water create associations with the hydrophilic groups of the surfactant facing outward and lipophilic groups facing inward. In oil, they create reverse micelles, where the hydrophilic groups and lipophilic groups face the opposite of micelles in water. The size of micelles is from several to tens of nanometers. In water, micelles can dissolve oil near the lipophilic groups in the associations. The product solution of micelle solubilization is called *microemulsion.*

Microemulsions have been systematically studied since they were reported by Schulman in the 1940s.[5] They are optically isotropic and are transparent, or they can show a slightly blue scattering light. Due to their appearance when they were first discovered, they were thought to be a disperse system of emulsion particles smaller than light wavelengths and thus were named microemulsions, but later studies found that microemulsions represent systems at thermodynamic equilibrium in which oils are solubilized in micelles or water is solubilized in reverse micelles. Here, a thermodynamic equilibrium is defined as a system for which the initial state is preserved as long as the temperature and pressure are constant.

For skin toners, oil solubilized in micelle solutions (continuous water types) is used, whereas reverse micelle–oil solutions with solubilized water are used for skin care oils and makeup cleansers.[6] Also, when the aggregation number of surfactants that form micelles increases, an infinite association structure is created in which water and oil have a continuous structure (Fig. 32.2). This structure is called a *bicontinuous microemulsion* and is used for makeup cleanser oils.[7]

The precondition of solubilization is that surfactants and solubilized substances are combined accordingly for the optimal results. For example, surfactants with dimethyl siloxane as their lipophilic group are used for solubilizing silicone oil, and surfactants with alkyl chains as their lipophilic group are used for solubilizing hydrocarbon oils. Further, the optimal surfactants for solubilizing substances such as fragrances, which have a small molecular weight and have polarity, are surfactants with propylene oxide as their lipophilic group.

## 32.5 ULTRAFINE EMULSIFICATION

Ultrafine emulsification methods are often used for skin toners, using nanosize emulsion formulation of microemulsions.[8]

The initial process of this method is to choose the oil and surfactant so that the microemulsion region is higher than room temperature (Fig. 32.3). In the microemulsion region, micelles with solubilized oils are dispersed in water. Although this solution leaves the microemulsion region when it is cooled, its microemulsion-like transparency is maintained, but only when the solution is rapidly cooled.

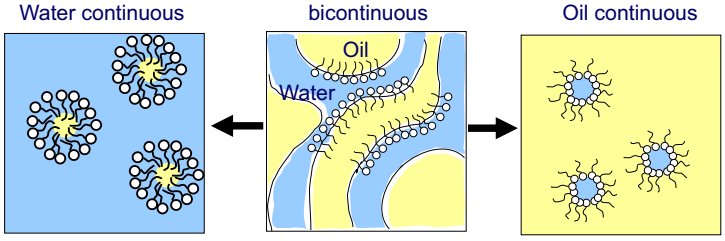



**FIGURE 32.2** Three types of microemulsion depending on HLB (hydrophile-lipophile balance).

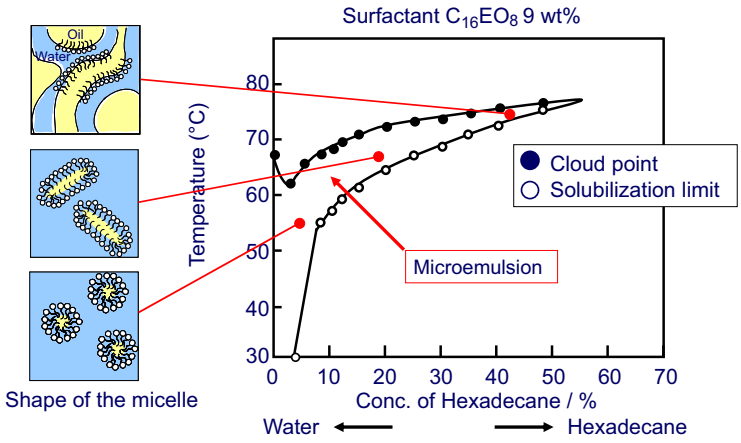



FIGURE 32.3 Dependency of solubilization limit of polyoxyethylene-type surfactant aqueous solution and the shape of the micelle.

This solution is an ultrafine emulsion in which the particle size of microemulsions remains small; although it is transparent, it is categorized as an emulsion. Thus it separates into two phases during long storage, but due to its extremely small particle size, its stability is suitable for practical use.

## 32.6 EMULSIONS

Emulsions are systems in which one of two insoluble liquid phases is dispersed into the other in the form of droplets. In most cases, these two liquid phases are water and oil.

The droplet size of emulsions is approximately 0.1−100 μm. The common types are O/W types, where oil droplets are dispersed in water, and W/O types, where water droplets are dispersed in oil. There are also O/W/O types, where O/W emulsions are dispersed into the oil phase,[9] and W/O/W types, where W/O emulsions are dispersed into the water phase; these types are called multiple emulsions.

To make an emulsion, one of the two liquids must be dispersed into the other, and the interfacial area increases in this process. There is interfacial tension between two liquid phases that do not mix with each other. Interfacial free energy is defined as the product of interfacial tension and interface area, and the interface tries to make its area size smaller to minimize the interfacial free energy. As a consequence, emulsions eventually separate into separate phases if given enough time.

The interfacial free energy increases when making emulsions, so energy must be applied from outside of the system to enable emusification. In general, homogenizers and other sources of mechanical energy are applied. Because the interfacial free energy is the product of the interfacial tension and interface area, decreasing the interfacial tension between the liquid phases can decrease the amount of required energy. In other words, the emulsion particle size becomes smaller when the same energy is applied, so surfactants are added to decrease the interfacial tension.

Having a smaller interfacial tension is better for formulating emulsions, but this does not necessarily mean that it is better to preserve the initial state of the emulsion for long-term storage (the stability of the emulsification). As such, formulation of emulsions and stabilization of emulsions must be considered separately.

Creaming, flocculation, coalescence, and Ostwald ripening are known phenomena that cause emulsions to become instable.

Creaming is a phenomenon in which the particles of the inner phase float or precipitate; it is caused by the specific gravity difference between the dispersed phase and the continuous phase. Stokes law is used to calculate the velocity of sedimentation and floating

$$V = 2gr^2\Delta\rho/9\eta \text{ (Stokes law)}$$

where V is the velocity of the particles, g is gravitational acceleration, r is the radius of the dispersed system particles, $\Delta\rho$ is the density difference between the dispersed phase and the continuous phase, and $\eta$ is the viscosity of the

continuous phase. This formula shows that the dispersed phase particle radius changes the velocity by a scaling factor of 2, indicating that decreasing the particle is extremely effective.

Flocculation is a phenomenon in which multiple particles aggregate, and it leads to an increase in the creaming velocity or to coalescence. Ionic surfactants are used to impart electrostatic repulsion between droplets, and nonionic surfactants with long hydrophilic groups are used for entropic repulsion to prevent flocculation.

Coalescence is a phenomenon in which separate particles merge into a larger particle when they make contact. To prevent coalescence, there are methods to avoid contact, such as by increasing the viscosity of the continuous phase or preventing coalescence even when they contact by adsorbing aggregates to interfaces.

Ostwald ripening is a phenomenon in which small particles disappear and the number of large particles increases when the components of particles with small radius dissolve into the continuous phase and dissolve back to larger particles. An effective method to prevent this phenomenon is to use substances that have low solubility to the outer phase as the component of the inner phase. For example, lowering the polarity of the oils is effective to prevent Ostwald ripening in O/W emulsions.

## 32.7 EMULSIFICATION

Even when emulsions have the same composition, they exhibit different properties (i.e., the diameter of the emulsion particles, viscosity) depending on the formulation method, and it is important to choose the proper emulsification method to meet the targeted purpose for emulsions in skin care cosmetics. In many cases, the main focus of emulsification is to increase stability because emulsions are thermodynamically nonequilibrium systems. Additionally, emulsification methods have been developed to target control of the condition of the emulsifying membrane after it is applied to the skin.[10]

O/W emulsions are formulated with methods such as phase inversion temperature emulsification,[11] D phase (surfactant phase) emulsification,[12] and liquid crystal emulsification.[13]

Phase inversion temperature emulsification is a method that uses the properties of polyoxyethylene hydrophilic nonionic surfactants. Polyoxyethylene hydrophilic surfactants show a high hydrophilic property at low temperature and form micelles in water. Conversely, the hydrophilic property decreases at higher temperatures and they form reverse micelles. The resulting emulsion is O/W at low temperatures and W/O at high temperatures. The temperature between these temperatures is known as the phase inversion temperature. Near the phase inversion temperature, the interfacial tension between oil and water becomes minimal and emulsions with small emulsion particles are formulated in this temperature range. However, the hydrophilic property of the surfactant is low near the phase inversion temperature, so the O/W emulsion is not suitable for maintaining its initial state and is unstable. By quickly cooling the emulsion after it is formulated, the hydrophilic property of the surfactant is restored and the emulsion can be stabilized. Phase inversion temperature emulsification is an excellent emulsification method that optimizes the formulation and stability with temperature control.

W/O emulsions are formulated by the use of methods such as amino acid gel emulsification,[14] liquid crystal emulsification, organic modified clay mineral emulsification,[15] and high inner water phase W/O emulsification using surfactants with hydroxyl groups.[10] Organic modified clay mineral emulsification is a method that uses organic modified clay minerals where lipophilic cationic surfactants are adsorbed to water soluble clay minerals (e.g., montmorillonite). When clay minerals are organically modified, they obtain a property by which the viscosity increases when dispersed in oil. W/O emulsions are formulated by adding proper surfactants to the oil gel formed by organic modified clay minerals with oil and then adding water to maintain the emulsion particles.

The key to formulating W/O emulsions is the gelling agent that increases the viscosity of the oil, which is the outer phase of the emulsions. Because there are various types of oils, it is important to choose the right gelling agent. When choosing the gelling agent, various aspects must be considered, such as the chemical species, molecular weight, and mechanism of network formation. The choice of the surfactant is also important; it should have a high lipophilic property while not having a negative influence on the structure of the oil gel.

## 32.8 RECENT PROGRESS OF OIL-IN-WATER EMULSIFICATION IN SKIN CARE COSMETICS

As an example of technology development based on scientific studies, we will look at our studies of advanced application of the previously introduced alpha gel emulsification using alpha-type hydrate crystals, where sodium

stearoyl methyltaurine, higher alcohol, and water systems were used to formulate alpha-type hydrate crystals; this research focuses on the characterization of gelling in water.

Alpha-type hydrate crystals are aggregations of surfactants (crystal hydrates), and they have a white color that is smooth with high viscosity. These crystals form in surfactant–water systems below the Krafft point. Further, they have been reported to form above the surfactant's Krafft point of surfactants when the surfactant is mixed with higher alcohols.[16,17] The long-period structure of alpha gels is a repeating (stacked) structure of bimolecular membranes. Additionally, the packing structure of the lipophilic groups (subcell structure) is a hexagonal crystal structure. A large amount of water is trapped between the hydrophilic groups of alpha-type hydrate crystals.

Alpha-type hydrate crystals made from higher alcohol, surfactant, and water are known to drastically change their properties depending on the mixture ratio of higher alcohols to surfactants. Detailed studies using differential scanning calorimetry show that alpha gels formulated with a three-component system of hexanol/octadecyl trimethyl ammonium chloride (OTAC)/water forms an alpha gel with a high melting point when the molar ratio of hexanol:OTAC reaches 3:1.[16,17]

Alpha-type hydrate crystals are known to create networks that gelate a solvent in a solvent that otherwise does not dissolve alpha gels.[18] For example, systems that have more water than the water-solubilizing capacity between the hydrophilic groups of alpha-type hydrate crystals (i.e., a two-phase phase equilibrium condition of alpha-type hydrate crystals and excess water phase) can often appear as a homogeneous gel state.[19,20] Further, gels made of alpha gels and excess water phase can emulsify oil in the gel, making a homogeneous gel state. This three-phase homogeneous gel of alpha-type hydrate crystals/water/oil can preserve the homogeneous mixed oil and water state for a long storage period and is an important system that can be applied to various industrial products such as skin care creams, shampoos, conditioners, and topical agents.

To preserve the uniform mixed state during a long period, the system must have sufficient alpha gels and the network structure must not change. However, there are not many studies that focus on the changes in water concentration and its effect on alpha-type hydrate crystal, amount of excess water phase, and network structure change.

In this study, alpha-type hydrate crystals formulated from sodium stearoyl methyltaurine (SMT)/behenyl alcohol/water were studied (Fig. 32.4), and characterization of the water concentration was studied in addition to the behenyl alcohol:SMT ratio. Further, evaluation of the self-diffusion coefficient by nuclear magnetic resonance (NMR)[21] was used to potentially characterize the water solubilized between the hydrophilic groups in the alpha-type hydrate crystals and the excess water stored in the network structure.

First, the change in alpha gel interlayer spacing with change in water concentration was studied. Fig. 32.5 shows the alpha gel–with–water concentration and the interlayer spacing of the gel made from the alpha gel and excess water phase when the ratio of behenyl alcohol:SMT was 3:1 (mol:mol). The plots show the values measured with small-angle X-ray scattering evaluation. When the water concentration was lowest at 20%, the interlayer spacing was approximately 8 nm, but the interlayer spacing increased with the increase in water concentration, and near the phase boundary of the two-phase region with a water concentration of 85%, the interlayer spacing was approximately 28 nm.

The solid line shows the theoretical value calculated from the following formula

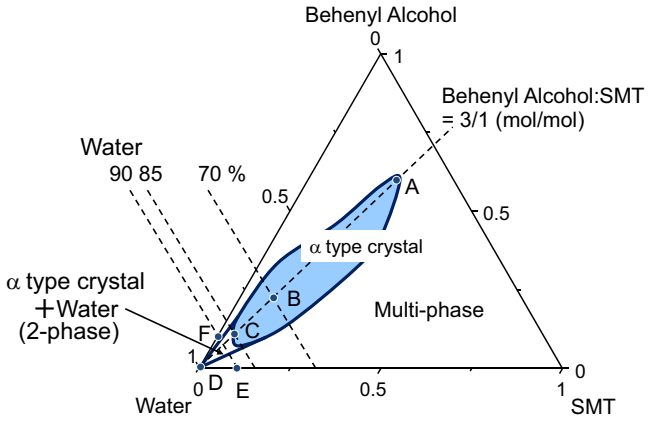



FIGURE 32.4 Phase diagram of sodium stearoyl methyltaurine/behenyl alcohol/water system. Compositions A to F will be discussed in other figures.

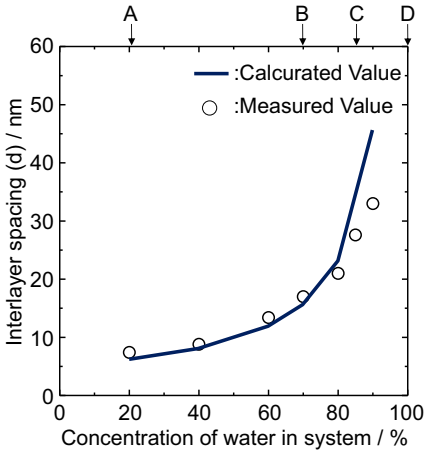



**FIGURE 32.5** Interlayer spacing (d) of alpha gel as a function of concentration of water in system. *Open circle* represents measured value by SAXS (small angle x-ray scattering). *Full line* represents calculated value from the equation. $d = \rho\ell/\varphi$, where $\rho$ is a the density of the alkyl chain that is assumed to be 0.9, $\ell$ is length of the alkyl chain that is assumed to be 2 nm, and $\varphi$ is weight ratio of sodium stearoyl methyltaurine plus behenyl alcohol in the system. Compositions A, B, C, and D correspond to those in the phase diagram (Fig. 32.4).

$$d = \rho\ell/\phi \tag{32.1}$$

where d is the interlayer spacing, $\rho$ is the specific gravity of the lipophilic group (here, the value was set to 0.9 $g/cm^3$ because the lipophilic group was an alkyl group), $\ell$ is the length of the lipophilic group (set to 2 nm), and $\phi$ is the mass ratio of the total mass of the surfactant and higher alcohol against the mass of the system. The theoretical value and actual values closely matched when the water concentration was from 20% to 80%, within the one-phase region. Further, when the water concentration was greater then 85%, a portion of the water did not solubilize and was stored in the alpha-type hydrate crystal's network structure as an excess a water phasean an excess water phase, and as a result it could not increase the interlayer spacing, leading to an observed difference from the theoretical value.

After the first test, an alpha-type hydrate crystal and a gel made from alpha-type hydrate crystal and excess water phase were treated with supercentrifugal separation at 40,000× *g* for 3 h; Fig. 32.6 shows the result of the volume of excess water phase separated from the alpha-type hydrate crystal. The water was not separated from samples with water concentrations of less than 80%. When the water concentration was 90%, 5 vol% was separated, and when the water concentration was 95%, 40 vol% was separated into the lower layer. The mass ratio of the water remaining in the upper layer gel was calculated as 0.89 and 0.91, respectively. These values were close to the maximum weight fraction of 0.85, where water can be solubilized between the hydrophilic groups of alpha-type hydrate crystals. These results show that the water separated in the lower layer was the excess water phase that was insoluble between the hydrophilic groups of the alpha-type hydrate crystals and was stored in the network structure of the alpha-type hydrate crystals. Further, the centrifugal separation condition shows that the water between the hydrophilic groups could not be separated from the bimolecular layer of the alpha-type hydrate crystals, indicating that the two types of water show different behavior in terms of stability from an industrial point of view. In other words, the water solubilized between the hydrophilic groups can be seen as water that is unlikely to separate, whereas the water stored in the network structure of the alpha-type hydrate crystals is more prone to separate.

The characterization of these two types of water with different behaviors can be important for industrial applications, and the self-diffusion coefficients of these two types were evaluated by using NMR.

Fig. 32.7 shows the self-diffusion coefficient of alpha-type hydrate crystals with a water concentration of 70% and gel with excess water phase and alpha-type hydrate crystal (90% water concentration). The fitting coefficient of the alpha-type hydrate crystals (70% alpha-type hydrate crystals) against the Gaussian function of the magnetic field strength decay curve was 0.997 and showed a positive correlation (Fig. 32.7A). On the other hand, the gel with excess water phase and alpha-type hydrate crystals (90% water concentration) showed a significantly lower coefficient correlation, and when the two curves were fit, there was high correlation (0.928 and 0.985) (Fig. 32.7B). The self-diffusion coefficient resulting from these two evaluations indicates the two different types of water in the alpha-type hydrate crystals.

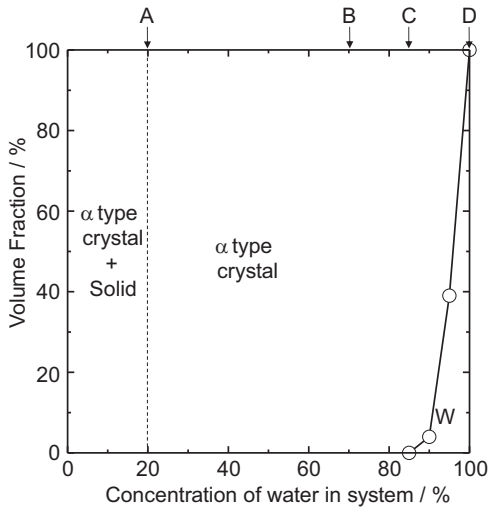



**FIGURE 32.6** Volume fraction of alpha gel and separated water as a function of concentration of water in system. Compositions A, B, C and D correspond to those in the phase diagram (Fig. 32.4).

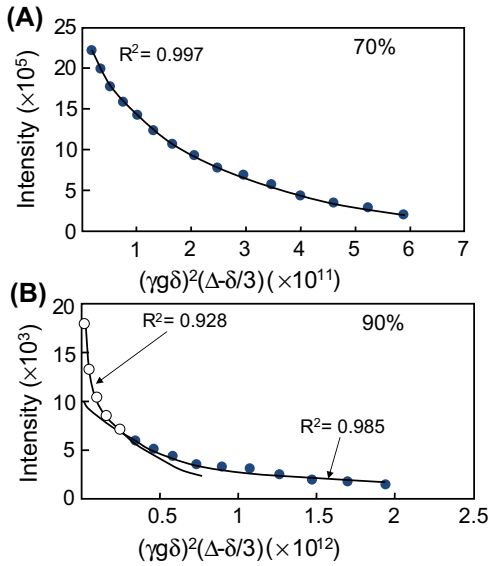



**FIGURE 32.7** Curve fitting of a decrease in signal intensity of NMR (nuclear magnetic resonance) to calculate self-diffusion coefficient ($D_{sel}$) of water in alpha gel one phase (A) and alpha gel plus water [two phase (B)], containing 70% and 90% of water, respectively.

Fig. 32.8 shows the dependency of the self-diffusion coefficient of water molecules with water concentration. When the water concentration was 70%, only "slow water" below $10^{-12}$ $m^2/s$ was found. The slow water self-diffusion coefficient increased with water concentration. On the other hand, "fast water" with a self-diffusion coefficient higher than $10^{-10}$ $m^2/s$ was found along with "slow water" when the water concentration was higher than 85%. The self-diffusion coefficient of "fast water" clearly increased with water concentration and became close to the self-diffusion coefficient of free water: $3.08 \times 10^{-9}$ $m^2/s$. Because the water concentration at 85% is on the phase boundary of the one-phase region of the alpha-type hydrate crystals and the two-phase region of alpha-type hydrate crystals with excess water phase, it was concluded that the "slow water" and "fast water" represent the water solubilized between the hydrophilic groups and the water stored in the network structure of the alpha-type hydrate crystals, respectively.

It is thought that the self-diffusion coefficient of the "slow water" solubilized between the hydrophilic groups of the alpha-type hydrate crystal was dependent on the water concentration due to the spread of interlayer spacing of the alpha gels. It was also understood that the self-diffusion coefficient of the "fast water" stored in the network

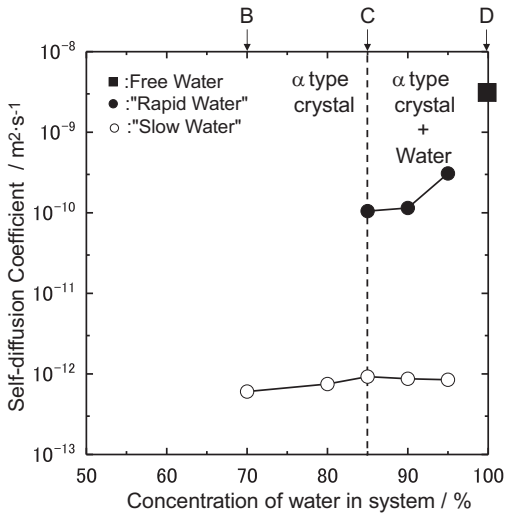



**FIGURE 32.8** Self-diffusion coefficient for water molecules as a function of water concentration in system.

structure of the alpha-type hydrate crystals clearly increased with the water concentration due to the increase of domain size in the water.

When the water concentration is the same, the network structure of the alpha-type hydrate crystal is packed when the domain size is smaller, indicating that a high viscosity can be expected and is stable against water separation. However, there were no methods previously known to compare the domain size in water. In this research using NMR to evaluate the self-diffusion coefficient, the exact domain size cannot be evaluated but comparison and evaluation of samples are allowed. With this method, we can evaluate the stability against water separation, which can be extremely helpful for industrial applications.

## 32.9 CONCLUSION

Skin care cosmetics have an important role in using "the self-preserving function of the skin to restore health, or in other words enhance the body's homeostasis." In addition to this fundamental role, chemical agents with mild effects are added to show various functions. Further, functionality is not the only focus; safety is a factor that must not be neglected, while the comfort of use is also an important factor for commercial products.

Among these various factors, comfort of use is closely related to the advancement of formulation technology. Because oil, water, and humectants are the main ingredients of skin care products, adding excessive surfactants to increase the stability tends to lead to uncomfortable application experiences.

As we have learned in this chapter, recent studies have greatly improved formulation technology and have contributed to establishing new formulation technologies, and now the formulation of skin care cosmetics with both stability and comfort of use has almost been realized. In future research, the focus of the development of skin care products should go beyond solely functional aspects and focus on products that provide a sense of happiness or satisfaction in the product itself.

## References

1. Elias PM. *Advances in Lipid Research*. Academic Press; 1991.
2. Koyama J, et al. *J Soc Cosmet Chem* 1984;**35**:183.
3. Nakayama Y, et al. *J Soc Cosmet Chem Jpn* 1986;**20**:111.
4. Shinoda K, Friberg S. *Emulsions and Solubilization*. New York: Wiley-Interscience; 1986.
5. Schulman JH, Cockbain EG. *Trans Faraday Soc* 1940;**36**:551.
6. Watanabe K, et al. *J Soc Cosmet Chem Jpn* 2012;**46**:287.
7. Watanabe K, et al. *IFSCC Magazine* 2004;**7**:309.
8. Tomomasa T, et al. *J Oleo Sci* 1988;**37**:1012.
9. Sekine T, et al. *J Surfactant and Deterg* 1999;**2**:309.

10. Watanabe K, et al. *J Soc Cosmet Chemists Jpn* 2009;**43**:185.
11. Shinoda K, et al. *J Colloid Interface Sci* 1969;**30**:258.
12. Sagitani H. *Dispersion Sci Technol* 1988;**9**:115.
13. Suzuki T, et al. *J Colloid Interface Sci* 1989;**129**:491.
14. Kumano Y, et al. *J Soc Cosmet Chemists* 1977;**28**:285.
15. Yamaguchi M, et al. *J Oleo Sci* 1991;**40**:491.
16. Watanabe K, et al. *J Oleo Sci* 2012;**61**:29.
17. Yamaguchi M, et al. *J Chem Soc of Jpn* 1989;**1**:26.
18. Yamagata Y, et al. *Langmuir* 1999;**15**:4388.
19. Suzuki T, et al. *J Colloid Interface Sci* 1989;**129**:491.
20. Junginger H, et al. *J Soc Cosmet Chem* 1984;**35**:45.
21. Lindman B, et al. *J Colloid Interface Sci* 1981;**83**:569.

CHAPTER

# 33

# Body Care Cosmetics

*T. Sakai*

**Material Science Research Laboratories, Kao Corporation, Wakayama-shi, Wakayama, Japan**

## 33.1 INTRODUCTION

The development of body care cosmetics has been driven by the pursuit for consumer-perceivable benefits that result in healthy, beautiful skin. Nowadays, body care cosmetics include not only body cleansers but also moisturizers, sunscreens, skin whiteners, and chemical peels. Cosmetics producers throughout the world continue to study and develop novel technologies and formulations to meet the diverse needs of consumers for healthy skin. The body care market, which is mainly in western Europe, North America, and Japan, is saturated compared with the facial care market. However, economic growth in the Middle East, Africa, and Latin America has opened up new markets for body care products.[1] Looking at body care technologies from a broader perspective, one can see that most of them considerably overlap facial care technologies. What is the most important original category in the field of body care cosmetics? It must be body cleansers. This section introduces the technologies and history of body cleansers.

## 33.2 BODY CLEANSERS

Body cleansers are classified into bar soaps and liquid body washes (liquid soaps, shower gels). Bar soaps are used in most areas of the world, but liquid body washes are preferred in East Asia. This preference may be attributed to the area's culture, the "hardness" of the water, personal preference for the feel of the skin made by the cleanser (which could also be related to the water hardness), and local bathing customs (i.e., bathing versus showering). Regardless of the type of body cleanser, the consumers' needs are the same. Namely, consumers desire mild cleansers with excellent foaming properties that leave the skin feeling clean and moist. The original purpose of keeping the body clean was the focus of body cleanser development in the distant past, and the development of technologies that can produce the previously mentioned sensations has been the most important challenge for a long time. The history of body cleansers is very different from that of household detergents like laundry detergents and dishwashing soaps. The goals for household detergents have been made to achieve environmentally safe and excellent detergency.

First, the technologies forming the basis of body cleansers are introduced along with the development history. How to design the excellent foaming properties and a reconsideration of detergency are then discussed.

## 33.3 MILDNESS TO SKIN AND SENSORY FEELING

### 33.3.1 History

The origin of washing the body and keeping it clean and beautiful is unclear. It may have stemmed from ancient religious rites, a latent demand to be clean, or medical care to heal wounds or promote relaxation. The ruins of large baths indicate bathing was a part of human culture in ancient Rome.

*Cosmetic Science and Technology: Theoretical Principles and Applications*
http://dx.doi.org/10.1016/B978-0-12-802005-0.00033-1



Copyright © 2017 Elsevier Inc. All rights reserved.

It is known that fatty acid soap was produced in ancient Babylon in approximately 3000 BC.[2] Records also show that it was used as a detergent by the ancient Romans almost 2000 years ago. The Romans used fatty acid soap made from fats and wood ash to wash their bodies.[3] In the 8th century, fatty acid soaps made from olive oil started being produced in Spain or Italy.[4] The soap industry developed in Europe by 800 AD, but soap was considered a luxury for nobility.[5]

All detergents were made from fatty acid soap until the 1920s. Fatty acid soap is actually an excellent detergent, having good foaming properties and high detergency. However, one of its drawbacks is that it easily forms a water-insoluble calcium salt "scum" when used in hard water. This solid precipitates on the surfaces of hair, skin and fabric, leading to a feeling of roughness. This scum also leaves a "bathtub ring" inside bathtubs after the water is drained. Moreover, fatty acid soap solutions can irritate the skin because of their alkaline pH. In the 1930s, German chemical companies developed neutral pH surfactants that were milder to the skin. Their efforts resulted in a variety of pH-neutral synthetic surfactants, called "detergents." At first, these detergents were industrialized as textile-treating agents that did not roughen the surface of fabrics. They were finally applied to shampoo or body cleansers as mild detergents in the 1950s.[6] The history of modern body cleansers that claim a mild effect on the skin (skin mildness) and distinct consumer-perceivable properties stemmed from these early mild detergents.

## 33.3.2 Skin Mildness

Although fatty acid soaps have excellent foaming properties, consumers dislike the scum deposits in hard water that give the solution a displeasing appearance and leave their skin feeling rough. This rough feeling does not convey an image of healthy, beautiful skin but rather an image of uncleanliness. "Combination bars" made of a mixture of fatty acid soaps and synthetic surfactants and "syndet bars" almost made entirely of synthetic surfactants were developed in North America and western Europe to be mild to the skin.

Synthetic surfactants, which have a lower pH in solution than fatty acid soaps, played a very important role in bringing the benefits of washing body using skin-milder bars to consumers. Cleansing the body with an alkaline solution is thought to easily damage the skin because the pH of the skin surface is weakly acidic. Therefore, cleansing at a neutral or much lower pH is preferred. Intercellular lipids and sebum contain an abundance of fatty acids. Cleansing skin using an alkaline solution results in excess degreasing due to saponification and self-emulsification of the fatty acids of the skin surface. This excessive degreasing is thought to vitiate the ability of the skin to act as a barrier and decrease skin moisture, resulting in rough, dry skin. Therefore, synthetic surfactants, which have a neutral pH, not only leave the skin feeling good but are also moisturizing and perceivably mild. Well-known anionic surfactants sodium cocoyl isethionate (SCI), sodium polyoxyethylene (POE) and alkyl ether sulfate (AES) have been developed based on this background and are still being applied to a number of body cleansers as primary surfactants.

## 33.3.3 Primary Surfactants for Body Cleansers

When synthetic surfactants appeared in the cosmetics field in the 1950s, consumers recognized the superior skin-mildness benefits for body cleansers. The following three surfactants have been applied to body cleansers for more than 50 years.

### *33.3.3.1 Sodium Alkyl Sulfate*

The molecular structure of sodium alkyl sulfate (AS) is shown in Fig. 33.1. AS having a hydrophobic dodecyl group is called sodium dodecyl sulfate (SDS) or sodium lauryl sulfate (SLS). It is easily produced from fatty alcohol. Because AS has good chemical stability, it can be used over a wide range of pH values.

SDS has excellent foaming properties regardless of water hardness.[7] AS commonly includes small amounts of fatty alcohol, which is the raw material, as an impurity. This impure AS product actually has better foaming properties than the highly pure product. This suggests that a small amount of fatty alcohol included as an impurity works as a foam booster.[8–10]

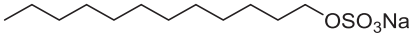



FIGURE 33.1 **Molecular structure of alkyl sulfate salt.** This structure shows sodium dodecyl sulfate.

Because AS has a comparatively high Krafft point compared with the other synthetic anionic surfactants, it is more suitable for a syndet or combination bar.

#### 33.3.3.2 *Sodium Cocoyl Isethionate*

SCI is the world's most common synthetic surfactant used for body cleansers, especially in bar form (Fig. 33.2). It can be directly prepared via dehydration−condensation of fatty acids and sodium isethionate at a high temperature. The ester-linkage is easily hydrolyzed to the above-mentioned two raw materials in an aqueous solution (especially in an alkaline solution). Therefore, SCI is preferably applied to syndet/combination bars rather than to liquid body washes, considering the preservation stability of the detergent products.

SCI has excellent properties regardless of pH and is not affected by water hardness when used as a detergent. It provides a very creamy and rich lather.

SCI not only provides a consumer-perceivable smooth and moisturizing feeling but also is actually one of the mildest surfactants for skin.[11] Numerous studies have shown the high tolerance of skin for SCI.[12]

#### 33.3.3.3 *Sodium Polyoxyethylene Alkyl Ether Sulfate*

The molecular structure of AES, which corresponds to AS having a POE unit between the hydrophobic group and the head unit, is very simple, as shown in Fig. 33.3. AES is chemically stable at almost all pH values, and the preservation stability of the solution is also excellent because its Krafft point is lower than that of fatty acid soaps and AS. Like AS, AES can be produced industrially very easily using a sulfation process.

AES exhibits greater water solubility and generates milder skin irritation compared with many other surfactants. Its properties remain stable in water over a wide range of pH values, levels of hardness, and electrolyte concentrations. Moreover, AES is very compatible with many kinds of anionic, cationic, nonionic and amphoteric surfactants and polymers in water and often exhibits some synergetic effects when with such other ingredients. Although its foam volume is slightly inferior to that of other anionic surfactants, the foam volume can be improved by mixing it with foam boosters. The usefulness and convenience of AES are directly linked to its reliability as a primary surfactant, leading to its use globally as a standard anionic surfactant. In fact, AES is a necessary primary surfactant for all liquid detergents worldwide, including liquid body washes, shampoos, and dishwashing detergents. The only potential weak point of AES is that it can only be applied to liquid detergents because it is very difficult to use in a solid state at a room temperature due to its low Krafft point and hygroscopicity.

### 33.3.4 Seeking Better Skin Mildness

As previously mentioned, the desire of consumers for a more comfortable skin feeling and better skin mildness led to the transition from fatty acid soaps to body cleansers with synthetic surfactants. As the market grew for such body cleansers using synthetic surfactants, the requirements for better skin mildness increased. Generally, anionic surfactants have been thought to irritate skin more than other types of surfactants, but they tend to exhibit good foaming, have high detergency for sebum due to their oil-dispersing ability, and produce a smooth and clean feeling. Nonionic surfactants, which commonly have weak foaming properties, could potentially offer better skin mildness. Therefore, formulations with better skin mildness could be produced by applying anionic surfactants as the primary surfactant and by mixing anionic surfactants and other materials to make the formulation more nonionic.

#### 33.3.4.1 *Superfatting*

"Superfatting" is the addition of small amounts of non-neutralized fatty acids to anionic surfactant-based (including fatty acid soaps) formulations. This has been applied to numerous body cleansers for a long time.

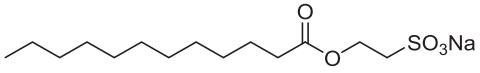



FIGURE 33.2 **Molecular structure of fatty acid isethionate salt.** This structure shows sodium cocoyl isethionate (SCI). SCI has the mixed hydrophobic acyl group, which has a coco-fatty acid composition (RCO═C8−C18).

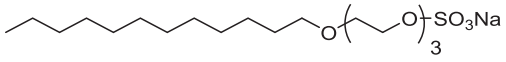



FIGURE 33.3 **Molecular structure of polyoxyethylene alkyl ether sulfate salt.** This structure shows sodium polyoxyethylene (3) dodecyl ether sulfate. Generally, the polyoxyethylene unit has a distribution of chain lengths.

Because superfatting can improve the foaming properties of body cleansers, it can prevent skin dryness. This effect is thought to be caused by the deposit and spontaneous barrier formation of a water-insoluble derivative, "acid soap"—consisting of fatty acids and neutralized fatty acids—onto the skin during the rinsing (diluting) process.[13] It is a very useful, convenient, and inexpensive way to produce formulations that improve both the skin mildness and foaming properties of body cleansers. However, adding an excess amount of fatty acid increases the antifoaming properties. Further, it likely has a negative effect on the preservation stability of liquid cleanser products because of the easy deposition of insoluble fatty acids in bottles.

#### *33.3.4.2 Mixed Surfactant System*

It is well known that the addition of cationic surfactants to anionic surfactant solutions can drastically change the solution characteristics. These effects are attributable to the formation of a complex consisting of anionic surfactant and cationic surfactant molecules over a wide range of mixing ratios. This complex so formed has often been called a "catanionic surfactant." The electrostatic neutralization between two opposite kinds of surfactants can provide a solution with nonionic characteristics and enhanced hydrophobicity. For example, there is a drastic decrease in the critical micelle concentration (CMC) and an increase in the detergency. Although these drastic changes in the properties can be achieved easily when quaternary ammonium salts or amine oxides are used as cationic surfactants, the systems become remarkably difficult to use due to the deposition of the hydrophobic complex or the excessive degreasing ability for cosmetic use. In liquid body wash systems, betaines, which are generally highly water soluble, are formulated commonly as cationic surfactants.

The skin irritation from surfactants might be related to the CMC. This is based on the hypothesis in physical chemistry that skin irritation might be caused by the adsorption and penetration of surfactant "monomers" into the skin and exacerbated by an increase in the monomer concentration (i.e., the CMC). There are a number of reports on this relationship for mixtures of anionic surfactants and betaines.[14,15] In fact, the skin irritation from mixtures of anionic surfactants and betaines decreases with the reduction of the CMC. This mixture system has been applied to not only body cleansers but also a number of liquid detergents. However, the recent progress of studies on the relationship between skin irritation and surfactants has suggested that lowering the charge density of anionic surfactants with nonionic surfactants and betaines stabilizes the mixed micelles and prevents the monomers from being released.[16] This is an ongoing discussion between chemists and biologists.

#### *33.3.4.3 Mild Anionic Surfactants*

In the 1980s, some Japanese companies were involved in the development of lesser-irritant anionic surfactants for cosmetic products. Acyl glutamate salt (Fig. 33.4), an amino acid derivative, and mono-alkyl phosphate salt (Fig. 33.5) were developed and used in many skin cleansers as supermild primary surfactants.[17–19] Both of these salts are weak-acid anionic surfactants. Interestingly, these new anionic surfactants are dibasic acid salts and can be used, when needed, for a monobasic or dibasic salt, respectively. These surfactants can be used not only at neutral pH but also at the same weakly acidic condition, such as the pH of human skin. Additionally, they have good foaming properties and make the skin feel comfortable. Because they improved the negative images associated with previous anionic surfactants, they helped the market for supermild liquid body washes grow remarkably in Japan and East Asian countries. Although liquid body wash was thought to be only a convenient detergent to use in the shower, such a highly functionalized body wash has been one of the leading cosmetic products in East Asia. These surfactants were applied to some bar soaps in the 1990s.

Recently, a much milder anionic surfactant, alkyl ether carboxylate salt (AEC; Fig. 33.6), has been applied to liquid body washes and facial cleansers as a primary anionic surfactant. This material can reduce the skin and eye irritation

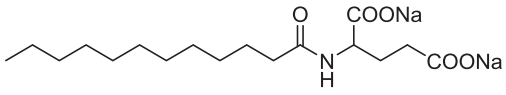



FIGURE 33.4 **Molecular structure of acyl glutamate salt.** This structure shows disodium dodecanoyl glutamate.

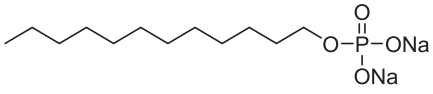



FIGURE 33.5 **Molecular structure of mono-alkyl phosphate salt.** This structure shows disodium mono-dodecyl phosphate.

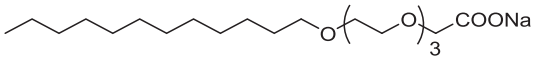



FIGURE 33.6 **Molecular structure of alkyl ether carboxylate salt.** This structure shows sodium polyoxyethylene (3) dodecylether carboxylate. Generally, the polyoxyethylene unit has a distribution of chain lengths, like alkyl ether sulfate.

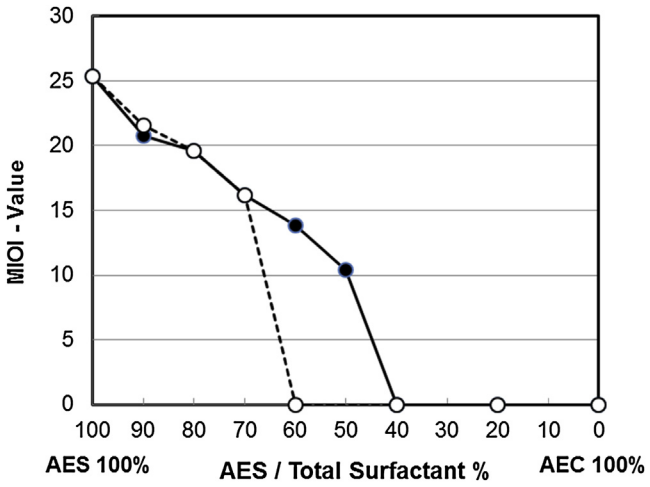



FIGURE 33.7 **Ability of alkyl ether carboxylate (AEC) to reduce eye (skin) irritation of alkyl ether sulfate by red blood cell test.**[20] The test substance (0.1%) is mixed with a suspension of isolated red blood cells and hemoglobin, and the denaturation of hemoglobin is photometrically determined. A mean index of ocular irritation (MIOI) value ≤5 indicates nonirritant; ≤10, slight irritant; ≤20, moderate irritant; ≤40, irritant; and >40, strong irritant.[21,22] Filled circle: AKYPO RLM45, open circle: AKYPO RML100; AKYPO is the trade name of AEC by Kao Chemicals Europe.

of the anionic surfactant, AES, synergistically.[20] Although the addition of a small amount of AEC only decreases the eye irritation in an additive manner, the addition of a certain ratio of AEC substantially reduces the irritation much like that of AEC itself (Fig. 33.7). This effect might be similar to that of the mixed system of anionic surfactants and betaines mentioned previously. While the electrostatic interaction works between the two kinds of surfactants, this characteristic interaction between AES and AEC is not expected. Novel technologies using anionic surfactants are under development.

### 33.3.5 Cultural Orientation

In some Asian countries, including Japan, that have soft water, the way fatty acid soaps make the skin feel has been positively accepted, this is in contrast to what has been accepted in western Europe and North America. In such countries, only small deposits of scum are formed even when fatty acid soaps are used with tap water. Rather than a smooth feeling, the scum results in a moderately squeaky feeling that evokes a feeling in Asian consumers of being clean and refreshed. There are still many countries with body cleansers that include fatty acid soap as the primary surfactant because many consumers prefer the way their skin feels after using these types of body cleansers. For liquid body wash, the potassium salt of fatty acids is generally preferred over the sodium salts, which have a higher Krafft point, because the formulations are easily stabilized. Further, the shorter hydrophobic chain length around C12 is generally selected rather than the C16−18 length used for bar soaps. As previously mentioned, the mainstream body cleansers in Japan are supermild liquid body washes. These products have the same weak-acid pH (5−6) as that of human skin. Of course, although synthetic surfactants have been used as the primary surfactants together with AES and other co-surfactants, the feeling they leave on the skin has been matched to the slightly squeaky feeling left by fatty acid soap.

## 33.4 FOAMING TECHNOLOGY

### 33.4.1 Foam Boosting

Generally, excellent foaming has not been thought to be directly related to the washing functions and properties of body cleansers. However, foaming can make people feel good and give them a sense of cleanliness while washing

their bodies. Therefore, excellent foaming is one of the most important sensory properties to consider when designing formulations. While fatty acid soap can basically provide creamy and voluminous foam, the excellent foaming properties are easily overshadowed by the deposit of scum under hard water conditions. Moreover, because human sebum contains a large amount of fatty acids, the raw materials of soaps, soaps have a remarkable affinity for human sebum. When a large amount of sebum is left on the skin surface, the foaming properties are substantially degraded because soap molecules are preferentially adsorbed onto the sebum surface.

Synthetic anionic surfactants, such as SCI and AES, are strong acid salts and do not easily form water-insoluble calcium or magnesium salts. Therefore, they lather well even in hard water. On the other hand, such foam is not resistant to fat and sebum, and the bubbles can easily rupture. To overcome this serious problem and provide a comfortable feeling to consumers, focus has been placed on the development of foam-boosting technologies.

### 33.4.2 Foam Boosters

"Foam boosting" means improving the foaming properties by the addition of small amounts of co-surfactants called "foam boosters." There are several kinds of foam boosters in the surfactant markets, with the main ones being nonionic and amphoteric boosters. The use and effects of these boosters are diverse.

Fatty acid monoethanolamide (MEA), fatty acid diethanolamide (DEA), and fatty acid *N*-methylethanolamide (NMEA) have often been applied as foam boosters (Fig. 33.8). NMEA is mainly used in liquid cleansers to increase the foam volume. Although DEA, which was the most useful booster for a number of years, is very mild to human skin, the use of DEA has decreased recently due to consumers' anxieties about the possible generation of nitrosoamines. MEA has a lower water solubility than DEA, which makes its formulation difficult. The foam-boosting properties of MEA are similar to but slightly weaker than those of DEA. NMEA has excellent foam-boosting properties.[21,22] Because it has low viscosity at room temperature, NMEA can provide good stability to liquid formulations but might be difficult to apply to bar soaps.

As amphoteric foam boosters, alkylamidopropyldimethyl betaines (APBs) and alkyldimethylbetaines (ABs) are mainly used for cosmetics (Fig. 33.9). They can give cleansers more-stable and richer foam. Nowadays, these are absolutely imperative for cosmetic cleansers. Their characteristics and foam-boosting abilities are very similar. The reason why APBs have been used more often is because of their excellent water solubility and compatibility with many other kinds of surfactants. When stronger foam-boosting effects are required, ABs might be a much better choice. Further, alkyldimethyl amine oxides (Fig. 33.9) are often chosen when detergents, such as household cleaners, require much better detergency.

### 33.4.3 Foaming Properties

Foaming properties are generally divided into foamability and foam stability.[23] "Foamability" refers to how rapidly the foam is generated. In other words, it is the ability to form bubbles easily. This property is recognizable by the large volume of foam that is generated instantaneously. Foam with excellent foamability is formed easily with only slight mechanical power, such as rubbing the hands together lightly. Foamability of surfactant aqueous solutions can be evaluated by the foam volume, which is measured by using the Ross–Miles method.[24] However, the results might be greatly affected by the effects of foam stability. Although correct foamability measurements are extremely difficult, methods to evaluate the foamability and foam stability, respectively, using both a custom

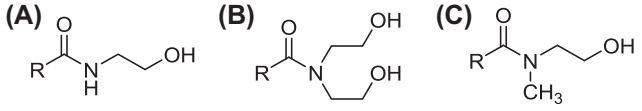



FIGURE 33.8 **Molecular structure of fatty acid alkanolamide derivatives:** (A) fatty acid monoethanolamide, (B) fatty acid diethanolamide, and (C) fatty acid *N*-methylethanolamide.

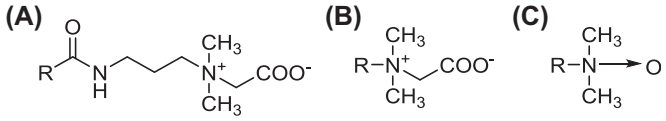



FIGURE 33.9 **Molecular structure of betaine derivatives:** (A) alkylamidopropyldimethyl betaine, (B) alkyldimethyl betaine, and (C) alkyldimethyl amine oxide.

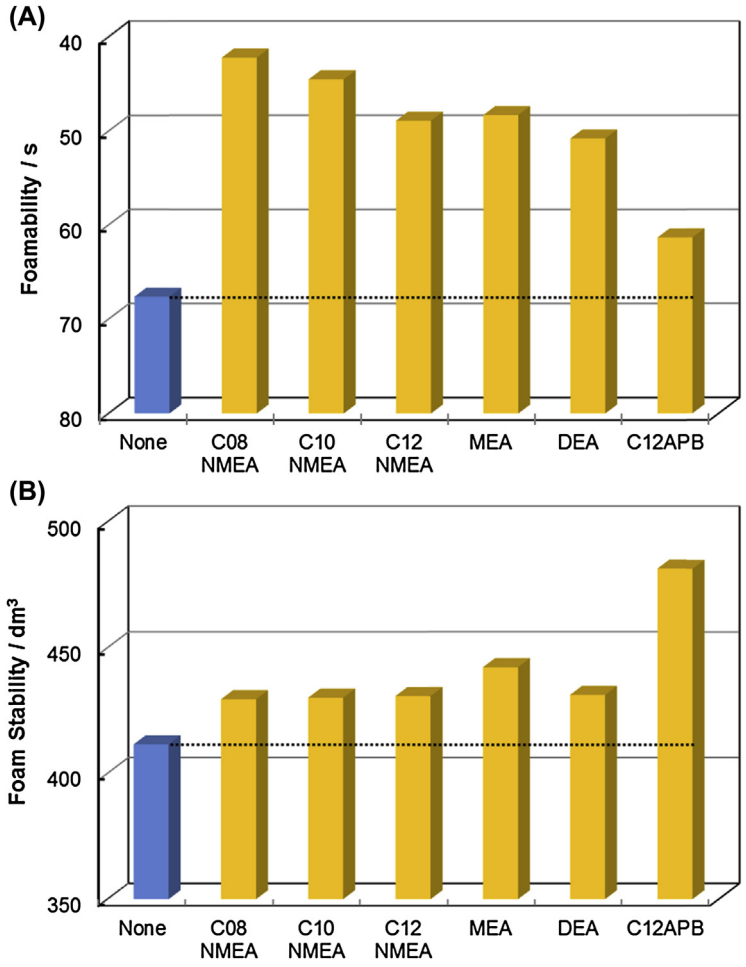



FIGURE 33.10 **Foam-boosting effects of co-surfactants for primary anionic surfactant, alkyl ether sulfate (AES), at 25°C.**[21,22] "None" indicates the AES alone in an aqueous solution without co-surfactants, and the others are the mixed solutions of AES and the respective co-surfactant. Each result represents the best foam-boosting ability of each co-surfactant at different mixed molar ratios of AES and co-surfactants, respectively. (A) Foamability test: Foamability is evaluated by the time to generate 50 mL of foam using a custom foam tester. Faster foam generation indicates better foamability. AES/co-surfactant molar ratios are C8 fatty acid *N*-methylethanolamide (NMEA): 0.9/0.1; C8 NMEA and C12 NMEA: 0.7/0.3; fatty acid monoethanolamide (MEA): 0.8/0.2: fatty acid diethanolamide (DEA), and alkylamidopropyldimethyl betaine (APB): 0.6/0.4. (B) Foam stability test: Foam stability is evaluated by the initial foam volume using the Ross–Miles method.

foam tester and the Ross–Miles method have been shown.[21,22] Nonionic foam boosters, such as DEA, MEA, and NMEA, are suitable as a foamability booster for anionic primary surfactants (Fig. 33.10A).

"Foam stability" refers to the ability to maintain the foam that has been already formed.[23] APBs and ABs are excellent foam stabilizers. The excellence of APB as a foam stabilizer for the commercial anionic primary surfactant, AES, can be seen in Fig. 33.10B. Primary anionic surfactants and betaine molecules co-adsorb at the air–water interface, and the electrostatic repulsion between anionic surfactant molecules is shielded by the cationic units of APB molecules. As a result, the stabilization ability of betaines might be attributable to the formation of closely packed monolayers with anionic surfactants at the air–water interface.

Unfortunately, foamability and foam stability might be contradictory properties, as shown in Fig. 33.10A and B.[21,22] Therefore, both characteristics cannot be improved by a single type of foam booster. This fact has been known empirically, and mixing nonionic boosters and amphoteric boosters together with the primary anionic surfactants has been used as the standard method globally to formulate liquid cleansers.

### 33.4.4 Superfatting for Foam Boosting

Because of their superfatting effects, fatty acids and fatty alcohols are used to improve both the foaming properties and skin mildness of mixed surfactant systems. Unfortunately, fatty acids and fatty alcohols have a lower water

solubility. Adding a large amount of them to formulations enhances the defoaming properties and increases the deposition of solids in the formulations. Therefore, only a small amount of them can be used.

Mixing fatty acids with anionic surfactants drastically increases the foam volume. Changing the pH of fatty acid soap aqueous solutions changes the amount of fatty acids included in the systems. Miles and Ross found specific pH values at which the maximum foam volume of fatty acid soap solutions is produced.[25] When AS includes fatty alcohol, one of the raw materials of AS, as an impurity, the AS solution generates more voluminous foam than the pure AS solution.[9] In this system, the rate of drainage of AS solution through foams decreases, leading to an increase in foam stability.[8] Vollhardt and Emrich studied the monolayer formed spontaneously on the air–water interface of an AS aqueous solution including some fatty alcohol and found that it resulted in a condensed monolayer of fatty alcohol on the surface.[26] This solid monolayer might prohibit the drainage of AS solution through the foam. Moreover, the addition of stearic acid to SCI bar soap forms a creamier and more-viscous foam with small-diameter bubbles.[27] In any case, the foam-boosting effects of superfatting might be attributed to the formation of a solid-like monolayer by fatty acids or fatty alcohols.

## 33.5 RECONSIDERATION FOR SATISFYING BOTH DETERGENCY AND SKIN MILDNESS

Cleansing, which is surely the most important role of body cleansers, has been overlooked as the main benefit that should be provided for consumers. More than a century ago, bar soaps, which focused on the hygiene benefits, were popular. Nowadays, the main benefits for consumers have shifted to more distinct perceivable properties, such as skin care, skin feel, medicinal properties, and foaming properties. With the growth of global markets for such body cleansers, manufacturers have also been involved in developing such commercial distinctions, which can only be evaluated by sensory evaluation tests. However, global disasters, advances in medicine, and the introduction of the latest mild body cleansers to developing countries have shifted the focus back to cleansing and hygiene. Body cleanser manufacturers now seem to be reconsidering studies on the original role of the "cleanser."

For more than a century, achieving both high detergency for dirt on the skin and mildness to the skin was considered to be difficult. Surfactants having a high detergency remove too much sebum and tend to defat the skin excessively. High detergency is also believed to irritate the skin and reduce the ability of the skin to act as a barrier. Therefore, for body wash products, developing formulations that provide the maximum sensuous cleanliness has been pursued using surfactants that are as mild to the skin as possible. Recently, advances in surfactant chemistry have driven the development of some novel technologies to achieve both good detergency and skin mildness.

As mentioned previously, the foam of surfactant solutions, which is one of the most important characteristics for body cleansers, was thought to be unrelated to detergency. However, studies on the functions of foam have shown that foam composed of small bubbles has two interesting abilities: detergency and skin mildness.[28,29]

Sonoda et al. studied the correlation among foam bubble size, the amount of surfactant in foam water drainage, and the amount of surfactant penetrating into the skin during washing with foam. The size of the foam bubbles affected the volume and concentration of the water drainage.[28] Smaller bubbles increase the air–water interface in the foam and allow the membrane to hold much more water, which maintains the foam structure and reduces water drainage. On the other hand, the amount of surfactant penetrating the skin increases with increasing size of the foam bubbles. This means that controlling the bubble size in foam can control the effects of surfactants on skin. These results provide a novel insight into a way to formulate milder skin cleansers. Moreover, researchers have discovered another novel phenomenon of foam that hints at a new way to formulate skin cleansers with mild and high detergency. Foam composed of small bubbles of a fatty acid soap solution spontaneously absorbs liquid oil without defoaming (Fig. 33.11).[29] This phenomenon does not occur with larger bubble sizes, which clearly indicates that foam with smaller bubbles can also provide excellent detergency for liquid sebum on the skin. Although the mechanisms have not been clarified yet, detailed observations of liquid oils in foam films have revealed that this phenomenon is not due to capillary action because the liquid oil does not wet the air–water interface in the foam. In this way, foam having much smaller bubbles might achieve both high detergency and skin mildness. It could be a "classic yet new" approach for body cleansers.

Generally, mild anionic surfactants, which have been commercially applied to numerous body cleansers throughout the world, have inferior detergency compared with other kinds of surfactants, such as nonionic surfactants. Although the anionic surfactant AEC is one of the mildest surfactants,[20] it has been recently clarified as having excellent detergency for the sebum on skin.[30] AEC molecules can aggregate to form acidic soap composing salt-type AEC and acid-type AEC.[31] The AEC molecules and fatty acids in sebum likely promote aggregation. This

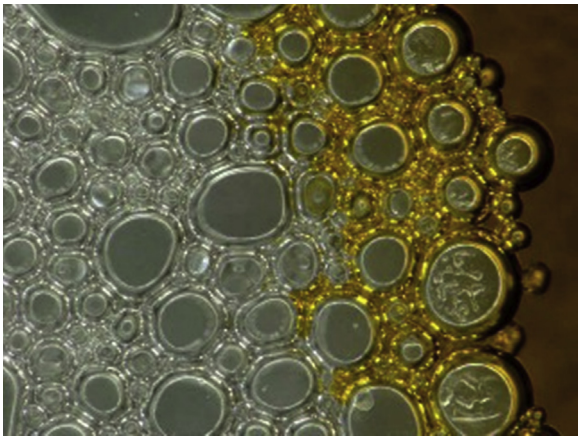


FIGURE 33.11 **Foam of a soap solution spontaneously absorbs a considerable volume of liquid oil without any external forces.** *This photograph was provided by the skin care research laboratories Kao Corporation.*

heterocomplex formation might drive the spontaneous penetration of AEC aqueous solution into the sebum phase, resulting in the lamellar formation in the oil phase. This characteristic of an AEC solution results in excellent detergency of sebum with only slight rubbing. Thus, even a mild surfactant can cleanse the skin well if it can interact specifically with the sebum components. This example highlights the potential for cleansers with high detergency and skin mildness.

## 33.6 CONCLUSION

The history of body cleanser development has been greatly influenced by consumers' desire for skin mildness and a comfortable feeling lather. Many synthetic surfactants and many mixing technologies for various surfactants have been developed to satisfy the diverse needs of consumers. Nowadays, focus has returned to the original purpose of body cleansers (i.e., high detergency) from the perspective of consumers' needs.

Further, society is becoming more concerned with safety for both people and the environment, and there is increasing demand for a shift to more natural products. Consequently, negative campaigns against surfactants without clear, science-backed reasons are frequently seen. Most of the present commercial surfactants for body wash products have been confirmed to be scientifically safe to humans and the environment. Therefore, most consumers can use them without concern. However, spread of the desire for safety into mainstream society may fuel criticism against surfactants, making it more difficult to development novel, functionalized surfactants. Consequently, scientists and formulators developing surfactants and body cleansers might be required to invent new technologies to make full use of the existing surfactants or levels of skin mildness.

## References


1. Tyrimou N. *Cosmet Toilet Sci Appl* 2015;**130**(8):8–9.
2. Willcox M. Soap. In: *Hilda Butler. Poucher's perfumes, cosmetics and soaps*. 10th ed. Dordrecht: Kluwer Academic Publishers; 2000. p. 453.
3. Aretaeus. *The Extant Works of Aretaeus, the Cappadocian*. tr. Francis Adams (London)**238 and 496**; 1856. noted in Dols MW. Leprosy in medieval Arabic medicine. *J Hist Med* 1979:316 note 9.
4. Bistline Jr RG. Anionic and Related Lime Soap Dispersants. In: Stache H, editor. *Anionic surfactants: organic chemistry. Surfactant science series*, vol. 56. CRC Press; 1996. p. 632 [Chapter 11].
5. Barel AO, Paye M, Maibach HI, editors. *Handbook of cosmetic science and technology.* Marcel Dekker; 2001 [Chapter 42].
6. Diez R. *IFSCC Mag* 2009;**12**(3):188–93.
7. Shore S, Bergen IR. In: Linfield WM, editor. *Anionic surfactants, part I*. New York: Mercel Dekker; 1976. p. 136–7.
8. Miles GD, Shedlovsky L, Ross J. *J Phys Chem* 1945;**49**:93.
9. Schick MJ, Fowkes FM. *J Phys Chem* 1957;**61**:1062.
10. Sawyer WM, Fowkes FM. *J Phys Chem* 1958;**62**:159.
11. Middleton JD, Soc J. *Cosmet Chem* 1969;**20**:399–412.
12. Frosch PJ, Kligman AM. *J Am Acad Dermatol* 1979;**1**:35–41.
13. Murahata RI, Aronson MP, Sharko PT, Greene AP. In: Rieger MM, Rhein LD, editors. *Surfactants in cosmetics*. 2nd ed. New York: Mercel Dekker; 1997. p. 315–6.

14. Lomax EG. In: Lomax EG, editor. *Amphoteric surfactants*. 2nd ed. New York: Marcell Dekker; 1996. pp.286–289.
15. Dominguez JG, Balaguer F, Parra JL, Palejero C. *Int J Cosmet Sci* 1981;**3**:57.
16. Cassiday L. *Inform* 2016;**27**:694–9.
17. Kaneko D, Sakamoto K. In: Barel AO, Paye M, Maibach HI, editors. *Handbook of cosmetic science and technology*. New York: Marcell Dekker; 2001. p. 499–510.
18. Imokawa G, Tsutsumi H, Kurosaki TJ. *Am Oil Chem Soc* 1978;**55**:839–42.
19. Thau P. In: *Surfactants in cosmetic*. 2nd ed. New York: Marcel Dekker; 1997. p. 297.
20. *Personal care booklet*. Kao Chemicals Europe; 2007.
21. Pape WJW, Pfannenbecker U, Hoppe U. *Mol Toxicol* 1987;**1**:525–36.
22. Sakai T, Kaneko Y. *J Surfact Deterg* 2004;**7**:291–5.
23. Wilson AJ. In: Prud'homme RK, Khan SA, editors. *Foams*. New York: Marcel Dekker; 1995. p. 259–68.
24. American Society of Testing and Materials Standards (ASTM Standard) D 1173.
25. Miles GD, Ross J. *J Phys Chem* 1944;**48**:280–90.
26. Vollhardt D, Emrich G. *Colloids Surf A* 2000;**161**:173.
27. Mukherjee S, Wiedersich H. *Colloids Surf* 1995;**95**:159–72.
28. Sonoda J, Sakai T, Inoue Y, Inomata Y. *J Surfact Deterg* 2014;**17**:59–65.
29. Sonoda J, Sakai T, Inomata Y. *J Phys Chem B* 2014;**118**:9438–44.
30. Kagaya M, Sakai T. In: *10th World Surfactant Congress and Business Convention (CESIO 2015 Istanbul)*; 2015. p. 32. Istanbul (Turkey).
31. Sakai T, Ikoshi R, Toshida N, Kagaya M. *J Phys Chem B* 2013;**117**:5081–9.

CHAPTER

# 34

# Makeup Cosmetics

*N. Nakamura*
**KISHI KASEI CO., LTD., Yokohama, Japan**

## 34.1 INTRODUCTION

Makeup cosmetics are used to protect the skin and to provide safety and comfort, but their main purpose is as a beauty product to make the face and skin attractive. There are base makeup products and decorative makeup products; the former are used to hide imperfections such as stains and wrinkles, to adjust skin tone, and to add firmness or translucence to make the skin look beautiful. The latter are used to color and decorate the body or for contouring to create a more healthy-looking or attractive impression.

As cosmetics that are applied to the face, skin care products and makeup products are often compared. The difference between these two is frequently discussed from various perspectives, but here we will define the two with the following: Skin care products are products that are valued even when used in complete darkness. For example, imagine if a person with dry skin applies skin lotion and feels reduced dryness and more moisture. This person will value its effect even if she or he uses it in complete darkness.

On the other hand, what is makeup? Needless to say, makeup cannot be appreciated in complete darkness. The effects of makeup cannot be appreciated if it is not seen. In other words, makeup can only be appreciated when there is light, and light is the most important factor that is unavoidable when discussing makeup.

In this chapter, we will first focus on foundations as the most prominent example of makeup cosmetics and look at their formulation methods and types.[1,2] Then, we will look at the cosmetic effects of makeup (visual effects) through recent studies in relation to light as mentioned earlier. Finally, consider some other effects (nonvisual effects) of makeup.

## 34.2 TYPES AND CHARACTERISTICS OF FOUNDATIONS

The technology involved in foundations and their formulations, functions, and optical effects in makeup finish has progressively advanced. The results of such progress have led to the introduction of various foundations at conferences such as the International Federation of Societies of Cosmetic Chemists congresses and conferences, and have greatly contributed to the cosmetics market. We will look at different formulations of foundations as well as their characteristics.[1]

### 34.2.1 Oil-in-Water Foundation

Oil-in-water (O/W) formulations were the most common type of foundation until the introduction of powder foundations, and they have various physical forms ranging from creams to emulsions. Previously, their covering property was weak compared with powder foundations, but various treatment pigments and formulation technologies have been developed and the difference between the two types of foundations is becoming negligible. These formulations tend to have stronger moisture-retaining properties and are especially popular among customers with dry skin. Although powder foundations are popular in Asian markets, O/W foundation is one of the most basic foundations in Europe and the Americas.

O/W foundations must be stabilized to prevent powder sedimentation, and materials such as fatty acid soaps are used to thicken or for gelling the water phase and to stabilize the powder/oil phase−water phase system. Alkalis

*Cosmetic Science and Technology: Theoretical Principles and Applications*
http://dx.doi.org/10.1016/B978-0-12-802005-0.00034-3

Copyright © 2017 Elsevier Inc. All rights reserved.

such as triethanolamine, KOH, and arginine are used for stabilization, but the content should be minimal due to safety issues and because products that feel good to the skin are preferred. Thus, it is important to consider the dispersion of surfactants and pigments that are also formulated in the product (e.g., even distribution, dispersion as ultrafine particles).

In recent years, ultraviolet (UV) protection also is a feature that is often requested and implemented, and the content of UV absorbers and fine particles with UV-scattering properties, such as titanium oxide or zinc oxide, is increasing. There are several UV absorbers in the market, but UVA absorbers are especially known to be difficult to formulate and are also unstable, so they must be carefully used in formulations. In recent years, premixed materials, which are stabilized systems made by mixing several UV absorbers with specific oily materials, have been introduced.[3] There are many ultrafine particles with UV-scattering properties, and they are marketed as nonchemical formulations and promoted by many cosmetic companies. Although they are widely used around the world, they still have many remaining challenges such as temporal condensation of ultrafine particles. Development of stable and easily dispersed premixed materials is anticipated.

### 34.2.2 Water-in-Oil Foundation

Unlike water-in-oil (W/O) used in skin care products, W/O foundations often use large amounts of volatile silicone. Because the silicone evaporates after the foundation is applied to the skin, the powder and solid fats/waxes become dense, thus showing a more powdery feel compared with typical O/W foundations. The film durability is also stronger, so the amount of fatty acid soaps or hydrophilic surfactants that are required in large volumes in O/W types can be drastically reduced, and this leads to higher water and sweat resistance. This type of formulation was first introduced to the market as cream-type products but was not very stable, and currently most products are separated types that must be shaken and evenly mixed before applying. The evolution of polyether-modified silicone directly contributed to the spread of W/O foundations, which has reduced the smell of early products; now many products with various structures or various Hydrophile-Lipophile Balance (HLB) values (in the range of 3–15) are available.

Although low-viscosity dimethyl silicone and cyclic tetramer silicone were previously used for this formulation, these materials have become difficult to use due to environmental safety aspects, and slow-volatile cyclic pentamer silicone is the only ingredient available for practical use. Thus, it has become difficult to differentiate the application feel of these products.

Once O/W foundations separate, the separated water can never mix back into the system, so the temporal change must be carefully considered in various temperature conditions. Further, typical temporal observation is insufficient, and currently various tests must be conducted such as vibration tests and kneading tests to simulate shipping and shearing tests to simulate the packing procedure.

### 34.2.3 Powder Foundations (Including Two-Way Types)

Powder-type foundations have become especially popular since the 1980s. As their name indicates, these formulations are mainly made of powders (more than 80% of their content), and the properties of powders strongly influence their properties. Thus, the development of better powders directly leads to increasing the value of these formulations. Surface treatment, composition with other materials, and modification of powders have improved the functions of powder foundations such as the makeup finish, UV blocking, and makeup durability. These functions will be described later in the chapter, and in Table 34.1 we have summarized items to consider during formulation other than aspects of application feel and makeup finish. These points affect all aspects of powder foundations

**TABLE 34.1** Heeding Point to Develop Powdery Foundation

| |
|---|
| Supply of in-process materials |
| Press molding property |
| Color property |
| Drop resistance |
| Vibration resistance |
| Glare of graininess during use |
| Pancake inflation(?) |
| Refill replacement cracking |
| Smell/color change with moist puffs |

including the balance of powders/pigments with oil bases, the balance of spherical powders and plate-like powders, surface treatment, mixing/dispersion conditions, molding pressure/speed, and container materials and shapes.

Among powder foundations, wet press molding foundations have become prominent in recent years. Wet press molding foundations are powder foundation products in which the powders are press molded in compact containers in the final production. Previous methods used a mixed dispersion of mixed powders with a small amount of oil-based binders as in-process materials and were packed in the final container with dry press molding. Wet press molding is a molding and packing method in which oil-based binders and mixed powders are mixed and dispersed in volatile solvents such as isopropanol, which are then poured into the compact containers and finished by absorbing the solvent while press molding. The product is stored in a dry room after packing to remove the solvents and then is shipped as the final products. Wet press molding foundations are preferred for their fine and moist feel, but they have a disadvantage when different products have a similar application feel.

### 34.2.4 Oil-Type Foundation

Although the popularity of these foundations declined for a while due to their oily and sticky feel, progress in formulation methods has brought them back to the market as a common type of foundation. Silicone oil bases, low-viscosity synthesized oils, and various spherical powders have become more common, and combined with the development and spread of kneading instruments with high torque and high shearing, products with rich powders and minimal oil content can now be formulated. Products made with these new methods are not oily but have a moist feel. Although the containers must be tightly sealed, using volatile silicone in the formulations can make even more powder-rich and refreshing finishes. Cool-feeling products can also be made by adding water.

Like powder foundations, the final products of these foundations are commonly packed by press molding in compact containers, but there are some stick-type products in the market as well.

Because the formulation of oil-type foundations are mixed systems of liquid oils, waxes, fats, and various pigments, it is important to remember that the liquid oils can separate at high temperatures (an effect called sweating) and the types and ratios of oils should be carefully chosen.

### 34.2.5 Water-Based Gel-Type Foundation

These formulations use agar and synthetic water-soluble polymers to make gels and are molded in compacts or stick-type foundations. Although they look similar to oil-type foundations, they have a refreshing and soft feel. The containers must be sealed, and preservative treatment is especially important in water gel-type foundations.

These foundations are especially preferred by customers who do not like oily products, but they have a disadvantage in their durability as makeup and can smear, especially with users with excess body oil or sweat. An increased number of consumers have both dry and oily skin on different parts of their faces, and these foundations should be used carefully because they can smear, especially at the T-zone and other areas with more facial oil.

### 34.2.6 Spray-Type Foundation

Spray-type foundations are relatively new foundations. These products use battery-operated devices to spray non—water-based foundations. Although they are still a niche product, they are unique products where foundations are not applied with the fingers or puffs.

## 34.3 MAKEUP FINISHES

As optical studies on makeup are becoming more active, many products based on these studies have been introduced to the market. It has become common to find information on the optical effects of cosmetics and new makeup finishes on cosmetic company websites, along with information on materials and their optical effects and their mechanisms. The main purpose of makeup is to have a satisfying finish. Because the finish can only be evaluated through sight, makeup studies are deeply integrated with optical studies. In the field of cosmetics, optics usually means visible rays and UV rays. Here, we will focus on visible ray in relation to makeup finishes.

It is commonly known that humans have sensitive eyesight. Unfortunately, instruments that can evaluate at the level of human sight are yet to be developed, and skin and makeup evaluation still relies on sensory evaluation in many cases. However, aside from complex and combined evaluation, relatively simple evaluation of color values (hues, chrome, value) and gloss values are now commonly evaluated with the development of new high-precision instruments. These optical evaluation instruments have made it possible to quantify data and objectify skin evaluation, which was not

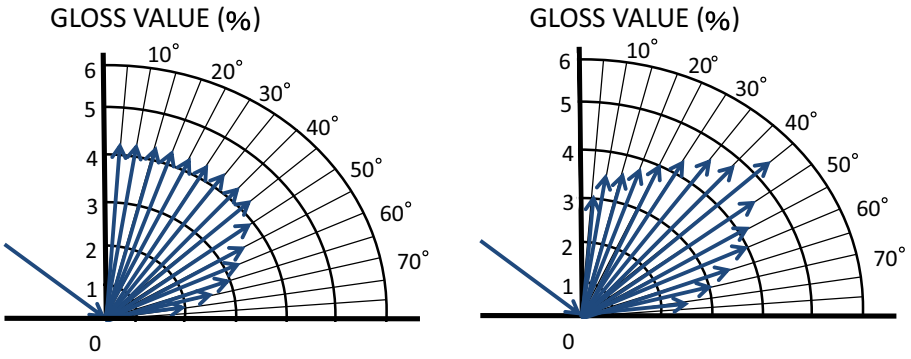



FIGURE 34.1 Reflection patterns of acrylic-coated talc and talc only.

possible with sensory evaluation, and they have greatly contributed to the development of makeup effects.[4] Here we look at the effect of makeup cosmetics through several examples of recently developed makeup finishes.

### 34.3.1 Soft-Focus Effect

The soft-focus effect is a method that makes wrinkles and other skin imperfections less visible. This new technology was studied from optical perspectives on both the skin and powders and has set a new direction for foundation research. Since its introduction in 1986, soft focus has become one of the most fundamental functions of foundations, as well as a common phrase.[5]

Strong concealing powders like titanium oxide or powders with regular reflection such as mica or talc do not show the soft-focus effect; powders that have diffused reflection are used to create this effect. The reflection patterns of commonly known powders are shown in Fig. 34.1.

The soft-focus effect is difficult to implement with spherical powders and is usually easier to create with plate-like powders. Various organic spherical powders that use suspension polymerization are now available in the market. However, as shown in Fig. 34.1, plate-like powders can also show soft-focus effects by coating the surface with resin. Further, it is also possible to make this effect by coating the surface with ultrafine particles.

In recent years, leakage of synthetic ultrafine particle resin powders into the environment has become an international issue. It is expected that the coated spherical powders mentioned earlier will be rapidly replaced with inorganic powders or natural materials such as cellulose.

The mixture ratio of powders and oil bases in the makeup film is also another important factor.

Figs. 34.2 and 34.3 show the DT (direct transmittance)/R (reflectance) curve of the thin film of mixed powder and oil bases. DT decreases when the oil base increases, but at a certain region (the *black-dotted* area in the figures) they reach a minimum and start to increase past this region. R decreases when the oil base increases, but at a certain region the decrease stops or becomes gradual. This region (shown with black dots) almost matches the dotted DT region if the powders and oil bases are the same and shifts to the left or right depending on the oil-absorbing property of the powders. The thin film of the mixtures shows unique optical properties in this region. Mixed systems in this dotted region are called soft-focus mixtures, and they can buff skin imperfections and wrinkle contours. Further, soft-focus mixture regions are known to show a unique TT (total light transmittance) curve (Fig. 34.4). The TT in the mixed systems increases with oil base content and becomes maximal at the soft-focus mixture region (shown in *black dots*). As such, this region is where the DT is minimal and the TT is maximal or, in other words, where the diffusing transmission is strong.

### 34.3.2 Natural-Looking Makeup (Bare-Skin Look)

Although makeup is commonly used globally, many consumers are unsatisfied and think that the finish looks artificial. Through a survey conducted in four major cities in the world, it became clear that there is a demand for makeup with a more natural-looking finish while keeping the basic functions such as coloring and concealing. As shown in the summary of this survey in Fig. 34.5, users responded that they are unsatisfied with the

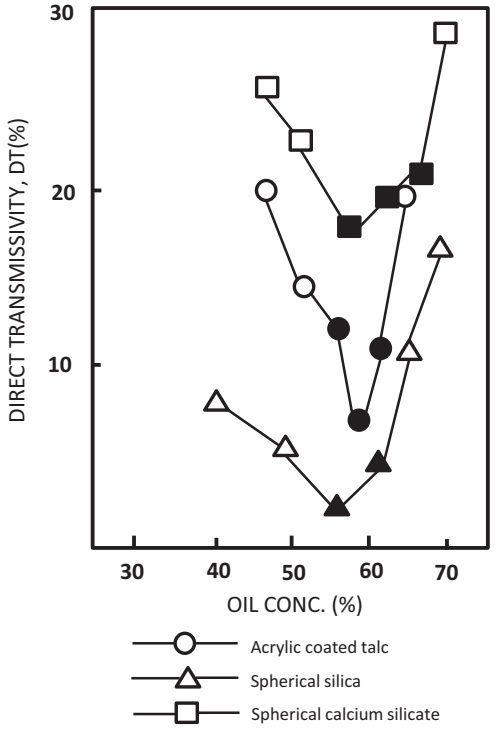



FIGURE 34.2 DT (straight part of transmitted light) curves of three mixtures.

artificial-looking finish in current foundations in the market. All women who participated in the survey answered that they would like to have beautiful bare skin, and evidently the need for more natural-looking makeup is strong in women. There is a method to analyze the color of a woman's cheek and then make a paper skin color chart that matches that color. In general color measurement, the colorimetric values (hue, value, and chrome from colorimetry)

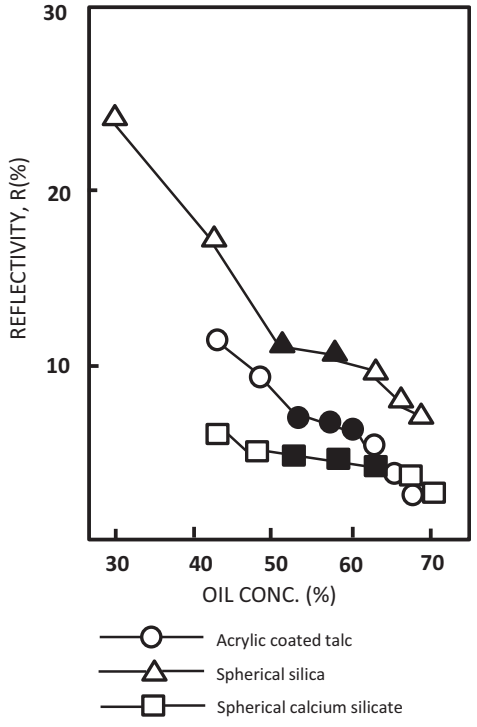



FIGURE 34.3 R (light reflectance) curves of three mixtures.

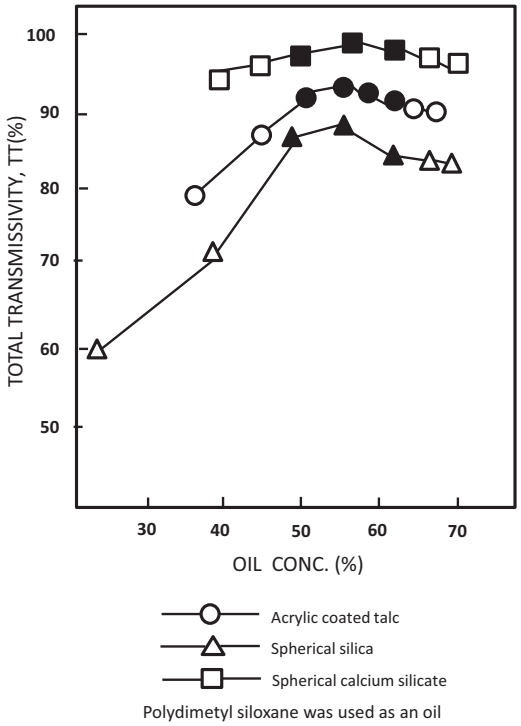



**FIGURE 34.4** TT (total transmitted light) curves of three mixtures.

are almost identical to those of the measured skin color, but most people will not mistake the paper skin color chart with real skin. This means that previous measurement methods were not able to determine the difference between skin and paper. Based on this fact, new parameters and new measurement methods are required to evaluate these differences. In this case, goniometric color measurement has been used to clear these challenges. Nishikata et al. used the Murakami Color Research Laboratory's CMS-500 to analyze the spectral reflectivity data for as many angles as possible (both incident and reflected) and discovered the following important factor.[6]

Fig. 34.6 compares data under two different experimental conditions (A and B). The three charts show the spectral reflectivity of (A) bare skin, (B) bare skin with generic foundation applied, and (C) skin-colored bricks. The experiment conditions of A and B are shown in Fig. 34.7. Condition A is close to regular experimental methods, where the incident angle and reflection angle are set close to a right angle. With condition B, the incident angle and reflection angle are both set to be close to parallel angles. The conditions were calibrated for both A and B, and the spectral reflectivity was evaluated. The angles of A and B are set to avoid the regular reflection angle. As seen in Fig. 34.6A–C, do not show a large difference under condition A, but under condition B the spectral reflectivity of bare skin is significantly higher than that of skin with makeup or with bricks. A similar result was confirmed with a model experiment using two layers of colored cellophane film (Fig. 34.8). As seen in Fig. 34.8, the color values were the same as the mixed color of the two films under condition A (the color values did not change drastically regardless of which film was on top). However, under condition B, the color of the film on top strongly influenced the color of the spectral curve. These results partially explain the optical aspects of natural-looking appearances compared with artificial-looking appearances. With layered materials like skin that have a highly transparent upper layer, the spectral reflectivity under condition A shows the overall color information, whereas the spectral reflectivity under condition B is strongly influenced by the color information of the upper layer, and the difference between these two conditions is a factor that makes skin look natural. The ratio of the spectral reflectivity of A and B was called RAO (ratio of acute incident angle/acute reflection angle to obtuse incident angle/obtuse reflection angle) and the maximum RAO at 400–700 nm was defined as the Max RAO. There was a correlation between the Max RAO and visual sensual evaluation, and the Max RAO of bare skin that was considered beautiful converged to a specific value range (4.3–6.5). The Max RAO is potentially an effective new parameter to evaluate the appearance of skin, and this index is now applied for new material development and new makeup cosmetics.

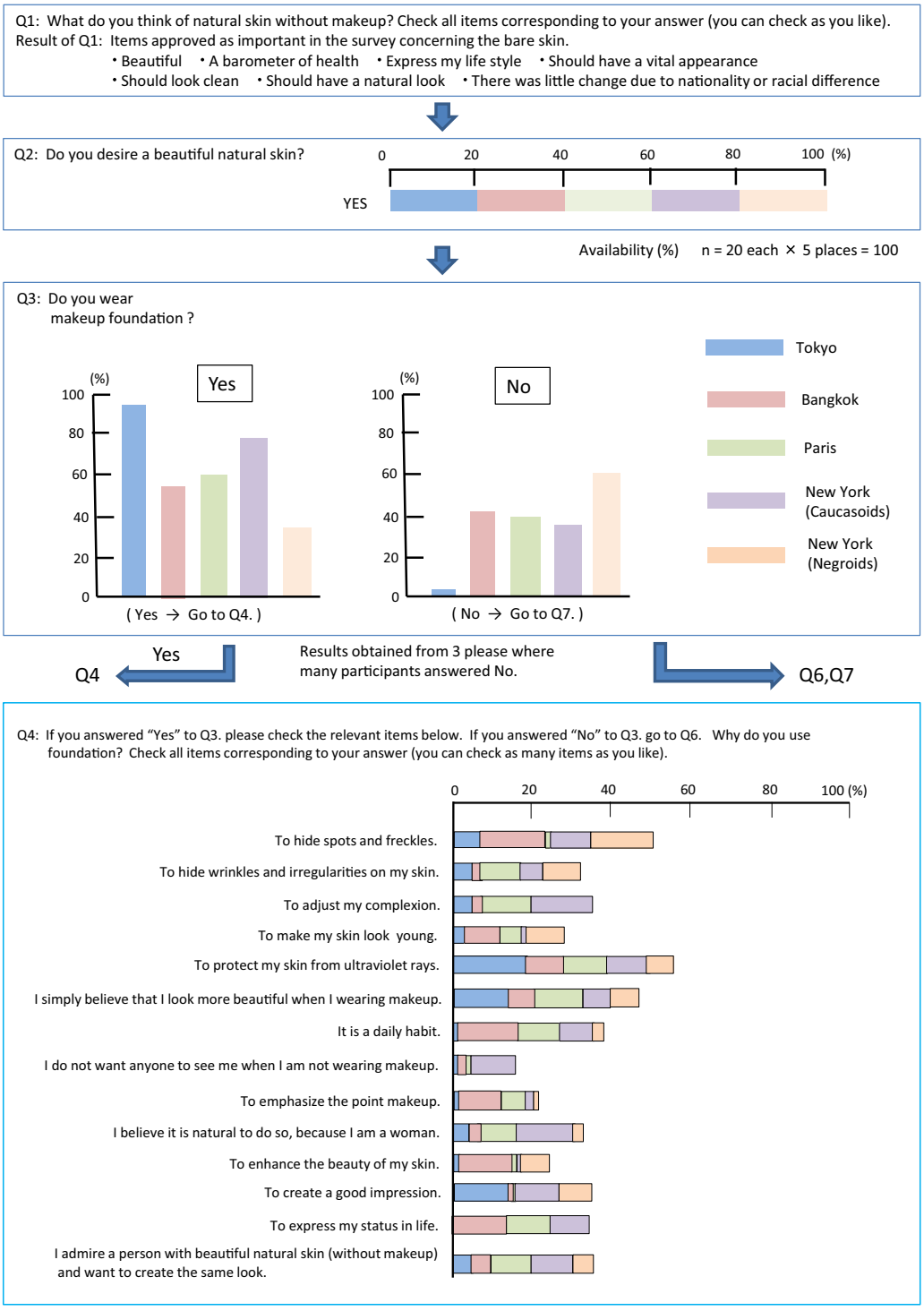



FIGURE 34.5 Opinion survey conducted in four countries in the world concerning the bare skin and foundation finish.

## 34.3.3 Supercovering Makeups

The Ota nevus (dark-blue to beige hyperpigmentation that can occur around the eyes or cheeks) could not be concealed with previous makeup products, but Shiozawa et al. developed makeup products to completely hide these marks.[7] Relying on the concealing property of titanium dioxide was insufficient to develop a makeup product with higher concealing properties, and various aspects such as the optical property of materials, formulation types, and

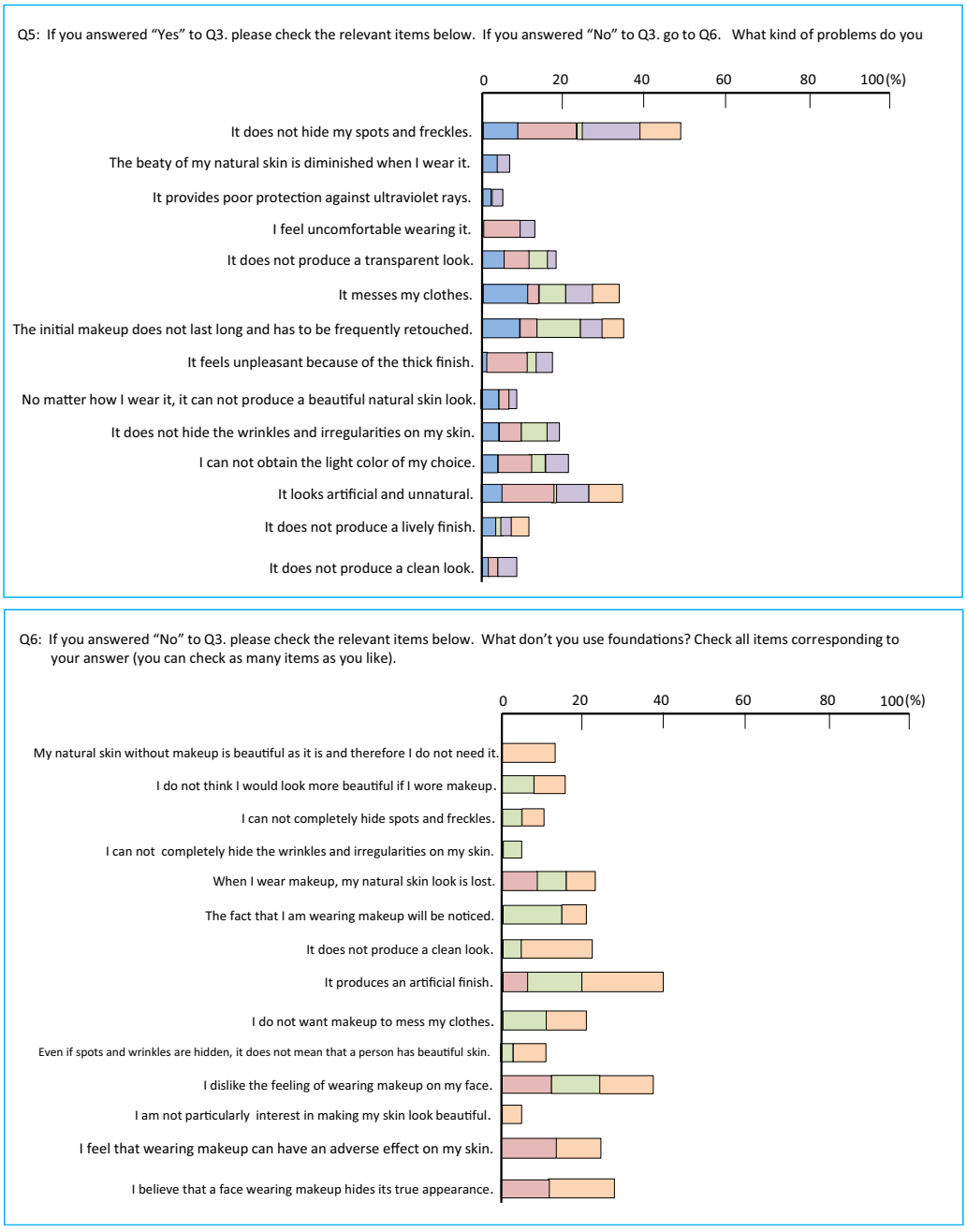



**FIGURE 34.5** Continued.

cosmetic films were required to make this new makeup. In their research, Shiozawa et al. used optical methods such as spectral colorimetry to examine the skin color and concealing property and scanning laser microscopes to measure the thickness of cosmetic film.

Supercovering makeup was developed as layered makeup by using acrylic polymers with viscosity as the makeup base layer, mixed powders with thin plate-like aluminum powder oriented in thin layers (leafing structure) as the main material, and oil-based foundations (layered with finishing powder if required) as the finishing layer. Due to this layering process, it is important to ensure that the cosmetic film is not too thick. The thickness of cosmetic film is measured by applying a layer of cosmetics on stained glass or leather, where the layer of cosmetics is scratched off with sharp needles and the thickness is measured with scanning laser microscope images. As shown in Table 34.2, the thickness of the cosmetic film of supercovering makeup was roughly the same as that of other makeup cosmetics. The concealing property was calculated by using spectral colorimetry to measure the spectral reflectivity on both

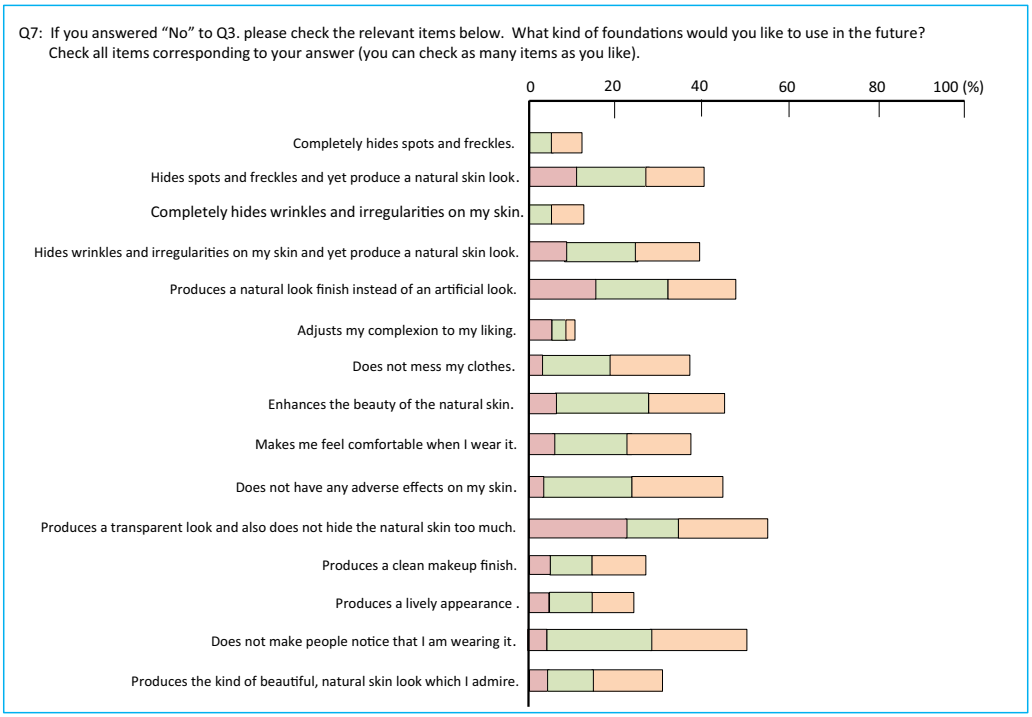



FIGURE 34.5 Continued.

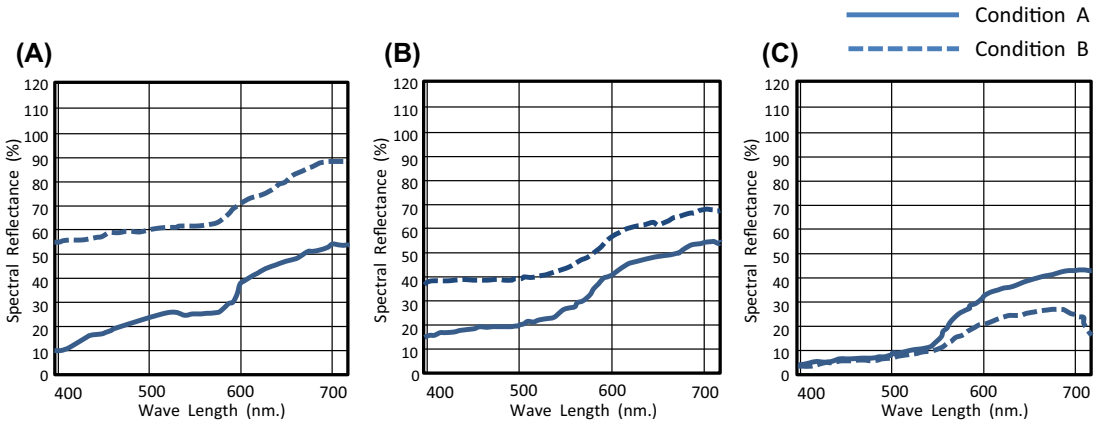



FIGURE 34.6 Spectral ratio between conditions A and B: (A) spectral ratio of the skin, (B) spectral ratio after application of conventional foundation, (C) spectral ratio of brick.

black and white surfaces and calculating the contrast ratio. Depending on the instrument, the contrast ratio can be measured in 5- or 10-nm increments, but in actual measurement, several points between 400 and 700 nm is sufficient. Tables 34.3 and 34.4 show the contrast ratio of dry and wet powders of various materials (kneaded and mixed silicone with controlled viscosity) applied on stained glass at a thickness of 0.5 mil using a surgical blade.

### 34.3.4 Creating Youthful-Looking Skin

Although it may be easy to finish young skin with makeup beautifully, skin on older persons sometimes looks more artificial and may not appear as youthful even if the same foundation is used. Sakazaki et al. analyzed the skin surface morphology of persons of various generations and found that the unevenness of the skin becomes flatter with chronological aging and the lateral diffusion of light on the skin decreases, and they proposed a new index, LDI (diffusion index of the light in the horizontal direction).[8] Powders with a high soft-focus effect are insufficient for this

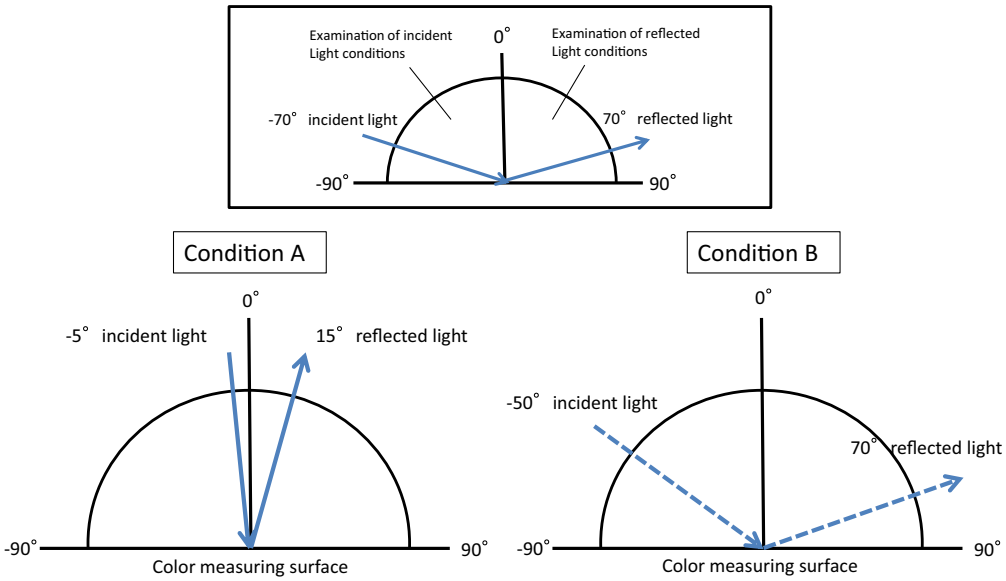



FIGURE 34.7 Measurement of spectral ratios under conditions A and B.

lateral diffusion and, unlike other generic powders, linear materials are required. Through their research focused on fibers, Sakazaki et al. found that 300-μm nylon fibers are effective. Fig. 34.9 shows the light diffusion on filters made from replicas of skin from young and old persons. The correlation with LDIs of various powders is shown in Fig. 34.10. These values show that the skin in older generations is flatter and the light diffusivity is lower. There are reports that the lateral diffusion property of fibers has a synergistic effect with red light rays that can make the skin look more beautiful.[9]

### 34.3.5 Effects on Face Shapes and Expressions

The soft-focus effect and bare skin—appearing effects are researched on how to make the skin look natural, and these studies focused on the optical properties of the skin surface. However, there are studies that focus on the visual effects of foundations on the face as a whole instead of focusing only on the surface, and these studies look into aspects such as expressions and impression.

It is evident that lighting influences expressions and impressions, and foundations can be used to make the face look smaller or larger, or flatter or more complex. Inoue et al. revealed that the size of the eyes and the impression of the facial outline below the eyes are the strongest indexes when humans recognize facial forms.[10]

Further, they used a measuring device for three-dimensional shapes to analyze human expressions (joy, anger, sadness, surprised) and found that compared with contour-enhancing makeup on the eyes or mouth, makeup that gradually changes the lightness and darkness of the face makes the impression of smiling stronger.[11] To develop foundations from this aspect that emphasizes the impression of smiles, a three-layered powder of titanium dioxide coated mica/aluminum oxide/silica has been developed.[12] This plate-like powder has been analyzed as having the following optical property. The L value was measured under a condition where light was exposed to the face from the front and an incident/reflecting condition and angle of incidence/reflection were set (L values LA: −15°/15°, LM: −25°/5°, LO: −55°/−25°) for the front of the face and side of the face. The differences in the L values LAM = LA − LM and LMO = LM − LO were calculated and compared with generic powders. The results of this analysis showed that this new powder had more brightness difference compared with generic powders. The correlations of LAM and LMO are shown in Fig. 34.11.

Additionally, a powder of titanium dioxide—coated mica coated with silica has been developed as a powder to adjust the lightness and darkness of the face without glaring when the face was lit from the front.[13] When the front of the face looks bright and the sides look darker, the face can appear slimmer or more complex. A similar effect is also possible with low-order oxide titanium—coated mica made through electric furnace reduction of metal titanium added to titanium dioxide—coated mica.[14]

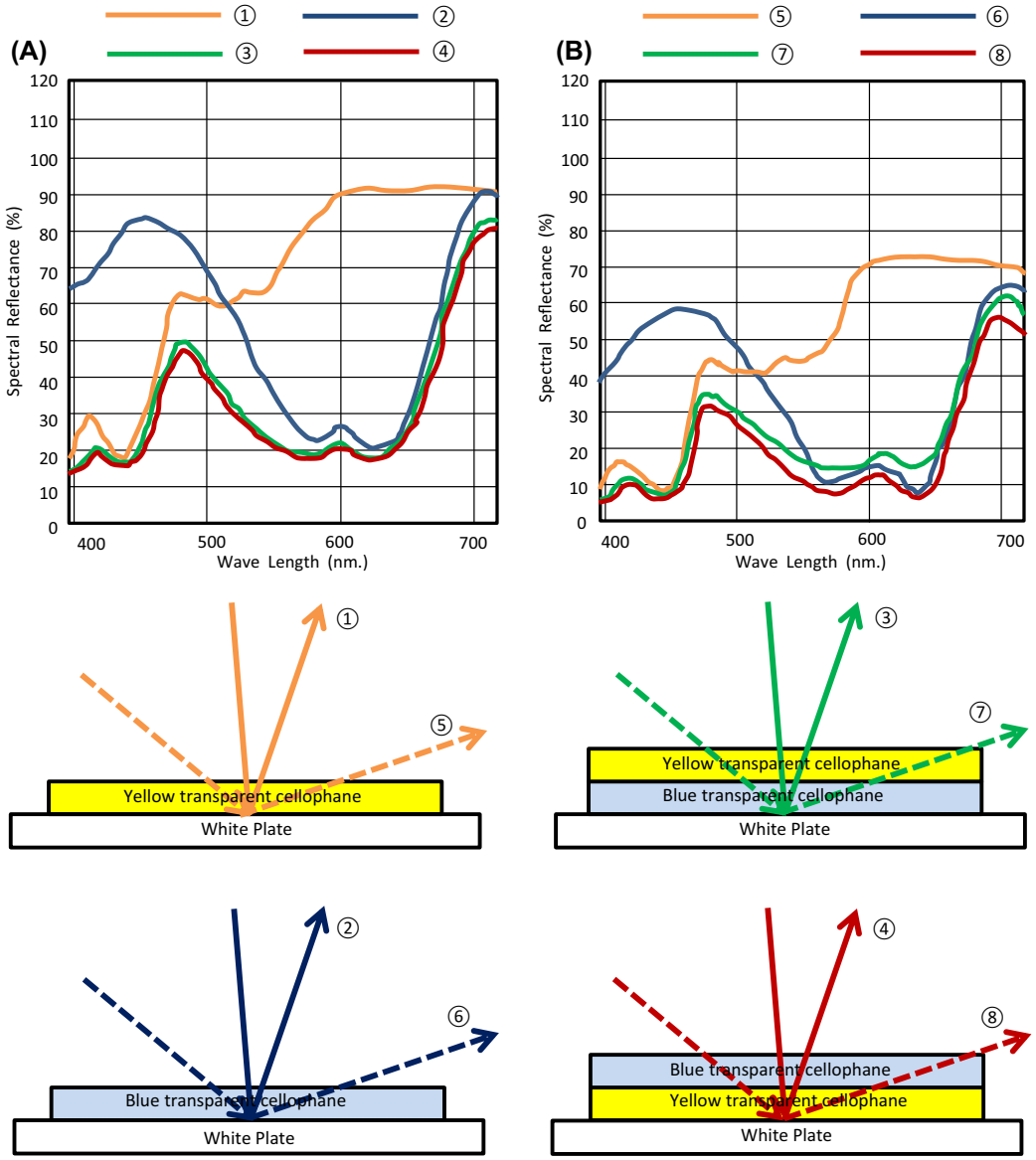



FIGURE 34.8 Spectral reflectance of the each transparent color cellophane between condition A and condition B. (A) Results of measurement under condition A. (B) Results of measurement under condition B.

TABLE 34.2 An Artificial Makeup Film Was Prepared on a Glass Slide Using the Weight of the Makeup Material Actually Applied to Cover of Ota's Nevus

| | Supercovering Makeup | Commercial Makeup (A) | Commercial Makeup (B) |
|---|---|---|---|
| Applied weight (g/cm$^2$) | $1.601 \times 10^{-3}$ | $1.357 \times 10^{-3}$ | $1.203 \times 10^{-3}$ |
| Film thickness (μm) | 8.08 | 8.12 | 9.36 |

*THICKNESS OF LAYER IN A SUPERCOVERING MAKEUP FILM*

| | Base material of metal–acrylic polymer | Aluminum powder mixture | Foundation for color compensation | Total |
|---|---|---|---|---|
| Film thickness (μm) | 2.48 | 1.52 | 4.08 | 8.08 |

**TABLE 34.3** Contrast Ratio of Dry Powder Films

| | CR-1 450 nm (%) | CR-2 550 nm (%) | CR 3 650 nm (%) |
|---|---|---|---|
| Copper | 100.0 | 100.0 | 100.0 |
| Aluminum powder | 91.4 | 93.3 | 90.6 |
| Silver | 71.8 | 71.4 | 71.4 |
| Iron sesquioxide | 50.0 | 66.7 | 66.7 |
| Black iron oxide | 66.7 | 50.0 | 66.7 |
| Gold | 50.0 | 55.6 | 51.1 |
| Yellow iron oxide | 63.6 | 27.4 | 21.4 |
| Titanium dioxide | 50.7 | 35.2 | 26.0 |
| Colored titanium mica | 25.0 | 13.6 | 17.6 |
| Mica treated with oxybismuth chloride | 15.7 | 14.3 | 12.5 |
| Zinc oxide | 15.1 | 10.3 | 7.4 |
| Barium sulfate | 8.5 | 5.9 | 6.0 |
| Micronized titanium dioxide | 6.1 | 3.5 | 4.0 |
| Cericite | 2.2 | 2.2 | 2.2 |
| Talc | 2.1 | 2.1 | 2.1 |

**TABLE 34.4** Contrast Ratio of Wet Powder Films

| | CR-1 450 nm (%) | CR-2 550 nm (%) | CR-3 650 nm (%) |
|---|---|---|---|
| Copper | 19.4 | 27.5 | 36.4 |
| Aluminum powder | 53.6 | 52.7 | 53.0 |
| Silver | 0 | 0 | 0 |
| Iron sesquioxide | 3.1 | 3.2 | 13.2 |
| Black iron oxide | 5.0 | 4.2 | 8.3 |
| Gold | 0 | 0 | 0 |
| Yellow iron oxide | 100.0 | 55.0 | 60.0 |
| Titanium dioxide | 52.9 | 50.7 | 50.0 |
| Colored titanium mica | 9.6 | 5.7 | 17.5 |
| Mica treated with oxybismuth chloride | 33.3 | 29.7 | 27.8 |
| Zinc oxide | 14.9 | 13.4 | 11.8 |
| Barium sulfate | 7.1 | 5.6 | 5.6 |
| Micronized titanium dioxide | 48.3 | 33.3 | 26.2 |
| Cericite | 1.3 | 1.3 | 1.3 |
| Talc | 1.3 | 1.3 | 1.3 |

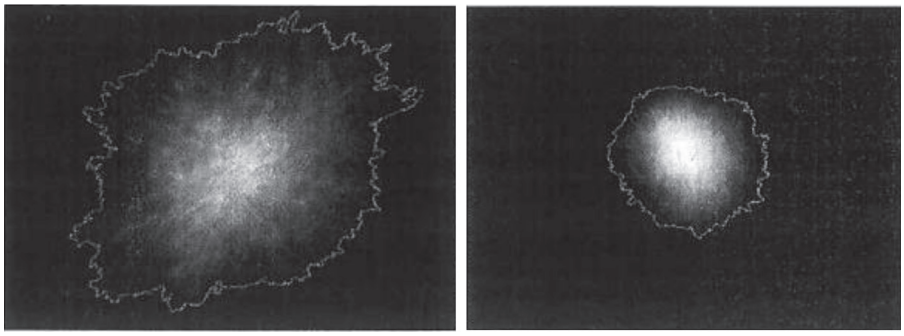



**FIGURE 34.9** Diffusion pattern of microrelief plate. Younger skin diffuses much more than does aged skin.

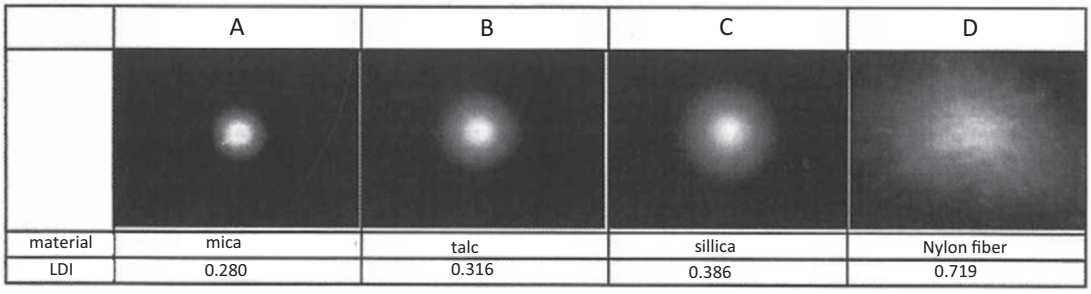



**FIGURE 34.10** The diffusion patterns and LDI values of pigments. Nylon fiber diffuses much more than ordinary powder.

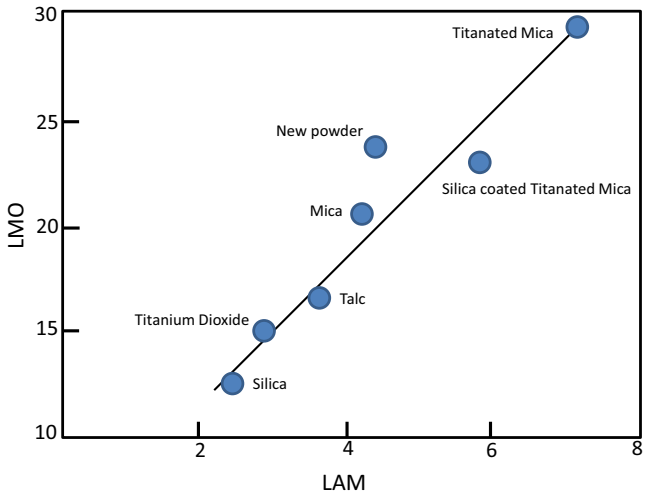



**FIGURE 34.11** The values of LAM and LMO on the various powders.

These makeup effects are a clever use of the light reflection properties of the face regarding visual characteristics. Although soft-focus effects are mainly found in spherical powders, this effect is seen with plate-like powders.

### 34.3.6 Photochromic Effect

Sometimes the finish of foundations looks different when inside versus when outside. Artificial light and sunlight have different spectra as well as brightness. Many people find that even though makeup was finished beautifully inside a room, they look whiter outside. Because foundations can appear different with sunlight versus artificial light, powders with photochromic effects have been developed to minimize this difference. Foundations with

powders made from baking anatase titanium dioxide with iron oxide lower their color value under sunlight, and the finish of this foundation looks similar under sunlight and inside.[15] Further, powders made from baking titanium dioxide–coated mica and iron oxide show blue-interfering light, and they change their color value and hue depending on UVA and minimize the look inside and outside.[16] These powders can create a bright and clear finish under fluorescent lamps and a natural and beautiful finish under sunlight. Having a finish that is not influenced by lighting conditions is another important function for foundations.

## 34.4 OTHER FACTORS

### 34.4.1 Makeup Durability

The durability of makeup is a function that is as important as the finish itself. Even if the makeup looks beautiful when it is applied, if the transparency increases or the coloring of pigments become stronger and darker over time, it will not only ruin the look but also weaken UV-blocking effects. Arimura et al.[17] and Toridzuka et al.[18] studied makeup deterioration with subjective analyses. Here, we will look at some technology through the viewpoint of actual foundation development.

#### *34.4.1.1 Improving Wettability (Water/Oil Resistance)*

The main cause of makeup smearing is sweat and body oils. The earliest technology for sweat resistance was methyl polysiloxane–coated powders and pigments. Foundations that used this method had a favorable feel and largely contributed to the evolution of powder foundations. Previously, there were issues of hydrogen gas forming due to incomplete coating, but these issues have been resolved and now the coating ratio can also be controlled. Currently, these materials are widely used for eye shadows and other decorative makeup products. Following this technology, surface treatment technology using fluorides such as polyfluoroalkyl phosphoric ester and perfluoroalkyl silane have been introduced.[19] These materials can inhibit transparency or coloring of powder and pigment caused by body oils.

However, these coated powders and pigments have low affinity with the oil bases in foundations, and the coloring can weaken or become uneven during production. When using such materials in formulations, their balance with oil bases and surfactants should be carefully considered.

#### *34.4.1.2 Body Oil Absorption*

Because body oils are one of the main causes of makeup smearing, there are some formulations that delay the smearing by absorbing oils into the makeup film. Powders with high oil-absorbing properties are used in this formulation to absorb body oils. Powders with large surface areas such as porous spherical powders or ultrafine particles are used for oil-absorbing powders, but the amount can be limited from their influence on the application feel or from molding limitations.

There are also proposed methods that target and selectively absorb specific substances in the body oil. Nomura et al. found that the unsaturated free fatty acids in the sebum or body oils cause makeup smearing, and zinc oxide–supported alumina pillared clay was developed to selectively absorb oleic acid as a new technology to improve the durability of cosmetics.[20] This method has been found to have a higher efficacy than porous cellulose or silica. The effects of formulations (the time until glaring was felt) of materials with and without zinc oxide–supported alumina pillared clay are shown in Fig. 34.12.

### 34.4.2 UV Blocking

As mentioned in the section on foundation types, applying makeup in the morning and removing it at night with cleansers is the common habit when wearing makeup. In other words, makeup is applied during the daytime. Because daytime is when we are most exposed to UV rays, adding UV blockers to cosmetics is a logical decision.

As mentioned earlier in this chapter, there are chemical methods (UV absorbers) and nonchemical methods (UV scattering with ultrafine particles), and there was a period when nonchemical methods were especially valued, but the current trend is to use both methods in balance.

Development of nonchemical powders was focused on producing ultrafine particles, combinations, and modification, but currently such powder development is not as active. The maximum SPF labeling is now set to 50+, and the PA value has changed from three-step labeling to four-step labeling. Thus, the current trend is shifting to an




**FIGURE 34.12** Comparison of time of spot observation on makeup film at 32°C (room temperature) and 70% relative humidity.

effective use of powders. In other words, the current trend is focusing on actual effects such as making the ideal dispersion, inhibiting condensation in the formulation, or effectively applying onto the skin while maintaining durability.[21] Premixed materials, mentioned earlier in this chapter, are expected to evolve even further.

### 34.4.3 Skin Protection

Foundations have the potential to protect the skin, beyond UV blocking. There are reports of technologies that can absorb skin-irritation factors and powders that do inhibit skin irritation.[22] There are patents that focus on pollinosis,[23] and studies on skin care effects of powders are expected to become even more active.

In modern society, social diversity has spread globally and many women work during the day. The skin is exposed to various stress factors during the daytime such as dryness in air-conditioned offices, so the cosmetics applied during the day are expected to have skin care (day care) functions. Protection against dehydration is an especially important function for makeup products, and more makeup products, not limited to foundations but including base makeup products and decorative makeup products, promote their moisture-retaining functions.

## 34.5 CONCLUSION

Why do people wear makeup? There are various theories to answer this simple question. Many wild animals such as birds and fishes are known to change their color to gorgeous nuptial colors during estrus. The purpose of this color change is clear—to find a mating partner and leave offspring. I am not one to judge whether this color change can be called makeup, but one thing is for certain: 99% of the wild animals that show nuptial colors are male. However, the majority of humans who wear makeup is women. The difference between nuptial colors in wildlife and human makeup is that the purpose of makeup is not limited to attract the opposite sex, but rather has many other purposes.

I personally believe that wearing makeup is an act that has a special and strong psychological effect. There are reports that productivity or outcome declines if a woman who usually works with makeup experimentally goes to the office without wearing makeup.[24] Nobody would want to go to work in their relaxed condition like they were at home without any makeup. Applying makeup and checking their faces in the morning may be a psychological ritual to switch their minds to a business mode. This effect is also seen in men, and even today there are tribes where men occasionally wear colorful makeup. This makeup is believed to have an uplifting effect for ceremonies or hunting (or historically for war with other tribes). This may be similar to heel wrestlers, where they are kind fathers at home but transform into villains the moment they wear their masks. Makeup is also believed to have ritual and religious meanings. Some clay figures from the stone ages (called *dogu* in Japan) have patterned cheeks, and there are theories that consider these patterns as ritual makeup. Perhaps they are like blushes today. Shaman are known to wear special makeup with costumes for rituals.

In recent years, the trend of the cosmetics market is shifting to natural-oriented cosmetics, and the number of organic or botanical products is rapidly increasing. However, this trend is not as strong in the makeup cosmetics

market compared with toiletry products or skin care products. One of the reasons may be that in makeup cosmetics, the makeup effects and functions are difficult to coexist with the natural-oriented trend. However, development in material technology will likely clear this obstacle. As we have learned in this chapter, the first and foremost function of makeup cosmetics is the visible makeup finish. We hope to see developments in material technology that have all the essential functions and finishes of makeup cosmetics and can meet the demands of natural cosmetics.

## References


1. Mitsui T. *New cosmetic science*. 1997.
2. Barel AO, paye M, Maibach HI. *Handbook of cosmetic science and technology*. 2014.
3. Published Japanese patent 2010-90041, Published Japanese patent 2010-197251.
4. Nishimura H, Takasuga Y, Yamamoto M. *Int J Cosmet Sci* 2007;**29**(1):67.
5. Nakamura N, Takasuga Y, Takatsuka I. *J Soc Cosmet Chem Jpn* 1987;**21**(119−126).
6. Nishikata K, Nishimura H, Mohri M, Nakamura N. *J Soc Cosmet Chem Jpn* 1997;**31**:276−96.
7. Shiozawa J, Nishikata K, Nakamura N. *J Soc Cosmet Chem Jpn* 1993;**27**(3):326−7.
8. Sakazaki Y, Nishikata K, Nakamura N. *J Soc Cosmet Chem Jpn* 2002;**36**:25−35.
9. Sakazaki Y, Suzuki Y, Nishikata K, Mohri M. *Int J Cosmet Sci* 2007;**29**(4):332.
10. Inoue S, Yamamoto M, Yamazaki K. *J Soc Cosmet Chem Jpn* 2000;**34**:,249−254.
11. Inoue S, Hirayama K, Yamazaki K. *IEICE Tech Rep, HIP 2000-47* 2001:15−21.
12. Ikeuchi M, Nishikata K, Inoue S, Yamazaki K, Nakamura N. *Paper abstracts 5th ASCS in Bangkok*. 2001. p. 53−5.
13. Nakamura N. *Fragr J 2289* 1996;**24**(10):64−8.
14. Tanaka T, Nishihama S, Kumagai S, Kimura A, Suzuki F. *J Soc Cosmet Chem Jpn* 1996;**29**:353−71.
15. Ohno K, Kumagai S, Tanaka T, Saito R, suzuki F. *J Soc Cosmet Chem Jpn* 1993;**27**:314−25.
16. Ogawa K, Sakurai O, Fuse S, Ohno K. *J Soc Cosmet Chem Jpn* 2000;**34**:387−94.
17. Arimura N, Hoshiya H, Hirai Y, Masaki H, Fjii M. *J Soc Cosmet Chem Jpn* 1988;**22**:149−54.
18. Torizuka M, Nagatani N, Shoji T, Asahi M, Takano S. *J Soc Cosmet Chem Jpn* 1995;**28**:350−8.
19. Horino M. *J Jpn Color Mater* 1992;**65**:492−9.
20. Nomura K, Takasuga Y, Nishimura H, Motoyoshi K, Yamanaka S. *J Soc Cosmet Chem Jpn* 1994;**33**:254−66.
21. Matsueda A. *J Soc Cosmet Chem Jpn* 1997;**31**:73−384.
22. Kawai E, Kohno Y, Ogawa K, Sakuma K, Yoshikawa N, Aso D. *Paper abstracts 22th IFSCC congress in Edinburgh*. 2002. p. 16−21.
23. Published Japanese patent 11-60441.
24. Korichi R, Pelle-de-Queral D, Gazano G, Aubert A. *J Cosmet Sci* 2008;**59**:127−37.

CHAPTER

# 35

# Ultraviolet Care Cosmetics

*N. Oguchi-Fujiwara*[1], *M. Hatao*[1], *K. Sakamoto*[2]

[1]Shiseido Global Innovation Center, Yokohama, Japan; [2]Tokyo University of Science, Chiba, Japan

## 35.1 IMPORTANCE OF SUN CARE COSMETICS

The Sun emits electromagnetic radiation including gamma ray, X-ray, ultraviolet (UV) ray, visible light, infrared light, and longer wavelength ray. UV, visible, infrared, and longer lights reach to the Earth's surface. UV radiation, considered to be harmful to the human body, represents ca. 6% of the solar spectrum. UV-C and part of UV-B covering 200–290 nm are absorbed by the ozone layer, and residual UV with 290–400 nm induces photo damage including sunburn, pigmentation, wrinkle formation, and cancer.[1–3] UV that reaches to the Earth's surface is divided into UV-B (290–320 nm)[4] and UV-A (320–400 nm)[5] based on their effect on the living system. Although total irradiance energy is predominantly larger for UV-A, biological effect such as acute erythema is much severe for UV-B. UV-B is sometimes called UV at leisure because seasonal variation is much larger than UV-A, and increases significantly during the summer season. DNA as a chromophore directly absorbs UV-B, which triggers acute and strong physiological changes such as solar erythema, which induces melanogenesis. Delayed tanning (DT) is a secondary skin reaction resulting from inflammation and melanogenesis. Excessive melanin production and residual inflammation could cause prolonged pigmentation.[6]

UV-A reaches to the Earth's surface and to the skin even through clouds and window glass because of its relatively long wavelength, so that the level of radiation is rather consistent year-round. UV-A also penetrates deep into skin to the dermis layer so that it causes immediate pigment darkening (IPD) or immediate tanning with even short periods of exposure, which eventually induce prolonged pigment darkening (PPD) without erythemal skin reactions.[7–9] It is well known that long-term exposure to UV-A causes deformation of collagen and elastin in the dermis, which results in skin darkening and deep wrinkle formation, which are typical signs of photoaging. Photoaging represents irreversible skin disintegration by solar UV radiation and is different from intrinsic aging that appears in the anatomic sights not exposed to UV.

As explained, it is important how to protect our skin from UV damage. Sun care cosmetics have been developed and utilized for this purpose, mostly against short-term UV-B exposure because of its relatively high energy to cause acute and reversible inflammation. Repeated UV-B exposure causes photoaging and eventually leads to skin cancer. Sun protection factor (SPF) is a measure to exhibit effectiveness of sun care products against short-term but strong UV-B exposure. It is a welcome trend that the necessity to protect skin from UV-B exposure is now well accepted and use of sunscreen products with appropriate SPF has become commonsense. However, the necessity to protect skin from UV-A, which causes every aspect of irreversible photoaging, is still not popularly accepted. New measures for the UV-A protection to ensure lifelong quality of life have recently been established. In this chapter, we will discuss every aspect of UV care cosmetics in relation to skin physiology.

## 35.2 SUNSCREEN AGENTS

Sun care cosmetics generally means cosmetic products expected to protect against solar UV radiation. In order for sun care cosmetic formulations to act, they must contain a sunscreen agent that either absorbs or scatters UV light. There are two types of sunscreen agents used in products: inorganic sunscreen powders[10–12] and organic UV absorbers.[13] Organic UV absorbers, also called UV-filters, can be classified as UV-B filters and UV-A filters based on their absorption profiles. Also there are different classifications by their origin as either synthetic or natural.

*Cosmetic Science and Technology: Theoretical Principles and Applications*
http://dx.doi.org/10.1016/B978-0-12-802005-0.00035-5



Copyright © 2017 Elsevier Inc. All rights reserved.

Sunscreen agents are used in the product alone or combined, depending on the formulation types and required level of UV protection.[14]

### 35.2.1 Sunscreen Powders

Titanium dioxide ($TiO_2$) and zinc oxide (ZnO) have been used for over 40 years as sunscreen powders.[11,12] These powders have high covering power together with effective scattering power for UV light and are widely used for sun care cosmetics and also decorative cosmetics such as makeups, foundations, mascaras, etc. In order to improve UV protection power along with avoiding powdery whitish look, reduction of powder size under nanometer scale has been a key objective of development since the 1990s. Since $TiO_2$ and ZnO have UV absorption capacity by its semiconductor optical absorption gap, development of functional sunscreen micropowders are focused in these materials. Points of development are to improve water resistance, sebum resistance, etc. by surface modification. $TiO_2$ and ZnO are transition metal oxides with photocatalytic activities to decompose cosmetic ingredients, so that effective surface treatment in this viewpoint is also important. Currently surface-treated micro or nano sunscreen powders to cover these drawbacks with improved dispensability in the formulae are available. Although these sunscreen powders have wide range of UV protection effect with durability on the skin, their drawbacks are uniform spreadability when applied on the skin. Incremental addition of these powders to the formula for better protection often cause deterioration of use feeling with rough surface. Combination with organic UV absorbers is often a solution to this problem.

### 35.2.2 UV Absorbers (UV Filters)

Most organic UV absorbers are oil soluble and a high amount of solubilizers is required to make a product that does not cause too oily a feeling when used. Furthermore, high content of UV absorbers causes coloration of the product because of the chromophore nature of absorbers, and fabric dyeing is a concern as sunscreen cosmetics are often used under sweating conditions.

There are strict regulatory requirements for sunscreen cosmetics and ingredients, so that the number of chemicals available in the market is limited to avoid adverse effects of generating harmful byproducts or decomposition of ingredients as side reactions at the time of releasing absorbed UV energy. Although the classification of sunscreen products is different in countries, products such as normal cosmetics, quasi cosmetics, OTC drugs, etc., UV absorbers are strictly restricted and only limited materials are approved for use. Table 35.1 shows the 10 most common types of molecules and details about them are explained in the following sections.

#### *35.2.2.1 Benzophenone Derivatives*

There are more than 10 derivatives developed. Benzophenone has wide range of UV absorption covering UV-B to UV-A incorporated with intramolecular hydrogen bond. Characteristic of benzophenone is its stability. Recently, diethylamino hydroxyl-benzoyl hexyl benzoate was developed and is now commonly used in Europe and other countries such as Japan, Mexico, and Taiwan, as an approved UV-A absorber.

#### *35.2.2.2 Salicylates*

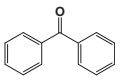
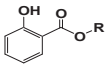
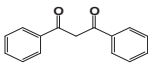
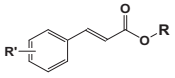
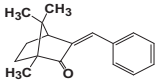
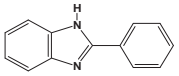
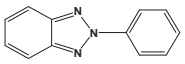
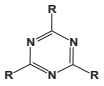
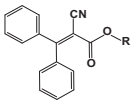
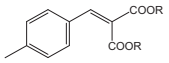
Intramolecular hydrogen bond between carbonyl in acid and ortho hydroxy make this structure a UV-B absorber. Although UV absorption level is rather low, liquid by itself and high compatibility with other cosmetic ingredients along with good solubilizing power to the relatively immiscible functional molecules make salicylate frequently used as a UV absorber.[15] As such, salicylate is easy to make formulations and stable in the system. Most typical salicylates are ethyl-hexyl-salicylate and homo-methyl-salicylate.

#### *35.2.2.3 Dibenzoylmethane Derivatives*

Within this category, butyl methoxy dibenzoylmethane (BMDBM) is used as an approved UV-A absorber. Basic structure provides absorption peak at UV-A with a wide range of UV absorption band extended to the higher wave length, which helps to develop superb sunscreen product with critical wavelength (λc) that exceeds the level settled by FDA guideline. λc is the wavelength at which the sunscreen allows 10% of the rays to penetrate. FDA defined a sunscreen with a critical wavelength over 370 nm as considered to provide excellent UV-A protection.

BMDBM also became an indispensable UV-A absorber to fulfill the European Union (EU) requirement to claim a product with broad spectrum protection for UV-B and UV-A to bear UV-A protection symbol on the package. The

**TABLE 35.1** Typical UV Absorbers Used in the Sun Care Cosmetic Products

| | Main Structure | UV Absorption Range | Approved Material |
|---|---|---|---|
| ① |  | UVB ~ UVA | • Benzophenone-5<br>• Diethylamino hydroxybenzoyl hexyl benzoate |
| ② |  | UVB | • Ethylhexyl Salicylate<br>• Homomenthyl Salicylate |
| ③ |  | UVA | • Butyl-Methoxydibenzoylmethane |
| ④ |  | UVB | • Ethylhexyl-Methoxycinnamate |
| ⑤ |  | UVB ~ UVA | • 4-Methylbenzylidene-Camphor<br>• Terephthalylidene Dicamphor Sulfonic Acid |
| ⑥ |  | UVB | • Phenylbenzimidazole Sulfonic Acid |
| ⑦ |  | UVB ~ UVA | • Drometrizole Trisiloxane |
| ⑧ |  | UVB ~ UVA | • Ethylhexyl Triazone<br>• Bis-Ethylhexyloxyphenol Methoxyphenyl Triazine |
| ⑨ |  | UVB | • OCTOCRYRENE |
| ⑩ |  | UVB | • polysilicone-15 |

UV-A protection is determined by the calculation based on the SPF of the product. A product that has one-third UV-A protection in relation to the UV-B protection may bear this symbol. However, BMDBM is well known for photo-instability under actual conditions of use. The commonly employed method for improving the photostability of BMDBM is based on the addition of other UV absorbers as stabilizer, or microencapsulation to protect BMDBM.[16–18]

#### *35.2.2.4 Cinnamates*

Octyl-4-methoxycinnamate (OMC) is the most widely used representative cinnnamate with strong UV-B absorption and easiness to handle as a liquid. A drawback of cinnamate is a reduction of absorption due to the *cis-trans* photoisomerization. There are many tips reported to prevent or suppress this disadvantage of OMC.[19,20]

#### *35.2.2.5 Benzyliden-Camphor Derivatives*

Combination of benzyliden structure with UV-B absorption and bulky camphor moiety to prevent *cis-trans* photoisomerization makes benzyliden-camphors stable UV-B absorbers against photoisomerization. The most typical material in this class is 4-methyl benzylidene camphor (MBC, λmax 300 nm, and E% = 920–1000 (1%, 1 cm) in ethanol),[13] and further development has been conducted such as dibenzyliden structure to extend resonance to be a UV-A absorber with wide range absorption spectrum.

#### 35.2.2.6 Phenylbenzimidasol Derivatives

Phenylbenzimidasol is a UV-B absorber and only 2-phenylbenzimidasol-5-sulfonic acid is used as approved absorber, which has unique water-soluble property with high absorption (λmax 310 nm (0.1 N NaOH) and E% = 920−1000 (1%, 1 cm) in ethanol)[13] and good photostability. Special care is required for the formulation to work as solubility varies by pH and sometime causes crystallization.

#### 35.2.2.7 Phenylbenzotriazol

OH substitution at 2-position makes phenylbenzotriazol a UV-A absorber. Drometrizole trisiloxane, bearing siloxane moiety, is compatible with silicon oils as popular solvent for sun care cosmetics, and has been used in the past. Recently, a dimerized molecule, methylene bis-benzotriazolyl tetramethylbutylphenol (bisoctrizole) was developed, which is insoluble both to oil and water and dispersed in the formula. Bisoctrizole is microfine organic particles (<200 nm), like microfine ZnO and $TiO_2$, whereas other organic UV absorbers are dissolved in either the oil or water phase.[21] Bisoctrizole is not approved by the US Food and Drug Administration (FDA), but is approved in the EU and other parts of the world.

#### 35.2.2.8 Triazine Derivatives

Three phenyl groups are substituted to triazine as UV-B absorber with high photostability. Ethyl-hexyl triazone with absorption maximum of 314 nm is the most common absorber widely used in sunscreen products. Bis-ethyl-hexyloylphenol methoxyphenyl triazone (ethylhexyl triazone (INCI)), a recently developed triazine derivative, has UV-A absorption with intramolecular hydrogen bond by two phenolic OH groups. Although UV absorption and photostability are high, low solubility to common cosmetic solvent and recrystallization in the formula are drawbacks of ethylhexyl triazone. Encapsulation of ethylhexyl triazone with poly-methacrylate to disperse in the aqueous phase is a recent development for ethylhexyl triazone.

#### 35.2.2.9 Diphenyl-acrylate Derivatives

Diphenyl-acrylate derivatives are UV-B absorbers and 2-ethylhexyl 2-cyano-3,3-diphenyl-2-propenoate (octocrylene; OCR) is the only approved UV absorber (E1%/1cm, methanol 340 to 370 at 303 nm)[13] with the characteristic stabilization effect for BMDBM with OCR's own high photostability. There are several advancements in the development of diphenyl-acrylate derivatives, which are ethyl-hexyl methoxy crylene with introduction of methoxy group at para position in phenyl moiety and Polyester-8, which is a copolymer composed of adipic acid and neopentyl glycol with terminal esterification by OCR.[22,23]

#### 35.2.2.10 Benzalmalonate

Benzalmalonate is a derivative of cinnamate bearing additional ester as a UV-B absorber with high photostability and compatibility to cosmetic oils. Polysilicone-15 is the only sunscreen approved for cosmetic use as a low-molecular-weight siloxane grafted with benzalmalonate.

Polysilicone-15 is mainly used in hair care formulations but also for sunscreens and cosmetics as UV absorber. As the UV chromophore part is relatively small within the whole molecule, UV protection by Polysilicone-15 (INCI)[24] is relatively weak compared to other absorbers.

## 35.3 REQUIRED FUNCTIONALITY AS SUN CARE COSMETICS

### 35.3.1 Basic Properties as Cosmetic Ingredients

There are extra requirements for sun care cosmetics to fit the consumer's needs such as feeling of use, stability, safety, etc. For example, UV absorbers are usually lipophilic materials, which require a high amount of oily solvent, but residual oily feeling is undesirable; also, powder sunscreen often leaves a whitish appearance. As a result, consumers tend to use less amounts of sun care cosmetics required to get the SPF value of the product. In order to overcome these problems, extensive efforts have been made and there are varieties of sun care products developed that are milky oil-in-water (O/W) lotion to waterproof water-in-oil (W/O) lotion, refreshing water-base gel, spray type, and stick type product easy for the point protection. Sun care cosmetics are often used during outdoor activities, which requires them to have waterproof and physically durable

properties. W/O formulations are advantageous to achieve these requirements and oil soluble sunscreen agents can evenly be spread on the skin. Along with technical developments on the formulations, improvement of ingredient properties such as water-repellent surface treatment for powder sunscreens has been conducted to increase efficacy.

## 35.3.2 Characteristic UV-Absorption Spectrum and Photostability

In order to reduce UV damage of the skin, appropriate balance of UV-B and UV-A protection is necessary for sun care cosmetics.[9] Inorganic powder sunscreen is effective to protect against a wide range of UV light, while organic UV absorbers tend to have narrow range of UV absorption profiles around λmax so that several absorbers are combined to cover wide range of UV.[9] UV absorbers in the cosmetic formula absorb UV light and then desirably release absorbed energy as heat, light, or in other not harmful ways.[25] In reality, there are side reactions happening such as isomerization, decomposition to reduce sunscreen potential, so that careful combination of absorbers to avoid decomposition or reduction of absorption potential have to be considered.[16,26–33]

As an example, typical combination for wide range cover is BMDBM for UV-A and OMC for UV-B. This combination has been applied for many products worldwide and photochemistry on the excitation and degradation has been intensively investigated.[31,34–38] The photoisomerization from *cis* to *trans* form occurs for OMC by UV radiation, and significant reduction of UV absorption is well known[20,25,39] (Fig. 35.1). This reduction of UV-B filter effect (reduction of absorption potential) is further accelerated in the combination of OMC with BMDBM. Furthermore, there is significant reduction of UV-A filter effect of BMDBM known in this combination because of keto-enol tautomerism, as shown in Fig. 35.1, to shift absorption spectrum to shorter wave length. This tautomerism and following photodecomposition of BMDBM is caused by energy transfer of triplet excited tautomer to OMC.[40] Therefore it is important to optimize combination of absorbers not just by their absorption spectra but to take account of the exited states and correlations between molecules.

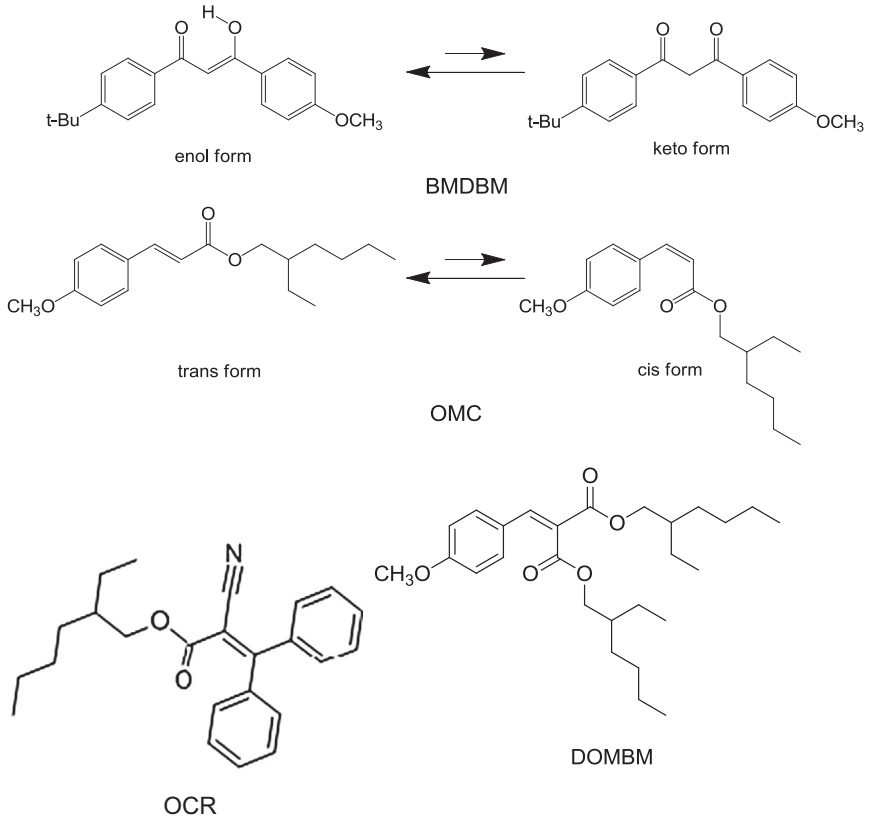



**FIGURE 35.1** Molecular structures of BMDBM, OMC, OCR, and DOMBM. *BMDBM*, butyl methoxy di-benzoylmethane; *DOMBM*, dioctyl-4-methoxy-benzylidene-malonate; *OCR*, 2-ethylhexyl 2-cyano-3,3-diphenyl-2-propenoate; *OMC*, octyl-4-methoxycinnamate; *Octocrylene*.

### 35.3.3 Development of Novel UV-B Absorber to Enhance the Efficacy of UV-A Protection Based on an Energy Transfer System

The most important characteristics of effective and safe UV absorbers in sunscreen products are photochemical stability and protection efficacy against broad range of UV radiation. Recent FDA amendment of the sunscreen monograph requires preirradiation for UV-A testing in order to evaluate the stability for the UV-A region. The European Commission has released a recommendation on the efficacy of sunscreen products to prove that a PFA must be higher than one-third of the SPF, and also a critical wavelength must be longer than 370 nm in order to claim UV-A protection. These trends clearly indicate that the importance of UV-A protection for public health has been recognized worldwide.

The most widely used organic UV-A absorber is BMDBM since it is the only absorber to cover UV-A 1 (340–400 nm) region satisfactorily. However, BMDBM is well known for photoinstability under actual conditions of use as mentioned before (Fig. 35.1). The commonly employed method for improving the photostability of BMDBM is based on the addition of other UV absorbers to protect BMDBM. 2-Ethylhexyl 2-cyano-3,3-diphenylpropenoate (OCR) has been found to be the most effective UV-B absorber for stabilizing BMDBM, though the stabilization mechanism has not been clarified.

In some sunscreen formulations, OMC, the most widely used representative UV-B absorber, is added to the combination of BMDBM and OCR in order to provide effective protection throughout the whole UV range of solar radiation to make up for the molar absorption coefficients of OCR that are small in the UV-B region (Fig. 35.2). However, the photostability of BMDBM in the BMDBM-OCR-OMC combination is significantly lower than that in the BMDBM-OCR combination (Fig. 35.3).

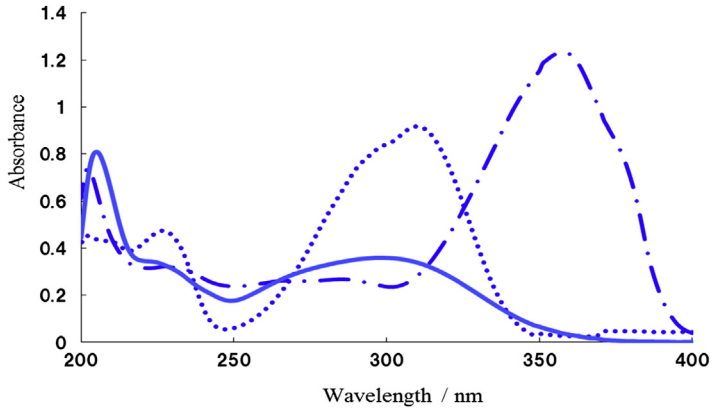



FIGURE 35.2 UV absorption spectra of OMC (*dotted line*), OCR (*solid line*), and BMDBM (*dash-dot-dash line*) in EtOH at 25°C. The sample solutions were prepared at a concentration of 10 mg/L.

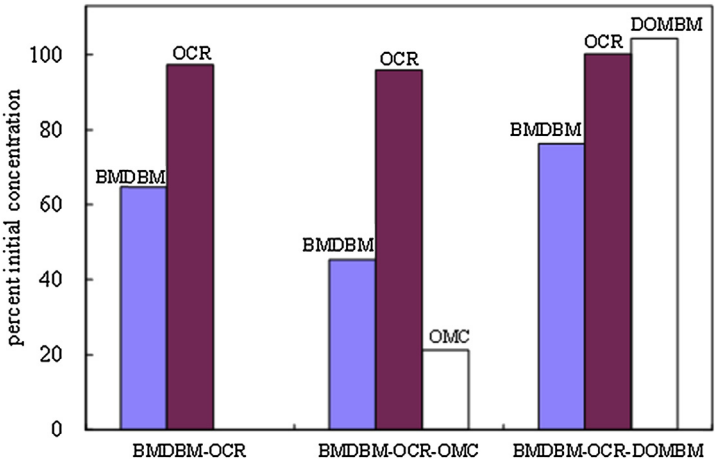



FIGURE 35.3 Photostability of BMDBM, OCR, *trans*-OMC, and DOMBM in BMDBM-OCR, BMDBM-OCR-OMC, and BMDBM-OCR-DOMBM after irradiation for 2 hours.

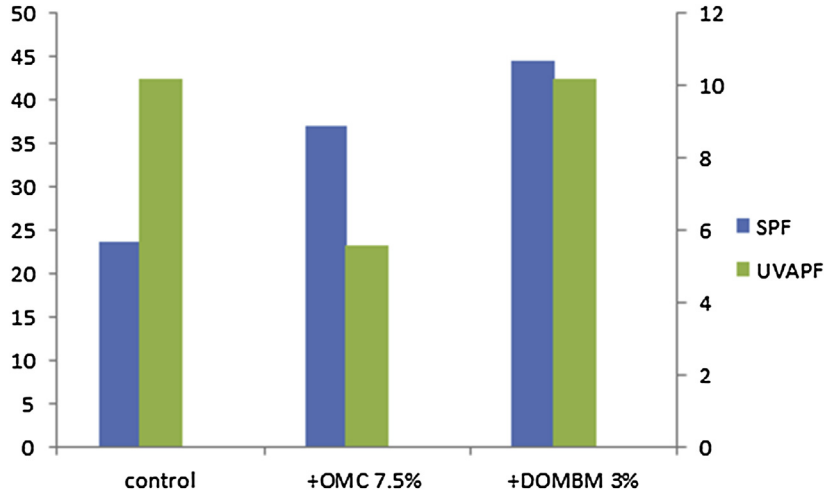



FIGURE 35.4 In vivo determination of UV-B and UV-A (SPF and UVAPF value).

Despite the fact that OCR effectively stabilizes BMDBM, the addition of OMC to OCR-BMDBM combination causes significant reduction of the stability of BMDBM. Oguchi et al. hypothesized that this was due to the triplet energy of BMDBM being transferred to other coexisting UV absorbers. In order to prove this hypothesis, they have conducted experiments to observe the triplet–triplet energy transfer from BMDBM to OMC and OCR to assure that OMC and OCR act as a triplet energy acceptor for BMDBM. They also verified the filter effect (the protecting efficacy) of OMC on the photostablity of BMDBM and found that the filter effect of OMC is reduced due to the isomerization, which is caused by accepting the triplet energy from BMDBM.[41–44]

To address this issue, they designed a new UV-B absorber, dioctyl-4-methoxy-benzylidene-malonate (DOMBM, Fig. 35.1), which has similar UV-B absorbing properties with OMC, but does not undergo *cis-trans* photoisomerization owing to the molecular structure. Triplet–triplet energy transfer measurements and photostability tests of DOMBM in the presence of BMDBM were performed in order to demonstrate the efficacy of DOMBM to stabilize BMDBM based on an ideal triplet–triplet energy transfer without photoisomerization.

DOMBM itself is stable even after UV irradiation since it does not undergo *trans* to *cis* photoisomerization, which is the main cause of the instability of OMC. DOMBM maintains the filter effect to protect BMDBM because of the structural stability. Furthermore, DOMBM significantly stabilizes BMDBM by accepting and releasing the triplet state energy, which destabilizes BMDBM as shown in Fig. 35.3. In vivo SPF measurements also gave evidence that DOMBM substantially improves the SPF of sunscreen formulations (Fig. 35.4). Since DOMBM is an oil-soluble liquid even in silicone, it does not require solvents though many other organic UV absorbers and crystalline solids that require suitable solvents. This property is a great advantage, which is applicable to a wide variety of formulations.[45]

The before-mentioned ideal photochemical properties of DOMBM meet requirements to provide innovative sunscreen products with high photochemical stability and high protection efficacy against a broad range of UV radiation. Understanding the mechanism of intermolecular energy transfer contributes to a new molecular design of UV absorbers to achieve high safety and efficacy for extended periods of time.

## 35.4 EVALUATION AND DECLARATION OF SUNSCREEN CAPACITY FOR COSMETICS

### 35.4.1 Determination of Effectiveness of Sun Care Products

There are two independent but closely related parameters for UV-B and UV-A that were developed to represent effectiveness of sun care products against solar UV exposure. SPF is a measure to quantify the level of UV-B (simulated solar radiation) exposure to cause erythema for individuals by assessing the minimum erythema dose (MED) of UV radiation. SPF can be determined as a ratio of MED for protected skin by the product to MED of unprotected skin. The first standardization of SPF was published by the FDA in 1978 in the Federal Register.[46] In FDA method the amount of application was set as 2 mg/cm$^2$, This method was followed by most of the other standards such as COLIPA (European), Australian/New Zealand, Japan but not by DIN (German standard with 1.5 mg/cm$^2$). SPF is a

measure to represent protection potential of sun care product but under the standardized condition, so that caution should be taken and that real protection depends on the situation of product use, level of solar radiation, amount applied, and duration of use. It is important to develop and promote sun care products so that consumers are not misled by the SPF number itself and that appropriate product information is delivered for practical use.

## 35.4.2 Determination Method of SPF

The principle of SPF determination is shown in Fig. 35.5. Each of six sights on the back (1 $cm^2 \times 6$) for without (A) or with (B) application of test product are irradiated by UV with progressive dose level as shown in Fig. 35.5. Minimum erythema dose ($MED^{A \text{ or } B}$) is determined at the sight that started to show erythema ($MED^A = 1.25$, and $MED^B = 14.1$) and then SPF was determined as 11.3 ($SPF = MED^B/MED^A = 14.1/1.25$).

As previously mentioned, there are individual methods set for SPF determination by countries based on the same principle but different test conditions. As a result, there are discrepancies between SPF values obtained by different methods. In order to avoid consumer inconvenience, international standardization for the SPF determination was developed and finally in 2010 the European Standardization Organization (CEN) published the Standard EN ISO 24444:2010 Cosmetics − Sun protection test methods − In vivo determination of the sun protection factor (SPF).[47] Although this standard minimized international discrepancies for the SPF value, careful attention should be paid that there are some countries including the United States that still did not adopt ISO 24444. Criteria important to compare each test method are listed in Table 35.2. Selection of skin type (or skin phototype) is important for the SPF determination. Skin phototype in Table 35.2 is based on the classification proposed by Fitzpatrick,[48] as shown Table 35.2.

Simulation of solar irradiation or distribution of UV spectrum is also important as each UV absorber has a characteristic absorption profile that directly relates to the SPF, and it is strongly recommended to follow test conditions by ISO 24444.

There are several in vitro SPF determination methods proposed and practiced to be time-saving and cost-effective alternatives to the in vivo test. In most of the cases for in vitro measurement, SPF is evaluated by the transmitted

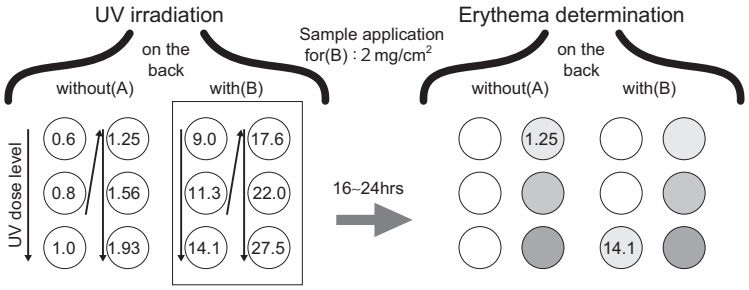



**FIGURE 35.5** Determination method of SPF.

**TABLE 35.2** Classification of Skin Type (Skin Phototype) by Fitzpatrick

| Skin Type | Typical Features | Tanning Ability |
|---|---|---|
| I | Pale white skin, blue/green eyes, blond/red hair | Always burns, does not tan |
| II | Fair skin, blue eyes | Burns easily, tans poorly |
| III | Darker white skin | Tans after initial burn |
| IV | Light brown skin | Burns minimally, tans easily |
| V | Brown skin | Rarely burns, tans darkly easily |
| VI | Dark brown or black skin | Never burns, always tans darkly |

spectrum thorough the quartz plate with test material spread onto it. Calculation of SPF varies by method and the most reliable one to the author's best knowledge would be the one proposed by Miura et al.[49] They developed an algorithm to estimate SPF in vitro by converting the amount of UV light transmission through the sunscreen layer into cumulative relative erythema effectiveness to obtain one minimal erythema algorithm using the same end point as in vivo SPF methods but with a photomultiplier tube as the detector instead of skin. The values obtained showed an excellent correlation with in vivo SPF values, even for high-SPF sunscreens exceeding SPF 50.

### 35.4.3 Determination of UV-A Protection

As explained in the first section of this chapter, necessity for UV-B protection can be easily recognized by consumers as UV-B damage is acute to generate erythema and inflammation. On the other hand, UV-A exposure would not cause such acute and severe reactions so that skin damage by long-term UV-A exposure to induce photoaging would be often overlooked. Increasing scientific evidence on the UV-A damage in dermis to cause photoaging has led to the awareness for necessary protection against UV-A. As a result, development and standardization of methods to determine UV-A exposure level and skin damage have been extensively conducted. PPD method as a biomarker is a one of the useful methods for the determination of UV-A exposure. Cause of PPD is considered to be the pigmentation of melanin precursors such as di-hydroxyl-indole carboxylic acid in the epidermis by oxidative polymerization in the stratum corneum.[50] Also, PPD is not directly related to the acute skin reactions, which makes it difficult for consumers to be aware of the importance of protection. Still, PPD was used to evaluate UV-A exposure level as a biomarker. Japan pioneered making a PPD method as an industrial standard,[51] then they were followed by Europe, and eventually this became ISO standard (ISO 24442) in 2011[52] after some improvement as an international de facto standard. The Japanese Cosmetic Industry Association (JCIA) adopted ISO 24442 as standard method in January 2013. Methods based on the ISO 24442 are also adopted in the EU and Asian countries such as Taiwan, Korea, and Thailand but not in China.

ISO 24442[52] specifies the procedure to determine the UV-A Protection Factor (UVAPF) of a sunscreen product using the PPD method according to the principles recommended by the JCIA in 1995.[51] The test method outlined in ISO 24442 is derived primarily from the UVAPF test methods as developed by the JCIA.[51] Modifications have been made to attempt to harmonize with other methodologies without changing the integrity of the fundamental underlying principles of the test method. Test conditions are summarized as follows:

**ultraviolet radiation**: electromagnetic radiation in the range of 290−400 nm.

**persistent pigment darkening (PPD)**: skin darkening that persists more than 2 h after the end of UV-A exposure.

**minimal persistent pigment darkening dose (MPPDD)**: lowest ultraviolet A (UV-A) dose that produces the first perceptible unambiguous persistent pigment darkening response with defined borders appearing over most of the field of UV-A exposure, observed between 2 and 24 h after the end of the UV-A exposure.

(Note): The MPPDD on unprotected skin is referenced as "MPPDDu," and the MPPDD on sunscreen-protected skin is referenced as "MPPDDp."

**individual Ultraviolet A protection factor (UVAPFi)**:

$$\mathrm{UVAPFi} = \frac{\mathrm{MPPDDp}}{\mathrm{MPPDDu}}$$

ratio of the minimal persistent pigment darkening dose on product-protected skin (MPPDDp) to the minimal persistent pigment darkening dose on unprotected skin (MPPDDu) of the same subject.

The outcome of this test method has been used to determine the UV-A classification of topical sunscreen products according to local regulatory requirements as mentioned before. The UVAPF value of a product provides information on the magnitude of the protection provided explicitly in the UV-A portion of the spectrum, independent of the SPF values. Labeling of UVAPF on the product is different by local regulatory bodies. In Japan, it is classified by grade symbols as PA+ through PA++++, where PA+:2≦UVAPF<4, PA++:4≦UVAPF<8, PA+++:8≦UVAPF<16, PA++++:16≦UVAPF.[51] The same classification was adopted in Taiwan and Korea where the highest grade is up to PA+++.

UVAPF is classified in combination with SPF in Europe as SPF is the primary factor to protect skin from UV-B, and UVAPF classifies the sunscreen potential to fortify the UV-A range that SPF would not cover. That is the reason labeling for UV-A protection is by standardized UV-A seal on its product labels in EU.[53] As explained in Section 35.3.3 of this chapter, UVAPF must be higher than one-third of its SPF in order to claim UV-A protection.

There are in vitro ISO standards such as ISO 24443:2012, which specifies an in vitro procedure to characterize the UV-A protection of sunscreen products.[54] These specifications are given to enable determination of the spectral

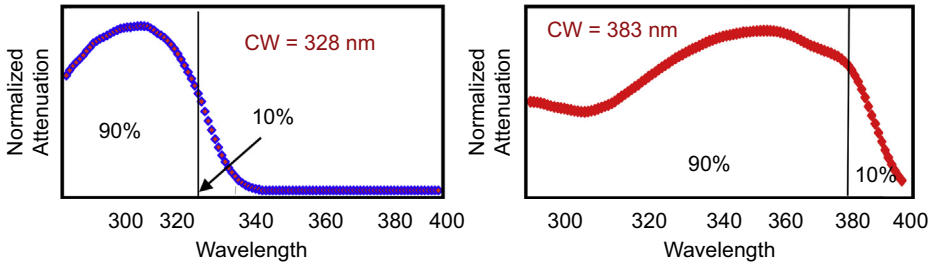



**FIGURE 35.6** Example spectra of critical wavelength (λc) and UV-A protection.

absorbance characteristics of UV-A protection in a reproducible manner. In order to determine relevant UV-A protection parameters, the method was created to provide a UV spectral absorbance curve from which a number of calculations and evaluations can be undertaken. This method relies on the use of in vivo SPF results for scaling the UV absorbance curve.[54] Another measure to show UV-A protection of the product is critical wavelength (λc) method as explained in Section 35.2.3 of this chapter. λc is the wavelength at which the sunscreen allows 10% of the rays to penetrate. FDA defined a sunscreen with λc over 370 nm as considered to provide excellent UV-A protection. Examples of λc are shown in Fig. 35.6. Products with λc = 383 nm shown right in Fig. 35.6 have better UV-A protection, even exceeding the FDA's recommendation.

λc is the wavelength at which the sunscreen allows 10% of the rays to penetrate. FDA defined a sunscreen with a critical wavelength over 370 nm as considered to provide excellent UV-A protection.

### 35.4.4 Classification of Sunscreen Product

Although there are progressive standardizations realized by ISO 24444 for the determination of SPF, and ISO 24442 and 24443 for UV-A, classification and labeling of product capacity are still being worked on. SPF calculation in the FDA's method is from the mean value minus the 95% one-sided confidence interval,[55] in COLIPA method is arithmetical mean,[56] and in Australian/New Zealand[57] method is mean MED to one decimal Std. error of mean <7% and round down of mean SPF. As such, careful attention should be paid for each product because determination and declaration of SPF classification on the label could be different under each regulatory definition.

In terms of regulatory status of sunscreen products, there are significant differences between countries. In Europe, New Zealand, and Japan sunscreen products are regulated under normal cosmetics. There is a special class of sunscreen products in Japan classified as a quasi-drug category in case the product includes active material designated in this category along with UV protection with sunscreen agents. Sunscreen products are classified as over-the-counter drugs in the United States, Canada, and Australia. In 2011, the FDA released a "final rule" for labeling and effectiveness testing of sunscreen products.[55]

### 35.4.5 Direct Measurement of Skin Reactions Toward UV Radiation by Specific BioMarkers

Although SPF and UVAPF are determined by standardized in vivo test with physiological reactions caused by UV radiation, they only represent protection potential of the product because there is no measurement of the results of consumers' actual use. The problem here is that consumers would not use designated amounts of product. A European Commission press release[53] tells consumers to "Apply sunscreen products in sufficient quantity. The correct application of the product is just as important as the choice of the product itself. To reach the protection indicated on the 'sun protection factor', a quantity of 2 mg/cm$^2$ needs to be applied. This is about 36 g (6full tea spoons) of sun cream for one adult body. Presently consumers use usually only about 1/2 of this quantity." Under these real situations, development of a noninvasive in vivo method with biomarkers directly reflecting the physiological changes caused by UV irradiation would be desirable.

Herring et al. reported a method to measure UV-generated free radicals/reactive oxygen species (ROS) in skin as a biomarker directly representing physiological functional changes by UV radiation by means of ESR spectroscopy.[58–62] Herring et al. explained their method and its usefulness as follows:[58]

> Free radicals/reactive oxygen species (ROS) generated in skin by UV irradiation were measured by electron spin resonance (ESR). To increase the sensitivity of measurement the short life free radicals/ROS were scavenged and accumulated by using the nitroxyl probe 3-carboxy-2,2,5,5-tetrametylpyrrolidine-1-oxyl (PCA). The spatial distribution of free radicals/ROS measured in pig skin biopsies with

ESR imaging after UV irradiation corresponds to the intensity decay of irradiance in the depth of the skin. The main part of free radicals/ROS were generated by UVA (320−400 nm) so that the spatial distribution of free radicals reaches up to the lower side of the dermis. In vivo measurements on human skin were performed with a L-band ESR spectrometer and a surface coil integrating the signal intensities from all skin layers to get a sufficient signal amplitude. Using this experimental arrangement the protection of UVB and UVA/B filter against the generation of free radicals/ROS in skin were measured. The protection against ROS and the repair of damages caused by them can be realized with active antioxidants characterized by a high antioxidative power (AP). The effect of UV filter and antioxidants corresponding to their protection against free radicals/ROS in skin generated by UVAB irradiation can be quantified by the new radical sun protection factor (RSF). The RSF indicates the increase of time for staying in the sun to generate the same number of free radicals/ROS in the skin like for the unprotected skin. Regarding the amount of generated free radicals/ROS in skin as a biophysical endpoint the RSF characterizes both the protection against UVB and UVA radiation.

Sakamoto et al. have noticed the *trans*-urocanic acid (t-UCA) in the stratum corneum as a potential biomarker of UV exposure. t-UCA is an end metabolite of histidine, a component of natural moisturizing factor as a hydrolysate of filaggrin. t-UCA has intrinsic UV-B absorption to convert to *cis* isomer (c-UCA) by photo isomerization and c-UCA is an intrinsic immune suppressor in the skin. They have established noninvasive surface corneometry (tape stripping of surface stratum corneum layers and following HPLC determination of *cis* and *trans* isomer ratio (*cis*/*trans*) of UCA recovered from the stripped tape), as isomer ratio is absolute value independent from the actual amount of UCA in the stratum corneum. With this method, they found that *cis*/*trans* ratio for UCA corresponds to the daily and seasonal level and fluctuating level of solar UV irradiation. Also *cis*/*trans* isomer ratio corresponded to the level of UV radiation generated by solar simulator, which confirms this ratio could be a useful biomarker to monitor the level of UV exposure to the skin. Furthermore, they have found that the ratio always saturates at the same level when radiation reaches the individual MED and this threshold level increases by the application of sunscreen product. This is a good indication that UCA could be a useful biomarker to evaluate actual exposure level on the skin and physiological response to the radiation.

## 35.5 SUMMARY

In this chapter a general view of basics, such as elemental technologies, evaluation methodologies, and regulatory concerns, necessary to develop sun care products are reviewed. Regulatory or organizational guidelines for the evaluation method for UV protection potential of products and labeling requirements for the protection capacity are recently updated by adapting scientific advancements in the various fields. As such, the necessity to avoid exposure to solar ultraviolet radiation became a well-accepted commonsense in society. As a reflection of these movements, product varieties are expanding to gel or spray from traditional O/W or W/O emulsions to explore products that are more convenient to use. Also, development of booster materials and improvements of formulation technologies to enhance UV absorption potential have significantly progressed.

Principle knowledge of the absorption mechanism and cross energy transfer to the other co-absorber has been extensively advanced. As a result, formulation tips to design better combinations of available absorbers to increase absorption potential and stability have been revealed. Furthermore, as an outcome of such investigations, the novel UV-A absorber DOMBM was developed. With all these advancements, we could expect further progress for UV protection not just by seeking superior formulation technology but also in situ evaluation with intelligent use of biomarkers existing in the skin to monitor actual physiological effects.

## References


1. Attard NR, Karran P. UVA photosensitization of thiopurines and skin cancer in organ transplant recipients. *Photochem Photobiol Sci* 2012;**11**: 62−8.
2. Pfeifer GP, Besaratinia A. UV wavelength-dependent DNA damage and human non-melanoma and melanoma skin cancer. *Photochem Photobiol Sci* 2012;**11**:90−7.
3. Matsumura Y, Ananthaswamy HN. Toxic effects of ultraviolet radiation on the skin. *Toxicol Appl Pharmacol* 2004;**195**:298−308.
4. Iwai I, Hatao M, Naganuma M, Kumano Y, Ichihashi M. UVA-induced immune suppression through an oxidative pathway. *J Invest Dermatol* 1999;**112**:19−24.
5. De Polo KF. *Composition of the solar radiation, reaching the surface of the earth, A short textbook of cosmetology, Chapter 3 Sunscreens*. Augsburg: Verlag fur chemische Industrie, H. Ziolkowsky Gmbh; 1998. p. 87−8.
6. Maeda K, Hatao M. Involvement of photooxidation of melanogenic precursors in prolonged pigmentation induced by ultraviolet A. *J Invest Dermatol* 2009;**122**:503−9.
7. Maeda K, Inoue Y, Nishikawa H, Miki S, Urushibata O, Miki T, et al. Involvement of melanin monomers in the skin persistent UVA-pigmentation and effectiveness of vitamin C ethyl on UVA-pigmentation. *J Jpn Cosmet Sci Soc* 2003;**27**:257−68.

8. Stanfield JW, Feldt PA, Csortan ES. Ultraviolet A screen evaluation in normal subjects. *J Am Acad Dermatol* 1989;**20**:744–8.
9. Gonzenbach HU, Mascotto RE, Cesarini JP. UVA sunscreen in vivo effectiveness measurements. *Cosmet Toilet* 1991;**106**:79–84.
10. Klein K. Encyclopedia of UVA absorbers for sunscreen products. *Cosmet Toilet* 1992;**107**:45–78.
11. Sayre REM, Nikiforos K, Roberts RL, Baqer A, Sadiq I. Physical sunscreens. *Soc Cosmet Chem* 1994;**41**:22–4.
12. Mitchnick MA. Zinc oxide, an old friend to the rescue. *Cosmet Toilet* 1992;**107**:111–6.
13. De Polo KF. *Chemical classification of UV filters, A short textbook of cosmetology, Chapter 3 Sunscreens*. Verlag fur chemische Industrie, H. Ziolkowsky Gmbh, Augsburgical; 1998. p. 101–6.
14. Hatao M, Oguchi N. Recent progress in sunscreen products. *Aesthet Dermatol* 2011;**21**:215–23.
15. Jaffe HH, Orchin M. *Theory and application of ultraviolet spectroscopy*. New York: John Wiley & Sons; 1964. p. 111–46.
16. Mendrok-Edinger C, Smith K, et al. The quest for avobenzone stabilizers and sunscreen photostability. *Cosmet Toiletries* 2009;**124**:47–54.
17. Scalia S, Mezzena M. Incorporation in lipid microparticles of the UVA filter, butyl methoxydibenzoylmethane combined with the UVB filter, octocrylene: effect on photostability. *AAPS Pharm Sci Tech* 2009;**10**:384–90.
18. Scalia S, Tursilli R, Sala N, Iannuccelli Va. Encapsulation in lipospheres of the complex between butyl methoxydibenzoylmethane and hydroxypropyl-β-cyclodextrin. *Int J harm* 2006;**320**:79–85. http://www.sciencedirect.com/science/article/pii/S0378517306003322.
19. Huong SP, Andrieu V, Reynier J-P, Rocher E. The photoisomerization of the sunscreen ethylhexyl p-methoxy cinnamate and its influence on the sun protection factor. *J Photochem Photobiol A* 2007;**186**:65–70.
20. Pattanaargson S, Munhapol T, Hirunsupachot P, Luangthongaram P. Photoisomerization of octyl methoxycinnamate. *J Photochem Photobiol A* 2004;**161**:269–74.
21. Herzog B, Mongiat S, Deshayes C, Neuhaus M, Sommer K, Mantler A. In vivo and in vitro assessment of UVA protection by sunscreen formulations containing either butyl methoxy dibenzoyl methane, methylene bis-benzotriazolyl tetramethylbutylphenol, or microfine ZnO. *Int J Cosmet Sci* 2002;**24**(3):170–85.
22. Kockler J, Oelgemöller M, Robertson S, Glass BD. Photostability of sunscreens. *J Photochem Photobiol C* 2012;**13**:91–110.
23. Labeling and Effectiveness Testing. Sunscreen drug products for over-the-counter human use: Final rule: Department of Health and Human Services, Food and Drug Administration. *Fed Regist* June 17, 2011;**76**(117).
24. Opinion on Polysilicone-15, COLIPA no. S74, SCCS/1346/10. In: *The SCCS adopted this opinion at its 7th plenary meeting*; June 22, 2010.
25. Bonda CA. Research pathways to photostable sunscreens. *Cosmet Toiletries* 2008;**123**:49–60.
26. Bonda CA. In: Shaath NA, editor. *Sunscreens: regulations and commercial development*. 3rd ed. Boca Raton: Tayler & Francis; 2005. p. 321–49.
27. Scalia S, Mezzena M. Photostabilization effect of quercetin on the UV filter combination, butyl methoxydibenzoylmethane-octyl methoxycinnamate. *Photochem Photobiol* 2010;**86**:273–8.
28. Herzog B, Wehrle M, Quass K. Photostability of UV absorber systems in sunscreens. *Photochem Photobiol* 2009;**85**:869–78.
29. Damiani E, Baschong W, Greci L. UV-Filter combinations under UV-A exposure: concomitant quantification of over-all spectral stability and molecular integrity. *J Photochem Photobiol B* 2007;**87**:95–104.
30. Damiani E, Rosati L, Castagna R, Carloni P, Greci L. Changes in ultraviolet absorbance and hence in protective efficacy against lipid peroxidation of organic sunscreens after UVA irradiation. *J Photochem Photobiol B* 2006;**82**:204–13.
31. Lhiaubet-Vallet V, Marin M, Jimenez O, Gorchs O, Trullas C, Miranda MA. Filter–filter interactions. Photostabilization, triplet quenching and reactivity with singlet oxygen. *Photochem Photobiol Sci* 2010;**9**:552–8.
32. Kockler K, Oelgemöller M, Robertson S, Glass BD. Photostability of sunscreens. *J Photochem Photobiol C* 2012;**13**:91–110.
33. Dondi D, Albini A, Serpone N. Interactions between different solar UVB/UVA filters contained in commercial suncreams and consequent loss of UV protection. *Photochem Photobiol Sci* 2006;**5**:835–43.
34. Alves LF, Gargano R, Alcanfor KBS, Romeiro LAS, Martins JBL. *Chem Phys Lett* 2011;**516**:162–5.
35. Paul BK, Guchhait N. A computational insight into the photophysics of a potent UV absorber Tinuvin P: Critical evaluation of the role of charge transfer interaction and topological properties of the intramolecular hydrogen bonding. *Comput Theor Chem* 2011;**966**:250–8. http://www.sciencedirect.com/science/article/pii/S2210271X11001435.
36. Morabito K, Steeley KG, Shapley NC, Mello C, Li D, Calvert P, Tripathi A. Proximal effects of ultraviolet light absorbers and polymer matrix in the photostability of β-carotene. *Dyes Pigm* 2012;**92**:509–16.
37. Kikuchi A, Yukimaru S, Oguchi N, Miyazawa K, Yagi M. Excited triplet state of a UV-B absorber, octyl methoxycinnamate. *Chem Lett* 2010;**39**:633–63.
38. Farkas R, Lhiaubet-Vallet V, Corbera J, Törincsi M, Gorchs O, Trullas C, Jiménez O, Miranda MA, Novak L. Synthesis of New 2-(2′-Hydroxyaryl) benzotriazoles and Evaluation of Their Photochemical Behavior as Potential UV-Filters. *Molecules* 2010;**15**:6205–16.
39. Pattanaargson S, Hongchinnagorn N, Hirunsupachot P, Sritana-anant Y. UV absorption and photoisomerixation of p-methoxycinnamate grafted silicone. *Photochem Photobiol* 2004;**80**:322–5.
40. Paris C, Lhiaubet-Vallet V, Jiménez O, Trullas C, Miranda MA. A blocked diketo form of avobenzone: photostability, photosensitizing properties and triplet quenching by a triazine-derived UVB-filter. *Photochem Photobiol* 2009;**85**:178–84.
41. Oguchi-Fujiyama N, Miyazawa K, Kikuchi A, Yagi M. Photophysical properties of dioctyl 4-methoxybenzylidenemalonate: UV-B absorber. *Photochem Photobiol Sci* 2012;**11**:1528–35.
42. Kikuchi A, Yagi M. Direct observation of the intermolecular triplet–triplet energy transfer from UV-A absorber 4-*tert*-butyl-4′-methoxydibenzoylmethane to UV-B absorber octyl methoxycinnamate. *Chem Phys Lett* 2011;**513**:63–6.
43. Kikuchi A, Oguchi-Fujiyama N, Miyazawa K, Yagi M. Triplet–triplet energy transfer from a UV-A absorber butylmethoxydibenzoylmethane to UV-B absorbers. *Photochem Photobiol* 2014;**90**:511–6.
44. Oguchi-Fujiyama N, Miyazawa K, Kikuchi A, Yagi M. Dioctyl 4-methoxybenzylidenemalonate: a new UV-B absorber. *J Soc Cosmet Chem Jpn* 2013;**47**:209–15.
45. Oguchi-Fujiyama N, Miyazawa K, Kikuchi A, Yagi M. *A novel UV-B absorber to enhance the efficacy of UV-A protection based on an energy transfer system: design and properties of dioctyl 4-methoxybenzylidenemalonate*. Paris: IFSCC Congress; 2014.
46. Sunscreen drug products for over-the-counter human drugs; proposed safety, effective and labeling conditions: Department of Health, Education and Welfare, Food and Drug Administration. *USA Fed Regist* August 25, 1978;**43**(166).

47. *Cosmetics-sun protection test methods-In vivo determination of the sun protection factor (SPF)*. The European Standardization Organization (CEN), the Standard EN ISO 24444:2010; 2010.
48. Fitzpatrick TB. The validity and practicality of sun-reactive skin types i through vi. *Arch Dermatol* 1988;**124**(6):869–71.
49. Miura Y, Takiguchi Y, Shirao M, Takata S, Yanagida T, Fukui H, et al. Algorithm for in vitro sun protection factor based on transmission spectrum measurement with concomitant evaluation of photostability. *Photochem Photobiol* 2008;**84**(6):1569–75.
50. Maeda K, Hatao M. Involvement of photooxidation of melanogenic precursors in prolonged pigmentation induced by ultraviolet A. *J Invest Dermatol* 2004;**122**:503–9.
51. Japan Cosmetic Industry Association Technical Bulletin. *Measurement standards for UVA protection efficacy* [Issued November 21, 1995 and effective as from January 1, 1996].
52. ISO 24442:2011. *Cosmetics—sun protection test methods—in vivo determination of sunscreen UVA protection*.
53. *European Commission Press Release, IP/09/1057 Brussels, 30 June 2009 Consumers, The new labelling requirements Labelled category Labelled sun protection factor Recommended minimum UVA protection factor "6 " "Low protection" "10" "15" "Medium protection" "20" "25" "30" "High protection" "50" "Very high protection" "50+" Projects co-funded by the European Commission on skin cancer*. http://ec.europa.eu/health/ph_information/dissemination/diseases/cancer_en.htm [Be sun-smart this summer].
54. ISO 24443. *Determination of sunscreen photoprotection in vitro*. 2012.
55. FDA, U.S.A. *Sunscreen drug products and over-the-counter human drugs. Proposed safety, effective and labeling conditions*. Final Tentative Monograph; May 1993. Federal Register 43/166, 38206-38269 (1978).
56. Ferguson J, Alert D, Bielfeldt S, Brown J, Brown M, Chardon A, et al. The COLIPA SPF test method; an advancement in SPF test methodologies IFSCC. *Venice A* 1994;**103**:28–41.
57. *Australian/New Zealand Standard: Sunscreen products evaluation and classification, AS/NZS 2604*. 1993.
58. Herrling T, Jung K, Fuchs J. Measurements of UV-generated free radicals/reactive oxygen species (ROS) in skin. *Spectrochim Acta A Mol Biomol Spectrosc* 2006;**63**:840–5.
59. Herrling T, Jung K, Chatelain E, Langenauer M. Radical skin/sun protection factor RSF – Protection against UV-induced free radicals in skin. *SÖFW-J* 2006;**132**:7.
60. Jung K, Seifert M, Herrling Th, Fuchs J. UV-generated free radicals (FR) in skin: their prevention by sunscreens and their induction by self-tanning agents. *Spectrochim Acta Part A* 2008;**69**:1423–8.
61. Lohan SB, Lauer A-C, Arnd S, Friedrich A, Tscherch K, Haag SF, et al. Determination of the antioxidant status of the skin by in vivo-electron paramagnetic resonance (EPR) spectroscopy. *Cosmetics* 2015;**2**:286–301.
62. Rhodes CJ, Tran TT, Morris H. A determination of antioxidant efficiencies using ESR and computational methods. *Spectrochim Acta A Mol Biomol Spectrosc* 2004;**60**(6):1401–10.
63. Yamashita Y, Hashimoto Y, Takemura M, Ohotaka Y, Sakamoto K. Quick photo-isomerization of urocanic acids in stratum corneum by solar UV irradiation. In: *39th Scientific Conference of Japanese Cosmetic Science Society in Tokyo*; June, 2014.
64. Obara W, Hashimoto Y, Yamashita Y, Ohotaka Y, Sakamoto K. Novel bio-index for the UV exposure by means of photo-isomerization of intrinsic urocanic acid in stratum corneum. In: *53th Scientific Conference of Japan Oil Chemist's Society in Sapporo*; September 2014.
65. Yamashita Y, Obara W, Hashimoto Y, Ohotaka Y, Hirao T, Sakamoto K. Proposal of a novel biomarker to indicate UV exposure level of skin by utilizing the kinetics of UCA photoisomerization. In: *The 15th Annual Meeting of Society Photoaging Research Japan in Kobe*; August 2016.

CHAPTER

# 36

# Hair Care Cosmetics

*J. Yang*

**Beauty Hi-tech Innovation Co., Ltd., Kobe, Japan**

## 36.1 FUNCTIONS OF HAIR CARE COSMETICS

Hair provides protective, sensory, and sexual attractiveness functions to human beings.[1] While the protective function of hair may not be as important as it used to be, beautiful hair is indeed an important part of personal beauty. Keeping hair in good conditions helps a person feeling comfortable and confident. Changing hair into a desired color and a designed shape can improve one's impression to others.

Hair cannot stand alone without the scalp. The relationship between the scalp and hair is similar to what is between the soil and plants. Therefore, maintaining good physiological conditions of the scalp is critical to hair growth and hair conditions.[2–4] Hair care cosmetics are designed and developed to keep hair feeling good and looking beautiful, and to maintain the scalp in a healthy condition Table 36.1.

Hair and scalp care cosmetics can be divided into several categories based on their functions and targeted consumer benefits.[5–8] The most fundamental consumer benefit is hair and scalp cleanliness, i.e., removing oil, dust, and dirt, keeping hair and scalp clean for good personal hygiene and appearance. Shampoo is basically designed for this purpose.

Antidandruff is another important aspect related to personal hygiene and appearance. Shampoo is also the most widely used cosmetic product for antidandruff. However, sometimes a conditioner or treatment may also have the function of antidandruff.

**TABLE 36.1** Hair Care Cosmetics

| Function | Consumer benefits | Cosmetic products |
|---|---|---|
| Hair and scalp cleansing | Keep hair and scalp clean for good personal hygiene and appearance | Shampoo |
| Antidandruff | Prevent and treat dandruff and itching scalp | Shampoo, conditioner |
| Hair conditioning | Make hair smooth, soft, easy to comb, and shine | Shampoo, conditioner, treatment, oil |
| Hair styling | Keep hairstyle temporarily | Styling mousse, gel, spray, lotion, wax |
| Hair coloring/bleaching | Cover gray hair, change to a desired color | Hair colorants (1st agent, 2nd agent) |
| Hair perming (permanent waving) | Create and keep hairstyle for a while | Perming agents (1st agent, 2nd agent) |
| Scalp and hair thinning care | Improve scalp conditions and reduce chance of hair fall | Hair tonic, scalp treatment |

*Cosmetic Science and Technology: Theoretical Principles and Applications*
http://dx.doi.org/10.1016/B978-0-12-802005-0.00036-7



Copyright © 2017 Elsevier Inc. All rights reserved.

Hair conditioning is a basic demand of most consumers. Making hair smooth, soft, easy to comb, and shine can help one feel comfortable and confident. It is almost unimaginable for a female consumer who has long and damaged hair not to use any hair conditioning cosmetics.

While cleansing, antidandruff, and conditioning are the fundamental consumer needs, making hair look good in color and shape can be defined as higher order consumer needs. Hair styling, coloring, and perming are designed for these purposes. Styling benefit can be delivered via various product forms such as mousse, gel, spray, lotion, wax, etc. On the other hand, permanent hair coloring and waving products are usually sold as a kit consisting of a first agent and a second agent.

Scalp and hair thinning care is another higher order consumer need, particularly to men. Hair tonic and scalp treatments are often used for this purpose.

The basic working mechanisms and key elements in shampoos, conditioners, styling products, coloring products, and permanent waving products will be introduced in this chapter. Scalp care and hair thinning care products will be separately described in a later section of this book.

## 36.2 SHAMPOOS

Shampoo is a basic hair care product representing the largest segment of hair care cosmetics. Shampoo is typically in the form of a viscous liquid with some exception of waterless solid form such as a bar. Shampoo was developed to replace soap for cleansing scalp and hair by removing unwanted sebum, dandruff, environmental dust, and residues of hair care products. Most of the dirt including sebum are water insoluble and cannot be effectively removed by water alone. Therefore, a shampoo containing a combination of surfactants is necessary. The content of surfactants in a shampoo is typically between 10% and 20%. An example of cleansing shampoo formula is given in Table 36.2.

Surfactants emulsify oily dirt on hair and scalp, then the dirt can be pulled into water and washed off easily (Fig. 36.1).[8] The cleansing effect of a shampoo can be observed by comparing the scalp image under a microscope before and after using shampoo (Fig. 36.2).[6] After shampooing, scalp becomes clean and free of the oily dirt until fresh sebum is regenerated. This action helps maintain personal hygiene and reduce the chance of scalp inflammation, itching, and odor.

A class of surfactants called anionic surfactants such as sodium laureth sulfate, ammonium laureth sulfate, sodium lauryl sulfate, and ammonium lauryl sulfate are the primary cleansing agents in shampoo. Amphoteric types of surfactants such as cocamidopropyl betaine and nonionic surfactants such as cocamide MEA are also often used as cosurfactants in shampoo to stabilize micelles formed, helping improve lather stability and viscosity building.

**TABLE 36.2** An Example of Conditioning Shampoo Formula

| Ingredient | Function | % (w/w) |
|---|---|---|
| Sodium laureth sulfate | Primary surfactant for lathering and cleansing | 16.0 |
| Cocamidopropyl betaine | Cosurfactant for lathering | 2.0 |
| Cocamide MEA | Cosurfactant for lathering | 2.0 |
| Glycol distearate | Pearling agent | 1.5 |
| Dimethicone | Conditioning agent for dry hair | 1.0 |
| Guar hydroxypropyltrimonium chloride | Conditioning agent for wet hair | 0.5 |
| Citric acid | pH adjuster | qs |
| Sodium chloride | Viscosity booster | qs |
| Preservatives | Preservation | qs |
| Perfume | Fragrance | qs |
| Deionized water | Solvent | qs to 100 |

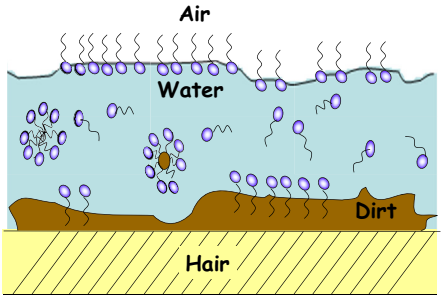



FIGURE 36.1 Cleansing mechanism of shampoo.

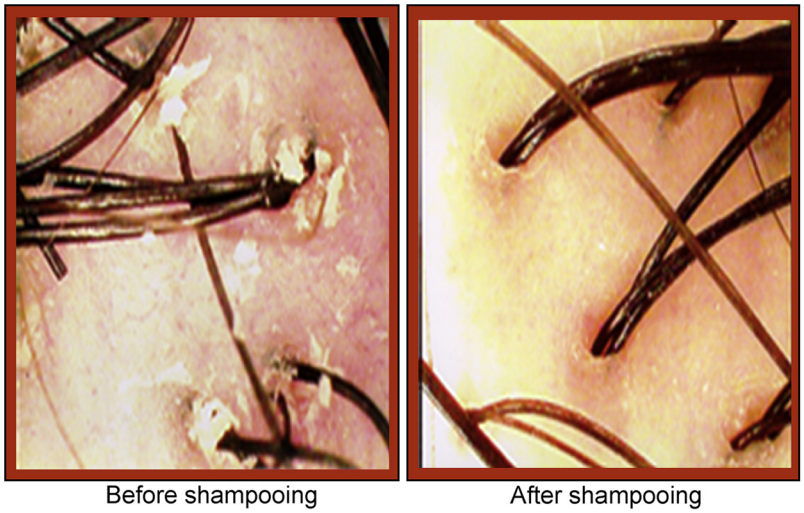



FIGURE 36.2 Cleansing effect of shampoo.

In addition to shampoo's primary cleansing function, antidandruff shampoos and conditioning shampoos also became popular decades ago.

Dandruff is a common scalp disorder often accompanied by scalp itching.[9] It is known that dandruff is associated with a scalp-specific fungus named Malassezia.[10–13] Malassezia metabolizes triglycerides in sebum by the expression of lipase, resulting in an unsaturated lipid byproduct. The unsaturated lipid penetrates into top layer of the epidermis, resulting in an inflammatory reaction. Dandruff is considered a result of the inflammatory reaction.

Not only can it wash off dandruff on scalp as ordinary shampoos do, an antidandruff shampoo usually contains antifungal actives for inhibition of Malassezia. Well-known antifungal actives include zinc pyrithione, piroctone olamine also known as octopirox, selenium sulfide, climbazole, ketoconazole, and ciclopirox. Sulfur, salicylic acid, and coal tar are also used sometimes, though they are relatively low in antifungal activity. Among these, zinc pyrithione and octopirox are the most widely applied antidandruff actives. Zinc pyrithione is typically used at a level of 0.5–1%, while octopirox is usually applied in a range of 0.2–0.5%.

Conditioning shampoos, sometimes called 2-in-1 shampoos, were introduced to global markets in the late 1980s. A conditioning shampoo is designed to deposit conditioning actives onto hair while washing off dirt at the same time. In order to make this happen, technology innovations were made in several areas: (1) stable dispersion of the water-insoluble conditioning actives such as silicones and conditioning oils; (2) efficient deposition of the conditioning actives onto hair; and (3) even distribution of the conditioning actives on hair surface.

Shampoo is generally used by applying it to wet hair, massaging the product into the hair, and then rinsing it out thoroughly. While some consumers may follow a shampooing with the use of hair conditioner, there are still consumers who may only use shampoo as daily hair washing and conditioning product. Hair conditioning effects such as making hair smooth, soft, easy to comb, etc. are expected from a shampoo by these consumers at both wet hair and dry hair stages. Wet hair conditioning of shampoo is mainly delivered by a colloid structure called coacervate formed by cationic polymer and anionic surfactant in water. On the other hand, dry hair conditioning is primarily the result of depositing silicones and conditioning oils on hair surface.

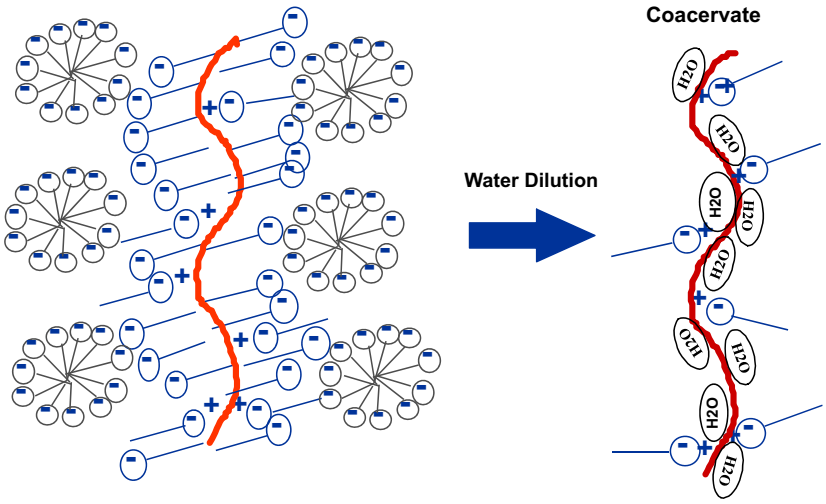



FIGURE 36.3 Coacervate formation.

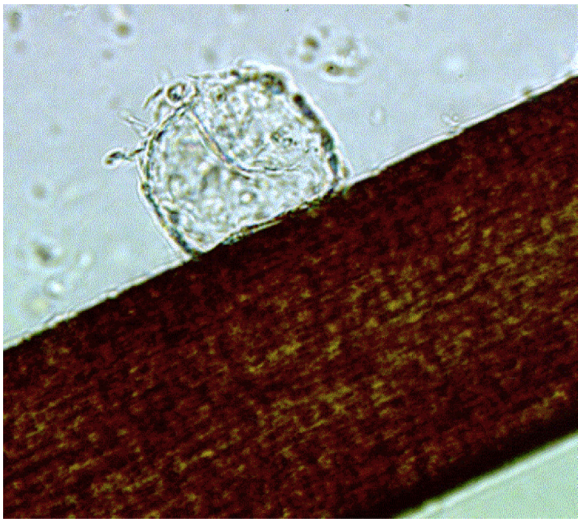


FIGURE 36.4 Coacervate absorbed onto hair surface.

Coacervation is a unique type of electrostatically driven liquid–liquid phase separation, resulting from the association of oppositely charged ions.[14–16] Coacervate formed during water dilution of shampoo while rinsing involves cationic polymers such as cationic cellulose or guar, and the anionic surfactants in shampoo (Fig. 36.3).[8] Anionic polymers such as Carbomer also can be used sometimes in addition to the anionic surfactants to enhance coacervate formation. Functioning as a cushion, the water-containing coacervates provide nonsqueaky hair feel during rinsing and protect the wet hair from being damaged (Fig. 36.4).[6]

Silicones and/or conditioning oils are usually formulated in a conditioning shampoo to provide smoothness, softness, and shine to dried hair. The hair surface lubrication effect is the basic reason for using these oils. One feels that hair is smooth because of lowered friction between the surfaces of hair and hand skin. When interfiber friction between hair fibers is reduced, there is less resistance to movement, so people may feel that hair is soft and easy to comb. Furthermore, alignment of hair can be improved by the same mechanism, allowing better reflection of hair surface to light, giving shiner looking hair.

Silicones such as dimethicone, dimethiconol, and amodimethicone are the most widely applied oils for conditioning dry hair. Its low surface tension, high hydrophobicity, and variety of molecular weights or viscosities make silicone unique among all of the conditioning oils. A comparison between silicone treated and untreated hair surfaces is shown on Fig. 36.5.[6] It is clearly observable that hair surface treated with silicone becomes smoother and covered with a thin protective layer. This is also the main reason for the color-protection effect claimed by some shampoos for consumers who color their hair.

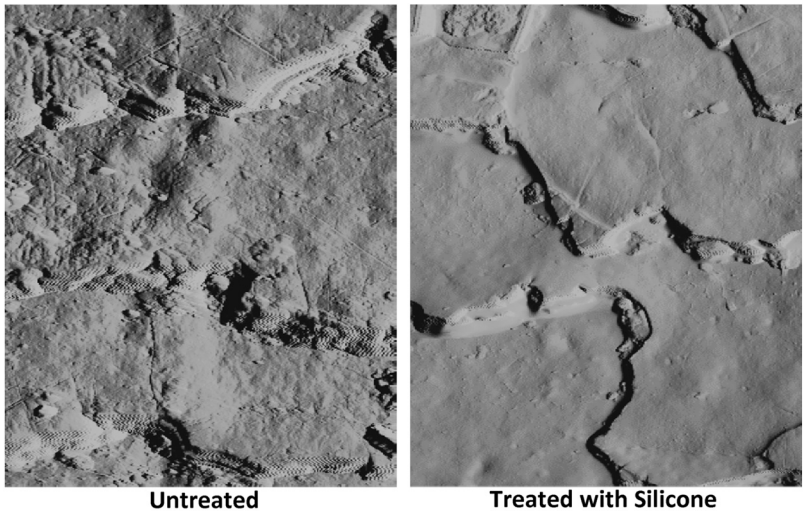



FIGURE 36.5 A comparison between silicone-treated and untreated hair surfaces.

In shampoo, silicones are often applied as preemulsified emulsions for better dispersion in the product. A variety of silicone emulsions are currently available from the silicone manufactures. Optimization of internal phase viscosity and particle size of the silicone droplets in emulsion is critical when selecting appropriate silicones to use. Measurement of hair friction or combing force is a typical tool used to screen silicones for their hair conditioning effect. Quantifying its deposition amount is also important to determine if a silicone is efficient in a given shampoo formula.[17]

Sulfate-based anionic surfactants, such as sodium laureth sulfate and sodium lauryl sulfate, and silicones have been the most applied ingredients in hair shampoo over the decades. However, recently sulfate-free and silicone-free shampoos are becoming popular in some markets. Consumers select sulfate-free shampoos for lower chance of skin and eye irritation or contact allergy. Some consumers also believe that silicone-free shampoo is a healthier or more environmentally friendly way to choose.

Sulfate-free shampoos and silicone-free shampoos may not be simply achieved by removing these ingredients from the shampoo, requiring new technology innovations. First, to be sulfate-free, low-irritation surfactants are needed to replace sulfate-based surfactants. Several classes of amino acid derivatives are often used for this purpose (Table 36.3). These amino acid-based anionic surfactants are reported to be milder than the traditional sulfate-based ones.[18–20] However, other than higher in cost, these amino acid-based surfactants are often found less efficient in building viscosity when used as a primary surfactant in shampoo. The large head group of the amino acid-based surfactants is an unfavorable factor in forming extensive wormlike micelles for high viscosity.[21] Adding sodium chloride usually is not

TABLE 36.3 Amino Acid-Based Anionic Surfactants

| Amino acid | Structure |
|---|---|
| Glutamic acid | $RCONHCHCOO^- M_1^+$ <br> $\quad\quad\quad

highly effective in increasing viscosity of the amino acid–based surfactant systems. In fact, most of the sulfate-free shampoos sold in market have relatively low viscosity compared with the traditional shampoos.

Thickening approaches are required to help build viscosity of the sulfate-free shampoos. Optimization of cationic polymers is the first option to explore. Molecular weight and charge density of cationic guar or cationic cellulose have a big impact on shampoo viscosity. Solution viscosity of the polymer per se is a useful parameter to which to refer, although there is not always a linear relationship with the viscosity of the final product.

Using amphoteric or nonionic surfactants as cosurfactants to balance the micelle packing parameter is another effective way to manipulate shampoo rheology.[22–25] Cosurfactants that are often used include cocamidopropyl betaine, cocamide MEA, cocamide DEA, lauramide MEA, lauramide DEA, cocamide methyl MEA, laureth-3, PEG-2 laurate, PEG-150 distearate, PEG-120 methyl glucose dioleate, PEG-160 sorbitan triisostearate, butylene glycol laurate, etc. Optimization of the ratio between anionic surfactant/amphoteric surfactant/nonionic surfactant is critical to obtain optimal viscosity.

Polymeric thickeners such as xanthan gum, hydroxyethyl cellulose, hydropropyl methylcellulose, etc. also can be added to increase shampoo viscosity. However, overdosage of these thickeners may cause negative hair feel. Sometimes pH also has an impact on viscosity of amino acid–based surfactant systems. Therefore, optimization of the pH range needs to be considered.

Other than the difficulty in gaining viscosity, amino acid–based surfactant systems can generally deliver equal or higher lathering and conditioning performances versus sulfate-based surfactants.

## 36.3 HAIR CONDITIONERS

Beyond the conditioning shampoos, hair conditioners are also widely applied as more effective hair conditioning cosmetics. Hair conditioner is usually used after washing the hair with shampoo. In general, conditioners are more effective for hair conditioning than 2-in-1 shampoos, because without having to take on the task of cleansing, a conditioner is purely designed to deliver varieties of conditioning actives onto hair.

Conditioners can be divided into several types as summarized in Table 36.4. Among these, rinse-off conditioner is the most used category. Rinse-off conditioners are designed to be used after shampooing in our daily life. With the help of water rinsing, the conditioning actives are more evenly distributed onto hair. Such hair treatment is mainly designed for intensive care of damaged hair, usually used once or twice a week. A rinse-off treatment can be simply a concentrated version of a conditioner. Leave-on conditioner or treatment is another category designed to be used conveniently at anytime and anywhere. Without rinsing, however, conditioning actives from a leave-on product may not be able to evenly cover the whole hair. Spray is another product form for leave-on conditioner.

There are three main classes of conditioning ingredients in a hair conditioner, cationic surfactants, fatty alcohols such as cetyl alcohol, stearyl alcohol, and behenyl alcohol, and silicones or other conditioning oils (Table 36.5). Among these ingredients, cationic surfactants and fatty alcohols are considered bifunctional, i.e., delivering conditioning benefit to both wet hair and dry hair, whereas silicones and other oils mainly contribute to dry hair conditioning.

Similar to the function of coacervates in shampoo, lamellar gel network in conditioner is the key factor for the slippery and smooth feel of wet hair. Gel networks comprise a lamellar phase consisting of cationic surfactants, fatty alcohols, and water under appropriate processing conditions, where the fatty alkyl chains adopt a frozen or

**TABLE 36.4** Classification of Hair Conditioners

| Type | Form | Character |
|---|---|---|
| Conditioner | Rinse-off | Mostly applied hair conditioning cosmetics for daily use, can evenly distribute conditioning actives on hair |
| Treatment | Rinse-off | For intensive care of damaged hair |
| Leave-on conditioner/treatment | Leave-on | Convenient to use, can be applied anytime, anywhere |
| Spray | Leave-on | Convenient to use, can be applied anytime, anywhere without getting hands dirty |

**TABLE 36.5** Key Ingredients in Hair Conditioning Cosmetics

| Ingredient | Function | Example | Usage amount |
|---|---|---|---|
| Water | Solvent | Deionized water | Up to 90% |
| Cationic surfactant | Surfactant, conditioning agent | Behetrimonium chloride, steartrimonium chloride, stearyl amidopropyldimethylamine, behenyl amidopropyldimethylamine, stearoxypropyl trimonium chloride, palmitamidopropyltrimonium chloride, | 0.5–3% |
| Fatty alcohol | Cosurfactant, conditioning agent | Cetyl alcohol, stearyl alcohol, behenyl alcohol | 0.5–10% |
| Silicone | Conditioning agent | Dimethicone, dimethiconol, amodimethicone | 0–10% |
| Oil | Conditioning agent | Cetyl esters, mineral oil, oleyl alcohol, cetyl ethylhexanoate, squalane | 0–5% |
| Polyol | Solvent, humectant | Glycerin, propylene glycol, dipropylene glycol, butylene alcohol | 0–5% |
| Polymer | Rheology modifier | Hydroxyethyl cellulose, PEGs | 0–2% |
| Organic acid | pH adjuster | Citric acid, lactic acid, glutamic acid | 0–1% |
| Scalp care active | Scalp care | Zinc pyrithione, octopirox, dipotassium glycyrrhizate | 0–1% |
| Preservative | Preservation | Methylparaben, phenoxyethanol, methylisothiazolinone | Less than 1% |
| Perfume | Fragrance | – | 0.1–1% |
| Color | Appearance modifier | – | 0–0.5% |

crystalline structure. This type of lamellar phase is also called Lβ phase. The layered structure of gel network with water in between each layer provides slippery feel when applied on wet hair.[14] Gel networks also help to stabilize dispersions of water-insoluble ingredients, such as silicone and perfume while acting as a deposition aid for the conditioning actives.

Cationic surfactants and fatty alcohols can also be deposited on hair to deliver a conditioning benefit to dry hair, along with silicones or oils. The function of silicone has already been described in the conditioning shampoo section. Cationic surfactants are uniquely used in hair conditioners as key conditioning and hair "repairing" agents. The most outer surface of pristine, undamaged hair is known to be covered by a naturally occurring hydrophobic protective layer or F-layer made of 18-methyleicosanoic acid (18-MEA). The F-layer can be easily peeled off through decomposition of the ester bond by coloring, bleaching, or perming the hair. Hair without the F-layer becomes less hydrophobic, and hence has higher surface friction due to the capillary bridging effect of atmosphere moisture attached to it. A cationic surfactant is a perfect "repairing" agent to hair that has lost its F-layer (or say hydrophobicity) as illustrated on Fig. 36.6.[7,8] Although having no cationic moiety, the long alkyl chain similar to those of the cationic surfactants, fatty alcohols can also deliver a hydrophobic modification effect to hair surface.

There are several commonly used types of cationic surfactants including monoalkyl quats, dialkyl quats, monoalkyl amidoamines, etc. Among these, the mostly applied cationic surfactants include steartrimonium chloride, behentrimonium chloride, stearyl amidopropyl dimethylamine, behenyl amidopropyl dimethylamine, palmitamidopropyltrimonium chloride, stearoxypropyl trimonium chloride, etc. Dialkyl quats, such as dicetyl dimonium chloride and distearyldimonium chloride, and ester quats, such as distearoylethyl dimonium chloride, are also

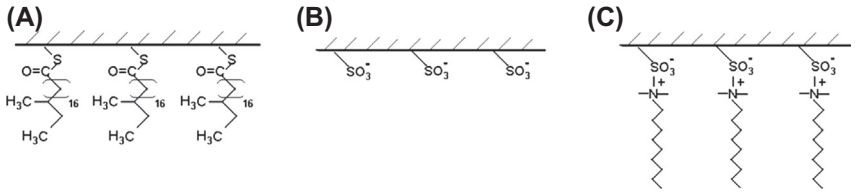



FIGURE 36.6 Hair "repairing" with cationic surfactants. (A) Undamaged hair is covered with a hydrophobic protective layer (F-layer). (B) F-layer is removed by coloring or bleaching. (C) Cationic surfactant absorb onto hair surface, recovering the lost hydrophobic protective layer.

used in some cases. When selecting a cationic surfactant for hair conditioning, in addition to its safety and cost, its deposition efficiency, hydrophobic modification capability, and lubrication efficacy need also to be considered. In general, a cationic surfactant with a longer alkyl chain favors higher conditioning effect, delivering lowering surface friction and higher surface hydrophobicity to the hair.

Silicones are often used as the dry hair conditioning agent in hair conditioners. Silicone is known for its ability for surface lubrication and hydrophobic modification.[26] Deposition efficiency of silicones from conditioners also needs to be considered as a key factor during the formulation process. Unmodified dimethicones are highly hydrophobic and therefore can be deposited easily onto undamaged hydrophobic hair surface. However, when hair is damaged, its surface becomes less hydrophobic. In such a case, amino-modified silicones, i.e., amodimethicones such as aminopropyl dimethicone, bisaminopropyl dimethicone, bis-hydroxyl/methoxy amodimethicone, silicone quaternium-22, etc. are often chosen to improve silicone deposition efficiency.

In addition to silicones, other oils including ester oils such as ethylhexyl palmitate, isopropyl myristate, caprylic/capric triglyceride, trimethylolpropane tricaprylate/tricaprate; polyolefin oils such as hydrogenated polydecene; and other oils such as mineral oil, jojoba oil, squalene, etc. are also sometimes used in hair conditioners as additional dry hair conditioning agents. Recently, using nonsilicone type of oils to replace silicones for silicone-free conditioners has been gaining attention. Unfortunately, most of the "natural oils" cannot fully match silicones in their properties such as surface tension and hydrophobicity. Efforts are continuously being made in developing silicone alternatives for hair conditioning with promising progresses. It is reported that when formulated into conditioner, a patent-pending mixture of oils consisting of cetyl ethylhexanoate, squalene, etc. (Trade name: DOCSilFee) delivers almost equal dry hair conditioning performance versus silicone.[27,28]

The conditioning effect of hair conditioners can be demonstrated via different approaches, such as comparing measurement data before and after conditioner treatment on static electricity, combing force, hair surface contact angle or surface energy, shine, etc. Fig. 36.7 shows how conditioning actives from a conditioner are deposited on hair surface, providing lubricating and protective coverage.[7,8] Surface smoothness and hydrophobicity are the fundamentals of all conditioning benefits. Soft feel, smooth feel, and ease of combing are the direct results of surface smoothness and hydrophobicity. Hair shine is an outcome of better hair alignment due to lower friction. Less flyaway or frizzy hair is also related to higher surface hydrophobicity and lower friction. Usually, the conditioning benefits of a hair conditioner can be easily noticed by consumers, particularly those who have long and damaged hair.

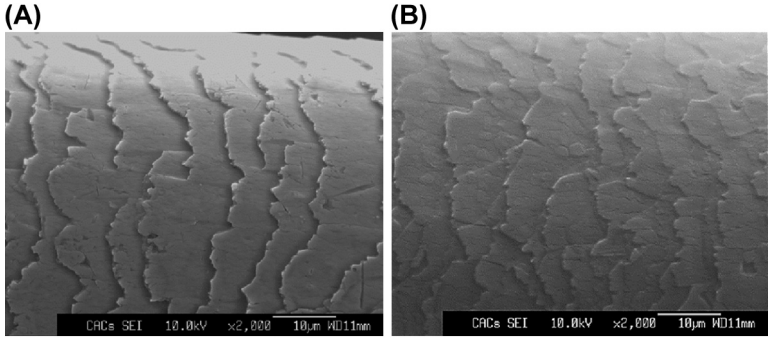



FIGURE 36.7 Hair images observed by scanning electronic microscopy (x2000). (A) Untreated. (B) Conditioner treated.

## 36.4 HAIR STYLING PRODUCTS

Hair styling products are designed to help tentatively create and hold a desired hairstyle. There are several product forms for hair styling products sold in the market, including styling mousse, styling spray, styling gel, styling water, styling wax, and styling oil. Some leave-on conditioning products may also have certain styling effects while providing smoothness and shine to hair. Each class can be further divided into several branches based on its style holding power, whether is multifunctional, and so on. Consumers can choose the right product based on their specific needs on styling and their desired balance between styling and conditioning benefits.

The main characteristics of the major styling products are summarized as follows.[5,8,29]

1. Styling mousse: The main characteristic of styling mousse is its foaming ability. When pumped out from the container, it appears as foam. A high-quality hair mousse should be able to generate rich, creamy, and soft foam. The foam is initially stable, and when applied on hair it disappears rapidly leaving the product on hair. Due to relatively low surface tension, upon slightly spreading a styling mousse can be easily and evenly distributed on hair surface. Styling mousse can be used either on wet hair or dry hair.
2. Styling spray: Styling sprays are usually ethanol-water solutions of styling polymers. As a main characteristic, styling spray can dry easily after it is applied on hair. Styling spray is often used on dry hair. After the hair is styled, it is sprayed on to fix the style. Styling spray has relative strong locally style-holding effect, and hence can be used to create hair curls, spiky hair, and hair buns.

   When sprayed out of a metal can, the small droplets of styling polymer solution attach to the hair surface to form thin films between hair fibers. Since ethanol is highly evaporative, the polymer film dries out rapidly, binding hair together to give a new style. The hairstyle can be held for a while, thanks to the strength of polymer film.

   Whether a styling spray product provides "super hold" styling effect or gives "soft hold" for a balanced styling-conditioning feel, the type of styling polymer used and the size of polymer solution droplets play important roles. In general, larger droplets favor strong styling effect, but take longer time to dry, leaving a relatively sticky and hard hair feel; smaller spray droplets leave better hair feel, but are weaker on styling. A high-quality spray should have a good balance between the two aspects and is also easily removable at next hair washing.
3. Styling gel: Styling gel is usually viscous and has relatively strong style-holding effect. Polymeric thickeners are often used in styling gel to provide viscosity, using water or water-ethanol as the solvent. Styling gel can be used on dry hair or wet hair, for whole hair or applied locally.
4. Styling water: Styling water is in principle similar to the styling gel but contains lower levels of polymeric thickener, and therefore is low in viscosity. Styling water usually gives relatively "soft" styling effect, feels cleaner, and is easy to rinse off.

While varying in product forms and levels of function, styling products have basically the same working mechanism as styling polymer. Key compositions of styling products are summarized as follows.

1. Styling polymer: Modern styling products share a common nature, i.e., using hair styling polymers, or sometimes called fixative polymers, as the key styling agents. Polymers are known to have film-forming ability and adhesive characteristics. Formation of either seam weld-like film or spot weld-like film between hair fibers to lock hair into a certain shape is the fundamental mechanism of hair styling by styling polymers (Fig. 36.8).[5] However, the film formed is breakable under hair movement (Fig. 36.9). Longevity of the styling effect depends on amount of polymer films formed, strength and flexibility of the polymer film, and type of the weld.

   Styling polymers are usually synthetic vinyl polymers, soluble in water or water-alcohol mixtures. They can be classified by charge type into anionic, cationic, nonionic, or amphoteric. Some often-used examples include: N-vinylpyrrolidone-vinyl acetate copolymer, acrylic acid-alkyl acrylate copolymer, methacrylic acid-methylacrylate-t-butylacrylate copolymer, methacrylic acid-methylacrylate-acrylic acid-ethyl acrylate-stearyl methacrylate copolymer, acrylic acid-methyl methacrylate-octyl acrylamide-t-butyl acrylamide-t-butyl aminoethyl methacrylate-3-hydroxypropyl methacrylate copolymer, methyl acrylate-butyl acrylate-methyl methacrylate-2-hydroxyethyl methacrylate copolymer, methyl vinyl ether-butyl/ethyl maleate copolymer, methylvinyl ether-ethyl maleate copolymer, cationic celluloses, cationic N-vinylpyrrolidone/acrylate or methacrylate copolymer (e.g., Polyquaternium-11), etc. To improve flexibility of the polymer film, "shape memory" copolymers having silicone moieties, polyurethanes, etc. have also been developed.

   Usage amount of the styling polymers depends on the type of product and desired level of styling effect, but usually is 0.5–4% in styling mousse, 2–12% in styling spray, 0.5–4% in styling gel, and less than 3% in styling water, respectively.

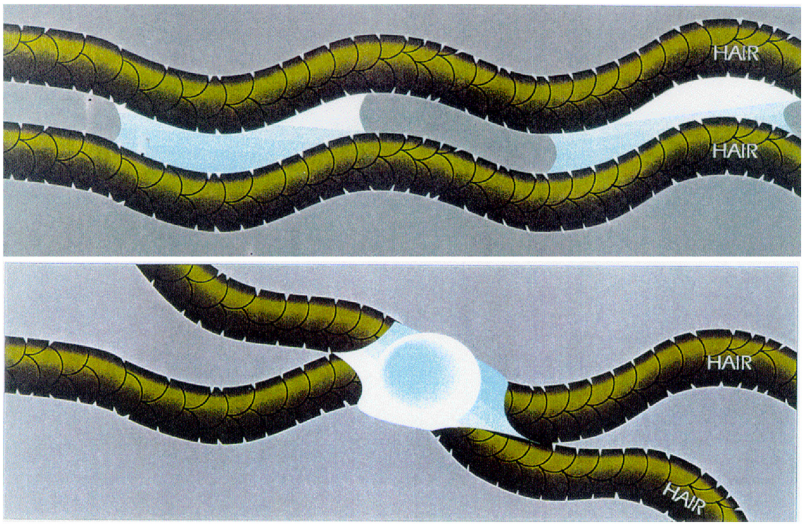



**FIGURE 36.8** Working mechanism of styling polymer via formation of seam weld-like film or spot weld-like film.

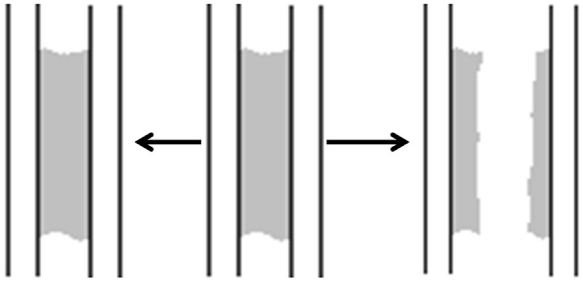


**FIGURE 36.9** Failure of styling polymer.

2. Solvent: As a carrier, the solvent's function is to help the styling polymer to evenly distribute on hair. The most commonly applied solvents include water, ethanol, propanol, and their mixtures.

   The selection of solvent and its usage level are based on the type of product. Styling spray usually uses alcohol as the main solvent for fast drying. The usage level of alcohol can be 40–80%.

   Styling mousse can be alcohol-free or contain alcohol. Even in the alcohol-containing case, the amount of ethanol usually is less than 20%.

   Other styling products such as styling gel and styling water usually use water as the only solvent and are alcohol-free.
3. Neutralizer: Anionic styling polymers and thickeners first need to be neutralized to function. Often-used neutralizers include 2-amino-2-methyl-1-propanol, triethanolamine, sodium hydroxide, potassium hydroxide, etc. Usage amount depends on the polymer to be neutralized, but usually is less than 1%.
4. Surfactant: In high water content styling products such as styling mousse and gel, surfactants are usually used at a level of 0.5–3%, to emulsify water-insoluble ingredients. Nonionic surfactants are often chosen.
5. Plasticizer: The function of a plasticizer is to help the film formed by the styling polymer to become more flexible and hence last longer, by lowering its glass transition temperature (Tg).

   Plasticizer is typically used at a level of 0.1–0.5%. Often-used plasticizers include propylene glycol, 2-methyl-1,3-propanediol, etc.
6. Propellant: In styling mousse or spray, liquefied gases such as dimethylether, isopentane, etc. are often used as a propellant to promote spraying or foaming. These propellants are highly volatile and flammable. As an alternative, carbon dioxide, nitrogen, condensed air, etc. can be used, but are not as effective in promoting foaming and spraying.

   Propellant is used at a level of 6–12% in mousse; in spray it can be as high as 15–35%.

7. Thickener: Styling gel uses thickener to build viscosity. The thickeners used are usually cross-linked polymers such as salts of lightly cross-linked polyacrylic acid known as Carbomer, Acrylates-C10-30 alkyl acrylate crosspolymer, etc. at a usage level of 0.25−1%.

In addition to the above ingredients, styling products may also contain a small amount of preservative (0−1%), perfume (0.1−0.5%), antirust agent (0−1%), etc.

## 36.5 HAIR COLORING PRODUCTS

Hair coloring is the practice of changing hair color. The reason for coloring is either to cover gray hair or to change hair color to a more fashionable or desirable one. Hair coloring can be done professionally at a hair salon or individually at home. Hair coloring products can be classified into three main categories. Key features of these hair coloring products are summarized in Table 36.6.[1,30−33] The differences in the working mechanisms between these coloring products are illustrated in Fig. 36.10.

1. Temporary coloring: Temporary coloring is often used to color hair for special occasions such as parties. It uses pigments, and the pigments directly adsorb onto hair epicuticle to give the color desired. The pigment molecules in temporary hair color are large and cannot penetrate into the cuticle layer, and hence are easily removed with one or several shampooings. Temporary coloring can be delivered via various product forms such as spray, mousse, gel, shampoo, and conditioner. Temporary coloring products are generally harmless to scalp and hair.
2. Semipermanent coloring: Compared to temporary dyes, semipermanent hair color has smaller molecules and can partially penetrate the hair shaft. For this reason, the color will survive repeated washing, lasting for a week or so. Semipermanent colors usually involve no chemical reaction, with some exceptions, and are relatively safer and cause less hair damage compared to permanent colorant.

**TABLE 36.6** Classification of Hair Coloring Products

| Function | Product form | Coloring agent | Mechanism |
|---|---|---|---|
| Permanent coloring | Colorant (1st agent, 2nd agent) | Oxidation dyes | Penetrate into cortex followed by chemical reactions |
| Semipermanent coloring | Hair manicure, conditioner | Pigments (smaller molecules) | Penetrate to cortex to some degree, but usually no chemical reaction |
| Temporary coloring | Spray, mousse, gel, shampoo, conditioner | Pigments (larger molecules) | Absorbed on hair surface, no penetration |

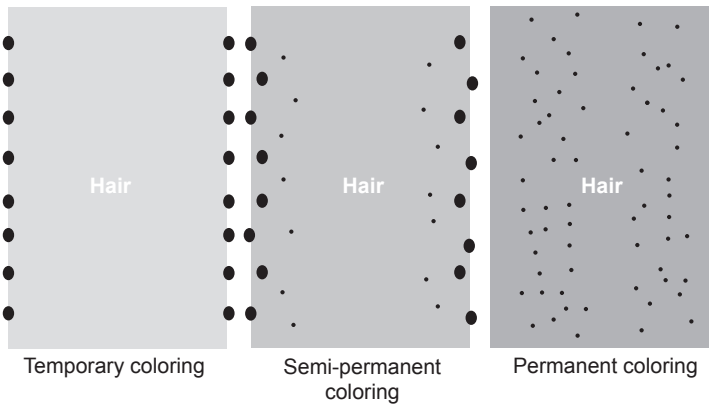



**FIGURE 36.10** Classification of hair coloring.

3. Permanent coloring: Permanent coloring using oxidation dyes is the most effective way to create color and is a long-lasting way to maintain the color created. Permanent coloring products usually consist of a dye precursor, a dye coupler, an oxidizing agent (usually hydrogen peroxide), and other ingredients such as surfactants, preservatives, pH-adjusting agents, and conditioning agents. The coloring process is typically performed under alkaline conditions (pH 8–10). Fig. 36.11 shows the reactions using 1,4-phenylenediamine as an example of precursor and 1,3-phenylenediamine as an example of coupler, involving three steps: (1) oxidation of 1,4-phenylenediamine to its quinone state, diiminium ion (Fig. 36.11A); (2 ) condensation reaction (Fig. 36.11B) of the diiminium ion with 1,3-phenylenediamine; and (3) oxidation of the resulting compound to give the final dye (Fig. 36.11C) having blueish purple color. When the dye precursor reacts with different couplers, different colors can be obtained. For example, when 1,4-phenylenediamine is mixed with 1,3-aminophenol, a light blue color is generated instead of blueish purple. 1,4-Phenylenediamine and resorcinol give a green-brown color. 1,4-Phenylenediamine and 1-naphthol also result in blueish purple. All of the chemical reactions occur inside the hair and the large dye molecules formed are locked inside of the hair cortex to give permanent color that can survive shampoo washing and last for months.[33]

Permanent coloring involves the use of hydrogen peroxide under alkaline conditions, therefore will almost inevitably cause hair damage. To minimize the impact of these harsh conditions, hair conditioning actives such as cationic conditioning actives, amodimethicones, or hydrolyzed proteins are formulated into the coloring products, or in an in-box intensive hair treatment product. Also, there is a risk that the reactive oxidation dye may cause skin irritation or allergy to certain people. Regulations in some countries are becoming more restrictive on permanent dyes that can be used. Therefore, efforts continually need to be made to improve the safety of oxidation dyes. In the meantime, as a healthy way of coloring, natural hair dyes such as henna seem to be attractive to certain consumers.

## 36.6 PERMANENT HAIR WAVING PRODUCTS

The keratin fibers of the hair shaft are held together by peptide bonds, salt bonds, disulfide bonds, and hydrogen bonds between the protein chains (Fig. 36.12). Changing hairstyle can be done via wetting hair to break hydrogen bonds, followed by drying to reform the hydrogen bonds while applying styling products to hold the new style. However, the hairstyle achieved in this way is only temporary. To permanently change hair shape, it is necessary to break the cross-linking disulfide bonds through a reducing reaction and reform the broken disulfide bonds on different positions of the keratin by oxidizing the two cysteine residues (Fig. 36.13).[5] This is the basic mechanism for the chemical part of permanent hair waving, while simultaneous physical action from wrapping hair is necessary to achieve the desired hairstyle.

Disulfide bonds can be broken relatively easily by reducing agents, whose electrons attack the bond. In a standard cold perming process, hair is first put into curlers and the reducing agent, typically ammonium thioglycolate, is

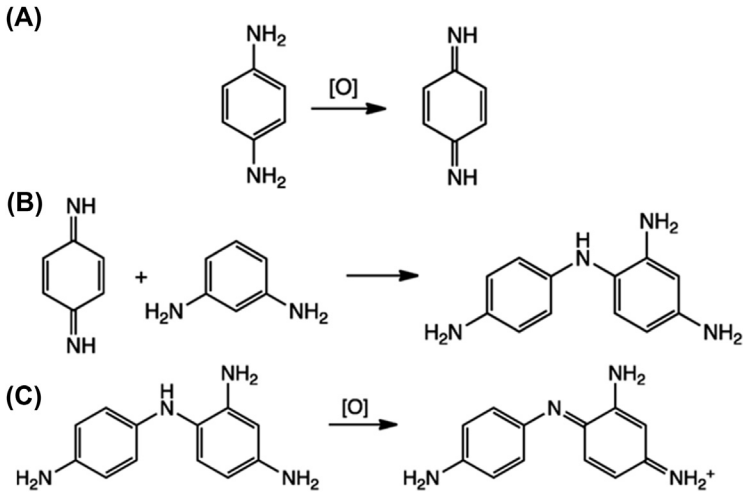



FIGURE 36.11 Chemistry of permanent coloring using 1,4-phenylenediamine as a precursor and 1,3-phenylenediamine as a coupler. (A) Oxidation of 1,4-phenylenediamine; (B) condensation with 1,3-phenylenediamine; and (C) oxidation of the resulting compound.

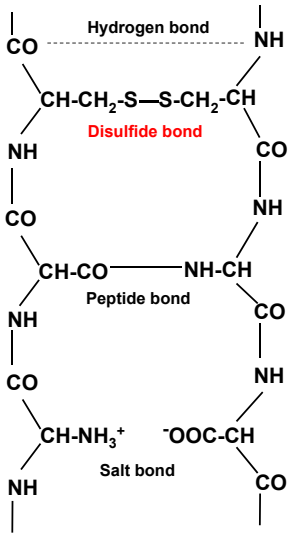



FIGURE 36.12 Chemical bonds between hair protein chains.

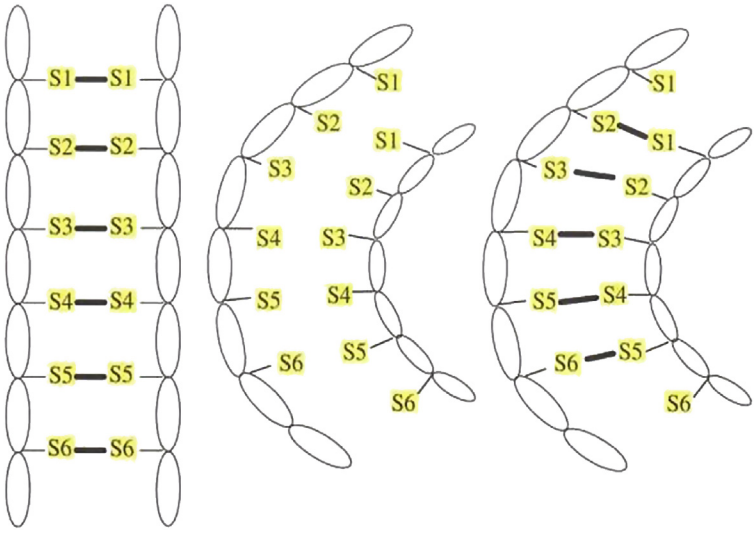



FIGURE 36.13 Mechanism of permanent waving.

added. The disulfide bonds break and keratin molecules are now free to move around and adjust to the shape of the curl. Then a neutralizer such as hydrogen peroxide is added to reverse the effect of the reducing agent. New disulfide bonds form so the keratin molecules are locked into the newly formed shape.

Permanent waving products typically consist of a first agent and a second agent. The first agent is designed for reduction of disulfide bonds, and the second agent is responsible for oxidation Table 36.7.

A typical composition of the first agent is as follows: (1) reducing agent such as thioglycolic acid, ammonium thioglycolate, monoethanolamide thioglycolate, L-cysteine, L-cysteine hydrochloride, N-acyl-L-cysteine, etc.; (2) alkali such as ammonium hydroxide, ethanolamine, ammonium hydrogen carbonate, L-arginine, etc.; and (3) other additives including chelating agents as such as EDTA salt, conditioning actives such as silicones and cationic celluloses, surfactants as emulsifiers, and pH-adjusting agents, UV absorbers, colors, thickeners, perfumes, etc.[1,34]

The second agent usually consists of oxidizing agents such as bromic acid salts, sodium perborate, and hydrogen peroxide along with other additives similar to those in the first agent.

The chemicals involved in the permanent waving process are generally harsh. Upper limits on usage level of the actives involved in permanent waving are regulated by many countries.[34]

**TABLE 36.7** Some Oxidation Dye Precursors and Couplers

| Function | Class | Chemical name |
|---|---|---|
| Precursor | Phenylenediamine derivatives | 1,4-Phenylenediamine |
| | | N,N-bis(Hydroxyethyl)-*p*-phenylenediamine sulfate |
| | | Toluene 2,5-diamine |
| | Phenol derivatives | 1,4-Amino phenol |
| | | 4-Amino-3-methylphenol |
| Coupler | Phenylenediamine derivatives | 2,4-Diaminophenoxyethanol Dihydrochloride |
| | Aminophenol derivatives | 1,3-Amino phenol |
| | | 4-Amino-2-hydroxytoluene |
| | | 5-Amino-2-methylphenol |
| | | 5-(2-Hydroxyethyl)amino-2-methylphenol |
| | Others | Resorcinol |
| | | 1-Naphthol |
| | | 2-Methylresorcinol |
| | | 4-Chlororesorinol |
| | | Gallic acid |

## 36.7 CONCLUSIONS

In the last few sections of this chapter, key functions and mechanisms of hair care cosmetics for hair cleansing, conditioning, styling, coloring, and perming were reviewed. It should be noted that hair diversity has a big impact on consumers' needs and their preferences on hair care cosmetics. For example, European hairs are generally thinner (having smaller diameters) and lighter in color, therefore it needs less conditioning (to avoid looking like it has lost volume) but more needs in coloring and styling. On the contrary, Asian hairs are usually thicker and rounder, so there are higher demands on conditioning to keep them smooth and well aligned. Also, since Asian hairs tend to be darker in color, bleaching is sometimes needed to color them to colors other than just covering gray, resulting in higher degree of hair damage which in turn will need even more conditioning. Although similar working mechanisms are applied across different hair types, there is no single product that will satisfy every consumer. When designing hair care cosmetics, carefully selection and balancing of the levels of benefit to fit specific consumer segments are necessary.

Consumer habits also play an important role in hair care cosmetic preferences. For example, among Asian consumers, Japanese tend to wash their hair every day using both shampoo and conditioner, whereas Chinese wash their hair every 2–3 days and many of them use shampoo only. As a result, Chinese consumers prefer shampoos with a higher conditioning effect and yet having sufficient antidandruff efficacy; versus Japanese consumers who simply want a shampoo that does its cleansing work (with certain wet hair conditioning effect) and let conditioners take care of dry hair conditioning. Most Japanese consumers need no antidandruff product as they wash their hair daily.

Given the diversity of hair type and habit, there is always a need for finer segmentation of hair care cosmetics to better meet consumers' specific needs. In the era of the Internet, customized hair care cosmetics could become a reality in the future. On the other hand, a trend to combining hair care with scalp care is drawing more attention over time. While it makes sense to focus more on the scalp, currently there is only limited understanding on the relationship between scalp conditions and hair appearance. More fundamental understanding need to be generated in this field.

## References

1. Robbins CR. *Chemical and physical behavior of human hair*. 4th edition. New York: Springer-verlag; 2002.
2. Soga H, Morita K, Arai K. Effects for scalp blood flow and properties from scalp massage. *J Soc Cosmet Chem Jpn* 2014;**48**(2):97–103.

3. Takahashi M, Yang JZ. Research on scalp physiology—current Status and future view. *Cosme Tech Japan* 2014;**4**(3):37.
4. Koyagi T, Hirohata R. Scalp care focusing on Lipid Peroxide. *Fragrance J* 2012;**40**(10):16–22.
5. Yang JZ, Luo XC. *Hair and hair care, chapters 6–8: shampoo, conditioner, styling products*. Nanjing: Phoenix Science Press; 1998.
6. Yang JZ. *Aesthetic dermatology: IV. Shampoo and conditioner.* 2nd Edition. Tokyo: Nanzando; 2009. p. 380–5.
7. Yang JZ. *Skin science and cosmetic efficacy evaluation, chapter 19: hair care and hair care cosmetics*. Beijing: Chemical Industry Press; 2005. p. 383–412.
8. Yang JZ. *Hair diseases, chapter 5: care and beauty of normal hair.* Nanjing: Southeast University Press; 2004. p. 113–46.
9. O'goshi K, Iguchi M, Tagami H. Functional analyses of the Stratum Corneum of scalp skin. *Arch Dermatol Res* 2000;**292**:605–11.
10. Schwartz JR, Cardin CW, Dawson Jr TW. *Textbook of cosmetic dermatology.* 3rd Ed. NY: Taylor & Francis; 2005. p. 264.
11. Yang JZ, Schwartz JR. Design of effective anti-dandruff shampoo technologies. *China Cosmet Rev* 2008;**254**:82.
12. Sei Y, Yang JZ, Luo X, Kato T. *Dermatology practice 5-skin care practice, chapter 6: dandruff and seborrheic dermatitis*. Tokyo: Bunkodo; 1999.
13. Yang JZ, Takahashi M. Scalp physiology and care–3. Scalp care. *Cosmet Tech Japan* 2012;**2**(4):86.
14. Lochhead RY. *Practical modern hair science, chapter 3: shampoo and conditioner science*. Carol Stream, Illinois: Allured Business Media; 2012.
15. Holmberg K, Jonsson B, Kronberg B, Lindman B. *Surfactants and polymers in aqueous solution*. New York: John Wiley & Sons; 1998.
16. Lochhead RY, Huisinga LR, Waller T. Deposition from conditioning shampoo: optimizing coacervate formation. *Cosmet Toiletries* 2006;**121**(3): 75–82.
17. Huang Q, Mei ZW, Takata K, Yang JZ. Analyzing deposition from rinse-off hair products. *Cosmet Toilet* 2013;**128**(11):810.
18. Megling A, Kleber M, Hensen H. Comparative studies on the ocular and dermal irritation potential of surfactants. *Food Chem Toxicol* 2007;**45**: 747–58.
19. Kimura T. Development of gentle cleansing products for skin. *J Soc Cosmet Chem Jpn* 2012;**46**(4):257–63.
20. Miyazawa K. Evaluation of haircare products; shampoo and rinse. *J Soc Cosmet Chem Jpn* 1995;**29**(2):95–105.
21. Yamasaki E, Ito S, Yang JZ. Technologies for Silicone-free hair care products. *Fine Chem* 2016;**45**(1):6.
22. Kawaguchi J. Fatty acid ester thickener with no amide bond for washing agents in personal care application. *Fragr J* 2014;**42**(7):48–53.
23. Suda H. Applications to cosmetic formulations of amino acid based surfactant using novel thickener. *Fragr J* 2014;**42**(7):43–7.
24. Miyamoto H, Iwasaki N, Kamata T. Application of Taurine for Body Care Products as a Unique Moisturizer. *Fragr J* 2010;**38**(3):15–21.
25. Matsuo S. *Oil Fat* 2015;**68**(8):65–70.
26. LaTorre C, Bhushan B, Yang JZ, Torgerson PM. Nanotribological effects of silicone type and deposition level and surfactant type on human hair using atomic force microscopy. *J Cosmet Sci* 2006;**57**:37.
27. Yamasaki E, Lin X, Yang JZ. Development of Sulfate-free shampoos. *Fine Chem* 2016;**45**(1):12.
28. Yang JZ. *Science of cosmetic to ensure the safety of cosmetics—paraben, silicone and new materials: 15. Towards the development of new hair care products*. Tokyo: CMC Publishing; 2014. p. 137–44.
29. Yang JZ, Luo X. *Gels Handbook, Vol. 3, Chapter 2: Cosmetics*. New York: Academic Press; 2000.
30. Arai Y. *The latest in hair coloring technologies*. 1st Ed. 2004. p. 101–210. Fragrance Journal, Tokyo.
31. Corbett JF. *Hair colorants: chemistry and toxicology.* Dorset, UK: Micelle Press; 1998.
32. Morel OJX, Christie RM. Current trends in the chemistry of permanent hair dyeing. *Chem Rev* 2011;**111**:2537–61.
33. Chan A, Kung S. Hair colorant technology advances further. *Pers Care* September, 2006:11–6.
34. Japan Permanent Wave Lotion Industry Association. *Science of perm*. Tokyo: Shinbiyo Press; 2015. p. 28–60.

CHAPTER

# 37

# Sensory Measurement—Evaluation and Testing of Cosmetic Products

*P. Huber*

**ZHAW Zurich University of Applied Sciences, Wädenswil, Switzerland**

## 37.1 INTRODUCTION—WHY SENSORY ANALYSIS?

The scientific discipline of sensory analysis describes the relationship between products (ingredients) and their perception and evaluation by the human senses. Sensorial characteristics are key quality criteria for both food and cosmetics.[11]

The Institute of Food Technologists in Chicago defined sensory evaluation in 1975 as: "… a scientific discipline used to evoke, measure, analyze and interpret reactions to those characteristics of foods and materials as they are perceived by the senses of sight, smell, taste, touch and hearing."

Product evaluation is a multistage process and hence the objective of any sensorial evaluation must be clearly defined and the method of assessment, which may involve the use of a sensory panel, a group of individuals who respond to and note the effects of a product stimulus in accordance with predetermined instructions, must be carefully selected.[41] Each stage of the evaluation process should be based on scientific principles if it is to withstand subsequent scrutiny. In this chapter, we will discuss some issues which can be raised by sensory analysis of cosmetic products and demonstrate how these issues can be addressed.

For many cost-oriented professionals in marketing and sales, sensory tests represent additional costs that do not provide value, but rather serve to reduce profitability.

For supporters of exact science, sensory tests are perceived as unsatisfactory because the accuracy of results can be compromised through working with people as "living sensors" and the innate biological variability in human judgment ("noise"). However, these concerns can be addressed when standardized test conditions are applied and the results verified through statistical analyses. In fact, a genuine, subjective response to a single product in a sensory test by actual product users may be highly desirable.

There is much discussion about the human factors involved in sensory testing and the fact that the use of panelists for training purposes can be too time-consuming. However, it is important to recognize that instrumental measurements of the physical and chemical properties of the product alone are limiting and cannot truly represent the application of the product by users in real situations.

Importantly, every product developer, raw material producer, and product marketing expert will inevitably be exposed to and will be required to use sensory data because sensorial descriptions represent the only credible link between the developer of a formulation and the product briefing by the marketing department on the one hand and the expectations and aspirations of the consumer on the other. If the objective of a sensory test is clearly defined, an appropriate test method selected, the test carried out according to specification, and the results statistically analyzed, valuable insights into a product's sensory characteristics can be gained that can be used to define the emotional benefits to the product users and to promote the acceptance of the product.[28] A sensory evaluation represents a common language that everyone involved in the value-added chain must learn and interpret to launch a product successfully. Early developers of fine fragrances, emollients, and polymer formers recognized and adapted findings from the food industry. The subsequent section of this chapter focuses on the development of the sensory sciences, their primary objectives and benefits.

*Cosmetic Science and Technology: Theoretical Principles and Applications*
http://dx.doi.org/10.1016/B978-0-12-802005-0.00037-9



Copyright © 2017 Elsevier Inc. All rights reserved.

Sensory science represents the interface between emotion/feeling and understanding ("Sense and Sensibility" as interpreted in the world-famous novel by Jane Austen). Scientifically, sensory science is an interdisciplinary approach to product assessment adopted from the methods and findings of the exact sciences and the humanities. The interdisciplinary approach is thus a key strength and requirement and not a weakness, but it does require that everyone involved in the sensory approach is aware of the implications. From neuroscience, we have benefitted from many recent studies about emotionally driven decision-making processes of humans for whom multisensory triggers can influence the "when" and "why" (purchase) decision. Here, thanks to noninvasive imaging measurement procedures, neuromedical specialists have literally been able to look into the human brain.

Nevertheless, the classical methods involving trained panelists and nontrained users continue to yield worthwhile results which provide the basis for further decisions in product development and market positioning. As a dynamic science, sensory science experts are continually developing classical timesaving methods which are cost-effective. An overview of the history of sensory science confirms this.

The origins of science-based sensory analysis can be found in Europe in the 19th century, coinciding with the rapid development of new organic substances such as sugar substitutes. But during the Second World War American catering logisticians faced new challenges and the science really became established. How could soldiers in far off lands be provided with microbiologically safe but tasty food? The qualitative analysis of food (spoilage) required a test for the senses because if the food did not taste good it was not eaten, and that was bad for morale[41]!

To summarize, sensory-testing methods represent important tools which enable issues associated with the development, quality assurance, marketing, and sales departments to be addressed. With selection of the appropriate testing method (see Section 1.6) the following questions can be answered:

- How should I modify my formulation so that it corresponds to a qualitative benchmark or market product? For example, how can I reduce the whitening of my cream or improve its velvety feel on the skin?
- How far can I replace a raw material for cost reduction or logistics reasons without regular customers being aware of the change?
- Do semifinished and/or end products correspond to internal company specifications? The sensorial product characteristics are understood to be part of product quality and a proof that the production process is controlled.
- Do consumers like the product and will they make a repeat purchase? If not, what are the reasons?
- Do we know our end consumers in the various regions of the world so well that we understand their individual needs (cross-cultural sensory)? In terms of globalization and multicultural experience, are there ethnic sensory similarities that can be considered as clusters? How can we best address emerging markets?
- Have both the actual product and the packaging been confirmed to be of high sensorial acceptance (sensory-driven)?
- Is there a difference between the sensory preferences of male and female consumers or are these preferences independent of gender? Do preferences in older consumers change analogous to their physiological changes (age-related sensory perception)?

Other factors that can influence the purchasing behavior of consumers at the point of sale include the brand, package, and the promised effectiveness. Subsequently, the sensorial experience dictates whether the consumer will purchase the product again. The immediate reaction to the product on being used, which can be called "compliance" (use of the product) or the "feel good factor," directly affects "adherence" (the continuing use of the product), which is critically important because the active ingredients of formulations frequently require prolonged use of the product and are only fully effective after several days or frequently after 4–12 weeks. In dermatological pharmaceuticals that are applied topically to treat acute skin problems, sensory properties such as texture or fragrance are secondary in importance. But even in these products, especially in the "over the counter" sector (medicines that are available without prescription), there is increasing consideration of sensory attributes to differentiate between competitive products. Interestingly, sunscreen occupies an intermediate position. Sunscreens complying with the legally defined, desired protective effect against high-energy ultraviolet (UV) radiation must be applied regularly and in a sufficiently high quantity to meet the expectations of each target customer group. Achieving the optimum sensorial properties together with good product performance is a challenge in this product group. However, combining both in the final product is crucial, as only combined regular and correct product application can provide appropriate protection against skin cancer. In this application, a pleasant texture with sufficient spreadability and potentially a non-tacky or dry-feeling residue on "compliance" by the consumer determines the loyalty of the consumer to the product, which consequently may affect the health of that consumer.[26,45]

In the cosmetics industry, sensory attributes of products are given high priority. This is especially true in the choice of the product fragrance but also applies to the selection of the ingredients for a new formulation, which

will affect the sensorial properties. The choice of a particular oil, for example, can generate either a rather dry or rather rich skinfeel. Not all products are subject to a full sensory optimization, however, as this usually requires both a detailed sensory analysis and correlation of the sensory profiles with consumer feedback. Sensory factors can be successfully integrated into a newly developed cosmetic series based on past experience. This process is quicker as only a comparison between the "old" and "new" formulations is required. The intelligent use of experience and an understanding of consumer preferences, coupled with the correct formulation, can result in the development of products which find so much favor with consumers based on their perception of the smell and the texture that the products become well established and are purchased again and again.[18]

Along with personal care products, sensory assessments are increasingly being conducted in the home-care sector. How do detergents and cleaners actually feel? In this case, it is the tactile properties of the packaging materials which come under scrutiny. It is crucially important that consumers experience a first, positive sensory impression when they are tempted to pick the product up from the supermarket shelf and feel the product in their hand. This may even provide a sensorial impression of the product content! For example, the fragrance within a package might be discernible through the application of special fragrance valves or scent capsules that release their fragrance due to mechanical pressure or rubbing, without the consumer actually opening the sealed package. Cosmetics especially are often assessed on the basis of a test of the product before the purchasing decision is made. If this is not possible at the first purchase opportunity, these products often do not end up in the consumer's shopping basket. This is even the case for products in lower price categories.

Seventy percent of a consumer's purchase decision is driven by emotional and subconscious factors. In the highly competitive cosmetics market in which product performance claims can be similar, sensory product features create potentially important product differentiation. In this case, the tactile properties and the scent perception are of central importance to the purchasing behavior and brand loyalty.[29]

The classical measurement methods are presented in this chapter, their advantages and disadvantages discussed, and reference made to the latest methods.

## 37.2 HAPTIC—SENSORY FUNDAMENTALS

Touch is separation and connection at the same time. ***Novalis***

### 37.2.1 Mouthfeel Versus Skinfeel

The sensations on the skin are the result of many individual stimuli recorded by a variety of sensors, which is similar to the sensations in the mouth when food is consumed. Although the term "mouthfeel" is used in connection with foods, "skinfeel" in the broadest sense is used in connection with cosmetics. With the intake of food the consistency of a product relates to a wealth of information. The situation is similar with cosmetic products; a lipstick based on color pigments must comprise particles of very fine grain size ($<10\ \mu$); otherwise, these would be troublesome when applied.[18]

The skin is our largest sense organ—weighing up to 8 kg and with a surface of 2 $m^2$ comprising millions of sensors registering diverse stimuli. There are up to 3000 min nerve-ending corpuscles in a square centimeter of skin. Tactile stimuli arrive via nerves in the somatosensory cortex of the cerebral cortex. Tactile cells already develop in the skin of an embryo. Thus, it is the first sense that forms in humans and probably is the last sense affected by aging.[12]

### 37.2.2 The Hierarchy of the Senses—The Sense of Touch

In a list of the five senses, touch is often the last of the human senses mentioned, although this represented an important sense during evolution.

There is a hierarchy of senses corresponding to each species, and reflects the sense which enabled that species to best survive. Today, the sense of sight is extremely pronounced in the human consciousness, but odor perception and hearing were much more important earlier as these senses enabled information to be perceived from large distances and were closely related to survival.[18]

From a philosophical point of view, the sense of touch occupies an ambivalent position. It is either the last or the first point in the hierarchy of the senses as rated by Aristotle (*according to his criteria of dignity?*) in his classic text "De Anima." The apple first touched Eve when she seduced Adam. The "Tactus" became the erotic symbol and only

from the 13th century increasingly received a negative interpretation. Perhaps, the observation described previously is one of the reasons why the assessment of tactile stimuli has not until recently received the same attention in research as the senses of sight and smell.[27]

### 37.2.3 The Resolution of Touch

Touch is the only sense perceived all over the body and it plays an important if not decisive role in both spatial and time awareness. For example, spatial distances are more apparent on the skin than from listening and time intervals more accurately perceived than by seeing. Physiologically, therefore, it occupies an intermediate position in the hierarchy of the senses. The skin passes on further information; where it is touched, how far apart distinguishable stimuli are, the shape of the touching object, and whether something on it is moving. However, all these capabilities can also be accompanied by delusions.[16]

Pressure and tactile sensations can only be triggered at certain points on the skin, the so-called touch points. It has been shown in experiments that touch to one body part can be resolved quite differently to touch on another part, the resolution being the highest at the fingertips and lips,[16] which makes these the "principal organ of tactile gnosis" (i.e., recognition by the sense of touch).[44]

Accordingly, the spatial difference thresholds, i.e., the shortest distances in which two stimuli are just perceived as separate, vary. Furthermore, stimuli applied at the same time result in a greater spatial difference threshold (simultaneous space threshold) than stimuli applied in succession (successive space threshold).[42] The structures on the fingertips, the skin ridges, send tactile sensations to the deeper lying skin receptors, thus increasing sensitivity.[44]

### 37.2.4 Skin Sensitivity

Each contact registered on the skin represents an interaction between the different corpuscles. Also the location and/or depth of each receptor in the skin layer provide specific information. The skin and mucosal surfaces are sensitive to:

- mechanoreception (touch)
- thermoreception (temperature)
- pain sensitivity (pain)

The sense of touch recognizes both tactile and kinesthetic impressions. Tactile stimuli are perceived by touches to the skin in the broad sense (surface sensitivity), whereas kinesthetic impressions (Fig. 37.1) are caused by a dynamic movement (for example, the depth sensitivity of a finger on the skin surface moving in a circular movement) or an application of force.[8,30]

Perceiving temperature, touch, pressure, pain, and vibration are the essential sensory abilities of the skin. In contrast to the autonomous (vegetative) nervous system of the skin, which is responsible for nervous controlled manifestations such as paling, blushing or bristling of the hair, the sensory (cerebrospinal) nerves are generally grouped together under the term "skin receptors". The sensory receptors described below (see Table 37.1) not



**FIGURE 37.1** The finger as a natural sensor (kinesthesia). *Picture credits P. Huber.*

**TABLE 37.1** The Sensitivity of Single Skin Receptors—Physiology (Overview)

| Sensitivity | Receptor | Characteristic |
|---|---|---|
| Touch | Meissner's corpuscles hair follicle receptors | Speed detector (differential sensor), fairly fast adaptation |
| Pressure | Merkel's discs Ruffini end organs | Proportional sensor, slow adaptation |
| Vibration | Pacinian corpuscles | Accelerator detector, very fast adaptation |
| Pain | Free nerve endings | No adaptation |
| Temperature | Free nerve endings (warmth), Krause end bulbs, among others (cold) | Proportional and differential sensors, adaptation between 20 and 40°C |

*According to T.H. Schiebler, U. Peiper, Fr. Schneider.* Histologie. *2nd ed. Springer Verlag; 1986.*

only perceive true stimuli in the skin and mucosa but also convey information from deeper organs such as intestines or the musculoskeletal system.[2,42]

The evaluation of products based solely on their tactile properties represents a challenge even for newly trained panelists, who are already experienced in the sensorial assessment of food, and there is still a gap to be filled with accurate characterizing test methods. Perhaps or because of this lack of suitable tests accompanied by the challenges encountered by panelists, the use of the sense of touch to test tactile and textural properties has been underestimated. Hence, the sensorial assessment of cosmetics has extended the range of additional test methods available. These methods have been applied to surface assessment of polished surfaces in the automotive, computer, and telephony industries, to mention just a few examples.[18]

## 37.3 APPLICATION OF SENSORY FOR COSMETICS

Sensory tests are afforded a high priority in the development of cosmetics. Whether the tests are outsourced or performed inhouse is usually a function of the size of the company and the available resources. During the early product development phase, descriptive tests like profiling are typically employed, or, if there is a lack of resources, the acceptance test, which is easier to conduct, is frequently used.[43]

The raw materials used in a product and the manufacturing processes affect the tactile-sensory properties of a cosmetic, allowing both the sensory attributes to be optimized and a desired sensory profile to be achieved. Natural cosmetic emulsions are a particular challenge, due to the limited number of raw materials available, and properties such as "whitening" or "film residue" which often have to be optimized.[22]

In subsequent product development processes, sensory impressions of fragrance are checked (smell, adhesion to the skin), because hydrophilic and lipophilic components of a product influence not only the scent impression, but also product stability (viscosity) due to their chemical–physical interaction.

Before product launch, specific consumer tests are conducted to predict at the very least the likely acceptance of the product. Sensory impressions can also be used for advertising and marketing purposes. Market research institutes regularly "map out" sensory product expectations of the various target markets through completion of surveys among typical consumers, which is known as "Preference Mapping." The acceptance data are correlated with the output from trained panelists and analyzed, for example, by means of principal component analysis to create the corresponding "Preference Map."

Once a product is launched, regular revisions to the product formulation may be required during the short product life cycles encountered in the cosmetics industry, for example, to incorporate new active ingredients or to switch to ingredients which simplify procurement or can be obtained from more sustainable sources. Currently, the cosmetics industry in the European Union (EU) is implementing new regulations, which require, for example, the use of alternative preservatives, adjustment to the limits of permissible parabens, and limits on the use of

particularly hypoallergenic fragrances. Here, difference tests are used, often with the (desired) objective of accepting the null hypothesis, so there is no perceived difference between the new and the original formulations.

Difference tests are applied during quality control and quality assurance checks, for example on raw material receipt and during the manufacturing process. For stability testing, the tactile and olfactory characteristics of reference samples are assessed and compared to standard components of a given specification.[18]

## 37.4 INFLUENCE OF RAW MATERIAL FORMULATION ON THE SENSOR

The cosmetics industry is required by legislation to produce high-quality products and to demonstrate their safety and efficacy. Cosmetics are classified according to their use as either rinse-off or leave-on products. Rinse-off cosmetics consist primarily of surfactants and encompass such products as shampoos and skin cleansers. The leave-on cosmetics include all toiletries that remain on the skin during their use. The raw material compositions and the categories of product corresponding to this form of cosmetics are more diverse and include emulsions, gels, serums, and solutions. In addition to the conventional emulsions, special emulsion types such as Pickering, microemulsions, and miniemulsions are also now used. Furthermore, the increasing demand for formulations of higher concentration and multipurpose products has led to the development of dermal delivery systems, such as liposomes, microparticles, and nanoparticles. The formulation type and raw material composition both strongly influence the sensory properties of a cosmetic product. [18,23]

Each formulation is adapted to meet specific customer needs. Consequently, there are diverse formulation variants, even if they generally correspond to recurring variations of emulsions and gels. Emulsions comprise at least two immiscible liquid phases, wherein one phase is finely dispersed in the other. Typically, these are oil-in-water mixtures (O/W), or more rarely, glycerol/silicone oil mixtures, or even triple emulsions. The particle size is determined by the manufacturing process, or more specifically by the energy input during homogenization, or the defined manufacturing process coupled with the selected emulsifiers which stabilize the newly created interfaces and prevent the droplets from coalescing. Droplet size and the choice and amount of the emulsifier, and thus of the resulting gel network, affect the sensory properties, especially the appearance stage, and pickup with respect to the emulsion's viscosity, appearance, and consistency. It is the choice of the oil, fat and wax components that most significantly affects the sensory stages of applying (rub-out) and feel of the skin after the product is withdrawn (afterfeel). The demand for natural raw materials has increased, challenging the raw material suppliers to source materials containing both the active compounds and the auxiliary substances such as emollients (oil components), emulsifiers, and surfactants from renewable plant material. Natural oils and butter have increasingly been used in formulations, but the choice of raw materials is much more restricted if the cosmetic formulation is to be considered from natural ingredients. Many raw materials that have the requisite sensory function cannot be used. This provides the formulator with a particularly tricky challenge when producing products with specific textures, examples of which include when the whitening effect must be minimized during application or the absorption improved. This can only be achieved by careful selection of fast-spreading and more polar emollients. In this way, the stickiness and oily or greasy residue on the skin are also minimized.

Gelling agents can be used, in addition to emulsifiers, to stabilize an emulsion by structuring the external continuous aqueous phase of an O/W emulsion and building a gel network, thereby stabilizing the dispersed droplets. The choice of the gelling agent and its concentration in the product can have a strong sensory impact and can cause diverse film-forming phenomena on the skin.

Emulsions can be used in many different ways in cosmetic formulations. Due to the formulation bandwidth and the possible viscosities that can be achieved, their application can result in low viscosity, "flowable" textures (sprayable emulsions or lotions), semisolid, or spreadable, butter-like formulations. Emulsions of the O/W type (with water as the external phase) account for an estimated 65% of the total market, whereas the W/O types represent approximately 35%. The latter are used for water-resistant formulations, products with "protection against the cold," in baby care, for very dry skin, and in the care of the elderly. They are not washed off after use and form a protective film on the skin. The water-rich O/W emulsions are used, for example, in moisture and antiaging creams. They can generally be more easily washed off the skin and their sensorial properties are usually preferred. Emulsions advertised as "emulsifier-free" are considered to be particularly suited to sensitive skin. But how can such a two-phase system be stabilized? Systems are regarded as emulsifier-free when stabilized with surfactant macromolecules and polymers (for example, a gelling agent) instead of amphiphilic emulsifiers. The latter form a film around each droplet, thus preventing the emulsions from phase separating. These emulsifier-containing emulsions are often characterized by their "lightness" and freshness, although they typically have an aqueous gel-like base.[18]

Support systems influence the sensory properties of a cream. Depending on the concentration and nature of the particles, this influence can lead to positive (dry-skin feeling) or negative (graininess, dullness) sensory effects. The particle size of these carriers typically varies between 200 nm and 500 μm. The most important support systems are liposomes, microparticles and nanoparticles, porous microparticles, cyclodextrins, and solid lipid nanoparticles (SLN).[37]

Unfortunately, sensory guidelines do not exist for all product categories. The American Society for Testing and Materials (ASTM) test provides procedures for emulsions and shampoos.

## 37.5 PROCEDURES AND GENERAL FACTORS INFLUENCING SENSORY TEST METHODS

### 37.5.1 Quality of Sensory Testing

Processes concerning the maintenance of quality in testing are described in the International Organization for Standardization (ISO) 9000 Series of Standards and by the ASTM.[3] The standards describe specific factors which affect quality, either partially or in depth, and describe how a quality framework designed to reduce the degrees of freedom and obtain reproducible results can be established.

The results from all studies must be relevant, reliable, and reproducible. A formal report should include the objective of the study, the experimental design and method including a statistical evaluation.

The testing of cosmetic products on adults generally corresponds to the application method typically used in practice and is noninvasive. Nevertheless, any country-specific or internal, company-specific testing requirements, which may necessitate the approval of test designs by an ethics committee, should be determined prior to initiating sensory tests. Any tests with children, pregnant women, or other specific target groups, or the use of raw materials which have not yet been classified as safe, are subject to initial clarification with the appropriate regulatory bodies.[28]

### 37.5.2 Validation of Panels

Consistent and reproducible test conditions are a prerequisite for all sensory measurements, which are often designed to evaluate the effects of a cosmetic over time (time intensity).

Panelists should be selected to ensure that they are not prejudiced in any way and that they are not subject to other pertinent influences. This is particularly important in the case of the selection of participants for “in-house” panels and for the development of new product formulations, for which neutral sample coding, such as a three-digit code, is essential.

Furthermore, each panelist must be cooperative and a team player and be prepared to conform to the assessment requirements of the panel. With long-term panelists, this can lead to discussions; on the one hand, their experience is normally valued, but on the other hand, routine habits may result in systematic misjudgments.[18]

The ASTM Methods E1490-03/E1490-11[4,5] offer product-specific supplements to the general recommendations described in Busch−Stockfish’s manual of practices[9] for the selection and training of panelists. Threshold tests (to determine the sensitivity of the sense organs) and certain ranking tests are used to identify suitable panelists and to help them develop in their roles.

### 37.5.3 Environmental Factors

As one would typically expect with a controlled measuring device, panelists require constant environmental conditions to be able to make consistent observations and they should not be distracted in any way. The premises in which the tests are carried out should be in accordance with ISO Standard 8589, odorless and without noise, and with good, constant, standardized lighting. In addition, the ASTM Committee E−18 makes specific recommendations for a high-quality setting for sensory testing in general.

The test samples are coded with three-digit random numbers and the allocation of the test sample is also usually randomized. Such steps are accordance with current good laboratory practice (GLP) and ISO Standards (ISO 6658, ISO 5497).

The ambient temperature (ideally 20−22°C) and relative humidity (ideally 50−55%) should not fluctuate by more than 3.4°C and 8%, respectively, during an assessment, according to ASTM.[5] Otherwise, the skin temperature of the

respective panelists must be re-checked. This requirement is especially important when testing formulations with temperature-sensitive melting behavior.

To ensure standardization of the tests as far as possible, the "substrate" skin must be configured and prepared as consistently as possible. Measurements at the Zurich University of Applied Sciences (ZHAW) have demonstrated that the moisture content of the skin of all panelists increases with repeated use of the same test zones after even just one application, despite protocol-compliant cleaning of the skin (degreasing with 50% ethanol) between test samples. Such variation in moisture content may affect the sensory perception of certain attributes.[24]

### 37.5.4 Application Site and Quantity

In practice, test products are frequently applied to the back of the hand. According to ASTM[4,5] the forearm is preferred because the skin in this region is type independent and has a regular pore distribution. There are, however, additional test zones available which can provide a direct comparison. The noticeable tendons and bones in the area of the middle forearm do not affect tactile sensitivity.

Regarding the quantity of the test product or references to be applied, the cosmetic panel at the ZHAW applies 0.1 mL to the fingertips ("pick-up" stage) and 0.04 mL (40 μL) to an area of about 19.6 $cm^2$ on the forearms, which is based on Cosmetics Europe (formerly the European Cosmetic, Toiletry and Perfumery Association, COLIPA) guidelines of 2 $mg/cm^2$. The American guidelines[4,5] are somewhat lower. Other references suggest amounts of up to 150 mg in the "pick-up" stage.[7]

### 37.5.5 Interactions With the Skin

As soon as a strong interaction with the stratum corneum of the epidermis occurs—during the stages of "rub-out" and "afterfeel"—individual differences are observed. The evaluation of all attributes in the "afterfeel" takes place after absorption of the product. This time dependence is a function of skin type; the absorption typically takes longer for a panelist with normal skin compared to a panelist with dry skin. In general, reference samples behave similarly on different skin types. Thus, potential panelists should not be excluded for reason of their skin type or because they have more mature skin. This observation was also confirmed by Busch and Gassenmeier.[7] According to ASTM,[4,5] the panelists with differing skin types should be selected such that products can also be tested with respect to skin type needs. The skin surface of the forearm comprises the "substrate," because the density of nerves in this area and the corresponding signal are low. The majority of sensory signals are perceived in the fingertip and these signals are then processed in the cerebrum in much greater detail. Nevertheless, formulations may react quite differently on the forearm depending on skin type.[18]

## 37.6 METHODS

Cosmetic products, whether leave-on or rinse-off types, stimulate the user in a multi-sensory way. In addition to tactile and visual stimuli, fragrances are also very important in the application of the product. The methods described below are largely suitable both for the evaluation of fragrances and haptics but may need to be adapted to the specific validated attributes (terms) and test procedures of interest. If neither a universal (and validated) attribute catalog for a product category nor a test design with accurate test instructions is available, it is worthwhile working with professionals experienced in sensory testing to develop an appropriate system with the objective of achieving reproducible measurement results, which can only be accomplished through standardization.

The objective of a sensory test must be clearly defined from the outset. The questions posed in the introduction section of this chapter will assist in selecting the most suitable test method or procedure. A valuable overview is also provided by the following authors: Meilgaard and Civille,[30] Stone et al.,[41] Kemp et al.,[28] and Moskowitz.[33]

Test methods can essentially be categorized as either subjective (hedonic, affective) or objective (analytical) (see Table 37.2). Typical users (consumers) are employed for the subjective methods, whereas the use of trained subjects (panelists) is preferred in the latter case to ensure reproducible results. Consumers may also be used for so-called discrimination tests, if a product developer wishes to simulate the user situation as closely as possible, which may be the case, for example, when assessing a revised formula that should differ as little as possible from the original recipe. Although the triangle test is widely used to determine if there is a sensory difference between samples, descriptive tests are used to describe the difference in sensory attributes using a variety of attributes/terms, which

are also used to quantify the intensity (magnitude) of the sensory attribute. In classical descriptive test methods, as in the profiling method, trained panelists are required. More recent methods such as Free Choice Profiling, the Flash Profile, Napping or Tabletop Profiling are more cost- and time-effective options which may be preferred by small businesses as they can be performed with fewer or even no trained panelists. Each simplification of the systematic testing approach is inevitably associated with some loss of information.[11]

### 37.6.1 Subjective Test Methods (Affective Tests)

The subjective test methods require untrained or inexperienced panelists such as typical product users. However, users are more susceptible to potential distractions or psychological factors, such as preference and multimodal sensory impressions, which must be taken into account or preferably prevented. If an "immediate" product efficacy (apart from physiological activity validation) has been defined as a test target, the product testing should occur in a real context, which may be the case in such products as a shampoo or a shaving product.[28]

Many different acceptance and preference tests can be included and can be carried out in a laboratory. If the test is completed in the home, it is called a "home use test." When completed near the place of purchase or in a neutral environment by invitation, this is called a "central location test." The sensory popularity of products can be determined by the acceptance test using a hedonic scale, as a paired comparison (for two products) or by means of a specified order of precedence (in the case of more than two products).[11] These methods address the questions (4) and (6) posed in Section 1.1. The response to question (6) can be elicited within a multisensory setting with the associated packaging or alternative triggers that affect consumer response.

The relative preference is determined using a preference test [question (7)]. This can be performed by means of a paired-preference test in which a user selects two of the presented samples, or by means of a ranking test, if more than two products are present.

New descriptive tests occupy an intermediate position between objective–descriptive and subjective methods and are less time-consuming and expensive as they require volunteers with little or no training. Originally applied in the food industry and now used for initial product trials in the personal care sector, the Free Choice Profiling method is a descriptive method that is counted among the objective test methods, which may involve, according to different sources, between 8 and 44 subjects. For a more rapid method, the Flash Profile, a modification of free-choice profiling, may be considered, in which panelists also assess each sample using their own vocabulary. During Napping and Tabletop Profiling, the test products are grouped and positioned on axes. In comparison with the classic profile test method described below, all these tests have an inherent simplification with a corresponding

**TABLE 37.2** Classification of Traditional Sensory Test Methods

| Test Methods | Examples |
|---|---|
| Subjective (affective) | Acceptance test |
| | Preference test and ranking test |
| Objective (analytical)—discriminatory | Triangle test |
| | Duo–trio test |
| | Difference-from-control test |
| | Same-different test |
| | "A", "not A" test |
| | Paired comparison (2-AFC) test |
| | Three-alternative forced-choice test |
| | Ranking test |
| | Difference-from-control test |
| | In/out test |
| Objective (analytical)—descriptive | Texture profile test |

*According to Derndorfer E. Lebensmittelsensorik. 4th ed. Wien: Facultas Verlag; 2012. p. 51.*

loss of attainable information.[11] The Check-All-That-Apply method (CATA) is a purely qualitative descriptive method, in which the consumers select their most sensitive parameter(s) from a catalog of attributes.[34]

If subjectively assessed product preferences are compared with objectively determined product descriptions with an intensity rating, a preference map is created. A statistical analysis can be carried out using Principal Component Analysis (PCA). The reader is also referred to initial question (5).

### 37.6.2 Objective Test Methods

In objective tests, trained panelists are used to generate objective data. The tests can be categorized as:

- Discrimination tests—determine if a sensory difference can be perceived or whether the samples are assessed as the same. This addresses initial question (2).
- Descriptive examination—describes the nature of the product using attributes and the intensity of expression. This classic profile examination (Fig. 37.3) addresses initial question (1).

The discriminatory test methods are usually quick to implement and can be performed by both trained and untrained assessors, depending on the question, because these involve comparisons between products.[28] These tests can also be used to confirm the sensitivity of panelists.

If small product differences are expected, the triangle test is appropriate. Three samples, two of which are identical, are compared with one another (e.g., with the following sample layout A-A-B, A-B-B, or A-B-A). The assessors are asked to select the odd sample, and are usually required by the test protocol to record the attribute which differentiates the selected sample from the other two. Depending on the level of significance (appropriate statistical tables provide the minimum number of passes, as can be found in Meilgaard and Civille[30] and Kemp et al.[28]), between 24 and 30 assessors are needed. A test designed to prove that the samples are the same requires a larger number of test runs than a test which determines lack of difference between the samples.

As with the triangle test, the duo–trio test examines whether a difference between two samples exists. A sample is provided as reference and a corresponding sample is selected from the remaining two samples. This test comparing samples has several variants, for example, the difference-from-control test, same-different test, and the "A", "not A" test, which are described in detail in Meilgaard and Civille,[30] Stone et al.,[41] and Kemp et al.[28] If a specific attribute is to be tested, a paired comparison or two-alternative forced-choice (2AFC) test is suitable. Two blind samples are compared—the assessor must determine the sample in which the selected attribute is most intense. If the number of blind samples increases, a three-alternative forced-choice test may be performed. As with the triangle test, two samples are identical. If three or more samples are to be checked for a specific attribute, a ranking test is used. Here, the attributes have to be classified according to their intensity. This test may also be helpful prior to conducting a descriptive profile test (Kemp et al.[28]). If a relative intensity scale is being considered, comparative tests, in which one sample represents the benchmark, are ideal quality tests. In a difference-from-control test, just two samples are compared with one another with one sample always being the control or benchmark sample. In this way, various samples can be compared with the benchmark product and any difference recorded with a verbal or numerical scale. The In/out test determines whether a newly produced batch sample corresponds exactly to the specification requirements and any approved deviations. These test methods address initial question (3).

A descriptive method, such as the texture profile test, is carried out in accordance with standardized instructions and conditions to ensure the same dynamic processes on the skin are used with each assessor.[8]

Various descriptive methods for the examination of leave-on products will be described in the following section, with a focus on the most commonly used classical techniques such as profiling methods. Newer descriptive methods are outlined at the end of the subjective methods section. Each of the product categories described is distinguished



FIGURE 37.2 Typical application site on the forearm with a well-characterized sequence of product application and palpation during the rub-out and afterfeel stages. *Picture credits ZHAW.*

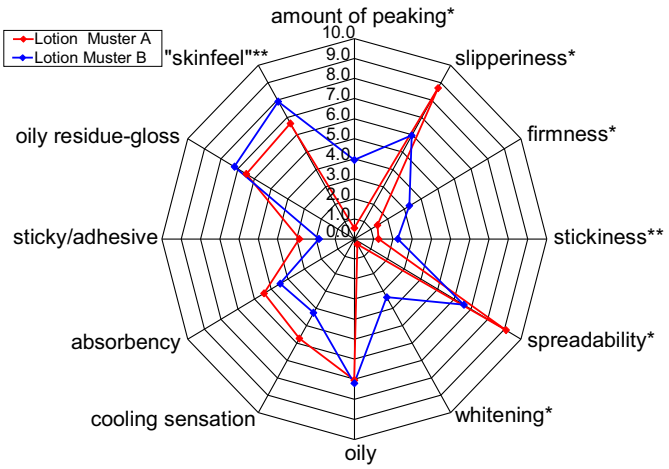



**FIGURE 37.3** Representation of a sensory profile of two lotions as a spider diagram, N = 10 (* significance level $p < 0.05$, ** "Trend" $0.05 < p < 0.01$).[24]

by its own sensory properties. The aim of descriptive tests is to obtain reproducible and repeatable data from panelists. It is assumed that terms used to describe a sensory attribute are universally understood and have a precise linguistic definition, so that the panelists recognize the appropriate property and can assess the intensity of a descriptive attribute.[24]

The Spectrum Descriptive Analysis Method offers a list of attributes that relate to various cosmetic products. These attributes can also be used as core questions for user testing. The complex descriptive analysis originates from the food industry ["Flavor Profile method" (FPM)]. In the late 1960s, consumers were interested in the texture of a food. This laid the foundation for the subsequent texture profile methods which were later adapted for cosmetics thanks to the introduction of appropriate terminology.[30] Since the 1980s, these tests have also been used for cosmetics.[8]

The method introduced by the Tragon Corporation called "Quantitative Descriptive Analysis (QDA)" was primarily designed for users, who were trained in a relatively short time with the actual products to be tested. This test assesses relative differences in intensity. In the "Spectrum Descriptive Analysis" method, the panel itself is calibrated with specific references so that absolute intensities are established and the products tested in this system can be compared reliably with each other. The corresponding training and coaching outlay is significant with 40−120 h of training required. Descriptive panels should comprise no fewer than six participants for statistical reasons, but a good compromise is a panel comprising 10 assessors.[17] However, logistical considerations frequently demand that at least 15 individuals are trained.

The properties of a product and their sensory impact need to be well defined and representative of the typical profile of a product category to facilitate training of the panelists. Because the sensorial impressions must always be associated with the same attribute, the distinguishing features of these attributes need to be supported with appropriate reference products. A selection of attributes is displayed in Fig. 37.3.

## 37.7 FOCUS TEST REQUIREMENTS OF THE DESCRIPTIVE PROFILE TEST

Our senses, including our sense of touch, are extraordinarily powerful detectors and operate virtually continuously and simultaneously. Classic sensory tests conducted by trained panelists can be regarded as very effective "instruments." The reading of the "signals," however, requires a thorough and well-documented procedure and regular training of the "measurement and output devices." After all, it is an entire panel group which is trained, not just individuals[11]! The advantage of using people as assessors—their multisensorial perception—can also be considered a weakness, because this perception can be affected positively or negatively by product properties such as color or perfume, thus influencing subsequent judgment.[6] This multimodal perception must be adequately addressed during test design. Experiments with food (coffee with milk of varying fat content) and a trained panel resulted in significant differences in terms of smell and taste under different optical conditions (red light/medium light).[46] A simple experiment with cosmetic face creams illustrates how individual senses are interdependent and can either

complement or detract from each other. When otherwise-identical formulations with variations in just perfume level (perfumed/non-perfumed) are assessed by untrained examiners, there is a slight tendency for the other sensory properties of the nonperfumed version to be evaluated as inferior and the two products to be determined to have different tactile properties. The risk of such a misjudgment is generally lower with trained assessors, but still cannot be ruled out. This test is also suitable for checking the influence of personal hedonism by providing the same recipe both colored and perfumed.

The validity of a measurement method is determined primarily by quality criteria like reliability and objectivity. Objectivity addresses the issue of whether the test results can be achieved independent of the observer, the reliability if the test result can also be repeated, both with the same, and with alternative, panelists. Reproducible values (reliability) require standardization of processes. Measuring sensory characteristics objectively means that the person is "instrumentalized." This requires intensive training, appropriate methods and the checking of the measurement results through sound statistical analysis. Statistical methods can be used in the training phase and for checking the quality of the panel. Such methods can also provide the panelists with valuable feedback on his/her "performance."[18]

### 37.7.1 Standardization Enables Reproducibility

Precise test procedures, which record and prescribe detail of a panelist's test sequence and control influencing factors, and thereby create similar conditions for all panelists, are a prerequisite. Only in this way is a test really meaningful. Specific requirements for the selection, training, and the accompaniment of assessors can be found in the ISO standard series 8586 or the ASTM. The diversity of influencing factors will now be discussed. Standard works such as the ASTM[4,5] or concepts such as the Spectrum Descriptive Analysis Method provide assistance in test implementation. In practice, many different methods are utilized with various amendments which have been introduced due to time or resource constraints. A direct comparison of the results is therefore difficult, but a relative comparison is possible.

### 37.7.2 Attributes—Verbalized Emotions

Language, the key to understanding among individuals, has many degrees of freedom. Semantics and the careful use of language is of critical importance. A word may have multiple interpretations so any free interpretation by an objective panel must be strictly limited by clear definitions. However, the situation is different in the so-called "Free Descriptive Panels," in which a wide diversity of languages is desirable.[7] More recent methods bypass the use of a common vocabulary and permit untrained panelists to use their own words. This may be useful in the early stages of product development for rapid assessments by consumers.

A word or phrase may be otherwise perceived and interpreted not only in the individual context but also due to language barriers and cultural affiliations. For example, the Japanese used to adopt in part completely contrary designations to describe the feeling of textiles to panelists from Australia, New Zealand, and India.[24] Another case in point, associated with language and cultural differences, is the attribute "greasy," describing a thick, sticky, sliding or tough film, and "oily" interpreted as a thin, sliding, nonsticky film.[6] In German, both these words can be translated as "greasy," an undifferentiated word, whereas "oily" is perceived as another form of fat.

The more subjective the interpretations of an attribute and its verbalization, the more diffuse the meaning of that descriptor. Examples of this are the attributes "skinfeel" or "softness." Interestingly, these are often the designations which are available to the user and most frequently communicated through advertising.

The way in which an attribute will be palpated and tested needs to be described in detail. In the "appearance" stage, only a purely visual comparison is possible, resulting in measurement observations among the panelists which are typically very homogeneous. A mechanical component is mainly used for the sequence stages "pick-up" and "rub-out." The movement of the hand must be constant, for example, at 2 revolutions/second (corresponds to 120 rpm). A faster or slower movement results in a change in shear rate and potentially a change in the viscosity of the cosmetic. This change in viscosity would alter the shear resistance perceived by the assessor. The higher the shear rate, the more fluid the product can be if it is a non-Newtonian system such as an emulsion. Most of the water in emulsions evaporates in the rub-out stage and sensory-relevant phase transformations can take place. As soon as there is direct contact due to the application of the product with the skin surface of the panelists ("rub-out" stage), there is an additional time factor. The attribute "greasiness" must be evaluated in both the "rub-out" as well as the "afterfeel" stages. The time intensity must always be taken into account. The test sample sequence must also be

recorded in accordance with a profile to avoid any initial misinterpretations. Attributes of the "appearance" and "pick-up" stages are based on detection of mechanical and physical properties. These are generally easily and quickly detected by the panelists. Correct interpretation of the attributes represents a real challenge for all parties, especially if there is a subjective component, such as aversion to the product, or the attribute term is not clearly defined. This can lead to invalidity of the sensory data. A clear definition of the attribute and the inclusion of reference samples help the individual panelist reproduce his or her feelings correctly and homogeneously in the group. The more accurate the description of the approach and test procedure, and the observed effect, the more homogeneous the statements of the panelists will be.[18]

From my own experience as well as that of various authors, it can be said that, in general, the costs associated with training a cosmetic panel in the pilot phase can be high; about 30 h are necessary to train a panel for 10 attributes[7] up to 100 h for about 20 sensory attributes including olfactory assessments.[6]

### 37.7.3 Reference Samples

The panelists need to be trained once the properties of the product and their sensory impact are sufficiently well defined and representative of the typical profile of a product category. Because the sensorial impressions must always be associated with the same features, the appearance of these features is supported importantly by reference products. This raises the issue of the merit of commercial or specially prepared "sensory libraries."

This brings us to the next challenge, the reference samples. These are used to "calibrate" panelists; no relative product comparison is made but these are the standards against which measurements are conducted. The question arises, how distinctive does the reference attribute need to be in the reference sample? On the one hand, the entire range that might be encountered in future test products, but on the other hand, the discrimination threshold (ability to detect a difference) should not suffer. The reference should be as similar to the products to be tested as possible regarding the absorption characteristics and appearance. Internationally available, marketed products, as detailed in part in ASTM[4,5] have provided a reliable benchmark historically. Standard formulations, which are internally developed and validated by a trained panel, can meet the needs of the panel, provided they conform to sufficiently, detailed physical–rheological data and further requirements such as microbiological safety are ensured.[18]

What is true for the reference samples should also be considered for the test samples. Their application must not jeopardize the panelists and therefore only those ingredients known to be safe may be used. A safety assessment of newly developed products must be completed; any potentially allergenic and/or sensitizing effects from dermal application must be excluded.

### 37.7.4 Notation Method

In the descriptive approach, scales with categories of numbers or words such as easy/medium/hard, can be denoted. Furthermore, horizontal lines with scales between 0 and 10, 0 and 100, or 0 and 15, but without any further markings, can also be used. This has the advantage that the resulting data can be subjected to a wider range of statistical tests.[30] A scale value at the maximum 10, 15, or 100 embodies a strong intensity of the attribute. The scale must be fully used by the panelists. Panelists tend to be reluctant to tick extreme values; reference samples which illustrate the extremes of the scale at both ends as well as at mid-scale avoid such distortions.

### 37.7.5 Statistical Data Analysis

The statistical analysis of sensory data is referred to as "sensometrics." Some issues are so complex that it is worthwhile utilizing the services of a statistician before commencing product testing. Interval or ratio data generated during testing should be checked for frequency. If the generated data is normally distributed, that is, it follows a Gaussian bell distribution, then so-called parametric tests such as the Student's t-test (to compare the means of two samples) and the ANOVA test (analysis of variance; to compare the means of more than two samples) are used to test for significant differences. If the aforementioned data is not normally distributed or is so-called nominal or ordinal data (such as classifying or grouping in discriminating tests like ranking tests), nonparametric tests such as the Wilcoxon test (also called Mann–Whitney-Use test for two samples) or the Friedmann's test (for more than two samples) must be used.[28] In descriptive statistics, values for the mean and median and/or the standard deviations (spread of data) are determined. These describe the study data from a population and can be compared

with each other and checked for differences [International Federation of Societies of Cosmetic Chemists (IFSCC) 1987].[25]

The decision to select a certain sensory-test method to achieve a specific objective, or answer a defined question, results in the definition of a test hypothesis. For example, when the test objective is that two samples are to be recognized as different, the test design will be based on the test hypothesis: "Are the samples different or not?". A so-called "null" hypothesis (usually this is that the samples are identical, or, alternatively phrased, the samples do not differ) differs from an alternative research hypothesis which confirms a statistical difference.[28] It should be noted that the latter is much more expensive!

Whether a difference exists in reality or is just a random error is indicated by the probability of error of the first order, the so-called significance level. This determines with which error probability, for example, the null hypothesis is proven or the alternative hypothesis rejected (Type I and Type II error). The significance level of $\alpha = 0.05$, which is typically required, corresponds to a significance level of 5%. Applied in scientific sensory practice, this level is acceptable to describe a result as "significant." However, this also means that when assessing 20 attributes, an accidental difference may occasionally occur, which is regarded as significant. "High significance" is the result with an error probability of $\alpha = 0.01$, respectively a $p$-value of 1%. If the statistical evaluation determines a difference between the test samples with a probability of error between 5% and 10%, then there is in truth most probably no difference.[30] In such cases, the most that can be described is a "trend." As noted above, this is also dependent on whether the measured data is normally or nonnormally distributed, or resulting from a particular type of scale, and which statistical test methods, such as the t test ("Student's t-test") or the analysis of variance (ANOVA), are used. Depending on the level of significance, a critical limit, or $p$ value must be established. This is compared with the results from the statistical calculation value. If the calculated value is greater than the critical value, the null hypothesis is rejected, that is, the samples are considered significantly different.[28]

The variance of the measurement results within the panel and the standard deviation from the mean are also good indicators of the quality of a panel. The sensory abilities of an individual panelist strongly depend on the number of training hours completed. Motivation through personal feedback and the improvement of results by calibration are indispensable over the entire "development career" of the panelist.

After statistical processing, the data, for example from a descriptive panel, may be displayed graphically. Significance levels for the individual attributes are usually marked with footnotes, as in the network diagram in Fig. 37.3.[24]

Gestures used during sensory evaluation should be as realistic as possible and mimic sequences adopted by cosmetic users to capture a maximum of sensations (see Figs. 37.2 and 37.4).

The standard methods mentioned here provide support for the implementation of a "sensory assessment," yet leave room for interpretation. This makes a direct comparison of results complicated. Busch and Gassenmeier[7] have already confirmed that methods are implemented inconsistently in the development laboratories of several large companies. This is not likely to have changed much since their study. For this reason, the presentation of results in the form of a spider chart is appropriate. In certain cases, the assessment of the attributes is necessary over time. This is especially so in the skinfeel/afterfeel stages. A time–intensity test identifies the change in the product on the skin.

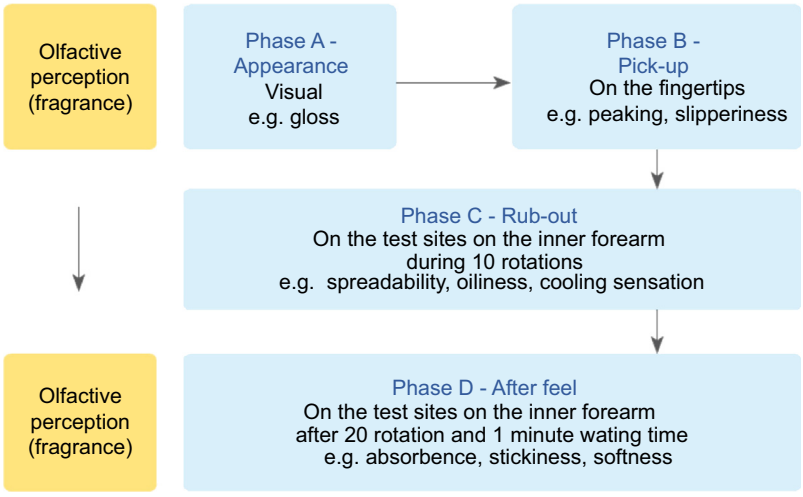



FIGURE 37.4 Sequence of a sensory product assessment according to ASTM[4,5] with examples of attributes (a selection from Huber[19,20]).

# 37.8 FUTURE OUTLOOK

## 37.8.1 Multisensory Approaches

In a manner similar to that used in the food industry, the cosmetics industry is attempting to record the emotional responses of users that occur with application of a product as accurately and objectively as possible. By combining psychological and physiological test methods, spontaneous sensations associated with cognitive processes can be partly decoupled and separately analyzed.[1,13] This requires the correct interpretation of a subject's physiological response. If responses at a cerebral level are included, the interpretation is even more demanding. Changes in response patterns that occur over time, for example, changes that occur because of the aging process, might also need to be evaluated.[15]

In making the transition from a one-dimensional, classical detection of, for example, haptics, smell, color, etc. (a classical sensory approach) to a multisensory, integrative approach, the influence of different sensory systems is captured. In this way, for example, tactile, olfactory, and visual impressions of the product and the packaging could be collected and analyzed simultaneously. This is rather a precise application scenario. For this multimodal recording of sensations, an entire catalog of responses from physiological, psychological, and hedonic test methods will need to be combined with neurological examinations resulting from imaging representations of the brain. Spence and Deroy[40] have studied the influence of music on the enjoyment of food categories and confirmed that the taste, for example, of pasta is particularly fine when enjoyed while listening to Italian classical music. This effect is similar to that already described relating to multimodal influences or other cross-modal effects.

## 37.8.2 Instrumental Data Modeling—Correlation Between Sensory and Measured Instrumental Data

The challenge in detecting sensory impressions is to achieve the appropriate balance between generating the most objective data possible and achieving the highest possible level of standardization, which may be compromised the further removed the test situation is from the actual user situation.[36] A person as an assessor inevitably brings his or her own experiences and inherent biological qualities into this area of tension between subjectivity and attempted objectivity.

An interesting field of research is the correlation between physicochemical properties of raw materials or cosmetic formulations and statistically derived measurements of sensory impressions.[35] If the correlation is significant, such methods of measurement, which can achieve considerable cost savings, can be used as a screening tool or as a quality control measure in the development process. In most cases, only a limited number of attributes can be correlated per assessment method because cosmetic formulations are typically complex, multicomponent systems. Using these techniques, for example, the absorbency of lipids in the skin could be correlated with the polarity and molecular size of the molecules,[39] likewise the spreadability. Quick-dispersing emollients are rapidly absorbed into the skin and have a light skin feel, whereas slow-spreading emollients remain longer on the skin surface and adhere, creating a greasy afterfeel.[14] Some stimuli that affect skin friction also have an impact on sensory properties such as softness, smoothness, and moist skin sensations. Rheological observations provide interesting correlations with product characteristics that occur during the early stages of applying an emulsion. In assessing the sensory properties of a skin cream, there is a correlation between a finger, which acts as a natural sensor similar to an old-style rheometer, the measured spreadability (fluidity), and viscometer values for viscosity and yield point.[19,20,38]

Furthermore, a review of the relationship between the perceived property of "absorbency" in the skin with Raman spectrometric measurements has provided interesting results, which require further detailed examination.[19,21] If nothing else, the work with panelists will benefit if instrumentally measured indicators can be used for sensory prescreening or to supplement the data created by testers. The research in this area is in its infancy.

In summary, it should be noted that the role of sensory science is undisputed in the cosmetic industry and the user market. According to market researchers, "sensory benefits have a high impact on consumer product choice"[10] and the use of descriptors like "texture" and "feel" on products increased from 1.2%, between 2003 and 2008, to 5.3%, from 2008 to 2013.[21,31] Referred to experts, sensory impressions are the new "consumer exciter." Market researchers explore how to enhance the connection between the product and user; they confirm that sensory experimentation is a primary purchase driver in beauty. For the future, they recommend to drive experimentation through multisensory experience including textures and scents, packaging and digital tools.[32] In the future, sensory-testing capabilities need to be enhanced to continue to support the cosmetics industry in its development of competence in sensory

methodology, so that sensory knowledge and understanding can be utilized to create value for both the consumer and the cosmetics industry.

## References


1. Abriat A, Barkat S, Bensafi M, Rouby C, Guillou V. Emotional and psychological effects of fragrance in men's skin care. *Int J Cosmet Sci* 2005; **27**(5):300.
2. Asmussen P. *Die Haut, Auszug aus Compendium medical, Band 1, BDF medical programm*. 1987.
3. ASTM. *Manual of sensory testing method*. Philadelphia: ASTM Special Technical Publication 434; 1968.
4. ASTM. *Standard practice for descriptive skinfeel analysis of creams and lotions E 1490−03*. Annual Book of the American Society for Testing and Materials Standards; 1997/2003.
5. ASTM. *Standard guide for two sensory descriptive analysis approaches for skin, creams and lotions E 1490−11*. Annual Book of the American society for testing and Materials Standards; 1997/2011.
6. Barkat S, Thomas-Danguin T, Bensafi M, Rouby C, Sicard G. Odor and color of cosmetic products: correlations between subjective judgement and autonomous nervous system response. *Int J of Cosmet Sci* 2003;**25**(6).
7. Busch P, Gassenmeier T. Sensory assessment in the cosmetic field. *Parfümerie und Kosmetik* 1997;**78**. Jahrgang, Nr. 7−8.
8. Busch-Stockfisch M. Sensorische Grundlagen, Kapitel 1. In: Busch-Stockfisch M, editor. *Praxis Handbuch Sensorik, 11 07 28*. Hamburg: Behr's Verlag; 2015.
9. Busch-Stockfisch M. Prüferauswahl, Prüferschulung, Prüfermotivation, Kapitel 2. In: Busch-Stockfisch M, editor. *Praxis Handbuch Sensorik, 11 07 28*. Hamburg: Behr's Verlag; 2015.
10. *Datamonitor, Sensory fusion trend sight*. 2011. p. 2011.
11. Derndorfer E. *Lebensmittelsensorik*. 4th ed. Wien: Facultas Verlag; 2012. p. 12−3. 51, 100ff.
12. Eberle U. Ich fühle, also bin ich. In: *Unsere Sinne, Geokompakt, Ausgabe***36**; 2013.
13. Eisfeld W, Schaefer F, Boucsein W, Stolz C. Tracking intersensory properties of cosmetic products via psycho-physiological assessment. *Int J Cosmet Sci* 2005;**27**(5):292.
14. Förster T. *Cosmetic lipids and the skin barrier*. Basel: Marcel Dekker, Inc.; 2002.
15. Freiherr J, Lundström JN, Habel U, Reetz K. Multisensory integration mechanisms during aging. *Front Hum Neurosci* December 13, 2013;**7**:863.
16. Geldard FA, Sherrick CE. Raum, Zeit und Tastsinn. In: *Physiologie der Sinne, in Spektrum der Wissenschaften*. Spektrum, Akademischer Verlag; 1986/1994.
17. Giboreau A. Cosmetics and the 5 senses, perception and description. *SÖFW* 2007;**133**:5.
18. Huber P. Anwendungsgebiete der Sensorik (V); Körperpflege und Kosmetika (Kapitel 2.3): Kosmetische Produkte. In: Busch-Stockfisch M, editor. *Praxishandbuch Sensorik. in der Produktentwicklung und Qualitätssicherung*. Hamburg: Behr's Verlag GmbH & Co. KG; 2015. p. 1−28.
19. Huber P. Sensorial assessments. In: Henning K, editor. *62nd SEPAWA Congress and 11th European Detergents Conference, Event Report, SOFW Journal*, **141**; 2015. 12/15.
20. Huber P. Sensorial assessments − what's going further than your fingertips?. In: *Proceedings, 62nd Sepawa Congress, Fulda*; 2015.
21. Huber P. Sensorik als Wirksamkeitsnachweis − Widerspruch oder Ergänzung?. In: *Proceedings, 6. Fresenius-Kosmetik Tagung, Mainz*; 2015.
22. Huber P. Sensorische «Traumwerte» bei Naturkosmetik. In: *Proceedings, Naturkosmetik Branchenkongress 2013 Berlin*. Naturkosmetik Verlag; 2013.
23. Huber P. *Vehikel und Trägersysteme in kosmetischen Produkten, online academy pnn, FPH-Fortbildungsprogramm in Offizin- und Spitalpharmazie*, Ausgabe 1/2010.
24. Huber P. Sense and sensibility. In: *der Kosmetik − die vielen Unbekannten sensorischer Testungen, Kosmetikjahrbuch SÖFW 2008*. Augsburg: Verlag für chemische Industrie H. Ziolkowsky GmbH; 2008.
25. IFSCC. Principle of product evaluation: objective sensory methods. In: *International Federation of Societies of Cosmetic Chemists IFSCC, IFSCC Monograph, Number 1*. Weymouth (GB): Micelle Press; 2005.
26. Jungman E, Maibach HI. Enhancing sunscreen efficacy for realistic application. *Cosmet Toilet* July 1, 2010.
27. Jütte R. *Klassifikationen: Die Hierarchie der Sinne, aus Robert Jütte: Geschichte der Sinne, München: Beck*. 2000S. 65−83.
28. Kemp S, Hollowood T, Hort J. *Sensory evaluation, a practical handbook*. Wiley Blackwell; 2009. p. 11−9. 25, 31, 66ff.
29. Lendenmann J. «*Markt und Menschen, Dem Apothekenkunden auf der Spur», OTX World, Nor*, **95**; August 2013.
30. Meilgaard MC, Civille GV, Thomas CB. *Sensory evaluation techniques*. 4th ed. CRC Press; 2007.
31. Mintel Global New Products Database (GNPD). *Analysis for product launches in skin care for sensory enablers, performer*. 2014.
32. Möglin E. Experience is all − connecting products with consumers through multi-sensory experiences. In: *Proceedings, in-cosmetics Asia 2015*. Mintel; 2015.
33. Moskowitz H. *Cosmetic product testing: a modern psychophysical approach*. New York: Dekker Vergl.; 1984. 216ff.
34. Parente ME, Ares G, Manzani AV. Application of two consumer profiling techniques to cosmetics emulsions. *J Sens Stud* 2010;**25**:685−705.
35. Parente ME, Gambaro A, Solana G. Study of sensory properties of emollients used in cosmetics and correlation with physicochemical properties. *J Cosmet Sci* 2005.
36. Prinz D. DGK Study group V; Sensory Assessment als verbindendes Tool zwischen Home Use Test und physikalischen Eigenschaften. In: *17.DGK-Symposium*; 2007.
37. Raschke T. Review of actual encapsulation technologies; encapsulation technologies in cosmetics. *SÖFW J* 2003;**4**:73−8.
38. Savary G, Grisel M, Picard C. Impact of emollients on the spreading properties of cosmetic products: a combined sensory and instrumental characterization. *Colloids Surf B: Biointerfaces* 2013;**102**:371−8.
39. Schiemann Y, Wegmann M, Lersch P, Heisler E, Farwick M. Polar emollients in cosmetic formulations enhance the penetration and biological effects of Phytosphingosine on skin. *Colloids Surf A: Physicochem Eng Asp* 2008;**331**:103−7.
40. Spence C, Deroy O. On why music changes what (we think) we taste. *i-Percept* 2013;**4**:137−40.

41. Stone H, Bleibaum NR, Thomas HA. *Sensory evaluation practices*. 4th ed. Elsevier; 2012. p. 5. 8ff.
42. Thews G, Mutschler E, Vaupel P. *Anatomie, Physiologie und Pathophysiologie des Menschen*. Wissenschaftliche Verlagsgesellschaft Stuttgart; 1991.
43. Treibel S. Sensorik im Produktentwicklungsprozess. *SÖFW* 2007:10.
44. Vögelin E. Die Hand als Tastorgan. In: *Unipress 113, Bern*; Juni 2002. p. 29−31.
45. Vollhardt J, Baltussen M, Oosterlinck F. The sensory experience of sunscreens − which properties matter? A descriptive sensory analysis study of more than 50 sunscreens. In: *Proceedings: 12th International Sun Protection Conference/London*; 2013.
46. Voirol E, Roberts D. Influence of colour on the flavour perception of a "Café au lait. In: *4th Pangborn Symposium, Dijon 2001, Poster*; 2001.

CHAPTER

# 38

# Structural Analysis of Formulations

*Y. Yamashita*[1], *K. Sakamoto*[2]

[1]Chiba Institute of Science, Choshi, Japan; [2]Tokyo University of Science, Chiba, Japan

## 38.1 INTRODUCTION

Different types of cosmetic formulations, such as solid, gel, liquid, emulsion, and aerosol, can exist as colloidal dispersion systems. The dispersed-phase particles (or droplets) in such colloidal systems have a diameter of approximately 1−1000 nm; the size of the dispersed phase controls appearance, functionality, tactile impression, and stability. These physical and physiologic effects can be adjusted by formulation even though the components in a cosmetic product are identical. To achieve the desired formulation, the optimal microscopic structure should be constructed from various components in the formulation. For such a project, it is important to select optimal analytical methods to characterize the system. This chapter will focus on various experimental methods to characterize physicochemical properties of the colloidal system—in particular, the microscopic self-assembly structure, and size.

## 38.2 COLLOIDAL DISPERSION SYSTEM

In brief, the thrust of this chapter is to explain colloidal dispersion systems. A basic colloidal system is a system in which one phase is homogeneously dispersed in another phase. Colloidal dispersions can be classified as two principal types; one is "molecular colloid" (lyophilic colloid) or "association colloid", and the other is "dispersed colloid" (lyophobic colloid). Molecular colloids comprise polymer solutions, such as starch and protein, and association colloids which are self-assembled micellar solutions of surfactant molecules. Polymer solutions and association colloids are thermodynamically stable systems that are spontaneously formed in a solvent. On the other hand, lyophobic colloids are thermodynamically unstable but kinetically stable, and these will separate into two phases eventually. Many cosmetic formulations, such as liquid−liquid emulsions and liquid−solid suspensions, are of the latter type.

In general, molecular colloids or association colloids consist of smaller droplets than dispersed colloids, and the dimension of sizes ranges from one to hundreds of nanometers for the association colloid (or molecular colloid), while common dispersed colloids often have dimensions that exceed 1 μm. It is important to understand that different measurement techniques can report different dimensions for the same colloidal system. This is due in part to the fact that most colloids are not monodispersed. Rather, they exist as statistical distributions of particle sizes. Different measurement techniques report different weighted averages of the distribution of particle sizes. Lyophobic colloidal systems are distinguished from solutions by the fact that the homogeneously dispersed phase consists of particles that are essentially insoluble in the continuous phase. On the contrary, for a solution, the solute is soluble in the continuous solvent phase. In the case of colloids, the dispersed phase and the continuous phase can be gas, liquid, solid states, and even a liquid crystal state. Generally, colloidal cosmetic products are categorized by these phase states (Fig. 38.1). Typically, such cosmetic products consist of oil (oil phase) and water (aqueous phase), namely being a liquid−liquid dispersion system. When one liquid is dispersed in another liquid, the dispersion system can be called either a "lotion" or an "emulsion."

*Cosmetic Science and Technology: Theoretical Principles and Applications*
http://dx.doi.org/10.1016/B978-0-12-802005-0.00038-0



Copyright © 2017 Elsevier Inc. All rights reserved.

| Dispersed Phase \ Continuous Phase | Gas | Liquid | Solid |
|---|---|---|---|
| Gas | None | (Foam) Hair mousse, Shave foam  | (Xerogel) Sponge, Styrofoam, Silica gel  |
| Liquid | (Aerosol) Hair spray  | (Emulsion) Cream, Lotion  | (Gel) Pomade, Food gelatin,   |
| Solid | (Aerosol) Powdery Spray  | (Suspension) Nail enamel, Foundation  | (Solid colloid) Colored glass  |

FIGURE 38.1 Various cosmetics consisting of colloidal dispersed systems.[1]

## 38.3 CHARACTERIZATION OF COLLOIDS

Table 38.1 lists various techniques that are used to characterize the size, structure, and structure of the discontinuous phase of colloids. Commonly, there are roughly three categories: atomic or molecular level (less than 1 nm), aggregate level (1 nm to hundreds of nanometers), and dispersion level (greater than 1 μm). This classification is not rigid since a few polymer molecules and association colloids can exceed 1 μm, and lyophobic colloids having nanometer particle sizes can now be prepared. Since evaluation methods at the molecular level are specifically described elsewhere in this book, this chapter will concentrate on the principles and applications of experimental methods for *soft* colloidal objects with sizes from 1 nm to 1 μm—that is, *micelles*, *liquid crystals*, and *emulsions*.

## 38.4 MICELLES

Surfactants form micelles only when they reach the a critical concentration, called the critical micelle concentration (CMC). (See Chapter 3 for a more complete description of the cause of micelle formation.) The CMC is a thermodynamically controlled variable. The importance of the CMC derives from the fact that solubilization of oils and fats occurs only above the CMC. Fig. 38.2 illustrates the changes in various physicochemical properties as a function of the surfactant concentration, and all of the properties show break points around the CMC. The CMC can be determined by measuring the abrupt change in these physical properties.

A common method to identify the CMC is the surface tension method. The defining characteristic of surfactants is their ability to lower surface tension at the air−water interface. Surface tension results from an imbalance in intermolecular forces at the surface of a liquid. There are also other methods to identify the presence of micelle in a solution, such as light scattering,[2] nuclear magnetic resonance,[3] and fluorescent probe spectroscopy[4] (Table 38.1). To determine the CMC, any specific parameters obtained by every method have to be expressed as a function of the surfactant concentration.[5]

The size of micelles depends on the geometric packing of the molecules in the micellar aggregate. (See the discussion on packing factor in Chapter 3.) Surfactant micelles adopt different shapes depending on the concentration of

**TABLE 38.1** Evaluation Methods of the Structure and Properties of Soft Colloidal Systems

| Properties | Colloid Type | Method and Apparatus |
|---|---|---|
| Size, shape, morphology | Micelle microemulsion | • Static/dynamic light scattering (SLS/DLS)<br>• Small angle X-ray/neutron scattering (SAXS/SANS)<br>• Nuclear magnetic resonance (PGSE-NMR)<br>• Transmission electron microscopy (TEM)<br>• Rheology |
| | Liquid crystal gel | • SAXS/SANS<br>• Polarized optical microscopy<br>• NMR<br>• TEM<br>• Rheology<br>• Staining method<br>• Phase study |
| | Emulsion | • Optical microscopy (visible light)<br>• Laser diffraction<br>• DLS<br>• Differential scanning calorimetry (DSC)<br>• TEM/scanning electron microscopy (SEM)<br>• Rheology<br>• PGSE-NMR |
| Interfacial structure | Micelle emulsion | • Zeta potential<br>• Fluorescence<br>• Electron spin resonance (ESR)<br>• NMR<br>• Wide X-ray scattering (WAXS)<br>• Interfacial rheology<br>• SEM, TEM |
| Micelle formation | | • Surface (interfacial) tension (pendant drop method, spinning drop method, Wilhelmy plate method, du Nouy ring method, bubble pressure method, etc.)<br>• Electric conductivity<br>• NMR<br>• Fluorescence<br>• Light scattering |

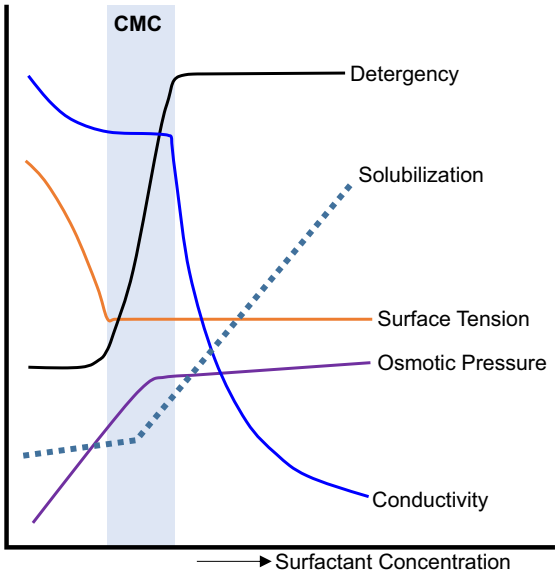



**FIGURE 38.2** Changes in various properties as a function of surfactant concentration. Many properties show the break point at CMC.

the surfactant and the presence of other components in the system. Although micelles are thermodynamically stable, the surfactant molecules are constantly exchanging between the micelles and solution. The rate of exchange is characteristic of the system. In general, the larger the micelle, the slower is the exchange rate.

### 38.4.1 Microscopy

As shown in Table 38.1, many methods are available to measure the size and shape of colloidal aggregates, while some have to be carefully selected according to the mesoscopic scale and internal structure of a colloidal droplet. A typical example is the microscope. Optical microscopy is usually not suitable for detecting and examining micelles because the scale of simple micelles is on the order of nanometers and this is below the resolution of optical microscopy. However, light microscopy can be used to observe colloidal particles and emulsion droplets around 1 μm in size. Thus, the scale of what you want to observe is the most important and may be presumed from the visual observation of a formulation.

The *transmission electron microscopy* (TEM) is one tool that can be used to elucidate the size and shape of micelles and offers a higher resolution than the *scanning electron microscopy* (SEM), typically being able to resolve 1-nm features. On the other hand, TEM cannot be used to observe the intact liquid state because of generation of the electron beam under a high vacuum condition, and therefore, a liquid sample should be pretreated via various methods such as the negatively staining method, freeze fracture method (FF-TEM), and cryofixation method (cryo-TEM). For the negatively staining method, the sample solution has to be stained by a staining agent such as uranyl acetate or phosphotungstic acid, because the electron density contrast of the soft colloidal solutions is insufficient to observe the structure. This method is used to examine sections of biological materials like the cell membrane and stratum corneum[6] and sometimes is applied to the observation of liposomes.[7] However, the addition of the staining agent to the sample and the drying process involved in this method are not always suitable for observing a precise structure of aggregate.

The latter two methods are often used to evaluate the aggregate structures of soft materials such as micelles, liquid crystals, and emulsions. In the preparation processes of both methods as shown in Fig. 38.3,[8] the sample is rapidly frozen with liquid propane or liquid ethane. In the case of FF-TEM, the sample is fractured by using a microtome at liquid nitrogen temperature (−150 to −120°C) and under high vacuum condition ($\sim 10^{-5}$ Pa), and then a replica coat of the fractured surface is prepared via evaporation of platinum and carbon. Therefore, FF-TEM can demonstrate only the structure of the fractured plane, excluding information on the entire aggregate. On the other hand, cryo-TEM does not require additional pretreatment after cryofixation, and the sample is directly transferred to the microscope apparatus under liquid nitrogen atmosphere. The aggregates are embedded in amorphous ice, and thus cryo-TEM would provide accurate information on the aggregate structure, being the most reliable optical

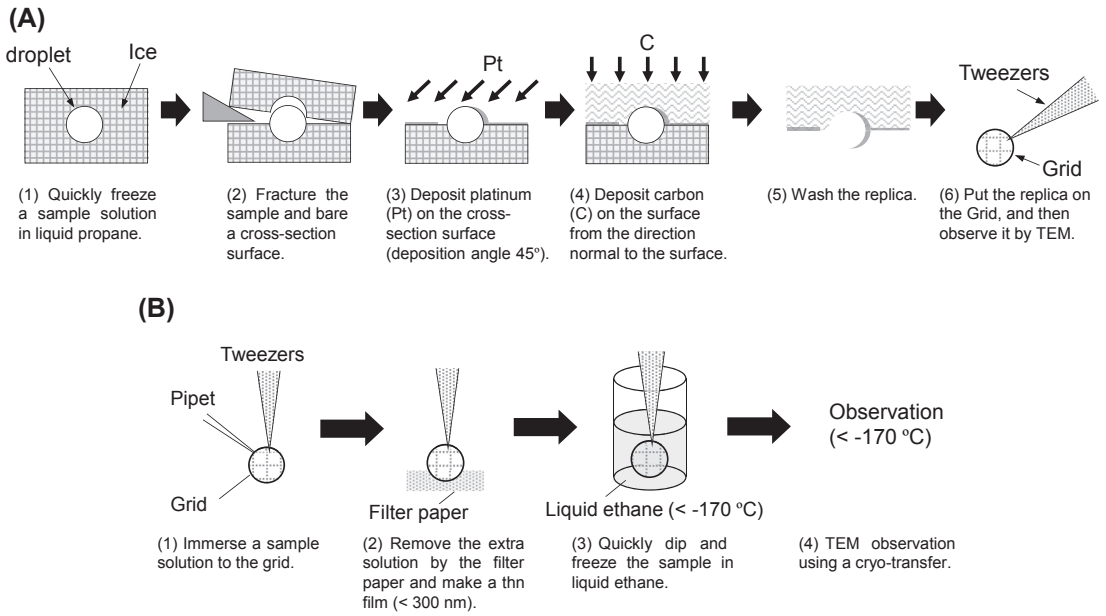



**FIGURE 38.3** Sample preparation procedure of (A) FF-TEM and (B) cryo-TEM.[8]

method at present. However, cryo-TEM is a technique that requires considerable practice and experience to distinguish fact from artifact.

## 38.4.2 Scattering Methods

Visible light, X-ray, and neutron diffraction are generally used to obtain structural information such as size, shape, internal structure, and interfacial roughness, and all use wave interference diffraction. The effective interference effect specifies a relationship between the absolute scattering vector $q$ ($4\pi\sin\theta/\lambda$) and micelle size, such as the structure of a cylindrical micelle with a short axis $d$ and a long axis $L$ has to be evaluated in the range of $1/L < q < 2\pi/d$, which would be attained by selecting the appropriate wavelength ($\lambda$) and scattering angle ($2\theta$). Table 38.2 shows the typical $\lambda$, measurable $2\theta$, and $q^{-1}$ ranges for the various scattering methods.[9] Note that the size range measurable by each method is limited, and small angle techniques may be necessary to measure the dimensions of colloid particles.

### *38.4.2.1 Light Scattering*

Light scattering of solutions measures the fluctuations in optical density that arise from thermal motion of solvent molecules and solute particles or from the differences in refractive index between solvent and polymer or micellar solutes. Modern light scattering methods generally use a He-Ne laser (632.8 nm) or argon laser (e.g., 488 nm). There are two different light scattering techniques: *static light scattering* (*SLS*) and *dynamic light scattering* (*DLS*). The former provides information on the droplet size and shape and molecular weight of micelles. In addition, SLS can be used to measure a relatively large dimension (approximately hundreds of nanometers), being useful for analyzing the hierarchical structure of a polymer.[10] In SLS, the intensity of elastically scattered light is measured as a function of scattering angle $\theta$. When the aggregates are much smaller than the wavelength, $d \ll \lambda$ (usually taken to be $d < \lambda/20$), the theory of so-called Rayleigh scattering is applicable for the analysis of scattering. Here, the scattered intensity ($I_\theta$) is different in the forward and back scattering directions (e.g., difference at 45 and 135 degree), and the ratio $I_{45}/I_{135}$ would relate to the particle size. The angular variation of $I_\theta$ can also provide information on the particle shape. Further, the association number of micelles can be determined by the intensity at $q = 0$, which is simply correlated to the root mean square of concentration fluctuation; therefore, SLS is a suitable method to determine the association number of micelles because the $q$ range is much smaller than those in the X-ray and neutron-ray scattering methods (Table 38.2). For this measurement, two theoretical treatments derive from the two prominent theories, and equations thus derived are given as follows[11,12]:

$$\text{Debye} \quad \frac{Kc}{R(\theta)} = \frac{1}{M_w} + 2A_2 \cdot c + \cdots \tag{38.1}$$

$$\text{Zimm Plot:} \quad \frac{Kc}{R(\theta)} = \frac{1}{M_w}\left(1 + \frac{1}{3}\left\langle R_g^2 \right\rangle q^2 + \cdots\right) + 2A_2 \cdot c + \cdots \tag{38.2}$$

where $K$ is the optical constant, $c$ is the concentration of solute, $R(\theta)$ is the reduced scattering intensity, $M_W$ is the weight-averaged molecular weight, $R_g$ is the radius of gyration, and $A_2$ is the second virial coefficient (the detailed explanation of these equation and parameters will be found elsewhere). The Debye plot is applied when the micelle size is sufficiently smaller than $\lambda$, typically $\lambda/20$, and the Zimm plot is used for larger micelles because the interference effect with angular dependency is not negligible. Therefore, the equation can be expressed as functions of $c$ and $q$ for the Zimm plot. The actual experimental plots of $Kc/R(\theta)$ versus $c$ or $q$ provide some physicochemical parameters, $A_2$, $R_g$, as well as $M_W$ of micelle.

DLS, on the other hand, measures the hydrodynamic volume of micelles. The principle is essentially different from that of SLS. DLS measures the temporal fluctuations of the intensity of scattered light. The number of photons

**TABLE 38.2** General $q^{-1}$ Ranges Measurable by Each Scattering Method[9]

| Light Scattering | Scattering Body | $\lambda$ (nm) | $2\theta$ (Degrees) | $q^{-1}$ (nm) |
|---|---|---|---|---|
| | | 400–500 | 20–150 | 30–200 |
| SANS | Neutron | 0.5–1.2 | 0.5–20 | 0.2–20 |
| SAXS | Electron | 0.15 (CuKa ray) | 0.2–7 | 0.2–7 |

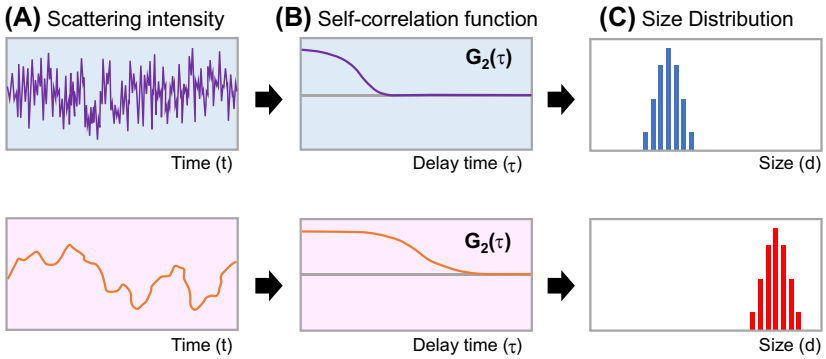



FIGURE 38.4 Schematic DLS data on (A) scattering intensity, (B) self-diffusion function, and (C) size distribution.[13] The scattering intensity sharply fluctuates with time for a small droplet (upper figure), whereby the self-correlation function steeply decreases. As the result of the fast relaxation mode, the smaller size distribution is obtained. For the larger droplet (bottom figure), their tendencies are of contrast.

entering a detector are recorded and analyzed by a digital correlator. The autocorrelation function of the intensity at an angle $\theta$ can be analyzed to yield the distribution of relaxation times. The autocorrelation function (secondary autocorrelation), $G_2(\tau)$ at a delay time ($\tau$) can be expressed as follows:

$$G_2(\tau) = \frac{\langle I(t)I(t+\tau)\rangle}{\langle I(t)\rangle^2} = 1 + \beta[G_1(\tau)]^2 \tag{38.3}$$

where $I(t)$ and $I(t+\tau)$ are the intensities at a given time ($t$) and $t+\tau$, respectively. The parameter $\beta$ is a correction factor depending on equipment. Fig. 38.4 shows a schematic example of the DLS measurement for a small or large micelle.[13] The smaller micelle exhibits very sharp intensity fluctuation, suggesting the faster Brownian motion is present. The $G_2(\tau)$ curve is obtained from the temporal intensity data and fitted by the following equation:

$$G_1(\tau) = \exp\left(-Dq^2\tau\right) \tag{38.4}$$

The decay rates of the relaxation modes provide translational diffusion coefficients of the micelles ($D$), and the $G_2(\tau)$ curve brings a number of $D$ values via a multinomial equation instead of Eq. (38.4). The hydrodynamic diameter of micelle ($d$) and size distribution are calculated from the $D$ values by using the Einstein–Stokes equation Eq. (38.5):

$$d = \frac{k_B T}{3\pi\eta D} \tag{38.5}$$

$k_B$ is the Boltzmann constant, $T$ is the absolute temperature, and $\eta$ is the viscosity of solvent. It should be noted that DLS provides only primitive data on the micelle size and does not take into account the shape.

### 38.4.2.2 *X-ray and Neutron Scattering*

Because X-ray and neutron beams have much smaller λ values than light (Table 38.2), their scattering experiments can be used to probe smaller features. The scattering species are the atomic electrons for X-ray and the atomic nuclei for neutron scattering. These scattering measurements for colloidal materials are carried out at small angles, typically less than $2\theta \sim 10$ degree, because the dimension of colloidal objects ranges from a few to tens of nanometers. Thus, the scattering measurement at small angles is commonly called *small angle X-ray scattering (SAXS)* or *small angle neutron scattering* (*SANS)*. In contrast, *wide angle X-ray scattering (WAXS)* means an X-ray scattering measurement at larger angles.

The small-angle region can be divided mainly into three parts in terms of the structural information obtainable from a dilute solution system (Fig. 38.5).[14] $I(q)$ in the Guinier region (Region I) relates to the "size" of micelle, which can be calculated as the radius of gyration by the Guinier approximation $\left(I(q) \propto \exp\left(-q^2R_g^2/3\right)\right)$.[15] In general, this approximation holds when $q < 1/R_g$. Region II, which corresponds to the slightly higher $q$ range than the Guinier region, expresses "shape" of micelle, being estimated by the power law. The slope in the double logarithm plot of $I(q)$ and $q$ indicate the shape: $q^{-4}$ for sphere, $q^{-2}$ for disk, $q^{-1}$ for rod. Region III is referred to surface configuration and also would be related to surface fractal dimension. The surface configuration can be expressed using the

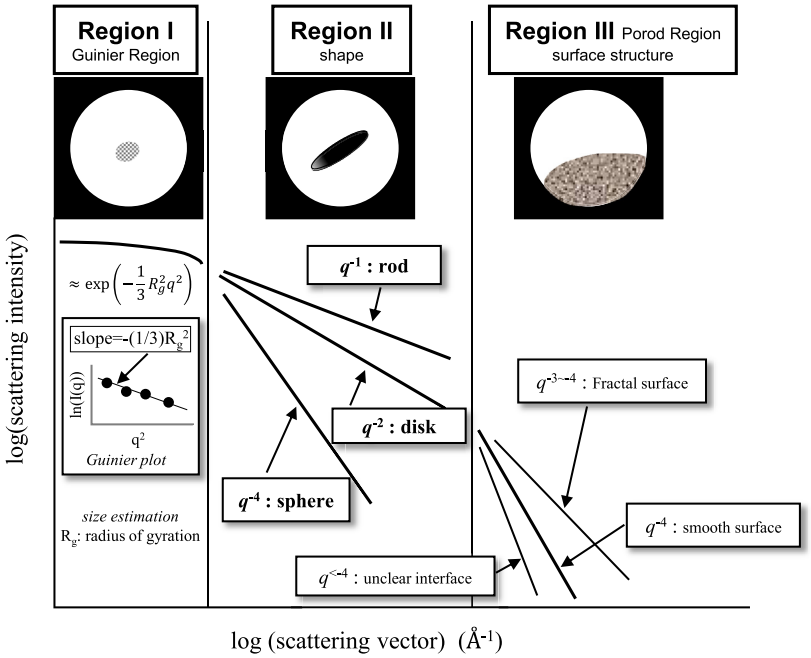



**FIGURE 38.5** Three $q$-regions in small-angle scattering data.[14]

equation, $I(q) \propto q^{-d}$ in the relatively higher $q$ range. When the micelle has a smooth surface and homogeneous distribution of electron density over the surface, the intensity $I(q)$ is proportional to $q^{-4}$. This is called the Porod rule.[16] The fractal dimension ($d_S$) equals $6 - d$, namely $d_S = 2$ for the smooth surface. When the surface becomes rough, $d_S$ approaches 3. Further, the diffuse interface of the colloidal object can have a smaller exponent of power law, $d < 4$.

On the other hand, SAXS or SANS analysis cannot be applied to practical systems at higher surfactant concentrations due to multiple coherent scattering between adjacent micelles. The coherent scattering effect can be called *structure factor* [$S(q)$], and the influence of $S(q)$ on the total scattering intensity $I(q)$ cannot be ignored even at 1 wt% of a nonionic surfactant. $I(q)$ is simply expressed as the product of the form factor $P(q)$ and $S(q)$ [more correctly $I(q) = nP(q)S(q)$, $n =$ number density of particle],[17] and therefore it should be essential to independently estimate $P(q)$ and $S(q)$. Recently, Glatter et al.[18–20] developed a new analytical method, *generalized indirect Fourier transformation* (*GIFT*), to exclude the bias and ambiguity that are inevitable for conventional SAXS researches. This method calculates $P(q)$ and $S(q)$ without any models, providing important information on size, shape, internal structure, polydispersity, interaction radius, and so on, from analysis of $P(q)$ and $S(q)$.

### 38.4.3 Pulsed-Gradient Spin-Echo Nuclear Magnetic Resonance

*Pulsed-gradient spin-echo nuclear magnetic resonance* (*PGSE-NMR*) can measure the self-diffusion coefficients ($D$) of selected components in solution, and it is one of practical methods to study micelle size and microstructure. In principle, the surfactant molecules are present both in the monodispersed state and in the micellar state, and the average $D$ can be defined as follows:

$$D = P \cdot D_1 + (1 - P) \cdot D_2 \tag{38.6}$$

where $D_1$ and $D_2$ are the self-diffusion coefficients of the micellized surfactant molecules and the monodispersed ones, respectively, and $P$ is the fraction of the micellized surfactant molecules in the total. In general, surfactants with longer hydrophobic chains have very low CMC values and $D$ approximately corresponds to $D_1$; this allows the hydrodynamic diameter ($d$) to be calculated from Eq. (38.5). The monodispersed molecules show a faster self-diffusion ($D_s$) than the micelle ($D_{mic}$); typically, $D_s$ and $D_{mic}$ are in the orders of $10^{-9}$ and $10^{-11}$ m$^2$/s, respectively.[21] However, $D_1$ and $D_2$ have to be separately interpreted when solvent-enhanced solubility of the surfactant with substances such as alcohol and oil is used. Also, it must be considered that the lateral diffusion within the micelle becomes dominant in a larger micelle such as worm-like micelle and bicontinuous micelle (sponge phase).

In a comparison with the other methods, PGSE-NMR can evaluate not only the surfactant but also the other constituents such as water and oil and therefore is very useful for various surfactant systems, since the measurements

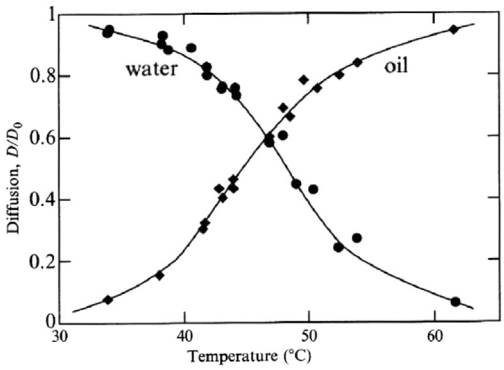



FIGURE 38.6 Changes in the relative self-diffusion coefficients ($D/D_0$) of water (●) and oil (◆) with temperature in a nonionic surfactant/water/oil system.[22] As temperature is increased through the microemulsion channel of a nonionic system, water diffusion is reduced from high to very low values, while the opposite applies to oil. The higher diffusions of both water and oil around 45°C are coincident with formation of the microemulsion phase.

are accurate and require essentially no assumptions. Microemulsions consisting of surfactants, water, and oil are representative examples. Fig. 38.6 shows the change in the relative self-diffusion coefficient ($D/D_0$) with temperature in a nonionic surfactant/water/oil system,[22] where an oil-in-water (O/W) emulsion transforms into an water-in-oil (W/O) emulsion via a bicontinuous microemulsion with increasing temperature(see Chapter 33, Emulsion and Emulsification Technology). The $D$ values of water and oil molecules strongly depend on the microstructures, and the O/W droplet structure with the discrete oil domain in water has an oil diffusion that is much slower than that of water, while water has a $D$ value of the same order of magnitude as that of pure water. At intermediate temperatures in Fig. 38.6, $D/D_0$ values of both solvents are high, which gives evidence for a bicontinuous microstructure (i.e., with both oil and water domains being connected). Based on these diffusion properties, the *staining method* is used to qualitatively identify continuity of the microstructure by using both water- and oil-soluble dyes.[23,24]

### 38.4.4 Rheology

Rheology plays a significant role in understanding tactile sensory attributes, which can be key properties for cosmetic products. The flow properties are important in most cosmetic applications of surfactant solutions as well as polymer solutions. Rheology deals with how materials respond to deformation, and the response will be varied depending on experimental conditions. Thus, rheology is not an easy subject, and experiments that give relevant information need to be carefully designed, especially for complex systems with viscoelasticity.

First, we have to acknowledge what types of liquids are present and can be distinguished in terms of their rheological features. Colloidal solutions can be divided into simple Newtonian fluids and non-Newtonian fluids. Newtonian fluids are characterized by a constant viscosity ($\eta$) while changing the shear rate, and the relationship of shear rate ($\dot{\gamma}$)—stress ($\sigma$) should be linear as shown in Fig. 38.7, where the slope corresponds to $\eta$. Newtonian behavior can be observed in simple liquids such as water ($\eta = 10^{-3}$ Pa s), glycerol ($10^{0}$ Pa s), and olive oil ($10^{-1}$ Pa s), which may

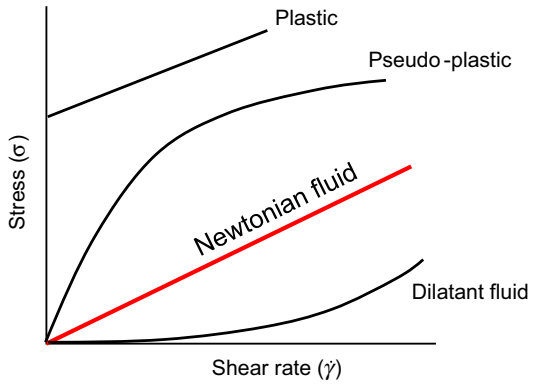



FIGURE 38.7 Schematic representation of Newtonian and non-Newtonian flow behaviors. The Newtonian fluid shows a linear relation between the shear rate ($\dot{\gamma}$) and shear stress ($\sigma$), while the non-Newtonian ones have non-linear dependencies of the shear stress on the shear rate.

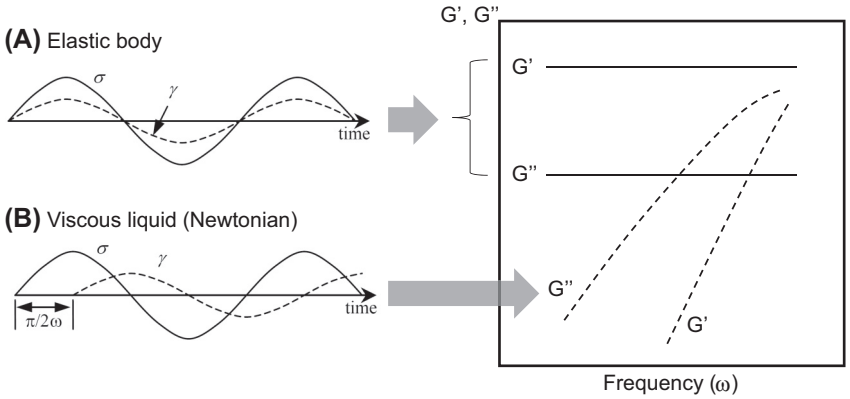



FIGURE 38.8 Phase difference between stress (σ) and strain (γ) for (A) an elastic body and (B) a viscous liquid (left figure). The corresponding rheograms of G′ and G″ as a function of frequency (ω) are shown on the right side: the elastic body (solid line) and viscous liquid (dotted line).

have only frictional obstruction against shear flow. Systems with a lower-volume fraction of micelles ($\phi_s$) exhibit Newtonian behavior but the rheology gradually changes to non-Newtonian behavior with increasing surfactant concentration. This can result from micelle growth from spherical to cylinder or worm-like morphology in addition to the increasing $\phi_s$. If the structure of spherical micelles remains unchanged, the relative viscosity $\eta/\eta_0$ can be expressed as a function of $\phi_s$ by Einstein's equation.[25]

Einstein showed that for a solution of spherical particles dispersed in a liquid medium (see Chapter 3), the relative viscosity was related to the volume fraction of spheres, $\phi_s$, by the relationship:

$$\eta/\eta_0 = 1 + 2.5\phi_s \tag{38.7}$$

where $\eta$ is the solution viscosity, and $\eta_0$ is the viscosity of solvent.

This equation is applicable only for hard, spherical, and noninteractive particles.

As seen in Fig. 38.7, there are different types of non-Newtonian fluids with different responses to deformation. Fig. 38.7 depicts $\dot{\gamma}-\sigma$ rheograms (static measurement), for Newtonian, plastic, pseudo-plastic, and dilatant fluids. For a pseudo-plastic system, $\eta$ decreases with increasing shear rate, called *shear-thinning*. Many cosmetic products are shear-thinning systems, for example, tooth paste and shampoo, which exhibit increased ease of flow upon application of a shear force, and the system will recover to the original state once the shear force is released. The shear thinning phenomenon is often observed in viscoelastic systems having internal structures such as entangled polymers (or worm-like micelles) or closely packed aggregates (see Chapter 32 Rheology of Cosmetic Formulations). In contrast to shear thinning, dilatant systems show shear-thickening behavior; the apparent viscosity increases with increasing shear rate. The mechanism is considered to arise from agglomeration of the colloidal particles under shear flow. A plastic liquid is characterized by a finite yield value (i.e., a minimal yield stress needed before it starts to flow). The yield stress is defined as the intercept of the flow curve. Real systems are often complex combinations of these three basic rheology types.

Besides the static measurement just described, dynamic experiments can be performed to obtain further information on the viscoelastic behavior of an aggregate system. Oscillatory measurement enables discernment of the elastic and viscous components of a viscoelastic fluid This measurement measures the phase shift (δ) between stress (σ) and strain (γ) when a sinusoidal deformation at a frequency (ω) is applied to the solution. For a viscous liquid, σ is maximum at $\gamma = 0$, meaning that σ is out-of-phase with respect to the deformation and the phase angle is 90 degree (Fig. 38.8A). For an elastic body, on the other hand, σ is maximum at the maximum γ, meaning that σ varies in phase with the deformation; that is, the phase angle $\delta = 0$ degree (Fig. 38.8B). A viscoelastic liquid can be characterized using these two components: out-of-phase (viscous component) and in-phase (elastic component), often called loss modulus ($G''$) and storage modulus ($G'$), respectively. Fig. 38.8 demonstrates schematic rheograms of the oscillatory measurements for a viscous liquid and an elastic liquid.

In practice, the rheological measurements provide indirect information on the structure of micelles, but additional structural properties such as persistent length of cylindrical micelles can be obtained by theoretical analyses of the rheogram. Many theories of rheology in the surfactant systems have been established based mainly on the polymer systems.[26] These theories allow fundamental analysis of micelle and liquid crystal systems. More information on this subject can be found in Chapter 32, Rheology of Cosmetic Formulations.

## 38.5 LIQUID CRYSTALS

In the nineteenth century, a new state of matter, liquid crystal, was discovered and it was descried as being structured in more dimensions than a liquid but in fewer dimensions than a crystalline solid. (see Chapter 24, Molecular Structure and Phase Behavior of Surfactants). Liquid crystals have intermediate properties of both solid (crystal) and liquid, and the degree of order is exactly intermediate between the molecular disorder of a liquid and the regular structure of a crystal. The most important property of liquid crystal phases is that the molecules have long-range orientational order.

Liquid crystals fall roughly into two categories: thermotropic and lyotropic series. Thermotropic liquid crystals have been widely used in industrial applications, particularly in liquid crystal displays. On the other hand, lyotropic liquid crystals have been used for life chemical products because amphiphiles, such as the component molecules of cell membranes, self-assemble into liquid crystals. These two type of liquid crystals show, in principle, the same physicochemical properties except for specific electrochemical phenomena, and the structural information for liquid crystals can be obtained via experimental methods.

### 38.5.1 Polarized Optical Microscope

Surfactant solutions form various assembly structures, including some birefringent liquid crystals. Birefringence of the liquid crystals can be macroscopically detected by viewing a sample between two crossed polarizing plates (polarizer and analyzer). A liquid crystal with birefringence exhibits brightness under polarization, and then simple observation of the shapes of the polarized light patterns (focal conics) gives preliminary information on the liquid crystal structure. By using a polarized microscope, the type of liquid crystal can be determined, since each liquid crystal possesses a characteristic texture when viewed in polarized light under a microscope. These textures or birefringences result mainly from structural anisotropy of the surfactant assembly. Representative liquid crystals with birefringence are hexagonal ($H_1$) and lamellar ($L_\alpha$) liquid crystals, showing different textures as seen in Fig. 38.9.[24] On the contrary, there exist optically isotropic liquid crystals such as cubic liquid crystals that do not exhibit any texture in the microscopic observation, but its isotropic feature is evidence for the presence of cubic liquid crystals. However, the type of the cubic liquid crystal, discontinuous type ($I_1$) and bicontinuous type ($V_1$), would be hardly distinguished by the polarized microscope, and thus TEM observation, SAXS measurement, PGSE-NMR measurement, or phase study (location of liquid crystal) is generally required.

### 38.5.2 Small Angle X-ray Scattering

To identify liquid crystal structures and obtain the structural parameters, SAXS is the most optimal method. X-ray waves are diffracted by specific planes that are characteristic of the particular Miller indices ($h$, $k$, $l$) in the Bravais lattice (Fig. 38.10) of a liquid crystal. Constructive interference takes place, and a scattering peak is observed in the case of a satisfactory Bragg's condition,[27] given by:

$$2d \sin\theta = n\lambda \tag{38.8}$$

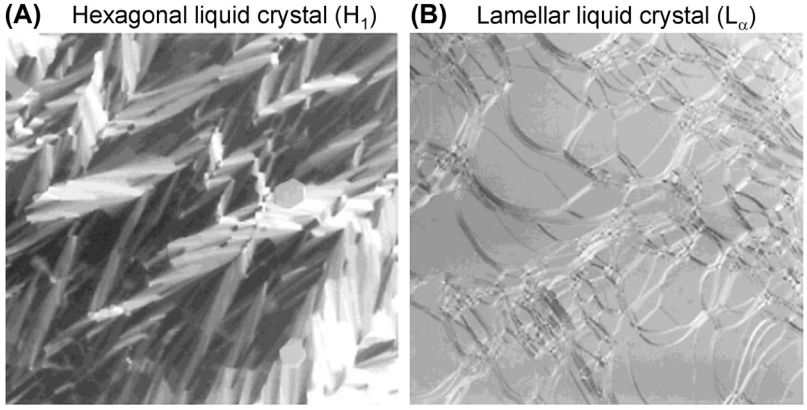



**FIGURE 38.9** Polarized micrographs of hexagonal and lamellar liquid crystals.[24]

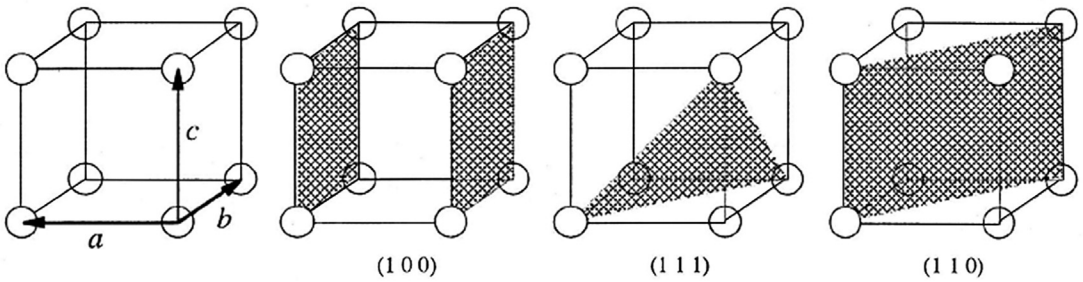



FIGURE 38.10 Miller indices in Bravais lattice.

where λ is the wavelength of X-ray, $\theta$ is the angle of incidence, $d$ is the interlayer spacing in a liquid crystal, and $n$ is the order of reflection. Miller indices and the interlayer spacing ($d$) of the lattice plane are correlated by the lattice parameter ($a$), which can be expressed by the following equation:

$$\frac{1}{d^2} = \frac{h^2 + k^2 + l^2}{a^2} \tag{38.9}$$

$$(\mathrm{L}_\alpha \text{ phase}) \quad d_1 : d_2 : d_3 : \cdots = 1 : \frac{1}{2} : \frac{1}{3} : \cdots$$

$$(\mathrm{H}_1 \text{ phase}) \quad d_1 : d_2 : d_3 : \cdots = 1 : \frac{1}{\sqrt{3}} : \frac{1}{\sqrt{4}} : \cdots$$

The peak intensity for a liquid crystal system decays with increase in the order of reflection because the structures of liquid crystals have the long-range periodicity but lose the order in the short range. Therefore, only a few scattering peaks are generally observed in the liquid crystal systems (Fig. 38.11).[28] The peak ratio is important to determine the type of liquid crystal because of the intrinsic symmetry. The peak ratios corresponding to $\mathrm{L}_\alpha$ and $\mathrm{H}_1$ (or $\mathrm{H}_2$) are shown in Fig. 38.11.

For cubic liquid crystals, the peak ratio is also defined by Eq. (38.9), but it cannot be unity, unlike $\mathrm{L}_\alpha$ and $\mathrm{H}_1$, due to the three-dimensional periodic structure. Crystal and cubic liquid crystals are classified in approximately 230 kinds of crystal lattices with different symmetries, called space groups. The space group is determined by the extinction rule, which states that the characteristic reflections do not occur in the case of translating symmetry element present in a complex lattice or crystal lattice. However, it is impossible in reality to determine a space group accurately because the same extinction rule is applied even for different space groups. The theoretical Miller indices and the space group are shown in Table 38.3, in which the cubic liquid crystals belonging to each space group are denoted by the marked Miller indices (●).[29]

Using the interlayer spacing ($d$) and the composition of the system (volume fraction of the surfactant), the micelle dimension of the liquid crystal ($r$) and the effective cross-sectional area per surfactant molecule at the water−micelle interface ($a_s$) can be calculated under the hypothesis that all surfactant molecules are arranged in a specific geometric

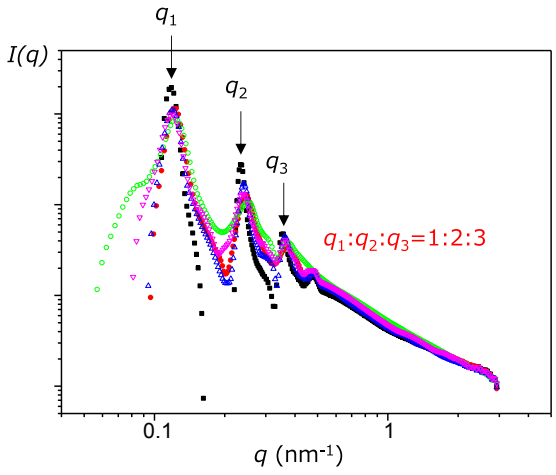



FIGURE 38.11 Representative SAXS spectra of lamellar liquid crystal.[28]

TABLE 38.3 Space Group and Miller Indices[29]

| h | k | l | s | s^(1/2) | Space group | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Pm3m | Pn3m | Pm3n | Pn3n | Im3m | Ia3d | Fm3m | Fd3m | Fm3c | Fd3c |
| 1 | 0 | 0 | 1 | 1 | ● | | | | | | | | | |
| 1 | 1 | 0 | 2 | 1.414214 | ● | ● | ● | ● | ● | | | | | |
| 1 | 1 | 1 | 3 | 1.732051 | ● | ● | | | | | ● | ● | | |
| 2 | 0 | 0 | 4 | 2 | ● | ● | ● | ● | ● | | ● | | ● | |
| 2 | 1 | 0 | 5 | 2.236068 | ● | | ● | | | | | | | |
| 2 | 1 | 1 | 6 | 2.44949 | ● | ● | ● | ● | ● | ● | | | | |
| 2 | 2 | 0 | 8 | 2.828427 | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● |
| 3 | 0 | 0 | 9 | 3 | ● | | | | | | | | | |
| 2 | 2 | 1 | 9 | 3 | ● | ● | | | | | | | | |
| 3 | 1 | 0 | 10 | 3.162278 | ● | ● | ● | ● | ● | | | | | |
| 3 | 1 | 1 | 11 | 3.316625 | ● | ● | | | | | ● | ● | | |
| 2 | 2 | 2 | 12 | 3.464102 | ● | ● | ● | ● | ● | | ● | ● | ● | ● |
| 3 | 2 | 0 | 13 | 3.605551 | ● | | ● | | | | | | | |
| 3 | 2 | 1 | 14 | 3.741657 | ● | ● | ● | ● | ● | ● | | | | |
| 4 | 0 | 0 | 16 | 4 | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● |
| 4 | 1 | 0 | 17 | 4.123106 | ● | | ● | | | | | | | |
| 3 | 2 | 2 | 17 | 4.123106 | ● | ● | | | | | | | | |
| 4 | 1 | 1 | 18 | 4.242641 | ● | ● | ● | ● | ● | | | | | |
| 3 | 3 | 0 | 18 | 4.242641 | ● | ● | ● | ● | ● | | | | | |
| 3 | 3 | 1 | 19 | 4.358899 | ● | ● | | | | | ● | ● | | |
| 4 | 2 | 0 | 20 | 4.472136 | ● | ● | ● | ● | ● | ● | ● | | ● | |
| 4 | 2 | 1 | 21 | 4.582576 | ● | ● | ● | ● | | | | | | |
| 3 | 3 | 2 | 22 | 4.690416 | ● | ● | ● | ● | ● | ● | | | | |
| 4 | 2 | 2 | 24 | 4.898979 | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● |
| 5 | 0 | 0 | 25 | 5 | ● | | | | | | | | | |
| 4 | 3 | 0 | 25 | 5 | ● | | ● | | | | | | | |
| 5 | 1 | 0 | 26 | 5.09902 | ● | ● | ● | ● | ● | | | | | |
| 4 | 3 | 1 | 26 | 5.09902 | ● | ● | ● | ● | ● | ● | | | | |
| 5 | 1 | 1 | 27 | 5.196152 | ● | ● | | | | | ● | ● | | |
| 3 | 3 | 3 | 27 | 5.196152 | ● | ● | ● | ● | | | ● | ● | | |
| 5 | 2 | 0 | 29 | 5.385165 | ● | | ● | | | | | | | |
| 4 | 3 | 2 | 29 | 5.385165 | ● | ● | ● | ● | | | | | | |
| 5 | 2 | 1 | 30 | 5.477226 | ● | ● | ● | ● | ● | ● | | | | |
| 4 | 4 | 0 | 32 | 5.656854 | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● |
| 5 | 2 | 2 | 33 | 5.744563 | ● | ● | | | | | | | | |
| 4 | 4 | 1 | 33 | 5.744563 | ● | ● | | | | | | | | |

s=h^2+k^2+l^2

lattice. These parameters are used to calculate the critical packing parameter (CPP), which controls the aggregate morphology (see Chapter 24, Molecular Structure and Phase Behavior of Surfactants).

### 38.5.3 Nuclear Magnetic Resonance

Nuclear magnetic resonance (NMR) spectroscopy is another technique to determine the type of liquid crystal. This method uses quadrupole splitting in deuterium NMR, and different patterns are observed for different phases and allow a direct identification, in particular, multiphase coexistence (Fig. 38.12).[30]

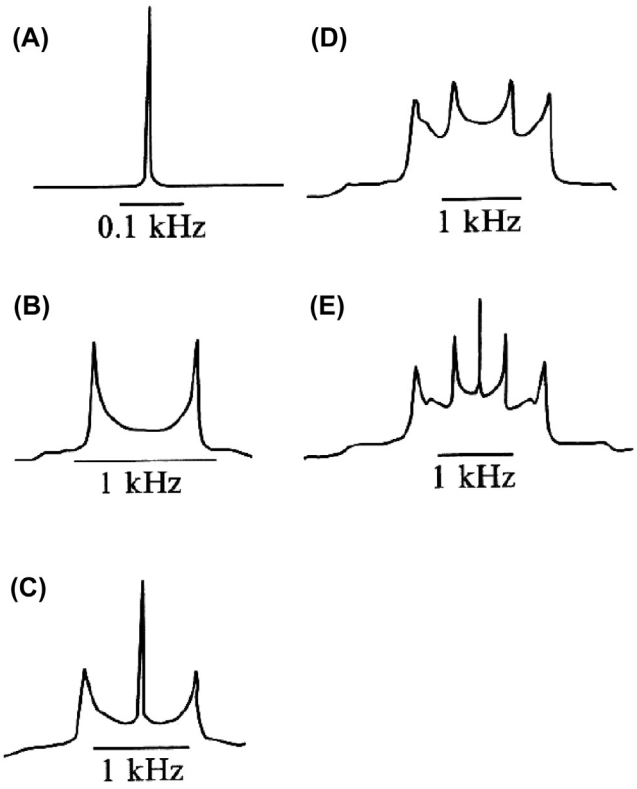



FIGURE 38.12 $^{2}H$ NMR spectra of various aggregates: (A) isotropic phases (micellar solution, sponge phase, cubic phase, or microemulsion), (B) lamellar phase ($L_\alpha$) or hexagonal phase ($H_1$), (C) two phase with one isotropic and one anisotropic phase, (D) two phase with $L_\alpha$ and $H_1$, and (E) three phase with two anisotropic and one isotropic phase coexisting.[30]

### 38.5.4 Other Methods to Identify Cubic Liquid Crystals

SAXS can provide the most precise information on the aggregate structure, while it may not give a conclusive judgment of the discontinuous type or bicontinuous type of the cubic liquid crystal, as mentioned previously. In general, identification of cubic liquid crystals would be made in combination with other methods, such as electron microscopy, phase study, and diffusion measurement.

In the phase diagram of a surfactant system, various liquid crystals generally appear depending on the composition and temperature (and pressure). The phase sequence, for example, with the composition can be expected from the change in the interfacial curvature; that is, increasing surfactant concentration induces a phase transition in the following order; $L_1$, $I_1$, $H_1$, $V_1$, $L_\alpha$, $V_2$, $H_2$, $I_2$, $L_2$ (refer to the notations in Chapter 24, Molecular Structure and Phase Behavior of Surfactants). This phase sequence indicates that the discontinuous-type cubic liquid crystal ($I_1$) phase is always present between $L_1$ and $H_1$ phases and the bicontinuous-type ($V_1$) is always present between $H_1$ and $L_\alpha$ phases.

The diffusion measurements such as PGSE-NMR and *staining method* would be definite methods to distinguish the two types of cubic liquid crystals. The discontinuous-type cubic liquid crystals, $I_1$ and $I_2$, have a discrete structure of micelles packed in a continuous phase, while the bicontinuous-type ($V_1$ and $V_2$) consists of the dual channel of water and oil. The diffusive motion of a molecule could be attributed to the aggregate structure. Fig. 38.13 demonstrates an example in which the staining method clearly identifies the discontinuous-type cubic liquid crystal present in a surfactant/water/oil system.[31]

## 38.6 EMULSIONS

Emulsions are thermodynamically unstable systems, and therefore, their structure often changes with time. However, quantitative analyses about emulsion structure are required to prepare a durable, stable emulsion product.

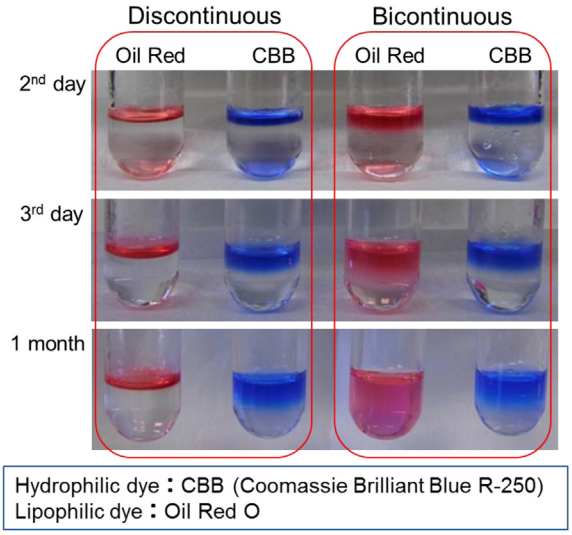



FIGURE 38.13 Dye staining method and identification of the type of cubic liquid crystals.[31] The discontinuous cubic liquid crystal is stained by the hydrophilic dye (CBB) solely, while the bicontinuous one can be stained by both the hydrophilic and lipophilic dyes (CBB and Oil Red).

## 38.6.1 Emulsion Type

Emulsions are classified roughly into two types—O/W and W/O; multiple emulsions are well known and can be formed through specific procedures. The fundamental concept to identify the emulsion type is to detect physicochemical properties of the continuous phase. Simple methods used to distinguish between O/W and W/O emulsions are (1) the *dilution method*, (2) the *electric conductivity method*, and (3) the *refractive index method*. Other methods such as diffusion methods (see Section 38.3) can be used, but here only these three methods will be interpreted briefly.

### *38.6.1.1 Dilution Method*

This method is based on the spreading or diffusive phenomenon when an emulsion is dropped onto a large amount of solvent being the same as the continuous phase of the emulsion. If the emulsion diffuses spontaneously and rapidly in water, the emulsion is likely to be O/W type; otherwise, it is W/O type (in this case, the emulsion just spreads over the surface or remains as it dropped).

### *38.6.1.2 Electric Conductivity Method*

This method uses the difference in the electric conductivity between water and oil. W/O emulsions have much lower conductivities than O/W emulsions.

### *38.6.1.3 Refractive Index Method*

In an emulsion state, the refractive index (RI) of the solution is determined by that of the continuous phase. The RI of water (1.333 at 25°C) differs from those of common oils (1.39−1.50), and thus the measured RI can identify the type of emulsion. However, it has to be noted that the RI value of the aqueous phase increases on the addition of water-soluble materials such as glycerin. When the RI of the aqueous phase is equivalent to that of the oil phase, a transparent emulsion can be formed, and then this method is not suitable for judging the type of emulsion.

## 38.6.2 Droplet Size of Dispersed Phase

The droplet size of a dispersed phase in an emulsion is an important factor that influences the properties as well as the stability of the emulsion. Since emulsions consists of relatively larger droplets than micelles and microemulsions, the evaluation methods for emulsions are different from those for small objects such as micelles at the nanometer scale. The droplet size of the emulsion typically ranges from a few to hundreds of micrometers and this is a suitable size for detection by visible light.

#### 38.6.2.1 Optical Microscope

*Optical microscope observation* can directly elucidate the emulsion state. Information on the size, morphology, and aggregation of droplets can be obtained within a minimal time after sample preparation. However, there is a limitation to the observable size: the practically lower limit for accurate measurement of the droplet size is around 1.0 μm, and then the image contrast may not be sufficient for evaluation. The contrast of the image can be improved by decreasing the aperture of the iris diaphragm and using an immersion objective.

Droplet sizing can be carried out using manual or automatic image analysis techniques. The size of spherical droplets is expressed by the diameter, and at least 100 droplets should be measured in order to attain the statistical accuracy.

#### 38.6.2.2 Laser Diffraction

This is a nonintrusive technique for determination of the droplet size and its distribution in the range of submicron to hundreds of micrometer, with good accuracy for most practical purposes. The *laser diffraction method* is based on Fraunhofer theory[32] or Mie theory[33] concerning the relationship between the particle size, the scattering angle, and the intensity of scattered light. In principle, the scattering angle of light becomes higher with increasing droplet size. In Fraunhofer theory, the diameter of the spherical droplet should be at least four times as large as the wavelength of the incident light, and the accuracy of droplet size determination would be unsuited when diameter is less than 10 μm. In such a case, Mie theory is more accurate, but some optical parameters, such as refractive index of the dispersed and continuous phases, are necessary to analyze the droplet size distribution.

#### 38.6.2.3 Dynamic Light Scattering

As mentioned, emulsion droplet size can be measured by using the photon correlation method. For emulsion systems, the dispersed phase volume is higher and then the interference effect is not negligible; in attempts to overcome interference from interparticle scattering, the emulsion sample has to be diluted by the continuous phase. However, such dilution can change the state of an emulsion. Alternatively, the back scattering technique can be applied, which allows one to measure at a high-volume fraction of the emulsion droplets. Usually, the scattered light is detected at an angle of 180 degrees.

#### 38.6.2.4 Laser Doppler

This method uses the Doppler shift (change in frequency) of back-scattered light from a laser beam shone on emulsion droplets. The Doppler shift ($\Delta v$) is expressed by the following equation:

$$\Delta v = \frac{2V \cdot n \cdot \sin(\theta/2)}{\lambda} \tag{38.10}$$

where $V$ is the rate of Brownian motion, $n$ is the refractive index, $\theta$ is the scattering angle, and λ is the wavelength of incident light.

#### 38.6.2.5 Differential Scanning Calorimetry

Calorimetry is the measurement of heat changes as the temperature of a substance is varied, and in general, *differential scanning calorimetry* (*DSC*) is used to determine phase transitions and their enthalpy changes in soft materials. The differential electrical power necessary to maintain a given temperature for two pans containing the sample and a reference is recorded. A discontinuous phase transition, being the first-order transition, is indicated by a sharp endotherm or exotherm, which causes changes in the differential power supplied to the sample.

To obtain the droplet size of emulsion, this method uses nucleation theory concerning freezing (i.e., freezing occurs at different temperatures, depending on the water sample size).[34] According to nucleation theory, the smaller the volume, the lower is the freezing temperature. For bulk water, freezing occurs around −14°C for a volume of 1 $cm^3$ and −24°C for a volume of 1 $mm^3$, while micro-sized droplets like emulsion freeze around −39°C (Fig. 38.14). Taking into consideration capillary phenomena, the relation between the radius of water droplet ($R$) and the freezing temperature ($T$) can be shown by the following equation:

$$R^3 = 0.69 \frac{3\dot{T}}{4\pi \int_{T_f}^{T} A \cdot \exp\left[-\frac{16\pi\gamma^3 V_s}{3L_f^2 \cdot \ln(T/T_f)} \frac{1}{k_B T}\right] dT} \tag{38.11}$$

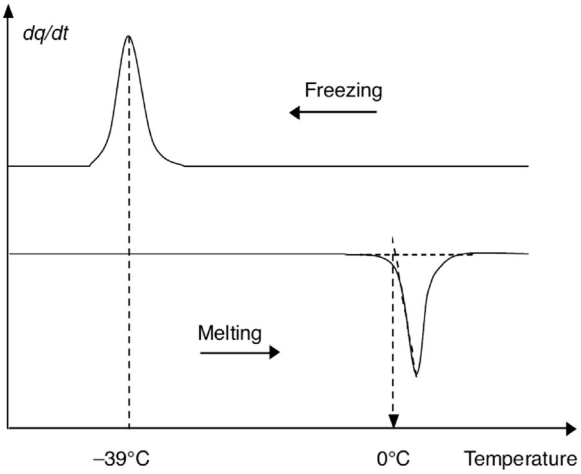



FIGURE 38.14 Cooling and heating thermograms of micro-sized droplets of water (W/O emulsion containing droplets of 1 $mm^3$).[34]

where $\dot{T}$ is the scanning rate, $A$ is the preexponential factor in the expression of the nucleation rate, $k_B$ is the Boltzman constant, $\gamma$ is the interfacial tension between water and the ice germ, $V_S$ is the molar volume of the germ, $L_f$ is the molar melting heat, and $T_f$ is the melting temperature.

#### 38.6.2.6 Other Microscopes

Besides optical microscopes, various microscopes have been used for the study of emulsions Electron microscopy is a powerful tool to investigate the size, morphology, and surface structure of emulsion droplets. SEM in particular can be used for emulsions to show droplet topography by scanning a very narrowly focused beam across the droplet surface. With a focused ion beam system and cryogenic freezing, SEM can provide more precise information on the internal morphology and three-dimensional structure (Fig. 38.15A),[35] and a very important advantage of SEM is elemental analysis by *energy dispersive X-ray analysis* (*EDX*).

Other methods to observe the three-dimensional structure of emulsions are *confocal laser scanning microscopy* (*CLSM*) and *tomographic microscopy*. CLSM uses a variable pin-hole aperture or variable-width slit to illuminate only the focal plane by the apex of a cone of laser light. The CLSM technique acquires images by laser scanning and uses computer software to subtract the out-of-focus images from the in-focus image. Since this method detects fluorescent light emitted from the sample, either the dispersed or continuous phase or interface (surfactant) in the emulsion has to contain a fluorescent probe as shown in Fig. 38.15B.[36] The use of *optical tomographic microscopy* (*OTM*) has been also reported recently to construct a three-dimensional image of emulsion (Fig. 38.15C).[37] This method may evaluate in situ emulsion dynamics such as Brownian motion.

### 38.6.3 Interfacial Layer

Emulsion stability can be controlled by interfacial properties that mostly rely on surfactant nature and orientation, or aggregate structure formed at the interface. Here, we focus on molecular mobility and viscoelasticity, interpreting some methods to evaluate them: (1) *zeta-potential*, (2) *fluorescent anisotropy*, (3) *electron spin resonance* (*ESR*), (4) *wide angle X-ray scattering* (*WAXS*), and (5) *interfacial rheology*. Some of the methods also can be useful for understanding molecular dynamics, for example, fluctuation and dislocation of bilayer membranes.[38]

#### 38.6.3.1 Zeta Potential

*Zeta potential* of small particles (or droplets) is approximately equivalent to surface potential, and six measuring methods are known so far: electrophoresis, electro-osmosis, streaming potential, sedimentation potential, electroacoustic sonic amplitude, and colloid vibration potential. The electrophoresis method is widely used and is a convenient method, being fast and accurate. This method is suitable for small droplets that undergo Brownian motion[39] based on the Doppler shift theory of scattered light (Eq. 38.10). If an electric field is placed

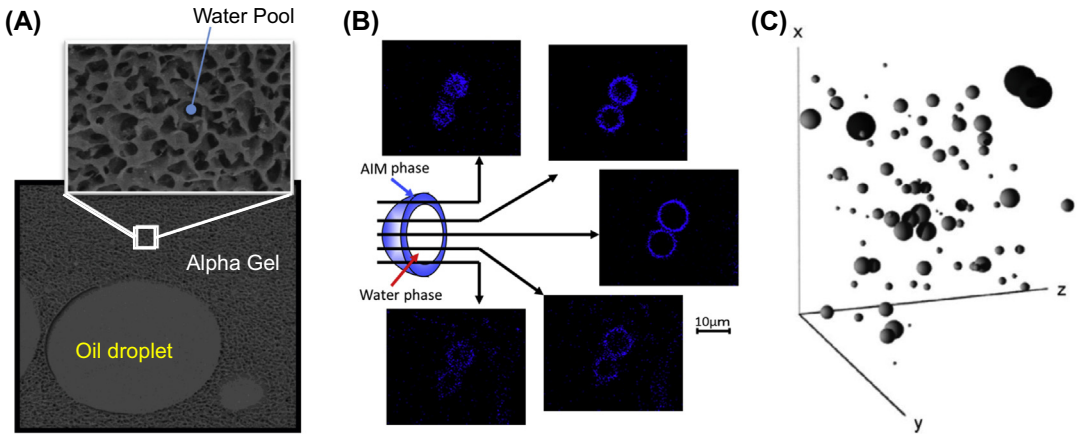



FIGURE 38.15 Various microscopic observation methods (A) FIM-cryo-scanning electron micrograph of the oil in alpha-gel emulsion,[35] (B) CLSM micrographs of the W/O emulsion,[36] and (C) three-dimensional images of the O/W emulsion by OTM.[37]

at a right angle to the incident light, the center of the scattered light frequency is shifted depending on the electrophoretic mobility ($\mu$). The magnitude of the Doppler shift ($\Delta$v) expressed by Eq. (38.10) can be modified using $\mu$ as follows:

$$\Delta v = \frac{2n \cdot sin(\theta/2)}{\lambda} \mu E \tag{38.12}$$

where $E$ is the electric field strength. Eventually, the zeta potential ($\zeta$) is calculated from $\mu$ using the Smoluchowski equation[40]:

$$\zeta = \frac{4\pi\eta}{\varepsilon} \mu \tag{38.13}$$

where $\eta$ and $\varepsilon$ are the viscosity and dielectric constant of solvent, respectively.

### 38.6.3.2 Fluorescent Anisotropy

The *fluorescence polarization* technique is often used to investigate membrane structure, based on the principle that if a fluorophore is immobile, fluoresced light is emitted in the same plane as the plane-polarized excited light. If the exciting light is polarized in the vertical direction, the fluoresced light will also be polarized in the vertical direction. However, this is dependent on movement of the fluorophore during its excited state.

1,6-Diphenylhexatriene (DPH) is used as a fluorophore to examine fluidity of interfacial membranes, and it can be solubilized between the hydrophobic chains of the surfactant molecules. If DPH is rapidly tumbling, *fluorescence anisotropy* ($f_A$) or polarization ($P$) is small. The $f_A$ value strongly depends on viscosity in the microenvironment and bound state (degree of freedom) of DPH; for example, $f_A$ has a large value when the surfactant molecules are in a gel state. Although $f_A$ and $P$ can be interconverted, $f_A$ is more frequently used and is obtained by using the following equation:

$$f_A = \frac{I_{VV} - G \cdot I_{VH}}{I_{VV} + 2G \cdot I_{VH}} \tag{38.14}$$

where $G$ is the apparatus constant ($=I_{VH}/I_{HH}$), and $I$ is the emitted intensity as measured through the vertical ($V$) or horizontal ($H$) polarizer detectors. Fig. 38.16 demonstrates an example of an anisotropy measurement that indicates the gel-to-liquid crystal transition with temperature.[38]

### 38.6.3.3 Electron Spin Resonance

*Electron spin resonance* (*ESR*), also called *electron paramagnetic resonance* (*EPR*), is generally used for the detection of a free radical generated by UV irradiation in a biological specimen, as well as for evaluation of dynamic changes in a local environment in the vicinity of the radical. The latter case uses spin probes that are chemically modified

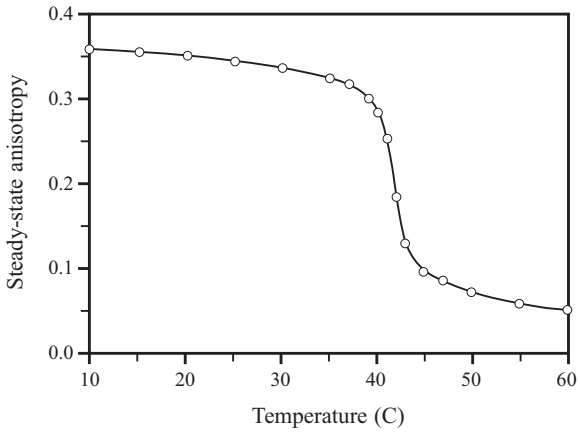



**FIGURE 38.16** Gel-to-liquid crystal transition of DPPC as followed by the steady state anisotropy of DPH.*[38]

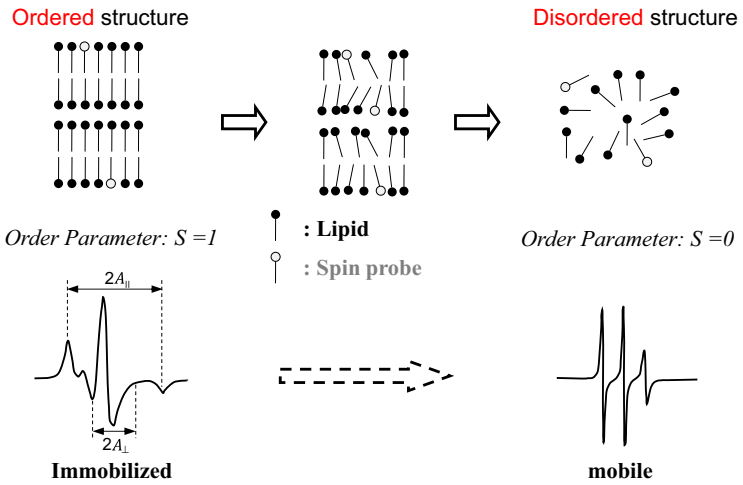



**FIGURE 38.17** Schematic representation of lipid bilayer structures as a function of lipid ordering.[45] The corresponding ESR spectral patterns were also indicated.

with a stable organic radical. For surfactant systems including emulsions, surfactant-like spin-labeled materials are useful to investigate the dynamic properties of the emulsion interface since they will self-arrange with surfactant molecules at the interface.[41] Various spin probes, with different positions of the alkyl chains labeled by a radical species, can provide information on the local mobility of alkyl chain in the depth direction. ESR measures the absorption of electromagnetic waves from the radical and thus can probe turbid solutions such as emulsions.

The ESR spectrum gives the order parameter ($S$) representing "softness (or hardness)" and "fluidity" of the interfacial membrane, being calculated as follows[42–44]:

$$S = \frac{A_{\parallel} - A_{\perp}}{A_{ZZ} - \frac{1}{2}(A_{XX} + A_{YY})} \cdot \frac{a}{a'} \tag{38.15}$$

where $A_{\parallel}$ and $A_{\perp}$ are the outer maximum and inner minimum hyperfine splitting, respectively (Fig. 38.17), $a$ is the isotropic hyperfine splitting constant for the spin label in solid state [$a = (A_{XX} + A_{YY} + A_{ZZ})/3$], $a'$ is the isotropic hyperfine splitting constant for the spin label in the membrane $\left[a' = (A_{\parallel} + 2A_{\perp})/3\right]$, and $A_{XX}$, $A_{YY}$, and $A_{ZZ}$ are

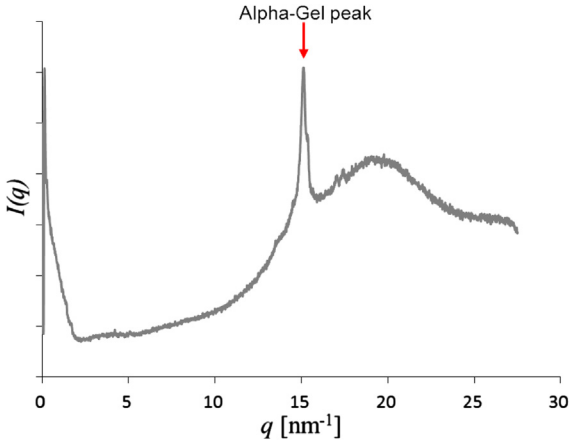



FIGURE 38.18 X-ray spectrum of the oil-in-alpha gel (O/αGel) emulsion (nonpublished data). The peak in the wide angle region (around $q = 15\ \text{nm}^{-1}$) indicate the presence of the αGel structure.

the experimental constants. As seen in Fig. 38.17,[45] the ESR spectra depends on the degree of molecular orientation assigned by the order parameter $S$.

#### 38.6.3.4 Wide Angle X-ray Scattering

The *wide angle X-ray scattering (WAXS)* technique, as well as SAXS, can be useful to identify the microstructure of emulsions, especially for specific emulsions using liquid crystals and alpha-gel (αGel). Since this scattering measurement is carried out at wide angles, typically $2\theta > 10$ degree, a WAXS spectrum shows molecular packing states. Fig. 38.18 demonstrates the WAXS spectrum of oil-in-αGel emulsion and proves the αGel structure is present in the continuous phase or at the interface.

#### 38.6.3.5 Interfacial Rheology[46]

Interfacial rheology has been found to be a key factor in the stability of emulsions, foams, and so on. In such cases, understanding the interfacial rheology over a broad range of frequencies and of the adsorption/desorption kinetics is important. For instance, the Ostwald-ripening mechanism of emulsion destabilization would be coupled to the interface viscosity and to the adsorption/desorption kinetics of surfactant (as well as solid particle) at the interface. In most practical applications, the interfaces are subject to external mechanical perturbations such as change in shape or size. The response of the interface to a change of size at constant shape is characterized by dilational elasticity and viscosity, whereas the response of the interface to a shape deformation at constant size is characterized by shear elasticity and viscosity.

Rheology is the science that investigates the system response when a mechanical perturbation is applied to the system. Therefore, the basal theory and measuring parameters are similar to those of bulk rheology (see Section 38.3). For dilational rheology, an infinitesimal change in the interfacial area ($\Delta A$) is the perturbation, and an oil or water droplet is perturbed by small harmonic oscillations of the interfacial area leading to harmonic oscillation of the surface (interfacial) tension. From the Fourier transform of the response relative to the perturbation, the complex viscoelastic modulus [$E(i\omega)$] is calculated by[47]:

$$E(i\omega) = \frac{F[\Delta\gamma]}{F[\ln(\Delta A)]} \tag{38.16}$$

$E(i\omega)$ can be also expressed using the storage modulus ($E'$, real part) and the loss modulus ($E''$, imaginary part).

$$E(i\omega) = E' + iE'' \tag{38.17}$$

$E'$ and $E''$ coincide with the dilational interfacial elasticity and viscosity, respectively. The schematic curves of the viscoelastic parameters are illustrated in Fig. 38.19, being very similar to the rheograms obtained from bulk rheology.

The study of the response of interfacial layers against shear deformation has not been sufficiently developed in comparison to dilational rheology, and in recent years some studies have been directed to the shear properties of interfaces. This is due to recognition of its importance in a wide range of technical aspects such as foaming, emulsification, oil

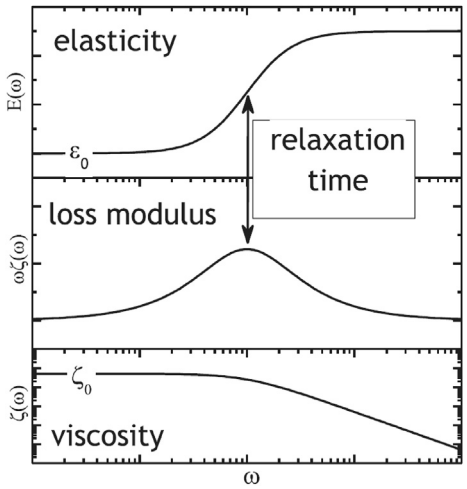



FIGURE 38.19 Typical frequency dependence of the elasticity [E(w)], loss modulus [wz(w)], and viscosity [z(w)] of a viscoelastic material undergoing a dynamic process.[46]

recovery, and so on.[48] The evaluation of the shear properties of interfacial layers applies the rheological concepts developed for three-dimensional systems (see Section 38.4 and Chapter 27, Rheology of Cosmetic Formulations).

## 38.7 CONCLUSION

In this chapter, we introduced and explained how to evaluate the structures of the colloidal objects (micelles, liquid crystals, and emulsions) focusing on the typical methods used in colloid science. In addition, as many as possible of the recent analytical methods were described to help your advanced research. Moreover, it was mentioned that novel instruments combined with two methods such as rheology−SAXS or −SANS[49] and rheology−Fourier transform infrared spectroscopy[50] have evolved continuously for kinetic studies. It is our expectation that these experimental techniques will lead to the discovery and creation of new functional formulations.

## References

1. Fukui H. *Cosmetics made absolutely simple (in Japanese)*. Tokyo: Nikkan Kogyo Shinbunsya; 2009. p. 59.
2. Debye P. Light scattering in soap solutions. *J Phys Chem* 1949;**53**(1):1−8.
3. Stilbs P, Lindman B. *J Phys Chem* 1981;**85**:2587−9.
4. Singer LA. Fluorescence probes of micellar systems − an overview. In: Mittal KL, Fendler EJ, editors. *Solution behavior of surfactants*, vol. 1. New York: Plenum Press; 1982. p. 73−112.
5. Holmberg K, et al. Kinetic of micelle formation. In: *Surfactants and polymer in aqueous solution*. 2nd ed. Chichester: John Wiley&Sons; 2003. p. 61−2.
6. Hayat MA. *Principles and techniques of electron microscopy: biological applications*. 4th ed. Cambridge University Press; 2000. p. 45−61.
7. Ruozi B, et al. AFM, ESEM, TEM, and CLSM in liposomal characterization: a comparative study. *Int J Nanomed* 2011;**6**:557−63.
8. Tsuchiya K. FF-TEM (chapter 13) & cryo-TEM (chapter 14). In: Abe M, editor. *Measurement techniques and practices of colloid and interface phenomena (in Japanese)*. Tokyo: Nikkan Kogyo Shinbunsya; 2016. p. 109−24.
9. The Chemical Society of Japan. *Introduction to modern interface and colloid chemistry (in Japanese)*. Tokyo: Maruzen; 2009. p. 47.
10. Disordered effects on relaxational process. In: Richert R, Blumen A, editors. *Glass, Polymer, Proteins*. Berlin: Springer; 1994.
11. Debye P. Light scattering in solutions. *J Appl Phys* 1944;**15**(4):338−42.
12. Zimm BH. Molecular theory of the scattering of light in fluids. *J Chem Phys* 1945;**13**(4):141−5.
13. Otsuka Electronics Homepage. https://www.otsukael.jp/product/detail/productid/92/category1id/37/category2id/30/category3id/81.
14. Matsuoka H. Introduction to small-angle X-ray and neutron scattering: analysis of nanostructure of polymer micelles. *Nihon Yukagaku Kaishi* 2000;**49**(10):1163−71.
15. Guinier A, Fournet G. Concept of radius of gyration of a particle. In: *Small angle scattering of X-ray*. New York: Wiley; 1955. p. 24−8.
16. Porod G. The small-angle X-ray scattering from densely packed colloidal systems. *Kolloid − Zeitschrift und Zeitschrift fur Polymere* 1951;**124**: 83−114.
17. Feigin LA, Svergun DI. *Structure analysis by small-angle X-ray and neutron scattering*. New York: Plenum Press; 1987.
18. Brunner-Popela J, Glatter O. Small-angle scattering of interacting particles. I. Basic principles of a global evaluation technique. *J Appl Crystallogr* 1997;**30**:431−42.

19. Weyerich B, et al. Small-angle scattering of interacting particles. II. Generalized indirect Fourier transformation under consideration of the effective structure factor for polydisperse systems. *J Appl Crystallogr* 1999;**32**:197–209.
20. Bergmann A, et al. Solving the generalized indirect Fourier transformation (GIFT) by Boltzmann simplex simulated annealing (BSSA). *J Appl Crystallogr* 2000;**33**:1212–6.
21. Holmberg K, et al. Confinement, obstruction and solvation determine solvent self-diffusion in microemulsions. In: *Surfactants and polymer in aqueous solution*. 2nd ed. Chichester: John Wiley&Sons; 2003. p. 148–51.
22. Olsson U, et al. Change of the structure of microemulsions with the hydrophile-lipophile balance of nonionic surfactant as revealed by NMR self-diffusion studies. *J Phys Chem* 1986;**90**(17):4083–8.
23. Watanabe K, et al. In: *Poster presentation in XXII IFSCC Congress, Edinburgh*; Sep. 2002.
24. Yamashita Y, et al. Phase behavior of N-Acylamino acid surfactant and N-Acylamino acid oil in water. *Langmuir* 2003;**19**(10):4070–8.
25. Hoffmann H. Viscoelastic Surfactant Solutions. In: Herb CA, Prud'homme RK, editors. *Structure and flow in surfactant solutions. ACS symposium series*, vol. 578. American Chemical Society; 1994. p. 3.
26. Doi M, Edwards SF. *The theory of polymer dynamics*. New York: Oxford; 1986.
27. Bragg WH, Bragg WL. The reflexion of X-rays by crystals. *Proc R Soc Lond A* 1913;**88**:428–38.
28. Yamashita Y, et al. Aggregation and phase behavior of a double-chain surfactant, N-dodecyl-N-octyl-N-methylamine oxide, as a function of the protonation degree. *Langmuir* 2007;**23**:1073–80.
29. Yamashita Y. *Phase behavior of amino-acid surfactant in water-oil system* [Master thesis]. 2002. p. 17.
30. Khan A, et al. Liquid crystallinity in a calcium surfactant system. phase equilibriums and phase structures in the system calcium octyl sulfate/decan-1-ol/water. *J Phys Chem* 1982;**86**:4266–71.
31. Yamashita Y, et al. Shear-response emulsion prepared through discontinuous cubic liquid crystal. *Chem Lett* 2013;**42**:433–5.
32. Jenkins FA, White HE. *Fundamentals of optics*. 3rd ed. New York: McGraw Hill; 1957. p. 288.
33. Wriedt T. Mie theory: a review. The Mie theory, basics and applications. In: Hergert W, Wriedt T, editors. *Springer series in optical sciences*, vol. 169. Berlin: Springer; 2012. p. 52–71.
34. Dalmazzone C, et al. Application of DSC for emulsified system characterization. *Oil Gas Sci Tech Rev IFP* 2009;**64**(5):543–55.
35. Miyamoto M, et al. Skin permeation promoting formulation based on novel bicontinuous alpha-gel structure with amphiphilic tranexamic acid derivative. In: *28th IFSCC2014 full paper*; 2014. p. 3440–5.
36. Sakai K, et al. Active interfacial modifier: stabilization mechanism of water in silicone oil emulsions by peptide-silicone hybrid polymers. *Langmuir* 2010;**26**(8):5349–54.
37. Antoni M, et al. Binary emulsion investigation by optical tomographic microscopy for FASES experiments. *Colloids Surfaces A Physicochem Eng Aspects* 2007;**309**:280–5.
38. Stillwell W. *An introduction to biological membranes*. London: Academic Press; 2013. p. 164–72.
39. Hunter RJ. *Zeta potential in colloid science: principle and application*. London: Academic Press; 1981.
40. Sze A, et al. Zeta-potential measurement using the Smoluchowski equation and the slope of the current–time relationship in electroosmotic flow. *J Colloid Interface Sci* 2003;**261**(2):402–10.
41. Ohnishi S. *Kagaku-to-Seibutsu (in Japanese)* 1976;**14**(2):108–16.
42. Griffith OH, Jost PC. Lipid spin labels in biological membrane. In: Berliner LJ, editor. *Spin labeling theory and applications*. New York: Academic Press; 1976. p. 453–523.
43. Hubbel WL, McConnell HM. Molecular motion in spin-labeled phospholipids and membranes. *J Am Chem Soc* 1971;**93**:314–26.
44. Marsh D. Electron paramagnetic resonance; spin labels. In: Grell E, editor. *Membrane spectroscopy*. Berlin: Springer; 1981. p. 51–142.
45. Nakagawa K. Lipid structure and dynamics investigated by modern ESR techniques (in Japanese). *OleoScience* 2010;**10**(4):133–9.
46. Mendoza AJ, et al. Particle laden fluid interfaces: dynamics and interfacial rheology. *Adv Colloid Interface Sci* 2014;**206**:303–19.
47. Zholob SA, et al. Determination of the dilatational elasticity and viscosity from the surface tension response to harmonic area perturbations. In: Miller R, Liggieri L, editors. *Interfacial rheology*. Leiden: Brill; 2009.
48. Krägel J, et al. Interfacial shear rheology. *Curr Opin Colloid Interface Sci* 2010;**15**:246–55. Fuller GG, et al. Complex fluid–fluid interfaces: rheology and structure. *Annu Rev Chem Biomol Eng* 2012;**3**:519–43.
49. Diat O, et al. Effect of shear on a lyotropic lamellar phase. *J Phys II Fr* 1993;**3**:1427–52.
50. Oldorp K. *Curing of an acrylate glue – rheology with simultaneous FTIR spectroscopy. Thermo fisher scientific application note V-254*. 2011.

CHAPTER

# 39

# Increasing Productivity by Reducing Carbon Footprint in Cosmetics Processing

*T Joseph Lin*

**T Joseph Lin Associates, Pacific Palisades, CA, United States**

## 39.1 INTRODUCTION

The cosmetics industry is dynamic and fast changing. New and improved products are constantly being introduced into the market, replacing old ones that have lost their appeal to consumers. Being a part of the beauty industry, changes in fashion color, for example, can affect decisions on new makeup products planned for the next season. Not long ago, our customers were satisfied with makeup products that promised only to make them look young and beautiful. Today, they demand more product performance and seek "antiaging" skin care or "cosmeceutical" products to make themselves look better, younger more naturally.[1] In addition, their awareness of environmental pollution and concern for global warming are becoming increasingly important to manufacturers, and this is affecting the direction of new product development and methods of manufacturing.

Many consumers now believe that natural or organic ingredients are safer for people and better for the environment than are synthetic chemicals. The share of natural/organic cosmetics has been growing globally, and increasingly cosmetic manufacturers are using more sustainable, natural ingredients in their products.[2]

In the 1960s, many surfactants and detergents widely used by the cosmetics and household products industries were found to be not biodegradable, contributing to environmental pollution. Manufacturers worked hard to replace them with more degradable substitutes. In the 1970s, the US cosmetics and household products industries were shocked by the discovery that some chlorofluorocarbons, widely used as propellants in popular aerosol products, could cause serious environmental harm, depleting the protective ozone in the stratosphere. Eventually, the use of these chemicals was banned and manufacturers were forced to use more degradable propellants or spray pumps without propellants.[2a]Compared to these environmental concerns of the past, our latest problem with global warming is much larger in scale and more serious, and finding a quick solution has been difficult.

Recently, representatives from nearly 200 countries met in Paris, France, to discuss ways to prevent average global temperature from rising 2°C above the pre-Industrial Revolution level. Energy conservation is becoming a very important issue for all industries, including ours, in manufacturing and marketing consumer products. Our consumers are becoming ever more aware of the danger of global warming and environmental pollution and are demanding us to make efforts to reduce our carbon footprint in manufacturing and marketing personal care products.

While energy conservation is becoming increasingly important to our industry, the solutions often require some sacrifice or compromise in production efficiency, product quality, or production cost. The focus of this chapter is to reexamine our use of energy and other resources in processing cosmetic products, and to suggest more effective ways to reduce energy consumption and carbon footprint without increasing production cost or compromising product quality.

The cosmetics industry is not generally energy intensive, and energy conservation has not been a particularly important consideration in manufacturing our products in the past. However, this traditional thinking is changing as global warming worsens, and increasingly consumers are demanding that our products should be not only safe and effective but also produced through environmentally friendly methods. In response, many raw material

*Cosmetic Science and Technology: Theoretical Principles and Applications*
http://dx.doi.org/10.1016/B978-0-12-802005-0.00039-2



Copyright © 2017 Elsevier Inc. All rights reserved.

suppliers have begun offering increasingly larger numbers of natural oils and other natural-based ingredients to replace synthetic ingredients traditionally used in manufacturing cosmetics.

## 39.2 UNDERSTANDING THE NATURE AND EFFECTS OF VARIABLES

In most single-phase solution-type products like hair oils, clear shampoos, and eau de colognes, replacing synthetic ingredients with natural materials will usually not cause manufacturing problems as long as all ingredients are compatible and soluble in the product to form a uniform phase. Two-phase products like emulsified moisturizers or facial creams are very popular in cosmetic preparations because they can contain both oil and water-soluble ingredients to form useful preparations that also feel nice on skin. However, emulsion products are more difficult to formulate and manufacture because they can often cause unexpected problems in formulation and manufacturing, or become unstable after the product is shipped to stores. Sometimes the problem can be serious enough to cause an expensive product recall.

Unfortunately, there is no reliable way to quickly test the stability of a freshly made emulsion. A commonly used test method is to place samples in stability ovens kept at different temperatures for about 3 months and to observe if any significant changes on viscosity, pH, or product appearance take place. The test is useful, but it unfortunately does not always accurately predict long-term stability.

The difficulty with stability tests of emulsion products stems from the fact they are not equilibrium systems, and their rheological properties and stability can change not only with the ingredients used but also with time and the processing methods employed. Due to fear of product failure and to assure product stability, we have a tendency to use more emulsifiers or apply more energy than necessary in manufacturing emulsion products. Since the stability of emulsions is often more dependent on the proper balance of hydrophilic and lipophilic surfactants than on their total quantity, addition of more surfactant can not only fail to stabilize the emulsion but it may actually promote instability, as will be discussed later in this chapter.

Since cosmetic manufacturers understand the strong desire of many consumers to buy totally “natural” products, it is often tempting to make claims that their products are “100% natural” or “chemical-free.” In reality, it is very difficult to make stable and functional skin care products that can meet such requirements, as most “natural” functional ingredients, including preservatives, surfactants, and emulsifiers, do not work as well as the synthetic chemicals, and the “all-natural” personal care products often experience serious product quality problems, resulting in product failure or trouble with government agencies for making unsubstantiated claims.

It will be shown in this chapter that we often use too much energy in manufacturing cosmetic emulsions. Potentially, emulsion-based products are troublemakers because they are not thermodynamically stable. This means that as soon as the product is made, it will start to degrade, sometimes quickly, sometimes not. Eventually, though, that freshly made, nice-looking cream will separate into an ugly mixture of oil and water. Depending on how long it takes for this to happen, this may or may not be a problem. We usually require emulsion products to remain stable for three years to avoid any complaints from customers. However, in spite of great progress in modern science, we have still not found a quick way to accurately predict emulsion stability.

A standard method for testing emulsion stability is to place a product sample at room temperature and also in ovens set at 40 and 45°C for 3 months to observe if any sign of phase separation takes place. This method is useful but unfortunately also time consuming and not always reliable. Few companies can afford to keep a freshly made production batch for 3 months before filling the product. Most companies will fill the product within a few days and ship it to the trade. Thus, if the sample of a new batch of a cream is found to separate in 3 days, the company is very lucky because the batch will most likely still be in the storage tank, not yet filled or packaged.

Frequently, a failed batch can be corrected by adding certain ingredients if the reason for the defect is known. However, if the batch sample is found to separate after 6 weeks of testing, it can be very bad news. Because by then, the batch is likely packaged and shipped. In this global market, the product may already be on store shelves in London or Tokyo, and a recall could be very expensive. Since the product is defective, most likely the unsold product from this batch will be discarded and not reused, a tremendous waste leaving a large carbon footprint.

However, by better understanding the nature and effects of both composition variables (CVs) and process variables (PVs) in processing cosmetic products, it is often possible to reduce energy and raw materials used in manufacturing without sacrificing product quality or increasing manufacturing cost. The main focus of this chapter is to introduce effective ways to reduce energy consumption and the use of functional chemicals such as surfactants in manufacturing cosmetic products without compromising product quality or increasing production time or cost.

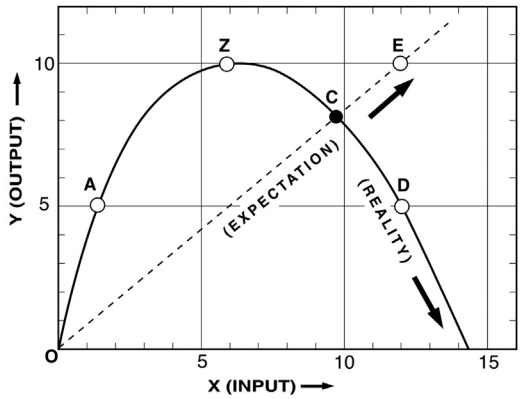



FIGURE 39.1 Linear expectation and nonlinear reality.

When it is discovered that there is something wrong with a freshly made batch of a product, which must be corrected before shipping, we tend to suspect that the problem is caused by a composition variable, such as use of incorrect or defective raw materials or possibly a weighing error. Indeed, CV can often be responsible for the problem, but equally possible are the effects of PVs, such as manufacturing procedures, processing time, temperature, or mixing intensity. Understanding the PVs and learning to control their effects can be very valuable in solving manufacturing problems because a PV solution usually does not require adding new ingredients, which might interact with other materials or cause other unexpected problems that affect product performance.

Examples will be shown to demonstrate that the energy-saving methods introduced here can be used to effectively solve many important processing problems in manufacturing different emulsion and nonemulsion products.

## 39.3 THE PRINCIPLE OF LESS IS MORE

Our minds often think linearly in an input–output relationship, namely "more input always produces more output," as illustrated in Fig. 39.1. However, we also know that nature does not always behave linearly. For example, if we are now at Point C and want to increase the output to reach Point E level, our linear thinking would likely suggest that we must increase the input. However, in this example, doing that would actually reduce output to a lower level at Point D. If we had conducted experiments to find that, in this case, nature follows the curve, AZCD, we would know that we are better off not to increase, but to reduce, input to the level of Point Z to reach a higher output level. This is the basic principle of "Less Is More," which can be applied to save energy while increasing the output.[3]

Note that the slope of the curve at Point A is a positive value. At Point C, it is a negative value. I named the Point Z in this graph, "Z-Point," because the slope is zero at this optimum point. It will be shown that we often use too much energy in our conventional ways of processing cosmetic emulsions, more than is actually required, and by conducting carefully planned experiments to understand the behavior of nature and to identify the Z-Point, it is often possible to save energy without sacrificing quality. This "Less Is More" principle can be applied to save energy and processing time in manufacturing cosmetic emulsions and certain nonemulsion products.

## 39.4 LOW-ENERGY EMULSIFICATION

Emulsion-based products are very popular in cosmetics as they combine water and many useful oils and other functional ingredients such as surfactants, humectants, antioxidants, and pigments to create a variety of interesting and novel creams, lotions, cleansers, makeup products, and sunscreens. The type and the amount of oils and surfactants can be adjusted in formulations to make oil-in-water (O/W) or water-in-oil (W/O)-type emulsions for different purposes. Most cosmetic emulsions are of the O/W type and typically contain 60–85% water in the external phase of the product. As illustrated in Fig. 39.2A, in processing O/W emulsions, both phases are heated separately in two kettles to dissolve solid or waxy ingredients before one of the phases is mixed into the other to start emulsification. After mixing and homogenizing the emulsion, the batch is usually cooled to about 35°C by introducing cold water into the kettle jacket before the product is pumped into a storage tank to complete the process.

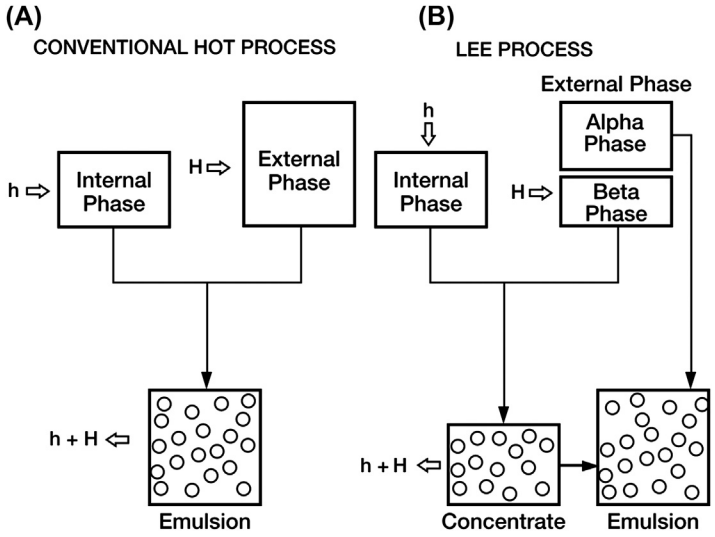



FIGURE 39.2 Conventional hot emulsification process and low-energy emulsification (LEE) process.

In low-energy emulsification (LEE), illustrated in Fig. 39.2B, the external phase, which is mostly water, is divided into two parts: alpha phase and beta phase. All water-soluble ingredients are dissolved in beta phase, which is first heated and combined with the hot oil phase to form an emulsion concentrate. The second stage of operation requires combining the warm emulsion concentrate with the cold alpha phase, which is usually pure water.[4]

It is easy to understand how the LEE process can save energy and processing time, particularly if the batch size is large. In this example, the size of the cold alpha phase is about 60% of the total water phase, and only 40% of the water in the external phase is heated to prepare the emulsion concentrate in the first stage. In manufacturing cosmetic emulsions, the most time-consuming step is usually the batch-cooling stage. To reduce the cost of emulsion processing, many manufacturers are increasing the batch size. One problem caused by increasing batch size is a reduction in cooling efficiency. In batch processing using a jacketed kettle, the cooling is done by passing cold water in the jacket. Increasing the size of the processing kettle reduces the heat-transfer surface area per unit volume and cooling efficiency.

If the batch size is large, say 20 tons, it can easily take more than 8 h just to cool the batch enough for storage or filling. To promote faster cooling, many companies use refrigerated water to cool the batch. Since the heat removed from the batch is usually not recovered, this process is wasteful because it is using more energy to discard energy. LEE is a very effective way to reduce waste of water and energy while reducing processing time, manufacturing cost, and carbon footprint.

## 39.5 DIFFERENT WAYS TO CARRY OUT LOW-ENERGY EMULSIFICATION

It is important to remember that there are many different ways to carry out LEE processing. The timing of adding the alpha phase can be controlled to promote efficient batch cooling, for example, by not adding the cold phase immediately after the emulsification but waiting instead until a later stage when the batch cooling efficiency is lower. Addition of the cold alpha phase will cool the batch very quickly to reduce the total processing time.

Another important variation in LEE processing is the method of combining the alpha phase and emulsion concentrate. As indicated in Fig. 39.3, there are two ways to combine them: alpha-into-concentrate and concentrate-into-Alpha. The quality of the emulsion made can be quite different depending on which method is used. LEE is quite flexible, and it is important to carry out pilot experiments to explore different ways of combining these two phases, as the method of addition can significantly affect the emulsion quality.[5]

## 39.6 THE IMPORTANCE OF FINDING THE Z-POINT

It is clear that a greater energy saving is possible by increasing the size of the cold alpha phase in relationship to the hot beta phase. However, it is important to know how far the alpha phase can be extended without adversely

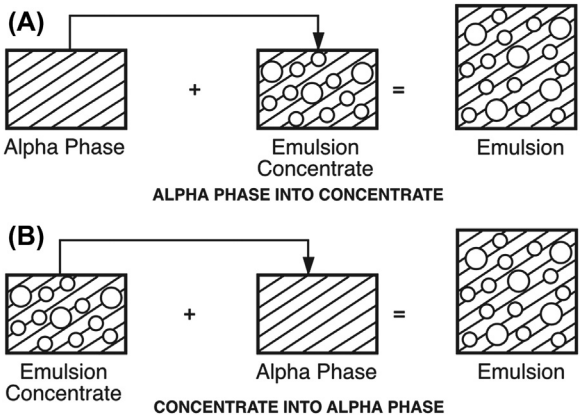



FIGURE 39.3 Two methods of combining alpha phase and emulsion concentrate.

affecting quality of the emulsion formed. Fig. 39.4 shows an example of an emulsion stabilized with an anionic surfactant, tested at two different emulsification temperatures, 70 and 80°C, to determine the limit of the alpha phase size before quality degradation, indicated by a sudden increase in the average droplet size of the emulsion.[6] The formulation used for this anionic O/W emulsion is shown here:

| | Wt% |
|---|---|
| Water | 87.0 |
| Light mineral oil | 8.0 |
| Stearic acid | 4.0 |
| Triethanolamine | 1.0 |
| Total | 100.0 |

From Fig. 39.4, it can be seen that when the emulsification temperature, Te, was set at 70°C, the degradation of the emulsion quality took place when the weight fraction of the alpha phase reached about 55%. This Z-Point for the quality degradation increased slightly to about 64% when the emulsification temperature was increased to 80°C. In this example, by increasing the emulsification temperature by 10°C, the experimental data suggested that we could produce a slightly finer emulsion and increase the alpha phase by about 9% to save more energy.

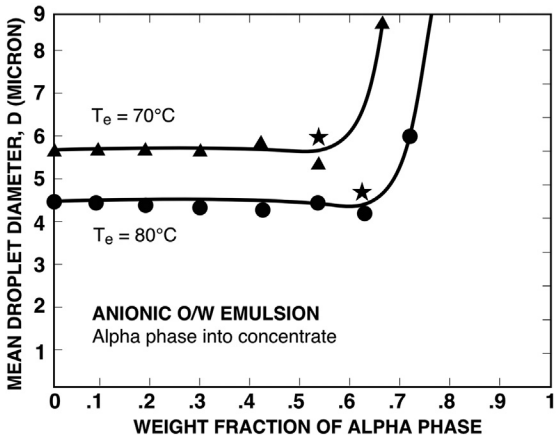



FIGURE 39.4 Effects of emulsification temperature and Z-point.

## 39.7 AN EXAMPLE OF "LESS IS MORE" LOW-ENERGY EMULSIFICATION PROCESSING

Here is an example of using a cationic surfactant for emulsification, utilizing a concentrate into alpha phase method, which produced a rather interesting result shown in Fig. 39.5. When the emulsification was carried out using a conventional method, with no withholding of the alpha phase, the average droplet size was about 6.8 μ. A series of emulsions were prepared by gradually increasing the size of the alpha phase from 0, but the change in the average droplet size of the emulsion was quite small until the alpha phase reached around 0.60.

The surprising result can be seen at this point as the emulsion droplets became much smaller, indicating that the emulsion quality actually significantly improved by increasing the size of the alpha phase, which also yielded a significant reduction in energy input. However, when the weight fraction of the alpha phase exceeded 0.8, a rapid degradation of the emulsion quality took place as indicated by a sudden increase in the average droplet size. The formulation for the cationic O/W emulsion used for the experiments in Fig. 39.5 is given here:

| | Wt% |
|---|---|
| Water | 91.5 |
| Stearyl dimethyl benzyl ammonium chloride (80%) | 2.0 |
| Light mineral oil | 4.0 |
| Stearyl alcohol | 2.5 |
| Total | 100.0 |

This "Less Is More " effect of producing a finer emulsion by using less energy at the point indicated by the black star in the graph (Z-Point), may appear surprising at first, because it means that a better, much finer emulsion was made by using much less energy. This example demonstrates that with an effective application of energy in emulsification, it is often possible to save energy while improving product quality.[7]

The effect of forming a very fine emulsion just before reaching the Z-Point shown here is due to a large withholding of the alpha phase. In this example, all water-soluble surfactant was added to the beta phase, leaving the alpha phase as pure water. The smaller beta phase means a higher concentration of the surfactant, which was responsible in forming the very fine emulsion until the weight fraction of the alpha phase exceeded 0.8. In this experiment, two variations of adding the alpha phase were tested as shown in Fig. 39.5.

In this example, the addition of the alpha phase into the concentrate was a better method than adding the concentrate into the alpha phase, as it produced finer emulsions without causing abrupt degradation of quality at the Z-Point, which was observed when the weight fraction of the alpha phase increased beyond 0.8. Clearly, it pays to conduct experiments to find out the Z-Points before deciding how to process the product. LEE processing is very flexible, and the method can be adjusted and modified to improve product quality while saving energy.

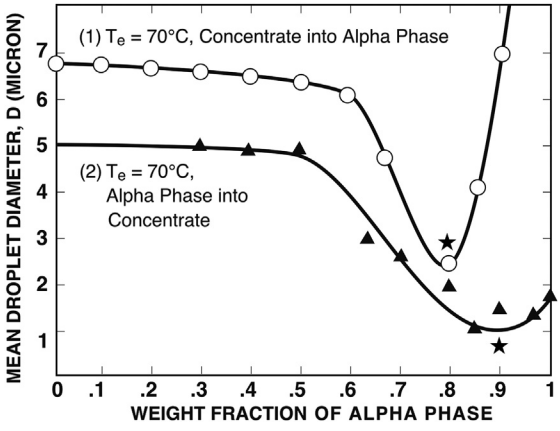



FIGURE 39.5 Using less energy to make better emulsions.

## 39.8 LOW-ENERGY EMULSIFICATION TO PREVENT BATCH FAILURE, IMPROVE PRODUCT QUALITY, AND SAVE ENERGY

Three examples will be presented here to show that LEE is not only useful in saving energy to make emulsions but it can also be used as an effective tool to solve difficult processing problems, to prevent batch failures, and increase productivity. The first example is solving a scale-up problem in making large batches.

### 39.8.1 Example 1: Solving Batch Failure Problem in Making a Large Batch of an O/W Emulsion

The company had been making an O/W moisturizing lotion in 200-gallon processing kettles for many years. To keep up with increasing demand, the company expanded production capacity by purchasing several new 500-gallon kettles. When the first batch was made using a new kettle, the viscosity of the product was too low and failed to pass quality control specifications. Since this product had a tendency to thicken with time, the manager thought that keeping the product in the storage tank for a few days might increase the viscosity sufficiently. It did not, and the batch remained too thin even after 1 month. I was asked to solve the problem without adding any thickeners or any other raw materials because it was a well-liked product and the company feared that any change introduced in the formulation might affect the product efficacy. This meant that I was only allowed to change the PVs and not CVs to solve the low-viscosity problem.

My initial investigation of the cause of the problem suggested that excess shearing action applied by the mixer due to prolonged cooling time stemming from the increased batch size probably contributed to excessive shear-thinning effect, reducing the viscosity of the product. I discovered that this emulsion was very shear sensitive, thixotropic, and excessive shear could reduce the viscosity sufficiently to make it difficult to recover. Since the new kettles were all equipped with mixers running at one speed, the shear-thinning effect of the mixer could not be overcome by operating the mixer at a lower speed. I decided to try an LEE procedure to reduce the total cooling time and thus reduce the shear-thinning effect of the mixer on the emulsion. This worked quite well, and I was able to produce consistently good product that passed all quality specifications.

### 39.8.2 Example 2: Problem Making Clear Hair Conditioner in Production

Even though LEE was conceived as a practical way to reduce processing time and the energy consumed in processing cosmetic emulsions, its "Less Is More" principle can be easily extended to save time and energy in making many nonemulsion products such as hair shampoos, conditioners, and liquid soaps. In my consulting work, I have encountered many unexpected process-related problems that I was able to solve by applying modified LEE processes.

The second example involves a company that developed a unique, clear hair conditioner that received favorable results in consumer testing. When they started production, some batches, filled in a clear bottle, became cloudy and could not be sold. My investigation revealed that the cloudy insoluble fine particles probably came from raw materials that were not completely soluble in the product. However, the manager assured me that every batch of the product was always filtered with fine filter paper after production to remove all insoluble particles. Strangely, the problem did not happen to every batch, only to certain ones, and they could not understand why.

My further investigation suggested that solubility of the insoluble particles in the finished product was temperature dependent, and that controlling the batch temperature at the time of filtration might be the key to solving the problem. In making lab samples or small pilot batches, the product cools quickly. By the time the product is filtered, the batch temperature is near room temperature, and all insoluble particles are removed quickly and easily by filtration. However, in making large production batches, the product cools more slowly, and the final batch temperature is usually around 40°C, which is much higher than room temperature.

If a freshly made batch is filtered soon after production when it is still warm, the solution may appear to be clear, but possibly be supersaturated with impurities, and the filtration process may not remove all insoluble materials. If a batch is luckily made on a Friday afternoon and filtered on the following Monday, the batch temperature at filtering time maybe sufficiently low enough to assure a more complete removal of impurities, avoiding the problem. After understanding the reason for the inconsistency in product quality, I suggested two solutions. The first was to continue cooling the batch to a lower temperature before filtering. The second approach, a greener method, was to use LEE to make the batch and use the cold alpha phase to bring down the temperature to a lower level to assure

complete removal of insoluble matters. This method not only saved the product but also saved energy, cooling water, and production time.

### 39.8.3 Example 3: Stability Problem in the Production of a Spray-Type Sunscreen Emulsion

As demonstrated in the last two examples, understanding the nature and ability to control PVs can be very important in solving many manufacturing problems. Being a nonequilibrium system, emulsion-based products, including many popular skin care, hair care, makeup, and sunscreen products, can be quite sensitive to PVs, causing manufacturing problems in the first production batch or when scaling up the batch size. Frequently, when a new formula is made in the laboratory, the product may appear to be trouble-free, with samples passing all tests and meeting all specifications. Frequently, the potential processing problem does not occur until the first full-scale production batch is made in the factory.

This third example involves using LEE to solve a processing problem related to making a large, 2000-gallon production batch of sunscreen emulsion in a factory. The product was a low-viscosity, oil-in-water-type emulsion having very fine droplet size distribution, designed for use in spray pump bottles. The product samples made in the laboratory were all very stable and performed well when tested. A 100-gallon pilot batch made in the factory also had good quality and passed all specifications.

However, when the first 2000-gallon production batch was made in the factory, the product quality was very poor, as the emulsion droplets were coarse and the product was unstable. Initially, the quality problem was thought to be caused by some defective or poor-quality raw materials used in the production batch, but further investigation conducted by the laboratory found this not to be the case. Using the same lot of raw materials used in the failed production batch, all laboratory test samples made were good and stable. It appeared that the difference in batch size was the main cause, and I was asked to find a way to quickly solve the problem.

I accepted the assignment but was worried about how to conduct my experiments. I was told that all small samples made in the lab were okay. Even the 100-gallon pilot batch sample was acceptable, but quality of the 2000-gallon production batch was very poor. If batch size matters, how could I design experiments to find the solution? Certainly, I would not be allowed to run experiments making 2000-gallon batches! Fortunately, in reviewing the formula used in this product, I realized that the production of the very fine sunscreen emulsion needed for this product was based on taking advantage of low interfacial tension produced by nonionic surfactants at the phase inversion temperature (PIT). In fact, I was once interested in this subject and had read a book on it written by two experts, Shinoda and Friberg.[8]

In thinking about the basic cause of the problem, I speculated that the slower cooling rate in processing a large 2000-gallon batch might be an important cause. In making lab samples, the batch is quite small and the product will cool quickly after emulsification even without use of a water bath. Making a full-scale, 2000-gallon production batch is a different story. Even circulating the kettle jacket with refrigerated water, the cooling rate can be very slow for a large production batch because of the reduced heat transfer efficiency.

I decided to investigate the effect of cooling rate in my laboratory by carefully controlling the cooling rates through use of a water bath to cool the batch. Instead of using cold water to cool the freshly made hot batch, I used warm water at different temperatures to cool the batch slowly for my experiments. I carefully measured the cooling rate for each experiment and studied its effect on emulsion quality.

I was happy to discover that the cooling rate for the batch indeed had a very important effect on quality of the emulsion produced as can be seen in the experimental data presented in Fig. 39.6. When the cooling rate, R, was greater than 1.5°C per minute, the droplets of the emulsion produced were extremely fine and the product was very stable. However, when I slowed the cooling rate to below 1°C per minute by using warmer cooling water as represented by R-3 in the figure, the emulsion quickly became unstable, and the average droplet size increased greatly. It was clear from the experiments that R-3 represented the Z-Point for the emulsion degradation for this O/W formulation.[9]

When the batch size is small, cooling is quite efficient and quick. But as the batch size is increased, the surface area of the kettle for heat transfer per unit volume of the product decreases rapidly, causing slow cooling while the batch temperature is still near PIT and resulting in poor emulsion quality. This was the reason why the potential manufacturing problem was not discovered in the laboratory or even when the 100-gallon pilot batch was made.

When the 2000-gallon production batch was made, however, the cooling rate slowed down so much that it caused production failure. The lesson here is that it is possible to prevent a potential problem by conducting small-scale laboratory experiments, but the experiments must be properly designed to allow discovery of the cause. And of course, good experimental design requires a good understanding of the laws of nature.

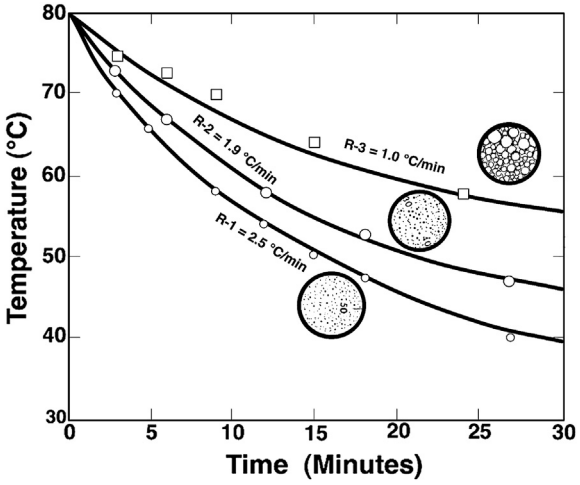



**FIGURE 39.6** Finding the Z-point of product degradation for a sunscreen emulsion.

Once the reason for the failure in making the large production batch became clear, finding a solution was not difficult. At the meeting when I reported my findings to manufacturing staff, someone suggested that we should accelerate cooling by purchasing a larger refrigerating unit to lower the cooling water temperature. However, I thought this would be a wasteful use of energy and water, needlessly using more mechanical energy to discard excess thermal energy faster. Moreover, my study also suggested that even a more powerful refrigerating unit might not accelerate the batch cooling rate to greater than 2°C per minute needed to solve the production problem.

I recommended that before buying an expensive new machine, we should try to see if we could use LEE to facilitate batch cooling to solve the problem. Since the product was an O/W emulsion containing a large amount of pure water, I reasoned that by withholding a sufficient amount of water as the cold alpha phase, and adding it during the critical period, shortly after emulsification, we should be able to shorten the time during which the batch temperature would remain near PIT to avoid quality degradation.

Fortunately, the test was successful. This is an example of an effective application of "Less Is More" principle, not only to prevent batch failure but also to save energy and processing cost, and significantly reduce carbon footprint without having to buy expensive new equipment. The success of this example was strongly dependent on a correct understanding of the basic theory and accurate determination of the Z-Point.

### 39.8.4 Low-Surfactant Emulsification

Surfactants are very important in formulating emulsions because they can reduce the interfacial tension between water and oil and adsorb at the interface to stabilize emulsions. However, the use of more surfactants does not always result in formulating a better or more stable product. In fact, using too much surfactant can not only make the product sticky, unpleasant to use, or even irritating to the skin, it can also make the product less stable and even shorten the shelf life.

Here again, the consideration of Z-Point can be crucial because the stability of an emulsion is not only dependent on the kind of emulsifiers used but it is also strongly related to the amount of each surface-active agent and how the surfactants are used in the formulation. This means that in processing emulsions, having a good formulation is important, but how the emulsion is made in the factory can also be critical in ensuring product stability. This means that by optimizing both CVs and PVs, we can actually reduce the amounts of surfactants, emulsifiers and polymer stabilizers in the formulation to manufacture better products while reducing product cost, production time, and carbon footprint.

However, because emulsion stability is difficult to predict accurately, there is a tendency for formulators to use more surfactant than necessary to assure product integrity. This means it is often possible to reduce the amount of a surfactant in a formulation to improve both product stability and performance. When successful, this may contribute significantly in reducing both product cost and carbon footprint while improving product quality.

In order to study the effects of surfactants and surfactant concentration on emulsion stability, I carried out a series of studies using different types of surfactants to make O/W-type emulsions, commonly used in formulating

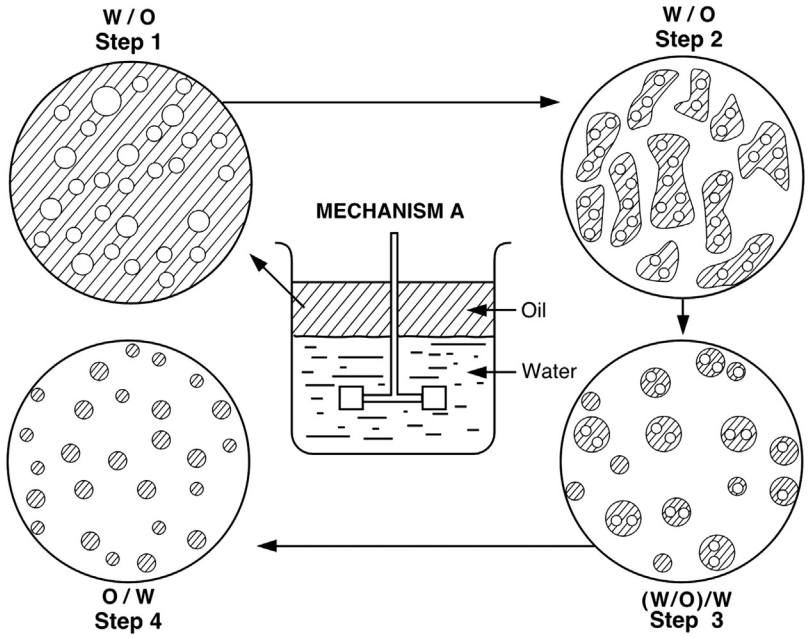



FIGURE 39.7 Illustration of Mechanism A, surfactant initially in oil phase.

different cosmetic products. I discovered that emulsion stability and quality can be affected not only by the surfactants and other ingredients in a formulation but also by the method by which the emulsions are processed. In other words, both CVs and PVs are important to the properties and the stability of the emulsion products manufactured.

Many surfactants are soluble in both water and oil. In a series of experiments conducted at room temperature, interestingly, I discovered that initial placing of the surfactant in the oil phase produced a finer and more stable emulsion than the same formulation made by initially placing the surfactant in the water phase. By carefully observing emulsion samples under a microscope at different stages of emulsification, I learned that possibly different mechanisms were involved in forming the emulsions, depending on the initial location of the surfactants.

When the surfactants are placed in the oil phase as illustrated in Fig. 39.7, there is a tendency for an initial formation of a (W/O)/W-type double emulsion. Continued mixing of this emulsion eventually promoted formation of an O/W final emulsion as illustrated in Step 4. I decided to call this Mechanism A to distinguish it from another mechanism observed when the initial surfactant location was changed.

A microphotograph of a (W/O)/W-type double-emulsion droplet is shown in Fig. 39.8.

Using the identical formulation, but simply introducing a PV in making the emulsion by placing the surfactants initially in the water phase, the effect on emulsion quality was quite significant. In this case, illustrated in Fig. 39.9, an initial formation of a double emulsion was not observed, but the emulsion formed had significantly larger emulsion droplets than did the same formulation made by initially placing the surfactant in the oil phase. An example of a final emulsion produced by Mechanism B is shown in Fig. 39.10, exhibiting a complete absence of double-emulsion droplets.

The results of these two experiments suggest that the initial surfactant location can be a very important factor in making emulsion products. Using more surfactants does not always assure better stability, but a better understanding of the basic mechanism and the Z-Point can help us to promote effective use of surfactants and improve product quality and stability. In conducting many experiments, I discovered the interesting fact that the stability of emulsions can be actually improved by reducing surfactants in the formulation.[11]

## 39.9 USING HYDROPHILE-LIPOPHILE BALANCE METHOD TO FIND OPTIMAL SURFACTANT COMBINATIONS FOR EMULSIFICATION

It is known that using pairs of surfactants with different hydrophile-lipophile balance (HLB) values is often better than using a single surfactant in making stable emulsions. The HLB system was introduced by Griffin to guide formulators in selecting effective surfactants in preparing emulsion products.[10] The basic idea was quite simple—by adjusting the HLB value of the surfactant blend to match the required HLB value of the oil blend, it should be

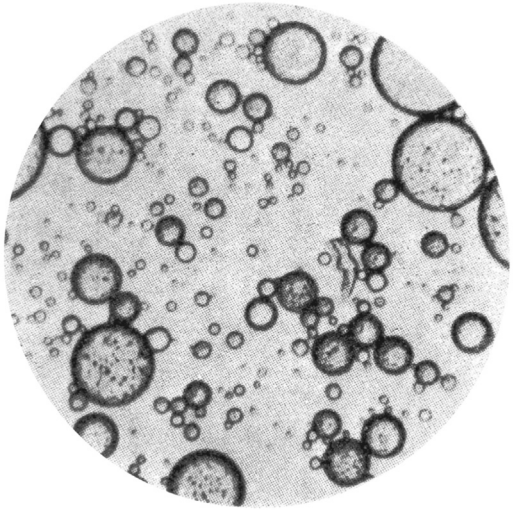


FIGURE 39.8 Microphotograph of a (W/O)/W-type double emulsion.

possible to determine the optimum composition of the surfactant blend to promote efficient emulsification and stable emulsions. The method worked well as long as the oil phase of the emulsion was limited to hydrocarbons and the surfactants were restricted to ethoxylated nonionics.

Unfortunately, as modern cosmetic emulsion formulations have become more complex and diversified, formulators have increasingly been forced to use various natural oils and different types of surfactants for which HLB values are unavailable or not reliable, and this simple method often fails to work. There was a time when I thought that by inputting all HLB and required HLB data for all cosmetic ingredients into a computer we could devise a program that would assist formulators to select the best surfactant combinations for a given project. Such a program would certainly save much time by reducing the usual trial-and-error process in the laboratory. Unfortunately, it does not appear that such a program will become available in the near future, as the use of HLB method in formulating emulsions appears to have lost popularity, and many companies no longer publish HLB data for their new surfactants.

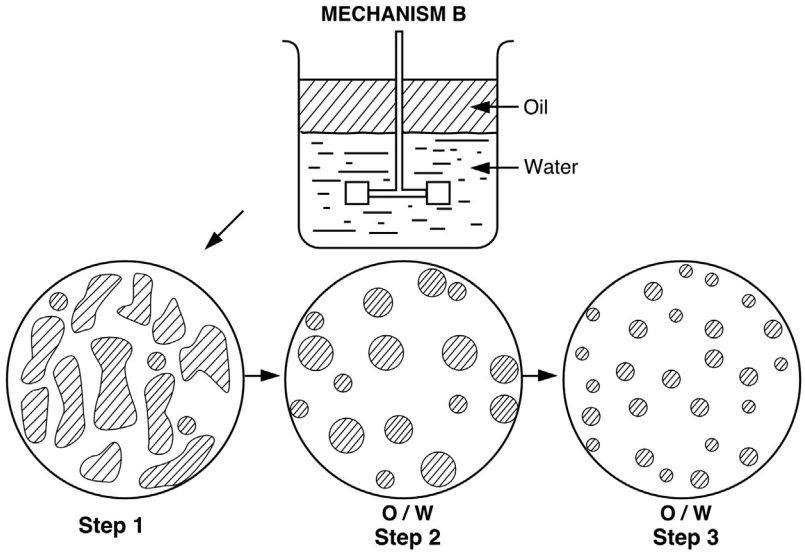



FIGURE 39.9 Illustration of Mechanism B, surfactant initially in water phase.

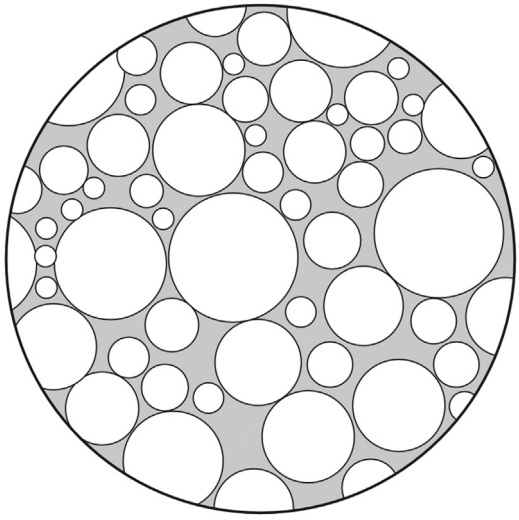


FIGURE 39.10 Example of an O/W emulsion form by Mechanism B.

## 3.10 SOLUBILIZATION METHOD IN LOW-SURFACTANT EMULSIFICATION

A useful way to find the optimum combination of a surfactant blend for making a good emulsion is the solubilization method, which I have tested by using many different surfactants and oils. This method involves determining the maximum amount of water solubilization in the oil containing surfactant blends used in emulsification. An example of finding the optimum surfactant blend for an O/W mineral oil emulsion, stabilized by a combination of Oleth-2 and Oleth-7, is shown in Fig. 39.11. By measuring the maximum amount of water solubilized in the oil containing different ratios of the two nonionic surfactants, we discovered that the maximum solubilization was observed at 70% Oleth-7 and 30% Oleth-2.

We then prepared a series of emulsions containing 30% mineral oil, 65% water, 5% total of the two nonionic surfactants used, while varying surfactant ratios as indicated in the figure. We measured the average droplet size for each emulsion prepared and discovered a very useful correlation between the amount of solubilization and the emulsion quality. We found that the best emulsion, having the smallest average droplet size, was formed by the surfactant blend corresponding to the highest solubilization point, indicated by the black and white stars shown in Fig. 39.11.

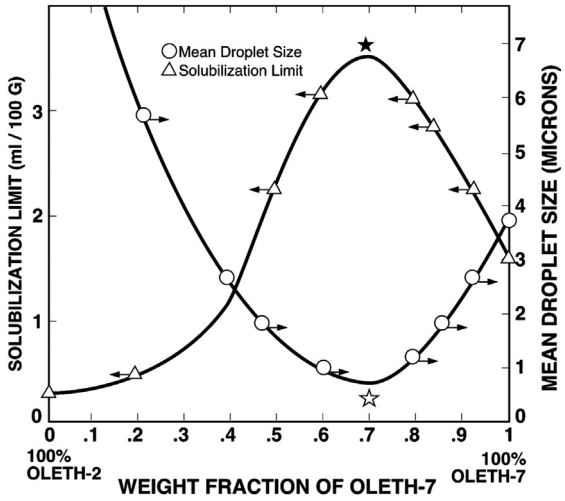



FIGURE 39.11 Solubilization and emulsion droplet size correlation for surfactant blends.

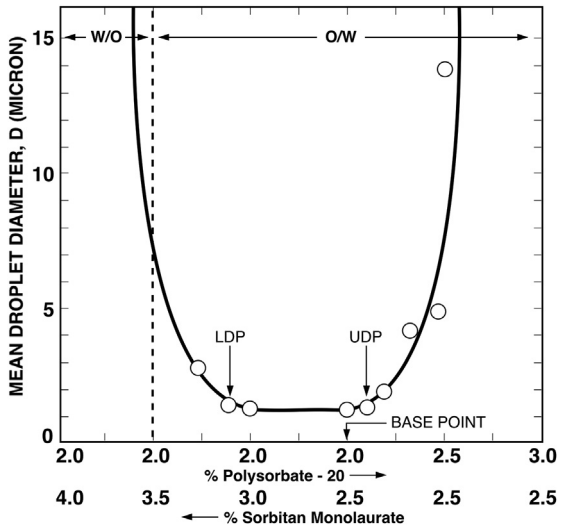



**FIGURE 39.12** Upper-degradation point (UDP) and lower-degradation point (LDP).

Another example showing the negative effects of using too much of the wrong surfactant can be seen in the experimental data presented in Fig. 39.12, using a combination of another two surfactants, polysorbate 20 and sorbitan monolaurate. As can be seen in the data presented, keeping the amount of high HLB polysorbate 20 constant, but increasing the low HLB sorbitan monolaurate gradually from 2.5% to 3.5%, produced a sudden increase of the emulsion droplet size, indicating a quality degradation indicated as LDP, a lower-degradation point. Similarly, increasing the hydrophilic surfactant, polysorbate 20, while keeping the low HLB surfactant, sorbitan monolaurate, constant, and increasing the amount of the high HLB surfactant, polysorbate 20, beyond 2% quickly degraded the emulsion, indicated as upper-degradation point (UDP). Clearly, addition of excess surfactants in both directions, higher or lower HLB, can make the emulsions unstable.

In these experiments, the sudden degradation at LDP is likely due to a phase inversion tendency caused by adding too much low HLB surfactants. The reason for the degradation at UDP appears to be more complex. In another series of experiments, I decided to focus on investigating the reasons for degradation by high HLB surfactants.

The results shown in Fig. 39.13 suggest that many surfactants can cause UDP degradation, and the likely cause appears to be the effect of adding high HLB surfactants, which interferes with the formation of primary double emulsion needed for Mechanism A to function, resulting in poor emulsification process. Further experiments indicated that any variable, whether CV or PV, that can interfere with functioning of Mechanism A will always cause degradation, and any factors that promote functioning of Mechanism A will improve the emulsification process. Therefore, understanding of the basic mechanisms was found to be highly valuable in manufacturing good emulsions while reducing the carbon footprint.

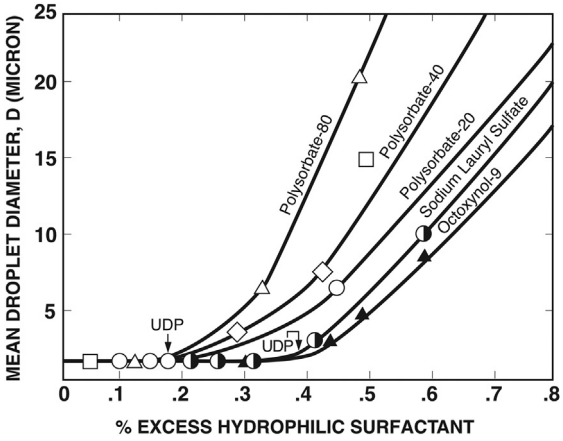



**FIGURE 39.13** Effects of excess hydrophilic surfactants on upper degradation points (UDPs).

## 39.11 OTHER APPLICATIONS OF "LESS IS MORE" PRINCIPLE AND LOW-ENERGY EMULSIFICATION

LEE was developed to increase production efficiency by reducing cooling time in processing large batches of emulsion products, but a similar method can be used to increase the productivity of many nonemulsions while reducing energy use. An example of using LEE to process a shower gel was presented at the 2014 IFSCC Congress in Paris. In this study, the energy and processing time saved in making a large 3-ton batch of a shower gel were calculated. This shower gel was based on fatty acid soap containing about 60% water. The original method of making the product was to heat all ingredients to 80°C before reacting the fatty acids with potassium hydroxide to form a soap. By heating only 20% of the water, leaving the remaining 40% as a cold alpha phase, we were able to reduce not only the processing energy by 30% but also the batch cooling time from 300 to 210 min.[12]

## 39.12 CONCLUSIONS

Global warming is a serious problem that will not go away soon, and the cost of clean energy and natural resources is expected to increase into the future. Conservation of energy and natural resources will continue to be increasingly important considerations in manufacturing our products. In this chapter, we have learned that using more energy or raw materials in manufacturing does not always lead to a better result. As demonstrated by many examples shown here, by learning to understand the laws of nature and by patiently carrying out experiments to determine the Z-Points for our formulations or process conditions, we can often not only find better solutions to our problems but also save energy and reduce processing time and cost.

## References


1. Lin TJ. Evolution of cosmetics: increased need for experimental clinical medicine. *J Exp Clin Med* 2010;**2**(2):49–52.
2. Grubow L, Jacobs V. The evolution of green in market and mind. In: Schroeder W, editor. *Sustainable cosmetic product development*. Carol Stream (IL, USA): Allured Business Media; 2011. p. 1–27.

   2a. The Montreal Protocol on Substances that Deplete the Ozone Layer. https://www.state.gov/e/oes/eqt/chemicalpollution/83007.htm.
3. Lin TJ. The Principle of less is more. In: *Manufacturing cosmetic emulsions: pragmatic troubleshooting and energy conservation*. Carol Stream (IL, USA): Allured Business Media; 2010. p. 109.
4. Lin TJ. Conventional hot processing and LEE. In: *Manufacturing cosmetic emulsions: pragmatic troubleshooting and energy conservation*. Carol Stream (IL, USA): Allured Business Media; 2010. p. 124.
5. Lin TJ. Two methods of combining alphas phase. In: *Manufacturing cosmetic emulsions: pragmatic troubleshooting and energy conservation*. Carol Stream (IL, USA): Allured Business Media; 2010. p. 126.
6. Lin TJ. Effects of emulsification temperature on anionic emulsion. In: *Manufacturing cosmetic emulsions: pragmatic troubleshooting and energy conservation*. Carol Stream (IL, USA): Allured Business Media; 2010. p. 137.
7. Lin TJ. Effect of dilution method of cationic emulsion. In: *Manufacturing cosmetic emulsions: pragmatic troubleshooting and energy conservation*. Carol Stream (IL, USA): Allured Business Media; 2010. p. 139.
8. Shinoda K, Friberg S. Stability of emulsion. In: *Emulsions and solubilization*. New York (USA): John Wiley & Sons; 1986. p. 125.
9. Lin TJ, Chang J, Pum G. Low-energy emulsification, 7: Improving emulsion quality by controlling phase-inversion and reducing energy application. In: *Paper presented at SCC Annual Scientific Meeting, New York, USA*; 2009.
10. Griffin WC. Classification of surface active agents by HLB. *J Soc Cosm Chem* 1949;**1**:311.
11. Lin TJ. Low-surfactant emulsification. In: *Manufacturing cosmetic emulsions: pragmatic troubleshooting and energy conservation*. Carol Stream (IL, USA): Allured Business Media; 2010. p. 149.
12. Lin TJ, Han AY, Lin H, Cho P. Low-energy emulsification 9: Reducing carbon footprint in cosmetic manufacturing though optimizing process variables. In: *Paper presented at IFSCC Congress, Paris, France*; 2014.

CHAPTER

# 40

# Structure and Function of Skin From a Cosmetic Aspect

*T. Hirao*

**Chiba Institute of Science, Choshi, Japan**

## 40.1 INTRODUCTION

The skin is a protective layer located at the outermost extent of the body. The purpose of cosmetics is to maintain healthy and beautiful skin. The skin is also a determinant of our appearance and is the target to which makeup cosmetics are applied. How can we keep our skin healthy? How do skin troubles occur? How can we keep our skin beautiful? Understanding the skin is essential to the development of better cosmetics and is one of the most important issues of cosmetic science.

The skin surrounds our body and is neither a simple membrane nor a cloak but has a composite structure consisting of various complex constituents well organized to play pivotal functions. In this chapter, the structure and function of the skin are described based on each of these functional constituents, and important points in understanding the relationship between skin and cosmetics discussed.

## 40.2 ROLE OF THE SKIN

The skin is located at the interface of our body and surrounding environment, protecting the body by appropriate adaptation to external environments. Although life is thought to have originated in the sea about 3 to 4 billion years ago, we now enjoy life on the land, acquiring the various benefits of sunlight directly and indirectly. However, terrestrial dry environments severely affect the maintenance of life, the retention of body water being essential. Thus, the most important and primitive function of the skin is to control water evaporation from the body to maintain life. It is proposed that life began in the marine environment and evolved to an air-breathing existence, similar to the development of a whole being from a fertilized egg via an embryo in amniotic fluid (Fig. 40.1). A discussion of the role of human skin from the viewpoint of comparative biological development is therefore appropriate.

### 40.2.1 Skin and Development

#### *40.2.1.1 The Skin in Aquatic Life*

Coelenterates, such as jellyfish, one of the simplest and most primitive multicellular biological entities, have a simple layer termed the ectoderm in their interface with surrounding seawater. Arthropods, such as crabs, have stiff shells made from hard materials to reinforce the protecting function against other stimuli. Fishes are aquatic vertebrates with a basic skin structure with dual layers: the epidermis and dermis. The epidermis, derived from ectoderm, is filled with cells. In contrast, the dermis, derived from mesoderm, has few cells and is filled with extracellular matrices including a collagen network. Fish scales cover the body, derived not from the epidermis but the dermis.

#### *40.2.1.2 The Skin in Terrestrial Life*

Amphibians such as frogs enjoy a partially terrestrial life, having developed an outermost structure resembling the stratum corneum (SC) consisting of only one cell layer. However, they have well-developed glands that secrete

*Cosmetic Science and Technology: Theoretical Principles and Applications*
http://dx.doi.org/10.1016/B978-0-12-802005-0.00040-9



Copyright © 2017 Elsevier Inc. All rights reserved.

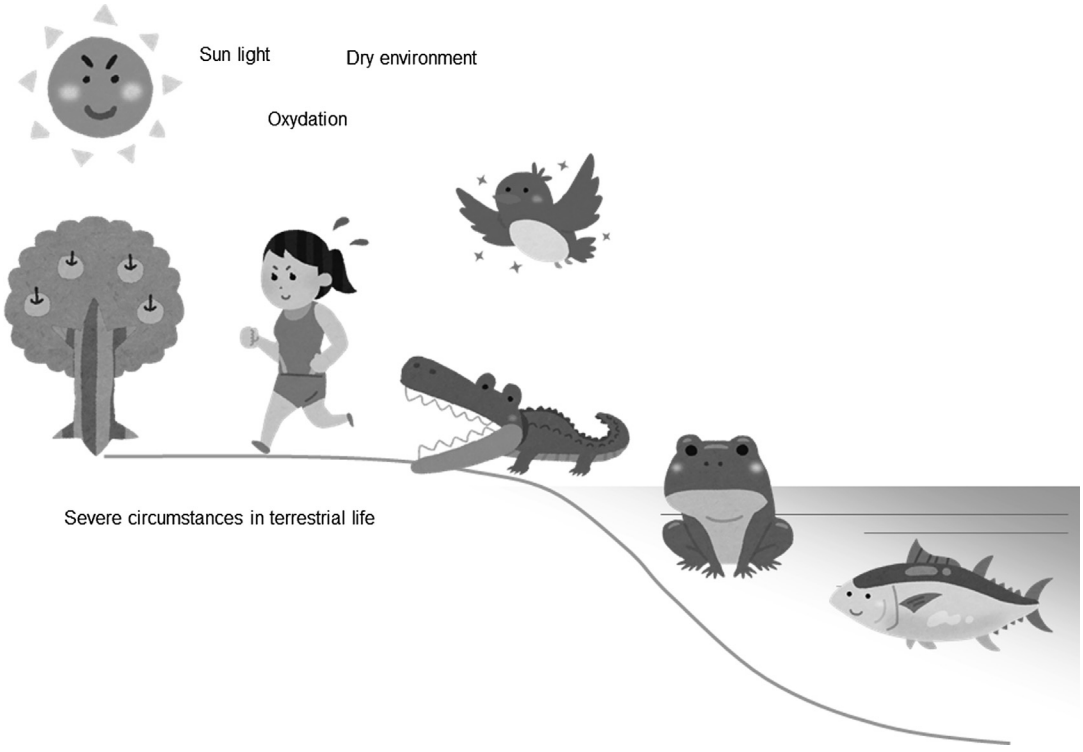



**FIGURE 40.1** Skin and development.

mucus to protect their skin from dry environments. Although the skin structure is not well developed, aspiration via the skin to incorporate oxygen from the air takes place to compensate incomplete lung function. While amphibians spend their larval stage in the aquatic environment, reptiles remain in the terrestrial environment throughout all stages of development. Reptiles have developed hard scales to confront a dry environment and prevent water evaporation from the body. They have adapted to the terrestrial environment by incorporating solar radiant heat to increase their body temperature as well as efficiently assimilating oxygen into the body via aspiration by well-developed lungs. In addition, their scales are arranged in several stratified layers of cornified epithelia whose intercellular spaces are filled with waxlike materials, the structure of which resembles the mammalian SC. Another similarity between reptiles and mammals is the continuous proliferation of epidermal cells, although replacement by molting occurs only in reptiles. Feathers, the most distinctive feature of birds, arise from the epidermis. The major constituent of feathers is so-called hard keratin, which exhibits several similarities with mammalian hair. Mammalian hairs, also derived from the epidermis, cover the body to maintain body temperature and alleviate external physical stimuli. Some hairs, such as whiskers in cats, perform a special function as an input sensor. Furthermore, in some species certain organs, including nail and hoof, are derived from the epidermis, while a horn or an antler specifically develops from a core derived from bone covered with an epidermal structure. In humans, areas covered with hair have become smaller in comparison with other mammals, with the remainder exposed directly to the external environment. Thus, the skin plays various important functions at the interface between body and environment. We now describe the principal functions of the skin.

## 40.2.2 Principal Functions of the Skin

### *40.2.2.1 Barrier Function*

Few people with healthy skin are aware that the barrier function of the skin is essential for daily life. The barrier function alleviates water evaporation from the body and controls the invasion of exogenous substances to maintain health. The human body consists of water (60−70%), protein (15%), and lipids (15%), with sugar and inorganic substances making up the remainder. It is indisputable that the water within the body is essential for life maintenance. In addition, the skin prevents the invasion of exogenous hazards, including various chemicals and pathogens such as viruses and microorganisms. A severe burn, for example, is dangerous and may be lethal in some cases depending

on the size of burned area. Damage to the barrier function by burned skin leads to loss of water from inside the body followed by invasion of exogenous microorganisms, resulting in the production of endotoxins and septic shock.

#### *40.2.2.2 Buffering Function*

The buffering function alleviates physical stimuli from outside the body. The skin acts as a cushion upon physical forces to prevent direct impact to the organs within the body. Another example of the buffering function is absorption and scattering of ultraviolet (UV) rays. Constituents in the skin, such as melanin, can absorb and scatter UV rays and protect viable cells from its hazardous effects.

#### *40.2.2.3 Control of Body Temperature*

Humans are homeothermic animal, meaning that the body temperature should be constant regardless of external temperature. A microvasculature network in the dermis delivers oxygen and nutrients to the skin. In the event of an increase in body temperature, accelerated peripheral blood circulation is initiated to promote heat loss. In addition, secretion of sweat from sweat glands via ducts is also effective in cooling the body by evaporation of secreted sweat from the skin surface. Conversely, in the case of lower external temperature than that of the body, the peripheral blood circulation decreases to prevent heat loss. Thus, the skin plays important functions as the controller of temperature difference between body and environment.

#### *40.2.2.4 Sensing Function*

The skin has sensory receptors and perceives tactile (or haptic) sense, which is one of the five senses (i.e., touch). Immediate transfer of specific stimuli, such as pressure conducted by touching something or hot and cold temperature, to the brain via the nervous system, is essential for our survival and communication.

#### *40.2.2.5 Immunological Function*

As already mentioned, the skin is equipped with a physical barrier against exogenous stimuli. Skin tissue also functions as an immunological barrier to exclude foreign invaders via inflammatory responses. Antigen-presenting cells in the epidermis, known as Langerhans cells (LCs), capture allergens and present the antigenic profiles to T lymphocytes, leading to recruitment of immune-competent cells to the skin to prevent further invasion.

#### *40.2.2.6 Determination of Appearance*

The skin is located at the outermost extent of the body and determines our appearance. Skin color is mainly controlled by two chromophores, melanin in the epidermis and hemoglobin in the erythrocytes, circulating within microvasculature in the dermis. Furthermore, skin surface morphology, such as microrelief consisting of ridges, furrows, and various wrinkles, can affect the appearance of the skin. Thus, skin appearance is determined by various factors and greatly affects human communication and kinship. The skin is also the main target of decorative makeup and plays a pivotal role in self-expression.

## 40.3 FUNDAMENTAL STRUCTURE OF THE SKIN

The skin is the largest organ in humans, its area reaching 1.6−1.8 $m^2$ in adults. The fundamental structure of the skin consists of three layers from outside to inside, namely the epidermis, dermis, and subcutaneous tissue (subcutis) (Fig. 40.2). The epidermis is 0.1−0.2 mm in thickness and is tightly filled with cells including epidermal keratinocytes. The dermis is 1−2 mm thick and contains fewer cells than the epidermis, but has abundant extracellular matrices such as collagens, affecting the physical properties of the skin. The blood circulation network operates in the dermis, providing oxygen and nutritional components to the skin. The subcutaneous tissue stores fats, its thickness varying among anatomical sites and individuals. Additional organs, collectively known as appendages, include hair follicles, sebaceous glands, and sweat ducts. A hair shaft is an exposed portion of the hair, whereas hair roots where continuous hair growth develops are buried within the skin, the deepest reaching toward the subcutis. Hair shafts in the skin are surrounded by hair follicles, and sebaceous glands open the duct to the follicle tissue. In the sebaceous glands, sebocytes actively synthesize and secrete sebum. Secreted sebum is delivered along the hair shaft and spreads to the skin surface. Sweat glands are independent organs, and synthesized sweat is secreted to the skin surface via sweat ducts. Nails, which originate in the epidermis, are also considered appendages.

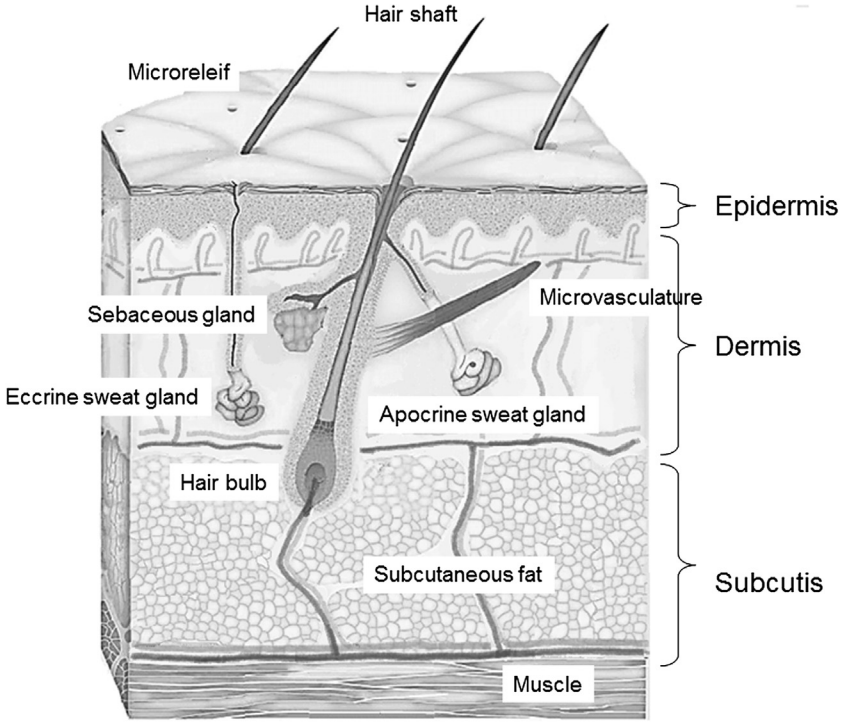



FIGURE 40.2 Fundamental structure of the skin.

## 40.4 EPIDERMIS

### 40.4.1 Homeostatic Proliferation and Differentiation of Epidermal Keratinocytes

The epidermis is 0.1−0.2 mm thick, and epidermal keratinocytes constitute 90% of epidermal cells. Based on morphological characteristics, the epidermis is divided into four layers, namely the basal layer, the spinous layer, the granular layer, and the SC (cornified layer), and cells in each layer are named basal cells, spinous cells, granular cells, and corneocytes (cornified cells), respectively. Cells other than epidermal keratinocytes in the epidermis consist of melanocytes (which produce melanin pigments), LCs (antigen-presenting cells initiating immune response), and Merkel cells (a type of neural crest cell), each of which occupy varying fractions interspersed throughout the epidermis.

The basement membrane is located at the interface between the epidermis and dermis, and comprises various proteins including type VI collagen and laminin 5, and basal cells are attached to the basement membrane by hemidesmosomes. The basal cells attached to the basement membrane proliferate and differentiate into spinous cells, granular cells, and corneocytes, with morphological changes and outer translocation, and finally detach in the outermost layer. This differentiation of epidermal keratinocytes is called keratinization or cornification, which is a continuous and consistent process. This constant renewal of the epidermis is known as epidermal turnover. Keratinization proceeds as follows.

#### *40.4.1.1 Retention of Basal cells and Undifferentiation*

In the basal layer, divided cells begin to differentiate but no subsequent cells appear if all of the divided cells initiate differentiation. In this case existence of epidermal stem cells is suggested, which maintain undifferentiated status and continuously provide new epidermal keratinocytes. Epidermal stem cells proliferate less and divided daughter cells are amplified transiently (transiently amplified cells) several times over, followed by differentiation into spinous cells. Basal cells attached to the basement membrane maintain undifferentiated status by integrin-mediated signal transduction.

#### *40.4.1.2 Differentiation into Spinous Cells and Granular Cells*

Epidermal keratinocytes detached from the basement membrane begin to differentiate into spinous cells, which are characterized morphologically by spinal adhesion structures around the cells called desmosomes, consisting of

proteins such as desmoglein and desmocollin. Gene-expression profiles of spinous cells differ markedly from those of basal cells. For example, keratins 5 and 14 expressed in the basal cells are replaced with keratins 1 and 10 in the spinous cells, and differentiation-induced genes, such as involucrin, are then expressed. These molecules can distinguish the differentiated from undifferentiated cells and are well known as differentiation markers. Next, spinous cells differentiate into granular cells, which exhibit flat morphology with abundant granules within the cytosol. The granules include two groups, lamellar granules and keratohyalin granules. Lamellar granules contain precursors of intercellular lipids as described following, in which the lamellar structure, a layered structure of organized lipids, can be observed by electron microscopy. Keratohyalin granules consist of aggregates of phosphorylated profilaggrin (a macroprotein with 10−12 repeats of filaggrin units) and insoluble protein aggregates such as loricrin.

#### *40.4.1.3 Differentiation into Corneocytes*

The development from granular cells to corneocytes represents a drastic change. Morphologically the nucleus and intracellular microorganisms are digested, and plasma membranes also disappear, so that the cornified envelope (CE), which is composed of various cross-linked proteins and has formed beneath the plasma membrane, comprises outermost corneocytes. Precursors of intercellular lipids, which are packed within lamellar granules in granular cells, are extruded into intercellular spaces between corneocytes. These events are accompanied by the death of the epidermal keratinocytes. Thus, corneocytes are dead cells but are still metabolically active so that components of corneocytes are continuously created. In other words, on transfer into the SC the corneocytes are immature, and maturation toward being fully equipped to accomplish barrier and moisturizing functions is continuously ongoing.

Thus, epidermal keratinocytes divided in the basal layer are differentiated from basal cells, spinous cells, granular cells, and corneocytes, and finally are shed in the outermost layer as squames. A balanced rate of proliferation and differentiation of keratinocytes and shedding of corneocytes results in homeostasis of the epidermis while cells in the epidermis are continuously renewed (epidermal turnover). The rate of epidermal turnover becomes slower with aging, whereas an accelerated turnover rate is observed under inflammatory conditions. An accelerated turnover rate sometimes results in an incomplete keratinization process, leading to a functionally abnormal SC (e.g., parakeratosis). Constant consecutive turnover of the epidermis at an appropriate rate is essential for healthy skin.

### 40.4.2 Structure and Function of the SC

#### *40.4.2.1 Composite Structure of the SC*

The SC is located at the outermost layer of the skin and is only 10−20 μm thick. This thin structure plays a pivotal role in the barrier function of the skin. The SC comprises flat dead corneocytes differentiated from epidermal keratinocytes and intercellular lipids filling spaces between the corneocytes, and the SC is often illustrated as bricks and mortar. Bricks correspond to corneocytes containing abundant fibrous protein, namely keratins, which determine physicochemical properties such as plasticity and elasticity of the SC itself, although the properties are largely affected by water content. In contrast, mortar corresponds to intercellular lipids consisting mainly of ceramides, cholesterol, and free fatty acids, which form a packing crystal structure and lamellar layers and play essential roles in the barrier function of the SC. Furthermore, the CE, which is the wrapping structure around corneocytes, also plays an indirect but important role in the barrier function of the SC by providing a scaffold for intercellular lipid organization (Fig. 40.3).

The SC is continuously renewed alongside epidermal turnover. In the SC corneocytes are stratified into 10−20 layers while the outermost corneocytes are shed habitually. Corneocytes within the SC are rigidly attached to each other via an adhesion structure, corneodesmosome, consisting of a protein complex with desmoglein,

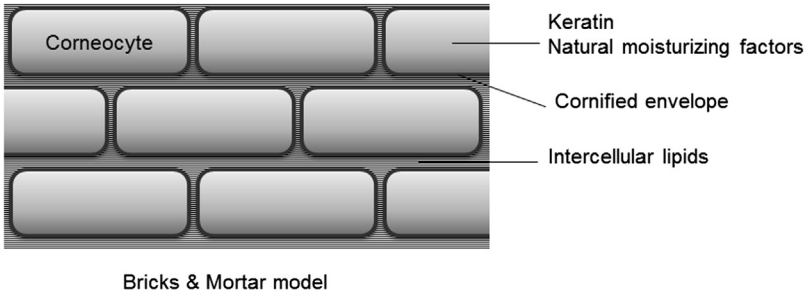



FIGURE 40.3 Structure of the stratum corneum.

desmochollin, and corneodesmosin, so that corneocytes scarcely dissociate. In contrast, corneocytes easily dissociate in the outermost layer because constituents of corneodesmosome have been digested by certain proteases. In healthy skin the rates of epidermal growth and corneocyte shedding are well balanced, so SC renewal continues unnoticed.

Imbalance, however, is often encountered in some individuals. For example, severe sunburn results in peeling skin. Severe sun exposure causes inflammation associated with temporal upregulated epidermal growth after which overgrown epidermal keratinocytes move to the SC, leading to incomplete dissociation of corneocytes and desquamation manifesting as aggregated squames. Similarly, rough skin is encountered in various situations such as imperceptible inflammation, imbalance of proliferation and differentiation of epidermal keratinocytes associated with incomplete keratinization, and retardation of corneodesmosome breakdown caused by decreased water content in the SC. These phenomena are often termed incomplete keratinization, although their clinical presentation varies widely. Parakeratosis is one of the typical features of incomplete keratinization and is characterized by remnant nuclei which, under healthy conditions, would be digested and disappear in corneocytes. A rough skin surface with squamous aggregate is not cosmetically acceptable because it presents with rough texture and a dirty appearance, and is less compatible with makeup.

As already described, the SC has a structure quite distinct from other viable cells in achieving barrier function, which is prepared gradually through the keratinization process. Various proteins including structural components and enzymes are synthesized readily according to genetic code and delivered to appropriate positions, thus to function promptly and create SC components. It is not an understatement to say that the epidermis is an extensive factory with the SC as its final product. The following describes the formation process of major components of the SC (Fig. 40.4).

### *40.4.2.2 Constituents of the SC*

#### 40.4.2.2.1 Keratin

Keratin is a group of fibrous proteins of 40−60 kDa molecular size, consisting of a cytoskeletal fiber network divided into two groups, type I (acidic) keratin and type II (basic) keratin. Besides the various numbers of keratins identified, in the epidermal keratinocytes keratins 5 and 14 are expressed in the basal layer, and keratins 1 and 10 are expressed in the differentiated layer after the spinous layer. These paired keratins form a heterodimer and assemble into intermediate filaments 10 nm in diameter. Thus, keratin fibers function as cytoskeletal components in living cells, while they form an insoluble rigid structure in the corneocytes by aggregation of filaments to keratin bundles. Keratin constitutes 80% of protein in the SC and is a major determinant of its physicochemical stiffness.

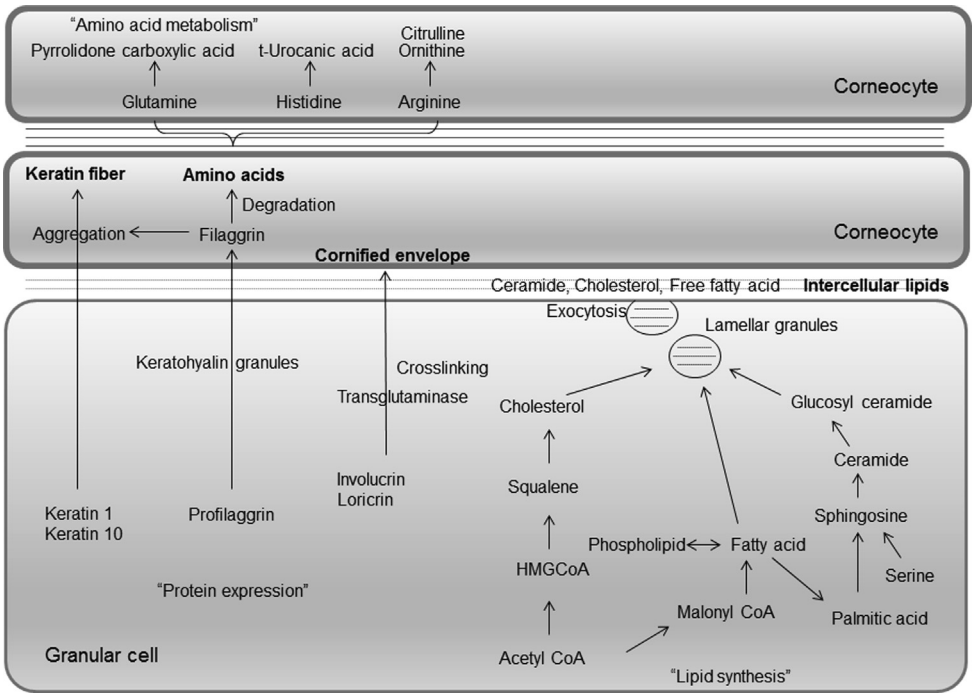



FIGURE 40.4 Biosynthetic process of constituents of the stratum corneum.

#### 40.4.2.2.2 Cornified Envelope

The CE is a membrane-like insoluble structure surrounding corneocytes formed by the cross-linking of various precursor proteins, including involucrin and loricrin, which are expressed in the spinous and granular layers along with keratinocyte differentiation. Cross-links are formed by transglutaminases between lysine residues and glutamine residues within precursor proteins. In living granular cells the CE is formed beneath the plasma membrane and becomes the outermost surrounding envelope-like structure of the corneocytes in the SC, because the plasma membrane is digested and disappears upon transition to the SC. Furthermore, ω-hydroxyceramides and ω-hydroxy fatty acids are bound to the outer component of CE by ester bonds to create corneocytes coated with lipids, for which the hydrophobic structure is assumed to provide a scaffold for organization of intercellular lipid matrices.

#### 40.4.2.2.3 Intercellular Lipids

Intercellular spaces between corneocytes are occupied by lipids mainly composed of ceramides, cholesterol (and its ester), and free fatty acids. These lipids are synthesized de novo along with differentiation of epidermal keratinocytes and are stored at lamellar granules appearing in the granular layers. Upon transition of granular cells to corneocytes, the content of lamellar granules is secreted by exocytosis into intercellular spaces; a recent study reported that this secretion does not depend on secretion of independent granules but on spatially contiguous architecture. In addition, these lipids construct highly organized crystals via enzymatic conversion of precursors into mature molecules.

Construction of organized crystals of intercellular lipids is essential for optimal barrier function in the SC. Each of the molecules, such as ceramides, cholesterol, and free fatty acids, have hydrophobic aliphatic hydrocarbon chain(s) and hydrophilic polar head(s), and alignment of the orientation of polar head groups with equimolar ceramides, cholesterol, and free fatty acids is necessary for packing of the crystal structure. In addition, this crystal structure is stratified into several layers forming a lamellar structure of intercellular lipids, which is not homogeneous but heterogeneous, with a characteristic domain. An X-ray diffraction study suggested that there is not only long-periodicity with a 13-nm interval but also short periodicity with a 6-nm interval. Furthermore, other factors reinforce the organization of lipid structure: ceramide 1, a long-chain fatty acid ester-type ceramide, penetrates lamellar layers to work like a rivet, and the CE provides a scaffold for intercellular lipids, as mentioned previously.

#### 40.4.2.2.4 Natural Moisturizing Factors

The SC has the potential to retain water in itself, i.e., the moisturizing function. The SC contains low-molecular-weight water-soluble molecules, which play an essential role in the moisturizing function and are called natural moisturizing factors (NMFs) because they occur endogenously in the SC. NMFs consist of amino acids (and their derivatives), organic acids (e.g., lactic acid, citric acid), and mineral salts. These small molecules are hydrophilic and moisturize originally hydrophobic keratin to retain water molecules. The production process of amino acids in the SC is noteworthy. Amino acids in the SC are not derived directly from penetration via blood circulation but are produced by degradation of a precursor protein, filaggrin, which is a huge molecule synthesized in the epidermal keratinocyte that is degraded by certain proteases into amino acids to function as NMF. In more detail, filaggrin is synthesized as profilaggrin with 10−12 repeats of filaggrin units and is stored in keratohyalin granules in the granular cells. Then, upon transition to the SC, profilaggrin is partially degraded into filaggrin to aggregate keratin fibers in the corneocytes, and filaggrin is finally degraded into small amino acids to function as NMF. Various proteases are involved in the processing of filaggrin into amino acids, including calpain, caspase 14, and bleomycin hydrolase. In other words, filaggrin plays two pivotal roles, reinforcing the physical properties of the SC by keratin aggregation and performing a moisturizing function in the SC by NMF production. NMFs consist of water-soluble molecules and are easily released upon cleansing with water or bathing, leading to a decrease in NMF and a less-moisturized SC. Under such dry skin conditions, skin care cosmetics are effective in improving the moisturizing function of the SC. Interestingly, it has been suggested that a filaggrin gene mutation(s) is related to the pathophysiology of a certain form of atopic dermatitis associated with dry skin and barrier disruption.

Some types of amino acids produced by degradation of filaggrin are further metabolized in the SC. Glutamine is converted to pyrrolidone carboxylic acid (PCA), which is hygroscopic and exhibits excellent water-retaining properties. Histidine is enzymatically converted to urocanic acid, which has UV-absorbing properties and is considered an endogenous sunscreen. Thus, the SC can produce essential components via sophisticated processes to maximize

its functions. In contrast, organic acids, such as lactic acid and citric acid, are found in the SC and are considered to be derived, at least in part, from sweat.

#### *40.4.2.3 Gradients in the SC*

While the SC is a thin structure of 10−20 μm depth with 10−20 cell layers, the SC is not homogeneous in perpendicular orientation and various gradients are observed within the SC. In the deeper layer of the SC, immediately after transition from granular layer, structural components are incomplete and immature, and thereafter are completed and matured in the middle portion of the SC. For instance, degradation of filaggrin proceeds within the SC and content of free amino acids peaks in the middle part of the SC. The structure of intercellular lipids is also well organized in the mid-SC. Cross-linking of CE proteins also depends on the depth of the SC, and immature CEs are abundantly detected in the deeper layer of the SC. In contrast to these maturation processes toward the mid-SC, some components exhibit alteration toward the outermost layer. Free amino acids such as NMF gradually decrease, presumably because of elution by washing routines, and the organized intercellular lipid structure is also perturbed in the outer SC. In line with these perpendicular changes, a water gradient is also observed within the SC. The deepest SC exhibits approximately 60% water content relative to the granular layer, gradually decreasing to about 30% in the outermost SC, which correlates with the NMF gradient peaking in the middle region of the SC. Corneodesmosomes, which are junctional protein components between corneocytes, are gradually degraded by various proteases toward the outermost SC. Many studies have revealed the complicated mechanisms of corneodesmosome degradation; various proteases and endogenous inhibitors are involved in the control of its degradation, resulting in final degradation of corneodesmosomes in the outermost SC shedding corneocytes by weakening their cohesiveness. Thus, various events occur dynamically in each portion of the SC, leading to maintenance of its homeostasis.

## 40.5 DERMIS

The greater part of the dermis is occupied by extracellular matrices. The major components are collagen, which mainly consists of type I and type III collagens. Collagens consist of fibrous proteins that form a triple-helical structure with three collagen molecules intermolecularly cross-linked, leading to hierarchical architecture of collagen matrices. The physicochemical stiffness of collagen matrices is easily assumed from the robustness of leather materials widely used in daily life. Another major protein component of the dermis is elastin, consisting of elastic fiber in the dermis, which exhibits elastic properties not unlike those of a spring. Elastic fibers, together with collagen fibers, construct network architecture in the dermis and provide physical properties for recovery upon deformation of the skin. Interspaces among these protein structures are occupied by various mucopolysaccharides, such as hyaluronic acid, chondroitin sulfate, and heparan sulfate, which can retain abundant water.

In contrast to the epidermis filled with cellular components, few cells exist in the dermis. These include fibroblasts producing extracellular constituents described earlier, endothelial cells consisting of microvasculature, mast cells located around the microvasculature and involved in allergic inflammation, and lymphatic endothelial cells of lymphatic vasculature, among others. Blood circulation via microvasculature in the dermis supplies oxygen and nutrient factors throughout skin tissues and is involved in the recovery of waste metabolites as well as lymphatic tissues.

The metabolic rate of extracellular components produced by dermal fibroblasts is slower than that of epidermal components, and turnover of the components determined by production and degradation in the dermis proceeds very slowly. While epidermal components are renewed within several weeks, renewal of dermal components requires longer than months, sometimes years. However, performance in synthesizing extracellular components gradually declines with age, leading to thinning of the skin, less elasticity, and further alteration as sagging accompanies declining performance of muscles.

In sun-exposed areas, characteristic symptoms of so-called photoaging can appear. One of the typical changes is a decrease in collagen in the dermis caused by degradation by enzymes such as matrix metalloproteinases, which are overexpressed by UV radiation. In contrast, elastic fibers are denatured and aggregated, so-called elastosis. These changes in the dermal components lead to a less elastic dermis with wrinkles, which are typical features of photoaged skin. Enzymes involved in proteolysis of collagen matrices are produced not only by dermal fibroblasts but also by leukocytes infiltrating from the microvasculature under inflammatory conditions. Dermal alterations associated with photoaging are prominent in the papillary dermis, easily reached by solar radiation rays. Alterations of

microvasculature in the papillary dermis associated with inflammation include fragility of capillary blood vessels, angiogenesis to compensate vascular damage, and leukocyte migration. These events accelerate dermal alterations in photoaging.

## 40.6 APPENDAGES

As already described, skin basically consists, from outer to inner, of a three-layered structure, the epidermis, dermis, and subcutaneous tissue. Skin structures other than this basic structure are called appendages, which include the sebaceous glands, sweat glands, hair (hair follicles), and nails. In this section, characteristics of sebaceous glands and sweat glands are described.

### 40.6.1 Sebaceous Gland

The sebaceous gland is located in the dermis, and the duct opens into the hair follicle to secrete sebum. Sebum contains triglycerides as major components, followed by wax esters (esters with higher alcohol and fatty acid), squalene, and cholesterol esters, and is synthesized in sebocytes, a type of epithelial cell mainly found in the sebaceous gland. Sebum ruptured by sebocytes upon cell apoptosis is secreted onto the skin surface along the hair shaft.

The quantity of sebum varies depending on genetic background and is acknowledged as one of the factors determining skin types. Skin types with rich sebum are generally classified as oily skin. The profile of sebum production is hormone dependent and actively produced by testosterone and progesterone. Therefore, sebum production in females increases in puberty, largely affected by menstrual cycles in adulthood, and gradually declines with age. It is noteworthy that activity of sebaceous glands varies depending on anatomical areas: scalp, forehead, and nose are the areas with active sebaceous glands, followed by the upper back. The forehead and nose are the so-called "T-zone," which is rich in sebum production. Excess production of sebum is often disliked in cosmetic terms because it causes makeup to crumble and be disturbed. Secreted sebum on the skin surface is thought to play a role in protecting the skin, but the contribution of the occlusive property of sebum to the barrier function of the skin is less dominant than that of intercellular lipids. Intercellular lipids form a packing crystal structure and lamellar structure, while sebum lipids are amorphous and do not form crystals. In contrast, sebum can affect the skin in terms of its physiological functions. The metabolism of sebum lipids by *Propionibacterium acnes*, one of the anaerobic microorganisms occurring in the sebaceous glands, should be considered. *P. acnes* produces lipases, which degrade triglycerides into free fatty acids and glycerol. Unsaturated fatty acids, such as oleic acid, as degradation products can cause hyperkeratinization of surrounding epidermal keratinocytes and promote inflammatory status, leading to generation of comedos, plumping of hair follicles, and acceleration of acne. Overproduction of sebum and overgrowth of *P. acnes* are thought to be major factors involved in the deterioration of acne, while their control is an effective acne remedy. In addition, glycerol produced by degradation of sebum triglyceride by lipase can act as an endogenous moisturizing factor. Thus, sebum has various contributory aspects in skin physiology.

### 40.6.2 Sweat Glands

Sweat glands can be classified as eccrine and apocrine glands. Eccrine glands directly open onto the skin surface and are distributed over every region of the anatomy, abundantly so over the face and palms. Eccrine sweat contains a high amount of water containing inorganic salts, such as NaCl, organic acids, such as lactic acid, and urea, in addition to trace amounts of antimicrobial peptides and bioactive proteins including cytokines and immunoglobulins. The most important and well-established role of eccrine sweat is control of skin-surface temperature by evaporation of the sweat. Eccrine sweating is regulated by the sympathetic neuronal system. Mental strain often induces sweating in the face and palms, so-called psychological sweating.

The apocrine glands are found only in the armpits and genital area, and open their ducts not to the skin surface but to hair follicles similar to sebaceous glands. Secretory mechanisms of apocrine sweat are similar to those of sebum by sebocytes; apocrine gland cells rupture sweat upon cell death. Therefore, apocrine sweat is somewhat viscous, containing more proteins in comparison with eccrine sweat. Apocrine sweat itself is not malodorous, but exhibits characteristic underarm odor upon degradation by microorganisms present in hair follicles and on the skin surface. Appropriate antimicrobial treatment can thus prevent the occurrence of underarm odor.

## 40.7 REGIONAL VARIATION OF THE SKIN

Human skin, in contrast to other mammalian skin, has coarse hair and is exposed directly to the outer atmosphere. Properties of human skin types may vary depending on anatomical region, although their basic structures are common. Palms and soles have strikingly thick SC to relieve external physical stimuli. In this section the characteristic features of the face are described, because this is a region to which many cosmetic products are applied.

The face is continuously exposed to the outer atmosphere and sunlight, is equipped with special sensory organs, is apportioned to create facial expressions to communicate with others, and is a major target of aesthetic treatment. In terms of physiological aspects, the face, compared with other anatomical regions, exhibits characteristic features with moderately thin thickness, accelerated epidermal turnover rate accompanied with relatively faster proliferation, and poor barrier function. The "epidermal factory" creating the SC for the face is always so busy that production lines work overtime, some constituents are overproduced, and the production lines are imbalanced and disorganized. Sebum is abundantly secreted in the face, although its secretion varies depending on the individual. Furthermore, according to our modern customs the face is the most exposed area to various external stimuli, including UV (sun) light, cold wind, and cleansers.

What happens in the skin on exposure to external stimuli? The most typical case is sunburn induced by sunlight. In daily life, people sometimes experience inflammation from sun exposure, accompanied with sunburn, sun tanning, and thereafter a troubling rough skin surface. These inflammatory changes are the biological responses made to exclude damaged tissue and recover. Major symptoms of skin inflammation include erythema, heat, edema, and ache, which are also present in UV-induced skin inflammation, followed by detachment of overgrown epidermis, with final recovery of healthy skin. As the face is continuously exposed to various stimuli, it is always prone to situations involving inflammatory responses, although this is not always associated with typical symptoms of inflammation as described herein. This situation is called subclinical inflammation. Subclinical inflammatory status is poorly characterized by conventional evaluation methods, although more sensitive and sophisticated techniques can distinguish and characterize subclinical inflammation of the face. Such measurements include corneocyte size, cytokines in the SC, and maturation status of the CE of corneocytes, which have revealed that the face SC has unique properties regarding subclinical inflammatory status in comparison with unexposed areas such as the abdomen, back, and inner upper arm. External stimuli, including sun exposure, dry air, and cleansers, as well as genetically determined properties of the skin, are potential complex factors affecting the subclinical inflammatory status of facial skin.

## 40.8 BARRIER FUNCTIONS OF THE SKIN

The barrier function is essential for maintaining life and is the most important function in the skin from a biological viewpoint. As described earlier, composite structure of the SC plays a central role in barrier function of the skin. In the next section, several topics regarding barrier function are described in detail.

### 40.8.1 Tight Junction

In addition to the barrier function of the SC, the tight junction, in the granular layer of the epidermis beneath the SC, also plays a role in regulating water evaporation. The tight junction is a form of adhesion structure between cells, forming a zipper-like continuous structure to regulate the translocation of molecules in extracellular spaces. It was originally discovered and studied in epithelial cells in gastrointestinal tissue separating the inside and outside of the body. Thereafter, it was revealed that the tight junction functions as a second barrier in the granular layer of the epidermis. Structural organization of the tight junction is disturbed upon UV irradiation as well as in certain forms of dermatitis, and the pathophysiological role of this junction has been reported.

### 40.8.2 Immunological Barrier

While the SC represents a physical barrier to invasion of exogenous substances, viable epidermis functions as a biological and immunological barrier to prevent further invasion of substances into the body. LCs in the epidermis, as antigen-presenting cells, play a central role as an immunological barrier; LCs capture exogenous invaders and then migrate to territorial lymph nodes to present antigenicity of the molecules to T lymphocytes. LCs are cells

derived from hematopoietic leukocytes, interspersed throughout the epidermis, and expand their dendrites, like antennae, to capture antigens efficiently. Upon reinvasion of antigens, LCs recruit T lymphocytes to induce local inflammation and thus exclude invading antigens. These responses form an immunological barrier to protect the body from exogenous hazardous substances. In this immunological barrier system, in addition to LCs as commanders, epidermal keratinocytes also play important roles in modifying immunological reaction in the skin. For example, epidermal keratinocytes abundantly express various cytokines to regulate immunological reactions depending on the phases of immune responses. In the effector phase, keratinocytes produce cytokines to activate immune responses, and in some situations produce inhibitory cytokines to suppress immune responses. Furthermore, epidermal keratinocytes express various adhesion molecules, such as ICAM-1, to create circumstances whereby lymphocytes can easily migrate to the inflammatory regions. Thus, the skin can be considered as a frontier immunological organ, and the concept of skin-associated lymphoid tissue (SALT) has been proposed. These immunological responses are essential events in a self-defense system, but sometimes are associated with an aesthetically unacceptable appearance such as rough skin. Improvement of barrier function of the skin without excessive inflammatory events is a cosmetically desirable goal in the maintenance of healthy skin.

### 40.8.3 Barrier Disruption by Excessive Moisturization

A dry environment leads to a decrease in water content of the SC and causes deterioration of SC function even though the SC is equipped with a specific moisturizing function. It is well established that moisturizers are effective in preventing dry skin and maintaining healthy skin, and that moisturization has a central role in skin care cosmetics. However, hypermoisturization with excessive water content in the SC may result in barrier disruption. Diaper dermatitis and glove dermatitis, which is induced by wearing a water-impermeable glove for a long period, are typical cases of hypermoisturization. Under these conditions, water evaporation from the skin is continuously suppressed by occlusion, resulting in hypermoisturized SC, which can incorporate abundant water. At first water is incorporated into corneocytes, which swell. Further incorporation of water in the SC results in breakdown of the lamellar structure of intercellular lipids, and a so-called water pool appears whereby the barrier function of the SC is severely disrupted and not only water, but also various chemical substances and hazards, can easily pass through the SC. Diaper dermatitis causes inflammation associated with damaged barrier function, and invasion of irritable substances and fecal microorganisms into the skin. Thus, while the SC should be moisturized to prevent dry skin and maximize its performance, overdosed, continuous moisturization might result in deterioration of barrier function.

### 40.8.4 Control of Percutaneous Penetration and Transdermal Drug Delivery

Barrier function is one of the pivotal functions of the skin in avoiding invasion of hazards in terms of biological defense. In contrast, excellent barrier function is a disadvantage for transdermal drug delivery, which transfers a drug effectively into the skin. The occlusive dressing technique is an empirically optimized method to facilitate transdermal delivery by occlusion of skin, topically applied with an appropriate formula and adequate coverage, which utilizes disruption of the barrier function of the SC by artificial hypermoisturization as described previously. Another approach to enhance percutaneous absorption is to loosen the crystal structure of intercellular lipids by chemical penetration enhancers, such as oleic acid, menthol, and azone. These techniques can be applied to cosmetics as well as clinical medicine to effectively deliver specific active agents. Selective control of the barrier function of the SC promises to be an important technical issue in the future.

## 40.9 CONCLUSIONS

This chapter describes the structure and function of the skin, focusing particularly on the issues related to cosmetic aspects. Nowadays various approaches can be applied to maintain healthy and beautiful skin. For the commercial use of cosmetics, the main target of treatments is the SC, located on the surface of the skin. In contrast, in medical treatment the targets include viable tissues from the epidermis and dermis downward to the deeper subcutis. According to current regulations, the targets of cosmetics are limited. In the future, however, the development of more innovative options to maintain healthy skin is expected, based on the expanding knowledge of mechanisms of the skin revealed by novel approaches.

CHAPTER

# 41

# Skin Lipids

*Y. Uchida*[1,2,3]

[1]University of California, San Francisco, CA, United States; [2]Department of Veterans Affairs Medical Center, San Francisco, CA, United States; [3]Northern California Institute for Research and Education, San Francisco, CA, United States

## 41.1 INTRODUCTION

Skin is comprised of four compartments: epidermis, dermis, subcutaneous fat, and skin appendages (sebaceous glands, hair, sweat glands). Lipids of each cutaneous compartment, as well as in extracutaneous cells, form membrane structures; and some lipid species serve as lipid modulators to regulate cellular functions such as cell proliferation, differentiation, cell death, cytokine production, and cell motility. In addition to these general roles that lipids play in cells, lipids in epidermis, sebaceous glands, and adipose (fat) tissue also have unique molecular structures, and play distinctive metabolic and biological roles in skin functions. These tissues' lipids are described herein, and because the roles of lipids and unique lipid species in hair remain unresolved, hair lipids are not discussed here. Additionally, since the majority of cosmetic products (moisturizers, sun protection, and makeup) maintain/improve normal skin conditions through epidermal treatment, the author is focusing on epidermal lipids in this chapter.

## 41.2 LIPIDS IN SKIN

Lipids are categorized as fatty acid (FA), glycerolipid, glycerophospholipid, sphingolipid, sterol, and wax in mammalian species. All classes of lipids are contained in the skin.

### 41.2.1 Lipids in the Sebaceous Gland

The sebaceous gland, characterized as an exocrine gland, is present in most skin sites except the soles and palms. In particular, an abundant number of sebaceous glands are distributed on the face and scalp. These glands produce sebum, which is comprised predominantly of triglycerides, wax ester, squalene, and free FA. The major FA compositions of both free FA and triglyceride in human are C16:0 (palmitic acid) and C14:0 (myristic acid).[1] The content of Δ9, 12 (linoleic acid) is decreased in the sebum of acne vulgaris patients, while C18:2 Δ5, 8 (Sebaleic acid) is increased.[2] Yet, the mechanism responsible for changes in these FA compositions is unknown. Sebaceous glands also contain relatively high amounts of squalene, which is enriched in some species of plants and in shark liver. Squalene is in the terpenoid family, consisting of 30 hydrocarbons with six unsaturated carbon bonds, and it becomes a precursor of sterol lipids. Because squalene is highly unsaturated, it is easily oxidized by oxidative stress, such as ultraviolet (UV) rays and oxidants. Such an oxidized hydrocarbon can produce a hydroxyl radical that could prompt inflammatory responses. Yet, it remains unknown whether oxidized squalene contributes to the inducement of inflammation in in vivo skin.

Free FA of sebum regulates skin surface acidification, in part to fortify the antimicrobial barrier in the skin. However, excess sebum production occurs in skin with acne and worsens acne symptoms.[3] Excess sebum production is also part of the pathogenesis of dandruff.[4] A fungus, *Malassezia* species, colonized in this diseased skin, produces and secretes lipases,[5,6] leading to hydrolysis of triglycerides enriched in sebaceous lipid to generate FA. These FAs show an inflammatory response that exacerbates dandruff conditions as well as utilizing FAS as nutrients for fungus.[7]


http://dx.doi.org/10.1016/B978-0-12-802005-0.00041-0

Copyright © 2017 Elsevier Inc. All rights reserved.

## 41.2.2 Lipid in the Cutaneous Adipose (Fat) Tissue

Cutaneous adipose (fat) tissues are classified by white adipose tissue (WAT) and brown adipose tissue (BAT).[8] WAT and BAT serve as thermal insulation and heat generators, respectively.[8] WAT is distributed in both subcutaneous and visceral areas. Visceral WAT is involved in various metabolic syndromes such as obesity and insulin resistance,[9] i.e., the WAT of visceral fat produces an inflammatory cytokine, TNF, as well as adiponectin, resistin, and leptin. Excessive TNFα compromises the insulin receptor in the muscle and adipose tissue, leading to insulin resistance. The mitochondria produce ATP through generation of a proton gradient due to the respiratory chain of oxidative phosphorylation, while the mitochondria in the BAT uncouple the respiratory chain of oxidative phosphorylation by uncoupling a protein resulting in the generation of heat instead of ATP production.

Triacylglyceride is a major lipid component of adipocytes. C16:0 (palmitic acid) and C18:1 (oleic acid) are major components of triglycerides in humans.[10] Carbon chain lengths of triacylglyceride species containing C18:2 (linoleic acid) are enriched in the epidermis.[11] FA composition is not significantly different in dissimilar depths of fat tissue in skin.[12] Studies of experimental animals and humans demonstrated that the FA composition of diet reflects triacylglyceride FA profile, e.g., Refs. [13,14]. However, how changes in the FA composition of triacylglycerol affect cellular functions remains unresolved.

## 41.2.3 Lipid in the Epidermis

### *41.2.3.1 Epidermal Structures*

Epidermis is comprised of stratum basale (basal cell layer), stratum spinosum (spinous or prickle cell layer), stratum granulosum (granular cell layer), and stratum corneum (horny cell layer). Epidermal cells consist of keratinocytes, melanocytes, and immune cells such as Langerhans cells and Merkel cells. Because >95% of epidermal cells are keratinocytes, lipids of keratinocytes represent epidermal lipids. Keratinocytes are proliferated at the basal cell layer and then differentiated to the suprabasal, granular, and horny cell layers.

The cuticle of terrestrial plants directly faces the external environment and is continuously exposed to external stress, such as UV irradiation and other types of oxidative stress, dryness, xenotoxic chemicals, and microbes. To protect host cells/tissues from these insults, the plant cuticle has acquired a barrier function during evolution.[15] Similar to plants, the epidermis of mammals living in a terrestrial environment has acquired protective barriers, with lipids being a critical component of these barriers in both plants and mammals. However, the responsible lipids are different in plants and mammals. Wax esters and alkanes are barrier constituents in plants, while cholesterol, FA, and ceramide are in mammals. Not only the mechanical removal of stratum corneum but also the extraction of lipids from stratum corneum using relatively mild conditions (i.e., acetone) disturbs epidermal permeability barrier function,[16] indicating that lipids are required for effective barrier formation. These barrier components are synthesized in nucleated epidermal cells, stratum basale, stratum spinosum, and stratum granulosum. Transitioned from granular to horny cell layer, keratinocytes are denucleated to become corneocytes. In contrast to other cells, including the nucleated layers of keratinocytes, corneocytes are not surrounded by plasma membranes comprised of lipid bilayer structures but instead are surrounded by cross-linked proteins, called the cornified envelope. The cornified envelope is distinct from other cellular membranes. It has a rigid structure, i.e., insoluble in 1% sodium dodecyl sulfate (SDS) containing reducing agent dithiothreitol at 100°C,[17] which likely allows it to resist mechanical stress.

### *41.2.3.2 Epidermal Lipids*

#### 41.2.3.2.1 Role of Epidermal Lipids: Nucleated Versus Denucleated Layers of Epidermal Lipids

Lipids of nucleated layers of epidermal keratinocytes are localized in plasma and cellular organelle membranes. In addition to these structural roles, some lipid species are lipid mediators (Table 41.1; and see Section 41.5). Lipids in the denucleated layers (stratum corneum) form an epidermal permeability barrier structure in the extracellular spaces.

#### 41.2.3.2.2 Alterations of Lipid Composition During Epidermal Differentiation

Free FA, cholesterol, cholesterol FA ester, ceramide, and glucosylceramide production are significantly increased in the stratum granulosum compared with stratum basale or stratum spinosum.[18] Cholesterol, free FA, and ceramide are dominant lipid species, which form epidermal permeability barrier structures in the stratum corneum. In particular, the amounts, as well as the molecular structures, of free FA and ceramide in the stratum corneum and of glucosylceramide in the stratum granulosum are unique to the epidermis. Triacylglycerol is not only important in the sebaceous glands and adipose tissue but is also a supplier of FA for omega-acyl residue of omega-O-acylceramide, which is a key barrier constituent in the stratum corneum (see Section 41.3.5.1).

TABLE 41.1 Lipid Modulator

| Lipid Modulator | Biological Effects | Involvement in Skin Disease |
|---|---|---|
| PGE2 | ↑Cell proliferation, ↑Cell migration, ↑Melanoma genesis, T Cell activation | Contact dermatitis,[110] psoriasis,[110] wound healing,[111] nonmelanoma skin cancer[112] |
| 15d-PGJ2 | ↑Sebum synthesis,[113] anti-inflammation[114] | Acne vulgaris? and seborrhea? |
| Endocannabinoid | ↓Cell proliferation, ↓sebum synthesis, antiinflammation[115] | C20:4-to-C22:4 |
| Sphingosine-1-phosphate | Antiinflammation,[116] ↑Cathelicidin antimicrobial peptide[106] | ↓S1P, atopic dermatitis?[117] |
| Ceramide-1-phosphate | ↑Human β-defensin 2 and 3 | |
| GM3, GD3, 9-O-acetyl GD3 and GD1b GT1b | ↓Keratinocyte proliferation[118] ↑Keratinocyte differentiation[119] | |

## 41.3 EPIDERMAL LIPID SYNTHESIS

### 41.3.1 Cholesterol Synthesis

Keratinocytes synthesize large amounts of cholesterol.[19] 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) synthesis from acetoacetyl-CoA by HMG-CoA synthase initiates cholesterol synthesis. HMG-CoA is then reduced to produce mevalonic acid by HMG-CoA reductase. HMG-CoA reductase is a rate-limiting enzyme of cholesterol. In addition, circulating cholesterol in low-density lipoproteins (LDL) can be incorporated by LDL receptor into keratinocytes.[20] Because statins and their derivatives inhibit HMG-CoA reductase, chemicals such as mevalotin and its derivatives are used in drugs to reduce cholesterol production. In murine skin, the epidermal permeability barrier is attenuated by topical application of statin drugs.[21] However, barrier abnormality has not been reported in human oral administration of a statin drug, suggesting that sufficient amounts of statin are not delivered into the epidermis. It also suggests that cholesterol synthesized in keratinocytes is a major source of barrier lipid.

### 41.3.2 Fatty Acid Synthesis

Fatty acids synthesized from acetyl-CoA through malonyl-CoA by FA synthase (FAS) are multienzymes of a homodimer of two protein subunits consisting of ketoacyl synthase, malonyl/acetyltransferase, dehydrase, enoyl reductase, ketoacyl reductase, acyl carrier protein, and thioesterase. FA synthase produces FA with carbon-chain lengths up to C16 (palmitic acid). Furthermore, longer FA (>C16) synthesis is conducted by FA elongation system, metabolically linked enzymes for chain elongation: 3-ketoacyl-CoA synthase (condensation), 3-keto-acyl-CoA reductase (reduction), 3-hydroxyacyl-CoA hydrase (dehydration), and 2,3 enoyl-CoA reductase (reduction). The first condensation step is catalyzed by a rate-limiting enzyme ELOVL (elongation of very long chain FAs protein).[22] Seven isoforms of ELOVL have been characterized in mammals.[23] Each isoform of ELOVL synthesizes different types of FAs, i.e., carbon chain length, saturation degrees with some overlapping of substrate specificity (Table 41.2). Pertinently, FA species over 26 carbon chain lengths (ultra very long chain FA; UVLFA) are catalyzed by only ELOVL4.[23,24] ELOVL4 is expressed in retina, brain, testis, and epidermis.[25] A rare form of autosomal dominant Stargardt macular dystrophy (STGD3) is due to a loss-of-function mutation of ELOVL4. A mutant gene knock-in homozygous transgenic mouse of STGD3 is neonatal lethal due to barrier defect-mediated dehydration.[24] The genetic status of recorded STGD3 patients is heterozygous and shows eye, but not skin, symptoms,[26] suggesting that approximately 50% of normal ELOVL4 level is sufficient to maintain epidermal barrier function, or the patients adapt to a terrestrial environment by an unknown compensating mechanism. Since ELOVL1 is required to synthesize >C24 FA (substrates of ELOVL4), ELOVL1-deficient mice are also neonatal lethal.[27] Ultra long chain FA (ULCFA) is expressed in certain tissues, i.e., retina, meibomian gland, brain, skin, liver, and testis.[28] ULCFAs are present as free FAs and also incorporated in amide-linked FA of ceramide and glucosylceramide (see Section 41.3.5). Because there are redundancies of ELOVLs to synthesize <C24 FA, ELOVL deficiencies other than ELOVL1 and

TABLE 41.2 FA Elongation

| FA | ELOVL | ELOVL | | ELOVL | |
|---|---|---|---|---|---|
| **Saturated** | **6, (3, 7)** | **Monounsaturated** | **3, (6, 7)** | **Polyunsaturated** | |
| C16:0-to-C18:0 | 3, (7) | C18:1-to-C20:1 | 1 | C18:3-to-C20:3 | 5 |
| C18:0-to-C20:0 | 1, 3 | C20:1-to-C22:1 | 1 | C20:4-to-C22:4 | 2,5 |
| C20:0-to-C22:0 | 1, 3, (7) | C22:1-to-C24:1 | 1 | C22:4-to-C24:4 | 2 |
| C22:0-to-C24:0 | 1, (3) | >C26:1 | 4 | C20:5-to-C22:5 | 2,5 |
| C22:0-to-C26:0 | 1, (4) | | | C22:5-to-C24:5 | 2 |
| >C26:0 | 4 | | | >C26:4, 26:5, 26:6 | 4 |

ELOVL without parenthesis and with parenthesis are primary and secondary (less activity), respectively.

ELOVL4 are not neonatal lethal but do cause an epidermal permeability barrier abnormality, indicating that ceramide species containing ULCFA are essential for effective permeability barrier formation.

#### *41.3.2.1 Hydroxylation of Fatty Acids*

In addition to nonhydroxy FAs, the epidermis contains 2(α)-hydroxy and omega (ω)-hydroxy FA.

##### 41.3.2.1.1 2(α)-Hydroxylation

2-hydroxy hydration is catalyzed by FA 2-hydroxylase (FA2H) to generate 2-hydroxy FA.[29] 2-hydroxy FA is enriched in sphingolipids (sphingomyelins, glucosylceramides, and ceramides) in epidermis.[24,30–32] Total amounts of 2-hydroxy FA are higher in differentiated human keratinocytes compared with undifferentiated keratinocytes.[32] Carbon chain lengths 16, 22, and 28 of 2-hydroxy FA are the major species in cultured human keratinocytes[32] and murine epidermis.[24] In addition, suppression of FA 2-hydroxylase expression in cultured keratinocytes shows partial abnormality of lamellar structures in the stratum corneum and of differentiation.[32] A mutation of FA 2-hydroxylase is a pathogenesis of neurodisorders, such as hereditary spastic paraplegia (SPG35) and brain iron accumulation.[33,34] However, skin abnormality has not been reported in SPG35 patients. Therefore another unidentified FA 2-hydroxylase synthesizes sufficient levels of free 2-hydorxy FA or other FA to maintain epidermal permeability barrier function.

##### 41.3.2.1.2 Omega (ω)-Hydroxylation

Prior study demonstrated that ω-hydroxylation of ULCFA is catalyzed by the cytochrome P450 gene 4 family (CYP4).[35] CYP4F22 was recently found to synthesize ULCFA.[36] ω-hydroxylated FA are found in carbon chain lengths of over 26 and incorporated into ceramide and glucosylceramide. CYP4F22 mutations are associated with a genetic skin disorder, autosomal recessive congenital ichthyosis (ARCI).[37,38] ARCI has significantly lower levels of ceramide containing ω-hydroxylated UVLFA.[36]

### 41.3.3 Triacylglyceride Synthesis

Diacylglyceride, which is an immediate precursor of triacylglyceride, is synthesized from monoacylglyceride by monoacylglycerol acyltransferase.[39] Diacylglyeride is also produced from monoacylglycerol phosphatidic acid by lipid phosphate phosphatase.[40] The latter, diacylglyeride, primarily serves as a lipid modulator to regulate cellular function.[40] Diacylglyceride is converted to triacylglyceride by diacylglyceride acyltransferase (DGAT). Two isoforms of diacylglyceride acyltransferase, DGAT1 and DGAT2, have been identified in mammals.[41] Importantly, DGAT2, but not DGAT1, deficient mice are neonatal lethal due to epidermal permeability barrier abnormalities.[42] As described in Section 41.3.5.1.1 ω-O-acylceramide synthesis, FA of omega-acyl residue of omega-O-acylceramide is derived from triacylglyceride.[43] Omega-O-acylceramide content is decreased in DGAT2 knockout mice epidermis.[42]

The FA composition of epidermal triacylglyceride is different in other cells/tissues. C16 and C18:1 are major FA components of triacylglyceride in epidermis, but in other skin compartments and extracutaneous tissues,[42,44] C18:2 (linoleic acid) of triacylglyceride is also enriched.[11] It has been well established that essential FA, i.e., linoleic acid, deficiency produces an epidermal permeability barrier abnormality,[45,46] suggesting that linoleic acid–enriched triglyceride, as well as ω-O-acylceramide, is a key lipid species in epidermis.

## 41.3.4 Wax Ester Synthesis

Wax esters consist of long-chain FA and alcohol. The synthetic pathway of wax esters in mammals is the same as in plants. Long-chain FA are synthesized through FA elongation systems (see details in Section 3.2) followed by conversion from FA to alcohol by fatty acyl-CoA esterase.[15] FA and alcohol are condensed by wax synthase.

## 41.3.5 Ceramide Synthesis

Ceramide is synthesized in all epidermal layers, while at a late stage of differentiation, keratinocytes synthesize heterogeneous molecular species of ceramide, including ceramide containing ULCFA and omega-hydroxylated ceramide.

### *41.3.5.1 De Novo Ceramide Synthesis Pathway*

De novo ceramide synthesis is initiated by condensation of L-serine and palmitoyl-CoA by serine palmitoyltransferase, which consists of two subunit proteins (SPTL1 and SPTL2). This condensation is a rate-limiting step. Generated 3-ketosphinganine is reduced to sphinganine (dihydrosphingosine) by 3-ketosphinganine reductase, and subsequent N-acylation of sphinganine by ceramide synthase(s).[15] Six isoforms of ceramide synthase (Cers1-6) have been identified in mammalian cells. Each of these ceramide synthases has substrate specificity (Table 41.3).[2] Following N-acylation, the sphinganine moiety is either desaturated to a sphingosine (sphingenine) backbone by desaturase-1 (DES-1) or hydroxylated to 4-OH sphinganine (phytosphingosine)[16] by desaturase-2 (or DES-2) or to 6-OH sphingosine by an enzyme, which has not yet been identified.[17] Ceramide species containing 6-OH sphingosine is unique to the differentiated epidermis. A variety of sphingoid bases and FA synthesize a total of 12 groups of ceramides, i.e., NS (Cer2), NDS, NP (Cer3), ADS, AS (Cer5), AP (Cer6), AH (Cer7), and NH (Cer8) (abbreviations indicate (1) Amide-linked FA: N, nonhydroxyl FA; A, 2-hydroxy FA and (2) Sphingoid base: D, dihydrosphingosine [sphinganine] S, sphingosine; P, phytosphingosine [dihydrosphingosine]; H, 6-hydroxy sphingosine).[47] In addition to these ceramides, four ω-O-acylceramides that contain very long-chain amide-linked FA (C28-34) with a terminal ω-hydroxyl group (ω-OH FA) are further esterified with some other FA (predominantly LA), i.e., EODS, EOS (Cer 1), EOH (Cer 4) and EOP (Cer 9).[47,48] ω-O-acylceramides are unique to the epidermis.

In addition to ω-O-acylceramide, 1-O-acylceramide is present in the stratum corneum.[49] 1-O-acyl FAs are carbon chain lengths of saturated 14−26 (C16 and C24 are major species).[49]

Genetic mutations of serine palmitoyltransferase (SPTL1 and SPTL2) and ceramide synthase 3 form the pathogenesis of hereditary sensory neuropathy, type 1[50] and autosomal recessive congenital ichthyosis associated with barrier abnormality,[51,52] respectively. The former causes distal sensory loss, foot ulcers, muscle weakness, distal motor involvement, and hypotonia. Patients carrying mutant serine palmitoyltransferase also express extra neuronal cells, including skin cells, but epidermal barrier and other skin abnormalities have not been reported. A subtype of autosomal recessive congenital ichthyosis is caused by ceramide synthase 3. Patient skin shows acanthosis with thickening of the stratum granulosum, with epidermal hyperplasia.[51] As shown in Table 41.3, ceramide synthase 3 is responsible for ceramide containing ULCFA that is utilized for omega-O-acylceramide synthesis, and mutations of this ceramide synthase show reduced acylceramide in epidermis.

#### 41.3.5.1.1 ω-O-Acylceramide Synthesis

Omega-hydroxy ULCFA and ceramide synthesis are catalyzed by CYP4F22 and ceramide synthase 3, respectively. Synthesized omega-hydroxy ultra long chain FA is conjugated with sphingosine, phytosphingosine, or

**TABLE 41.3** Ceramide Synthase

| Ceramide Synthase | FA Specificity |
|---|---|
| CerS1 | C16, C18 |
| CerS2 | C20−C24 |
| CerS3 | C24, C26, and longer. Synthesize ceramide containing ULCFA |
| CerS4 | C18−C22 |
| CerS5 | C16 |
| CerS6 | C14, C16 |

6-hydroxy sphingosine to produce omega-hydroxy ceramide by ceramide synthase 3.[52] Subsequently, the omega-hydroxy group is esterified by FA, which is derived from triacylglyceride[43] to synthesize EOS, EODS, EOH, and EOP. Linoleic acid is a predominant esterified FA of ω-O-acylceramide.[53,54] As described earlier (Section 41.3.3), triglyceride synthesized by DGAT2 from diacylglyceride releases FA by triacylglyceride lipase activated by CGI-58 (α/β-hydrolase domain containing protein 5, ABHD5) that is an activator protein of adipocyte triacylglyceride lipase (ATGL). A loss-of-function mutation in CGI-58 genes causes Dorfman—Chanarin syndrome (DCS), an autosomal recessive, neutral lipid storage disorder with ichthyosis.[55] Both DCS patient skin and knockout mouse of CGI-58 show significant decreases in acylceramide, accumulation of triacylglyceride, and defective epidermal permeability barrier function, while ATGL deficiency does not develop barrier defects.[56] Therefore, an unidentified triacylglyceride lipase, which requires CGI-58, should be responsible for FA release from triacylglyceride utilized for omega-O-acylceramide synthesis in epidermis. In parallel, omega-O-esterified linoleic acid of omega-acylceramide and C16: Δ1 (sapienic acids) are decreased and increased in acne vulgaris patient skin, respectively.[2] Although topical application of linoleic acid reduces acne microcomedones,[57] oral administration of FA including linoleic acid and antibiotics does not suffice to change esterified FA (wax ester, cholesterol ester, and triglyceride) composition[58] (probably due to delivering insufficient levels of FA to skin). Hence, topical (percutaneous) administration of skin care products or drugs is more efficient to deliver FA to the skin in some cases.[58] Yet, the following remain unknown: (1) what changes in FA composition of triacylglyceride in sebum and epidermis; (2) whether lipids from sebum are utilized for epidermal triglyceride production; (3) why changes in FA species occur in acne vulgaris; (4) what mechanism is responsible for changes in FA; and (5) how topically applied linoleic acid reduces microcomedones.

#### *41.3.5.2 Salvage Synthesis (or Sphingosine Recycling) Pathway*

Ceramides are produced from glucosylceramide and sphingomyelin by β-glucocerebrosidase and sphingomyelinases, respectively. It has been shown that ceramide generated from sphingomyelin by sphingomyelinase activation in response to stimuli serves as a lipid modulator.[59] Ceramidase hydrolyzes ceramide to sphingosine base and FA. Five ceramidase isoforms, which show different pH optimal and cellular distributions, have been characterized in mammals, i.e., (1) acid ceramidase, lysosomal distribution; (2) neutral ceramidase, plasma, and mitochondrial membrane distribution[60,61]; (3) alkaline ceramidase 1, a differentiated keratinocyte specific isoform, Golgi apparatus, and endoplasmic reticulum (ER)[62]; (4) alkaline ceramidase 2, Golgi apparatus, and ER[63]; and (5) alkaline ceramidase 3 (or phytoalkaline ceramidase), which catalyzes ceramide species containing dihydrosphingosine (sphinganine), 1,3,4-trihydroxydihydrosphingosine (phytosphingosine), and amide-linked unsaturated FAs, localized in Golgi apparatus and ER.[64] Epidermal keratinocytes express all five isoforms of ceramidase with different expression profiles of each isomer across the epidermis, i.e., acid ceramidase and alkaline ceramidase 1, and alkaline ceramidase 3 expression are increased and decreased, respectively, during keratinocyte differentiation, while expression levels of both neutral ceramidase and alkaline ceramidase 2 are not altered in nucleated layers of epidermis.[62,65] Sphingoid bases that are generated by this salvage pathway can then be reutilized as substrates for Cer formation. This salvage pathway could remodel preformed ceramide, e.g., ceramide-to-sphingoid base and FA. Produced sphingoid base is acylated by various FA species.[66] (see Section 41.3.7 and also Fig. 41.1). Similar to other tissues and skin components, ceramides containing N-acyl nonhydroxy and 2-hydroxy FAs are present across epidermis, while the stratum granulosum and stratum corneum exhibit heterogeneity of ceramides and glucosylceramide.

### 41.3.6 Glucosylceramide and Sphingomyelin Synthesis

Most synthesized ceramides in the ER are transferred to the Golgi apparatus (Golgi complex) by vesicle transport for sphingomyelin and ceramide transfer protein (CERT) for glucosylceramide.[67] Ceramide is converted to sphingomyelin and glucosylceramide by sphingomyelin synthases and β-glucosylceramide synthase, respectively. Two isoforms of sphingomyelin synthases are identified in mammalian cells including epidermal cells. Whereas complex glycosphingolipids, including ceramide dihexoside and sialoglycosphingolipids, are present in the epidermis, these complex glycosphingolipids are minor components.[68] Sialoglycosphingolipids become membrane constituents and also can serve as lipid modulators.

### 41.3.7 Barrier Ceramide Synthesis

Heterogeneous ceramide species in the stratum corneum forms epidermal permeability structures. To distinguish from the ceramide that comprises cellular membranes or becomes a lipid mediator in the nucleated layers of epidermis, the author terms ceramide in the stratum corneum as "barrier ceramide."

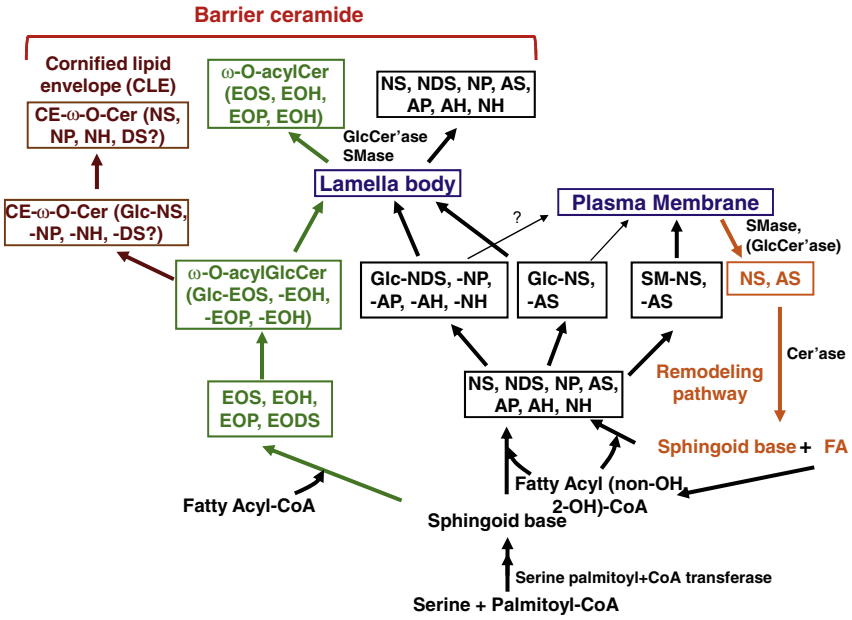



FIGURE 41.1 **Barrier ceramide formation.** Ceramide nomenclature is as reported by Motta et al.[48] and Masukawa et al.[47] Abbreviations indicate (1) Amide-linked FA: N, nonhydroxyl FA; A, 2-hydroxy FA and (2) Sphingoid base: D, dihydrosphingosine (sphinganine) S, sphingosine; P, phytosphingosine (dihydrosphingosine); H, 6-hydroxy sphingosine as nutrients. Some synthesized sphingomyelin and glucosylceramide consisting of NS, AS backbone, are incorporated plasma membrane. Glucosylceramides are minor components in the plasma membranes. These sphingomyelin and glucosylceramide are endocytosed and hydrolyzed in lysosomes. Generated sphingosine and FA are reutilized for the synthesis of heterogenous ceramide species (remodeling pathway).[56] Cer'ase, ceramidase; CE, cornified envelope; GlCer'ase, β-glucocerebrosidase; SM'ase, sphingomyelinase; SM-, sphingomyelin.[127,128]

Some synthesized glucosylceramides and probably most synthesized sphingomyelin are utilized as membrane constituents, while other pools of glucosylceramides and sphingomyelin are sequestrated into epidermal lamellar bodies with certain other lipids such as glycerophospholipids, cholesterol, and cholesterol ester. Lamellar bodies also contain hydrolytic enzymes, including proteases and lipases (secretary phospholipase A2, sphingomyelinase, β-glucocerebrosidase), which do not hydrolyze lipids in the lamellar body probably due to less-than-optimal pH for catalysis or absence and presence of endogenous activators and inhibitors.[69] Glucosylceramide is transferred from cytosol to the lamellar body by ABCA12 (a subfamily of ATP-binding cassette transporter).[70] A loss-of-function mutation of ABCA12 leads to the pathogenesis of Harlequin ichthyosis that displays epidermal permeability barrier defects.[70] Lamellar bodies are also present in lung alveoli. Differing from the epidermal lamellar body, the lung lamellar body stores pulmonary surfactants comprised of phosphatidylcholine (80–90%) and phosphatidylglycerol (5–10%).[71]

Lamellar bodies are formed in the granular layer and are diffused to the apical face of plasma membranes and contents then are extruded into extracellular spaces of the stratum corneum.[72] Transmission electron microscopy (TEM) analysis demonstrated ovoid structures of lamellar body,[72] while cryotransmission microscope study revealed that the lamellar body is likely a part of the tubuloreticular membrane network in cytosol and continues to the plasma membrane rather than to discrete vesicles.[73] In addition, different lamellar body contents such as glucosylceramide, corneodesmosin, cathepsin D, and kallikrein are present in distinct amounts.[73] These observations were confirmed by three-dimensional electron microscopy.[74] Moreover, Rab11, a class of GTPase protein, which regulates intracellular vesicular trafficking, i.e., recycling endosome and exocytosis of secretary proteins from trans-Golgi network, is associated with lamellar body contents.[75] The structural abnormalities of lamellar bodies assessed by TEM analysis are associated with epidermal permeability defects. What effect lamellar body abnormalities have on the tubuloreticular membrane network is not known.

Secreted sphingomyelin and glucosylceramide are hydrolyzed to ceramide by sphingomyelinases and β-glucocerebrosidase, respectively. Phosphoglycerolipids are hydrolyzed to produce FA by phospholipases. Generated ceramide and FA along with cholesterol assemble lamellar membrane structures in the extracellular spaces of the stratum corneum.

Sphingoid bases are present in the stratum corneum, and they form lamellar membrane structures with ceramide, cholesterol, and FAs.[76] Ceramide is hydrolyzed to sphingoid bases and FA by ceramidase (Fig. 41.1). Acidic and alkaline ceramidase, which are enriched in the stratum corneum,[62,65] could produce a sphingoid base in the stratum corneum. However, it is unclear that hydrolysis of ceramide occurs in the stratum corneum at physiological conditions. Alternatively, because free sphingoid bases are present in keratinocytes,[77] presynthesized sphingoid bases in nucleated layers of epidermis are a source of sphingoid bases in the stratum corneum. It also is unclear that the increase in ceramide hydrolysis at the upper part of the stratum corneum results in formation of the ceramide gradient in the stratum corneum.

All ceramide and omega-O-acylceramide in the stratum corneum can be derived from glucosylceramide and omega-O-acylglucosylceramide, respectively, but only two ceramide species, NS (Cer 2) and AS (Cer 5), are derived from SM[21,22] (Fig. 41.1). These studies suggest a reason why the lack of β-glucocerebrosidase activity in Gaucher disease patients leads to a more severe barrier abnormality than that in patients lacking sphingomyelinase.[78]

### 41.3.8 Bound Cer Formation

The ω-position of the amide-linked FA moiety of ω-O-hydroxyceramide becomes covalently bound to the carboxy termini of cornified envelope proteins (primarily involucrin) on the external surface of the corneocyte, forming the corneocyte lipid envelope (CLE) (i.e., bound form of ω-OH ceramide). CLE is formed as follows: (1) omega-O-acyl residue is released from omega-O-acylglucosylceramides; (2) omega-hydroxyl residue of ω-hydroxyglucosylceramides is covalently bound to cornified envelope proteins (primarily to glutamate residues in cornified envelope protein, mainly involucrin)[79]; (3) cornified envelope-omega-hydroxyglucosylceramides are deglucosylated by β-glucocerebrosidase to cornified envelope-omega-hydroxy ceramides; (4) some cornified envelope-omega-O-hydroxyceramides are hydrolyzed to omega-hydroxy free FA by ceramidase(s).[80,81] Release of linoleic acid residue of omega-O-linoleoyl glucosylceramides is required for 12R lipoxygenase (12R-LOX) and lipoxygenase 3 in the epidermis, which produces hydroperoxy linoleic acid of omega-O-linoleoyl glucosylceramides. This oxidized form is enzymatically catalyzed to bind to cornified envelope proteins.[82] Mutation of these lipoxygenases is associated with nonbullous congenital ichthyosiform erythroderma.[83] Transglutaminase 1, which generates isopeptide bonds between cross-linked proteins of the cornified envelope, is catalyzed by the formation of an ester linkage between involucrin and a synthetic pseudo-omega-hydroxy ceramide.[79] Yet, CLE is evident in the stratum corneum of lamellar ichthyosis patients that show trace levels of TG1 activities.[84] Hence, other transglutaminase(s), other enzyme(s), or nonenzymatic transesterification might also serve in CLE formation.[84] A role for CLE as a scaffold to form lamellar membrane structures (see Section 41.3.9) has been proposed.[84,85] It is also possible that CLE regulates egress of hydrophilic substances from corneocytes. CLE is visualized using preextraction of unbound lipids using pyridine solution followed by electron microscopic analysis.[84]

### 41.3.9 Lamellar Membrane Structure

Lamellar membrane structures comprised of cholesterol, free FA, heterogeneous ceramide species, and minor lipid components, such as sphingoid base, are required for formation of the epidermal permeability barrier. The molecular ratio of cholesterol, free FA, and ceramide (1:1:1) is critical to form a functional, competent epidermal permeability barrier.[86] In addition to this ratio, increases in shorter carbon chain length of ceramide occur in atopic dermatitis on the stratum corneum leading to changes in lipid organization and epidermal barrier abnormality.[87] It has been demonstrated that changes in the sphingosine and dihydrosphingosine ratio occur in the stratum corneum of the atopic dermatitis mouse model and that a certain ratio of sphingosine and dihydrosphingosine (sphinganine) is also important to form stable lamellar structures in vitro (reconstructing lamellar membrane structures using liposomes).[76] Other minor lipid species and/or endogenous hydrophobic molecules such as peptides may also contribute to form and/or influence lamellar membrane structures.

Electron microscope, X-ray diffraction, neutron diffraction, Fourier transform infrared spectroscopy (FT-IR), and differential scanning calorimetry (DSC) analyses characterize lamellar membrane structures. In transmission electron microscopic analysis, both reduced osmium and ruthenium postfixation visualize epidermal structures, including lamellar membrane structures of lamellar body and stratum corneum. Distribution of specific molecules in skin is assessed by immunostaining using specific antibodies and electron microscopy. X-ray diffraction, neutron diffraction, FT-IR, and DSC analyses characterize further details of lamellar membrane structures in the stratum corneum. Two lamellar phases are comprised of approximately 6 nm (short-periodicity) and 13 nm (long-periodicity) phase.[88] Humidity-dependent swallowing occurs in the lipid lamellar structure, suggesting that lamellar membrane structures contain water.[89] The short-periodicity phase is changed following incorporation of water.[90] In addition to these analyses indicating two-dimensional structures of lamellar membrane structures, three-dimensional structures show lamellar packing (hydrocarbon packing).[91] Both hexagonal and tightly-packed orthorhombic structures are present in the stratum corneum.[91] Moreover, a study using the low-flux electron diffraction analysis demonstrated the presence of a different type of orthorhombic structure, which was showing a different packing space distance, in the lamellar membrane structures in the stratum corneum.[92] Alterations of the lamellar organization have been shown in skin diseases associated with compromised permeability barrier function (e.g., atopic dermatitis).[87]

**TABLE 41.4** Skin Diseases Associated With Lipid Abnormality

| Disease | Responsible Metabolic Enzyme | Lipid Abnormality |
|---|---|---|
| Autosomal recessive congenital ichthyosis | Ceramide synthase 3 | Ceramides containing ULVFA, including omega-O-acylceramide and bound lipids[51,52,120] |
| Autosomal recessive congenital ichthyosis | CYP4F22 | Omega-O-acylceramide and bound lipids[36–38] |
| Ichthyosiform erythroderma | 12R lipoxygenase (12R-LOX), lipoxygenase 3 | Decreased bound lipids[82] |
| Gaucher disease type 2 | β-glucocerebrosidase | Ceramide deficiencies, including omega-O-acylceramide and bound lipids[78] |
| Atopic dermatitis | Not well characterized. | Decreased ceramide/Cholesterol[121,122]; decreased ceramide (EOS, NP, NH) and increased (NS, AS, AH, AP, ADS) deficiencies[121–124]<br>Increased shorter FA (C < 18), ceramide (shorter chain of FA) and mono saturated FA and decreased longer chain length FA and ceramide[87,123–125] |
| X-linked ichthyosis | Cholesterol sulfotransferase | Accumulation of cholesterol sulfate[126] |

### 41.3.10 Lipid-Mediated Epidermal Permeability Barrier Defects in Skin Disease

Abnormal lamellar bilayer structure in the stratum corneum is a pathogenesis of skin disease–associated epidermal permeability defects. The rate of abnormal lamellar structures likely correlates with the degree of barrier functional defects. Compromised barrier function occurs in atopic dermatitis, while electron microscopic analyses show that abnormal lamellar structures are present in certain parts of the stratum corneum. Lethal levels of barrier abnormality, such as Gaucher disease[93,94] and harlequin ichthyosis[95,96] show large areas of abnormal lamellar structures. Lipid-mediated epidermal permeability in skin diseases is summarized in Table 41.4.

## 41.4 SKIN SURFACE LIPID

Skin surface lipid is generated from sebum lipids. Skin surface lipid thickness is dependent on amounts of sebum production, i.e., low and high sebum production in facial skin is <0.5 μm and >4 μm, respectively.[97] Skin surface lipids show amorphous structures.[97] Lipids of lamellar membrane structure and corneocyte lipid envelope (at the outer layers of stratum corneum) are localized adjacent to amorphous structures,[97] suggesting that skin surface lipids can be mixed with lipids derived from stratum corneum. Yet, these amorphous structures are not observed in the stratum corneum of palmoplantar skin.[97] Therefore, sebum is a major contributor in forming the amorphous structures in the outer layers of stratum corneum. Skin surface lipid amounts increase in the development from newborn to adult and then decline during aging.[98] Skin surface lipid levels are also low in atopic dermatitis skin.[99] Although barrier recovery following acute barrier perturbation by tape stripping or acetone treatment of stratum corneum is attenuated in aged populations,[100] basal water content and transepidermal water loss are not significantly decreased. Therefore lamellar membrane structures in the stratum corneum play a major role in transepidermal permeability barrier function, and skin surface lipids additively enhance barrier function.

Skin surface lipids in sheep and horse contain a giant lactone composed of omega-hydroxyl UVLFA and free omega-hydroxy UVLFA.[101,102] The lactone in musk deer has pheromonal function,[103] and while both female and male horses have a giant lactone composed of omega-hydroxyl UVLFA,[104] it is not likely that an omega-hydroxyl giant lactone has pheromonal function. A lactone composed of omega-hydroxy UVLFA is present on the plant surface. Therefore, such lactone is likely responsible for barrier formation.

## 41.5 LIPID MEDIATORS

Certain lipids, including prostanoids, leukotriene, lysophospholipids, resolvins, and endocannabinoids, initiate signal transduction leading to modulation of cellular function. These lipids are called lipid mediators and are

categorized into three groups: Class 1, prostaglandins and leukotrienes; Class 2, lysophospholipids (platelet-activating factor, lysophosphatidic acid, sphingosine-1-phosphate and ceramide-1-phosphate); and Class 3, omega-3 polyunsaturated acid-derived antiinflammatory lipids (resolvins). In addition to these three groups, endocannabinoids are also lipid mediators. Cannabinoids modulate cellular function through cannabinoid receptor (CB)1 or CB2 activation. Cannabinoids show antiinflammatory effect in human sebocytes,[105] and potentially can be used for acne vulgaris treatment. Lipid mediator levels are relatively low in cells under basal conditions. However, in specific cellular compartments, i.e., cellular membranes, relatively small changes in levels of lipid mediator generated in membrane or in cytosol, through stimuli such as cytokine/chemokine, oxidative stress, or external perturbants, are sufficient to alter cellular function through multiple pathways, e.g., protein kinase activation, protease activation, and binding to specific receptor. Immediate downstream effectors of lipid mediators likely depend upon stimuli and cell types. All of these lipid modulators are generated in cutaneous tissues. Lipid mediators initiate positive and negative outcomes for host cells, e.g., sphingosine-1-phosphate induces endogenous antimicrobial substances, the antimicrobial peptide, cathelicidin antimicrobial peptide.[106,107] Cathelicidin antimicrobial peptide is a multifunctional peptide that shows not only antimicrobial activity but also stimulates cell proliferation, motility, inflammation, and cancer cell growth and development.[108] Although antimicrobial peptides are synthesized in nucleated layers of epidermis, these peptides are secreted into extracellular spaces in the stratum corneum.

## 41.6 LIPIDS IN COSMETICS

FA, FA ester, fatty alcohol (carbon chain lengths $\geq$8), mono-, di-, and triglyceride, petroleum jelly, sterol, lanolin (wool wax), sterol ester, squalene, and phosphatidylcholine (lecithin; which is derived from plants, eggs and petroleum and also is chemically synthesized) are used in cosmetic formulations. It is unclear if topical lanolin, which contains ω-hydroxy UVLFA, is utilized for endogenous omega-hydroxyceramide production. Yet, both topically applied lanolin and petroleum in cosmetics cover the skin surface and protect it from dryness, xenotoxic chemicals, and microbial pathogens. In addition, ceramide, and cholesterol (both major permeability barrier constituents) have been used as active ingredients.

## 41.7 BARRIER CARE (REPAIR) USING COSMETICS TO IMPROVE SKIN DISEASE

Biologically active materials have been formulated in skin care products, which maintain and improve the skin condition of normal or relatively mild, damaged skin, including dry skin and sunburn. The US Food and Drug Administration (FDA) and other nations' federal regulators control these potential drug types of cosmetics. However, users of skin care cosmetics can expect cosmeceutical and drug effects even using products that are not formulated with potent biological molecules. Prior studies demonstrated that epidermal permeability barrier defects perturb normal proliferation and differentiation of keratinocytes. In parallel, production of epidermal cytokines, chemokines, and certain protease activities are increased in the epidermis. These molecules affect immune cells, leading to induction of inflammatory responses in certain conditions. Inflammation triggers abnormal keratinocyte proliferation and differentiation and results in attenuating epidermal permeability barrier formation, per se leading to a vicious cycle; barrier defects → disruption of skin homeostasis → barrier defects. This cycle is also initiated by primary inflammation.[109] Hence, maintaining and/or improving epidermal permeability barrier function improves total skin condition and suppresses occurrences of skin diseases associated with epidermal permeability barrier abnormalities. In clinical settings, after treatment or cotreatment of atopic dermatitis with antiinflammatory drugs, steroids, and immune suppressors, maintenance of epidermal permeability barrier function by cosmetics can additively increase drug efficacy, but drug use should be decreased if there are adverse side effects from long-term usage. Lipids are a critical barrier constituent and therefore are a primary target for skin care treatment in both cosmetics and cosmeceuticals. In addition, topical lanolin and petrolatum in cosmetics contribute to maintaining barrier function. Lipid mediators can be used as cosmeceuticals, but because most lipid mediators are unstable, stabilization or chemically synthesized derivatives should be required.

## Acknowledgments

The author gratefully thanks Dr. Mari Itoh-Nogami (Tokyo Medical University and Imperial College of Science, Technology and Medicine), Dr. Akio Kihara (Hokkaido University), and Dr. Sumiko Hamanaka (Hamanaka Dermatological Clinic and Josai University). The author acknowledges the superb editorial assistance of Ms. Joan Wakefield.

## References


1. Nordstrom KM, Labows JN, McGinley KJ, Leyden JJ. Characterization of wax esters, triglycerides, and free fatty acids of follicular casts. *J Invest Dermatol* 1986;**86**:700–5.
2. Stewart ME, Grahek MO, Cambier LS, Wertz PW, Downing DT. Dilutional effect of increased sebaceous gland activity on the proportion of linoleic acid in sebaceous wax esters and in epidermal acylceramides. *J Invest Dermatol* 1986;**87**:733–6.
3. Williams HC, Dellavalle RP, Garner S. Acne vulgaris. *Lancet* 2012;**379**:361–72.
4. Pochi PE, Strauss JS. Endocrinologic control of the development and activity of the human sebaceous gland. *J Invest Dermatol* 1974;**62**: 191–201.
5. Juntachai W, Oura T, Kajiwara S. Purification and characterization of a secretory lipolytic enzyme, MgLIP2, from *Malassezia globosa*. *Microbiology* 2011;**157**:3492–9.
6. Lee YW, Lee SY, Lee Y, Jung WH. Evaluation of Expression of Lipases and Phospholipases of *Malassezia restricta* in Patients with Seborrheic Dermatitis. *Ann Dermatol* 2013;**25**:310–4.
7. DeAngelis YM, Saunders CW, Johnstone KR, Reeder NL, Coleman CG, Kaczvinsky Jr JR, et al. Isolation and expression of a *Malassezia globosa* lipase gene, LIP1. *J Invest Dermatol* 2007;**127**:2138–46.
8. Saely CH, Geiger K, Drexel H. Brown versus white adipose tissue: a mini-review. *Gerontology* 2012;**58**:15–23.
9. Gustafson B, Hedjazifar S, Gogg S, Hammarstedt A, Smith U. Insulin resistance and impaired adipogenesis. *Trends Endocrinol Metab* 2015;**26**: 193–200.
10. Beynen AC, Hermus RJ, Hautvast JG. A mathematical relationship between the fatty acid composition of the diet and that of the adipose tissue in man. *Am J Clin Nutr* 1980;**33**:81–5.
11. Goto-Inoue N, Hayasaka T, Zaima N, Nakajima K, Holleran WM, Sano S, et al. Imaging mass spectrometry visualizes ceramides and the pathogenesis of Dorfman–Chanarin syndrome due to ceramide metabolic abnormality in the skin. *PLoS One* 2012;**7**:e49519.
12. Body DR. The lipid composition of adipose tissue. *Prog Lipid Res* 1988;**27**:39–60.
13. Brockerhoff H, Hoyle RJ, Hwang PC. Incorporation of fatty acids of marine origin into triglycerides and phospholipids of mammals. *Biochim Biophys Acta* 1967;**144**:541–8.
14. Shorland FB, Czochanska Z, Prior IA. Studies on fatty acid composition of adipose tissue and blood lipids of Polynesians. *Am J Clin Nutr* 1969; **22**:594–605.
15. Samuels L, Kunst L, Jetter R. Sealing plant surfaces: cuticular wax formation by epidermal cells. *Annu Rev Plant Biol* 2008;**59**:683–707.
16. Grubauer G, Feingold KR, Harris RM, Elias PM. Lipid content and lipid type as determinants of the epidermal permeability barrier. *J Lipid Res* 1989;**30**:89–96.
17. Rice RH, Green H. The cornified envelope of terminally differentiated human epidermal keratinocytes consists of cross-linked protein. *Cell* 1977;**11**:417–22.
18. Yardley HJ. Epidermal lipids. *Int J Cosmet Sci* 1987;**9**:13–9.
19. Feingold KR, Brown BE, Lear SR, Moser AH, Elias PM. Localization of de novo sterologenesis in mammalian skin. *J Invest Dermatol* 1983;**81**: 365–9.
20. Jackson SM, Wood LC, Lauer S, Taylor JM, Cooper AD, Elias PM, et al. Effect of cutaneous permeability barrier disruption on HMG-CoA reductase, LDL receptor, and apolipoprotein E mRNA levels in the epidermis of hairless mice. *J Lipid Res* 1992;**33**:1307–14.
21. Feingold KR, Man MQ, Menon GK, Cho SS, Brown BE, Elias PM. Cholesterol synthesis is required for cutaneous barrier function in mice. *J Clin Invest* 1990;**86**:1738–45.
22. Uchida Y. The role of fatty acid elongation in epidermal structure and function. *Dermatoendocrinol* 2011;**3**:65–9.
23. Sassa T, Kihara A. Metabolism of very long-chain Fatty acids: genes and pathophysiology. *Biomol Ther (Seoul)* 2014;**22**:83–92.
24. Vasireddy V, Uchida Y, Salem Jr N, Kim SY, Mandal MN, Reddy GB, et al. Loss of functional ELOVL4 depletes very long-chain fatty acids (>=C28) and the unique {omega}-O-acylceramides in skin leading to neonatal death. *Hum Mol Genet* 2007;**16**:471–82.
25. Mandal MN, Ambasudhan R, Wong PW, Gage PJ, Sieving PA, Ayyagari R. Characterization of mouse orthologue of ELOVL4: genomic organization and spatial and temporal expression. *Genomics* 2004;**83**:626–35.
26. Vasireddy V, Wong P, Ayyagari R. Genetics and molecular pathology of Stargardt-like macular degeneration. *Prog Retin Eye Res* 2010;**29**:191–207.
27. Sassa T, Ohno Y, Suzuki S, Nomura T, Nishioka C, Kashiwagi T, et al. Impaired epidermal permeability barrier in mice lacking elovl1, the gene responsible for very-long-chain fatty acid production. *Mol Cell Biol* 2013;**33**:2787–96.
28. Agbaga MP, Logan S, Brush RS, Anderson RE. Biosynthesis of very long-chain polyunsaturated fatty acids in hepatocytes expressing ELOVL4. *Adv Exp Med Biol* 2014;**801**:631–6.
29. Alderson NL, Rembiesa BM, Walla MD, Bielawska A, Bielawski J, Hama H. The human FA2H gene encodes a fatty acid 2-hydroxylase. *J Biol Chem* 2004;**279**:48562–8.
30. Gray GM, Yardley HJ. Lipid compositions of cells isolated from pig, human, and rat epidermis. *J Lipid Res* 1975;**16**:434–40.
31. Uchida Y, Hara M, Nishio H, Sidransky E, Inoue S, Otsuka F, et al. Epidermal sphingomyelins are precursors for selected stratum corneum ceramides. *J Lipid Res* 2000;**41**:2071–82.
32. Uchida Y, Hama H, Alderson NL, Douangpanya S, Wang Y, Crumrine DA, et al. Fatty acid 2-hydroxylase, encoded by FA2H, accounts for differentiation-associated increase in 2-OH ceramides during keratinocyte differentiation. *J Biol Chem* 2007;**282**:13211–9.
33. Kruer MC, Paisan-Ruiz C, Boddaert N, Yoon MY, Hama H, Gregory A, et al. Defective FA2H leads to a novel form of neurodegeneration with brain iron accumulation (NBIA). *Ann Neurol* 2010;**68**:611–8.
34. Kota V, Hama H. 2'-Hydroxy ceramide in membrane homeostasis and cell signaling. *Adv Biol Regul* 2014;**54**:223–30.
35. Behne M, Uchida Y, Seki T, de Montellano PO, Elias PM, Holleran WM. Omega-hydroxyceramides are required for corneocyte lipid envelope (CLE) formation and normal epidermal permeability barrier function. *J Invest Dermatol* 2000;**114**:185–92.
36. Ohno Y, Nakamichi S, Ohkuni A, Kamiyama N, Naoe A, Tsujimura H, et al. Essential role of the cytochrome P450 $CYP_4F_{22}$ in the production of acylceramide, the key lipid for skin permeability barrier formation. *Proc Natl Acad Sci USA* 2015;**112**:7707–12.
37. Lefevre C, Bouadjar B, Ferrand V, Tadini G, Megarbane A, Lathrop M, et al. Mutations in a new cytochrome P450 gene in lamellar ichthyosis type 3. *Hum Mol Genet* 2006;**15**:767–76.

38. Sugiura K, Takeichi T, Tanahashi K, Ito Y, Kosho T, Saida K, et al. Lamellar ichthyosis in a collodion baby caused by *CYP$_4$F$_{22}$* mutations in a non-consanguineous family outside the Mediterranean. *J Dermatol Sci* 2013;**72**:193–5.
39. Polheim D, David JS, Schultz FM, Wylie MB, Johnston JM. Regulation of triglyceride biosynthesis in adipose and intestinal tissue. *J Lipid Res* 1973;**14**:415–21.
40. Giusto NM, Pasquare SJ, Salvador GA, Ilincheta de Boschero MG. Lipid second messengers and related enzymes in vertebrate rod outer segments. *J Lipid Res* 2010;**51**:685–700.
41. Yen CL, Stone SJ, Koliwad S, Harris C, Farese Jr RV. Thematic review series: glycerolipids. DGAT enzymes and triacylglycerol biosynthesis. *J Lipid Res* 2008;**49**:2283–301.
42. Stone SJ, Myers HM, Watkins SM, Brown BE, Feingold KR, Elias PM, et al. Lipopenia and skin barrier abnormalities in DGAT2-deficient mice. *J Biol Chem* 2004;**279**:11767–76.
43. Uchida Y, Cho Y, Moradian S, Kim J, Nakajima K, Crumrine D, et al. Neutral lipid storage leads to acylceramide deficiency, likely contributing to the pathogenesis of Dorfman–Chanarin syndrome. *J Invest Dermatol* 2010;**130**:2497–9.
44. Dawkins MJ, Stevens JF. Fatty acid composition of triglycerides from adipose tissue. *Nature* 1966;**209**:1145–6.
45. Hansen HS, Jensen B. Essential function of linoleic acid esterified in acylglucosylceramide and acylceramide in maintaining the epidermal water permeability barrier. Evidence from feeding studies with oleate, linoleate, arachidonate, columbinate and alpha-linolenate. *Biochim Biophys Acta* 1985;**834**:357–63.
46. Burr GO. The essential fatty acids fifty years ago. *Prog Lipid Res* 1981;**20**:xxvii–xxix.
47. Masukawa Y, Narita H, Shimizu E, Kondo N, Sugai Y, Oba T, et al. Characterization of overall ceramide species in human stratum corneum. *J Lipid Res* 2008;**49**(7):1466–76.
48. Motta S, Monti M, Sesana S, Caputo R, Carelli S, Ghidoni R. Ceramide composition of the psoriatic scale. *Biochim Biophys Acta* 1993;**1182**:147–51.
49. Rabionet M, Bayerle A, Marsching C, Jennemann R, Grone HJ, Yildiz Y, et al. 1-O-acylceramides are natural components of human and mouse epidermis. *J Lipid Res* 2013;**54**:3312–21.
50. Bejaoui K, Wu C, Scheffler MD, Haan G, Ashby P, Wu L, et al. SPTLC1 is mutated in hereditary sensory neuropathy, type 1. *Nat Genet* 2001;**27**:261–2.
51. Radner FP, Marrakchi S, Kirchmeier P, Kim GJ, Ribierre F, Kamoun B, et al. Mutations in CERS3 cause autosomal recessive congenital ichthyosis in humans. *PLoS Genet* 2013;**9**:e1003536.
52. Jennemann R, Rabionet M, Gorgas K, Epstein S, Dalpke A, Rothermel U, et al. Loss of ceramide synthase 3 causes lethal skin barrier disruption. *Hum Mol Genet* 2012;**21**:586–608.
53. Abraham W, Wertz PW, Downing DT. Linoleate-rich acylglucosylceramides of pig epidermis: structure determination by proton magnetic resonance. *J Lipid Res* 1985;**26**:761–6.
54. Hamanaka S, Hara M, Nishio H, Otsuka F, Suzuki A, Uchida Y. Human epidermal glucosylceramides are major precursors of stratum corneum ceramides. *J Invest Dermatol* 2002;**119**:416–23.
55. Demerjian M, Crumrine DA, Milstone LM, Williams ML, Elias PM. Barrier dysfunction and pathogenesis of neutral lipid storage disease with ichthyosis (Chanarin–Dorfman syndrome). *J Invest Dermatol* 2006;**126**:2032–8.
56. Fischer J, Lefevre C, Morava E, Mussini JM, Laforet P, Negre-Salvayre A, et al. The gene encoding adipose triglyceride lipase (PNPLA2) is mutated in neutral lipid storage disease with myopathy. *Nat Genet* 2007;**39**:28–30.
57. Letawe C, Boone M, Pierard GE. Digital image analysis of the effect of topically applied linoleic acid on acne microcomedones. *Clin Exp Dermatol* 1998;**23**:56–8.
58. Costa A, Siqueira Talarico A, Parra Duarte Cde O, Silva Pereira C, de Souza Weimann ET, Sabino de Matos L, et al. Evaluation of the Quantitative and Qualitative Alterations in the Fatty Acid Contents of the Sebum of Patients with Inflammatory Acne during Treatment with Systemic Lymecycline and/or Oral Fatty Acid Supplementation. *Dermatol Res Pract* 2013;**2013**, 120475.
59. Hannun YA, Bell RM. The sphingomyelin cycle: a prototypic sphingolipid signaling pathway. *Adv Lipid Res* 1993;**25**:27–41.
60. Mitsutake S, Tani M, Okino N, Mori K, Ichinose S, Omori A, et al. Purification, characterization, molecular cloning, and subcellular distribution of neutral ceramidase of rat kidney. *J Biol Chem* 2001;**276**:26249–59.
61. el Bawab S, Mao C, Obeid LM, Hannun YA. Ceramidases in the regulation of ceramide levels and function. *Subcell Biochem* 2002;**36**:187–205.
62. Houben E, Holleran WM, Yaginuma T, Mao C, Obeid LM, Rogiers V, et al. Differentiation-associated expression of ceramidase isoforms in cultured keratinocytes and epidermis. *J Lipid Res* 2006;**47**:1063–70.
63. Xu R, Jin J, Hu W, Sun W, Bielawski J, Szulc Z, et al. Golgi alkaline ceramidase regulates cell proliferation and survival by controlling levels of sphingosine and S1P. *FASEB J* 2006;**20**:1813–25.
64. Mao C, Xu R, Szulc ZM, Bielawska A, Galadari SH, Obeid LM. Cloning and characterization of a novel human alkaline ceramidase. A mammalian enzyme that hydrolyzes phytoceramide. *J Biol Chem* 2001;**276**:26577–88.
65. Lin TK, Crumrine D, Ackerman LD, Santiago JL, Roelandt T, Uchida Y, et al. Cellular changes that accompany shedding of human corneocytes. *J Invest Dermatol* 2012;**132**:2430–9.
66. Hamanaka S, Nakazawa S, Yamanaka M, Uchida Y, Otsuka F. Glucosylceramide accumulates preferentially in lamellar bodies in differentiated keratinocytes. *Br J Dermatol* 2005;**152**:426–34.
67. Hanada K, Kumagai K, Yasuda S, Miura Y, Kawano M, Fukasawa M, et al. Molecular machinery for non-vesicular trafficking of ceramide. *Nature* 2003;**426**:803–9.
68. Uchida Y, Iwamori M, Nagai Y. Distinct differences in lipid composition between epidermis and dermis from footpad and dorsal skin of guinea pigs. *Jpn J Exp Med* 1988;**58**:153–61.
69. Feingold KR. Thematic review series: skin lipids. The role of epidermal lipids in cutaneous permeability barrier homeostasis. *J Lipid Res* 2007; **48**:2531–46.
70. Akiyama M, Sugiyama-Nakagiri Y, Sakai K, McMillan JR, Goto M, Arita K, et al. Mutations in lipid transporter ABCA12 in harlequin ichthyosis and functional recovery by corrective gene transfer. *J Clin Invest* 2005;**115**:1777–84.
71. Schmitz G, Müller G. Structure and function of lamellar bodies, lipid-protein complexes involved in storage and secretion of cellular lipids. *J Lipid Res* 1991;**32**:1539–70.
72. Elias PM, Gruber R, Crumrine D, Menon G, Williams ML, Wakefield JS, et al. Formation and functions of the corneocyte lipid envelope (CLE). *Biochim Biophys Acta* 2014;**1841**:314–8.

73. Ishida-Yamamoto A, Simon M, Kishibe M, Miyauchi Y, Takahashi H, Yoshida S, et al. Epidermal lamellar granules transport different cargoes as distinct aggregates. *J Invest Dermatol* 2004;**122**:1137–44.
74. den Hollander L, Han H, de Winter M, Svensson L, Masich S, Daneholt B, et al. Skin Lamellar Bodies are not Discrete Vesicles but Part of a Tubuloreticular Network. *Acta Derm Venereol* 2015;**96**(3):303–8.
75. Ishida-Yamamoto A, Kishibe M, Takahashi H, Iizuka H. Rab11 is associated with epidermal lamellar granules. *J Invest Dermatol* 2007;**127**: 2166–70.
76. Loiseau N, Obata Y, Moradian S, Sano H, Yoshino S, Aburai K, et al. Altered sphingoid base profiles predict compromised membrane structure and permeability in atopic dermatitis. *J Dermatol Sci* 2013;**72**:296–303.
77. Uchida Y, Houben E, Park K, Douangpanya S, Lee YM, Wu BX, et al. Hydrolytic pathway protects against ceramide-induced apoptosis in keratinocytes exposed to UVB. *J Invest Dermatol* 2010;**130**:2472–80.
78. Chan A, Holleran WM, Ferguson T, Crumrine D, Goker-Alpan O, Schiffmann R, et al. Skin ultrastructural findings in type 2 Gaucher disease: diagnostic implications. *Mol Genet Metab* 2011;**104**(4):631–6.
79. Nemes Z, Marekov LN, Fésüs L, Steinert PM. A novel function for transglutaminase 1: attachment of long-chain omega-hydroxyceramides to involucrin by ester bond formation. *Proc Natl Acad Sci USA* 1999;**96**:8402–7.
80. Doering T, Holleran WM, Potratz A, Vielhaber G, Elias PM, Suzuki K, et al. Sphingolipid activator proteins are required for epidermal permeability barrier formation. *J Biol Chem* 1999;**274**:11038–45.
81. Uchida Y, Holleran WM. Omega-O-acylceramide, a lipid essential for mammalian survival. *J Dermatol Sci* 2008;**51**:77–87.
82. Zheng Y, Yin H, Boeglin WE, Elias PM, Crumrine D, Beier DR, et al. Lipoxygenases mediate the effect of essential fatty acid in skin barrier formation: a proposed role in releasing omega-hydroxyceramide for construction of the corneocyte lipid envelope. *J Biol Chem* 2011;**286**: 24046–56.
83. Yu Z, Schneider C, Boeglin WE, Brash AR. Mutations associated with a congenital form of ichthyosis (NCIE) inactivate the epidermal lipoxygenases 12R-LOX and eLOX3. *Biochim Biophys Acta* 2005;**1686**:238–47.
84. Elias PM, Schmuth M, Uchida Y, Rice RH, Behne M, Crumrine D, et al. Basis for the permeability barrier abnormality in lamellar ichthyosis. *Exp Dermatol* 2002;**11**:248–56.
85. Wertz PW, Downing DT. Covalently bound omega-hydroxyacylsphingosine in the stratum corneum. *Biochim Biophys Acta* 1987;**917**:108–11.
86. Man MM, Feingold KR, Thornfeldt CR, Elias PM. Optimization of physiological lipid mixtures for barrier repair. *JInvest Dermatol* 1996;**106**: 1096–101.
87. Janssens M, van Smeden J, Gooris GS, Bras W, Portale G, Caspers PJ, et al. Increase in short-chain ceramides correlates with an altered lipid organization and decreased barrier function in atopic eczema patients. *J Lipid Res* 2012;**53**:2755–66.
88. Bouwstra JA, Gooris GS, Cheng K, Weerheim A, Bras W, Ponec M. Phase behavior of isolated skin lipids. *J Lipid Res* 1996;**37**:999–1011.
89. Charalambopoulou GC, Steriotis TA, Mitropoulos AC, Stefanopoulos KL, Kanellopoulos NK, Ioffe A. Investigation of water sorption on porcine stratum corneum by very small angle neutron scattering. *J Invest Dermatol* 1998;**110**:988–90.
90. Nakazawa H, Ohta N, Hatta I. A possible regulation mechanism of water content in human stratum corneum via intercellular lipid matrix. *Chem Phys Lipids* 2012;**165**:238–43.
91. Bouwstra JA, Honeywell-Nguyen PL, Gooris GS, Ponec M. Structure of the skin barrier and its modulation by vesicular formulations. *Prog Lipid Res* 2003;**42**:1–36.
92. Nakazawa H, Imai T, Hatta I, Sakai S, Inoue S, Kato S. Low-flux electron diffraction study for the intercellular lipid organization on a human corneocyte. *Biochim Biophys Acta* 2013;**1828**:1424–31.
93. Sidransky E, Fartasch M, Lee RE, Metlay LA, Abella S, Zimran A, et al. Epidermal abnormalities may distinguish type 2 from type 1 and type 3 of Gaucher disease. *Pediatr Res* 1996;**39**:134–41.
94. Holleran WM, Ginns EI, Menon GK, Grundmann JU, Fartasch M, McKinney CE, et al. Consequences of beta-glucocerebrosidase deficiency in epidermis. Ultrastructure and permeability barrier alterations in Gaucher disease. *J Clin Invest* 1994;**93**:1756–64.
95. Fleck RM, Barnadas M, Schulz WW, Roberts LJ, Freeman RG. Harlequin ichthyosis: an ultrastructural study. *J Am Acad Dermatol* 1989;**21**: 999–1006.
96. Elias PM, Fartasch M, Crumrine D, Behne M, Uchida Y, Holleran WM. Origin of the corneocyte lipid envelope (CLE): observations in harlequin ichthyosis and cultured human keratinocytes. *J Invest Dermatol* 2000;**115**:765–9.
97. Sheu HM, Chao SC, Wong TW, Yu-Yun Lee J, Tsai JC. Human skin surface lipid film: an ultrastructural study and interaction with corneocytes and intercellular lipid lamellae of the stratum corneum. *Br J Dermatol* 1999;**140**:385–91.
98. Hayashi N, Togawa K, Yanagisawa M, Hosogi J, Mimura D, Yamamoto Y. Effect of sunlight exposure and aging on skin surface lipids and urate. *Exp Dermatol* 2003;**12**(Suppl. 2):13–7.
99. Sator PG, Schmidt JB, Honigsmann H. Comparison of epidermal hydration and skin surface lipids in healthy individuals and in patients with atopic dermatitis. *J Am Acad Dermatol* 2003;**48**:352–8.
100. Ghadially R, Brown BE, Sequeira-Martin SM, Feingold KR, Elias PM. The aged epidermal permeability barrier. Structural, functional, and lipid biochemical abnormalities in humans and a senescent murine model. *J Clin Invest* 1995;**95**:2281–90.
101. Wertz PW, Colton SWt, Downing DT. Comparison of the hydroxyacids from the epidermis and from the sebaceous glands of the horse. *Comp Biochem Physiol B Comp Biochem* 1983;**75**:217–20.
102. Colton SW, Downing DT. Variation in skin surface lipid composition among the Equidae. *Comp Biochem Physiol B* 1983;**75**:429–33.
103. Wood WF. Volatile components in metatarsal glands of sika deer, *Cervus nippon*. *J Chem Ecol* 2003;**29**:2729–33.
104. Downing DT, Colton SW. Skin surface lipids of the horse. *Lipids* 1980;**15**:323–7.
105. Olah A, Toth BI, Borbiro I, Sugawara K, Szollosi AG, Czifra G, et al. Cannabidiol exerts sebostatic and antiinflammatory effects on human sebocytes. *J Clin Invest* 2014;**124**:3713–24.
106. Park K, Elias PM, Shin KO, Lee YM, Hupe M, Borkowski AW, et al. A novel role of a lipid species, sphingosine-1-phosphate, in epithelial innate immunity. *Mol Cell Biol* 2013;**33**:752–62.
107. Park K, Ikushiro H, Seo HS, Shin KO, Kim YI, Kim JY, et al. ER stress stimulates production of the key antimicrobial peptide, cathelicidin, by forming a previously unidentified intracellular S1P signaling complex. *Proc Natl Acad Sci USA* 2016;**113**(10):E1334–42.
108. Nakatsuji T, Gallo RL. Antimicrobial peptides: old molecules with new ideas. *J Invest Dermatol* 2012;**132**:887–95.

109. Elias PM, Hatano Y, Williams ML. Basis for the barrier abnormality in atopic dermatitis: outside-inside-outside pathogenic mechanisms. *J Allergy Clin Immunol* 2008;**121**:1337–43.
110. Kawahara K, Hohjoh H, Inazumi T, Tsuchiya S, Sugimoto Y. Prostaglandin E2-induced inflammation: relevance of prostaglandin E receptors. *Biochim Biophys Acta* 2015;**1851**:414–21.
111. Su WH, Cheng MH, Lee WL, Tsou TS, Chang WH, Chen CS, et al. Nonsteroidal anti-inflammatory drugs for wounds: pain relief or excessive scar formation? *Mediat Inflamm* 2010;**2010**, 413238.
112. Rundhaug JE, Simper MS, Surh I, Fischer SM. The role of the EP receptors for prostaglandin E2 in skin and skin cancer. *Cancer Metastasis Rev* 2011;**30**:465–80.
113. Iwata C, Akimoto N, Sato T, Morokuma Y, Ito A. Augmentation of lipogenesis by 15-deoxy-Delta12,14-prostaglandin J2 in hamster sebaceous glands: identification of cytochrome P-450-mediated 15-deoxy-Delta12,14-prostaglandin J2 production. *J Invest Dermatol* 2005;**125**:865–72.
114. Garcia-Bueno B, Madrigal JL, Lizasoain I, Moro MA, Lorenzo P, Leza JC. The anti-inflammatory prostaglandin 15d-PGJ2 decreases oxidative/nitrosative mediators in brain after acute stress in rats. *Psychopharmacology (Berl)* 2005;**180**:513–22.
115. Biro T, Toth BI, Hasko G, Paus R, Pacher P. The endocannabinoid system of the skin in health and disease: novel perspectives and therapeutic opportunities. *Trends Pharmacol Sci* 2009;**30**:411–20.
116. Reines I, Kietzmann M, Mischke R, Tschernig T, Luth A, Kleuser B, et al. Topical application of sphingosine-1-phosphate and FTY720 attenuate allergic contact dermatitis reaction through inhibition of dendritic cell migration. *J Invest Dermatol* 2009;**129**:1954–62.
117. Baumer W, Rossbach K, Mischke R, Reines I, Langbein-Detsch I, Luth A, et al. Decreased concentration and enhanced metabolism of sphingosine-1-phosphate in lesional skin of dogs with atopic dermatitis: disturbed sphingosine-1-phosphate homeostasis in atopic dermatitis. *J Invest Dermatol* 2011;**131**:266–8.
118. Paller AS, Arnsmeier SL, Alvarez-Franco M, Bremer EG. Ganglioside GM3 inhibits the proliferation of cultured keratinocytes. *J Invest Dermatol* 1993;**100**:841–5.
119. Paller AS, Arnsmeier SL, Fisher GJ, Yu QC. Ganglioside GT1b induces keratinocyte differentiation without activating protein kinase C. *Exp Cell Res* 1995;**217**:118–24.
120. Eckl KM, Tidhar R, Thiele H, Oji V, Hausser I, Brodesser S, et al. Impaired epidermal ceramide synthesis causes autosomal recessive congenital ichthyosis and reveals the importance of ceramide acyl chain length. *J Invest Dermatol* 2013;**133**:2202–11.
121. Di Nardo A, Wertz P, Giannetti A, Seidenari S. Ceramide and cholesterol composition of the skin of patients with atopic dermatitis. *Acta Derm Venereol* 1998;**78**:27–30.
122. Angelova-Fischer I, Mannheimer AC, Hinder A, Ruether A, Franke A, Neubert RH, et al. Distinct barrier integrity phenotypes in filaggrin-related atopic eczema following sequential tape stripping and lipid profiling. *Exp Dermatol* 2011;**20**:351–6.
123. Imokawa G, Abe A, Jin K, Higaki Y, Kawashima M, Hidano A. Decreased level of ceramides in stratum corneum of atopic dermatitis: an etiologic factor in atopic dry skin? *J Invest Dermatol* 1991;**96**:523–6.
124. Bleck O, Abeck D, Ring J, Hoppe U, Vietzke JP, Wolber R, et al. Two ceramide subfractions detectable in Cer(AS) position by HPTLC in skin surface lipids of non-lesional skin of atopic eczema. *J Invest Dermatol* 1999;**113**:894–900.
125. Thakoersing VS, van Smeden J, Mulder AA, Vreeken RJ, El Ghalbzouri A, Bouwstra JA. Increased presence of monounsaturated fatty acids in the stratum corneum of human skin equivalents. *J Invest Dermatol* 2012;**133**(1):59–67.
126. Elias PM, Williams ML, Choi EH, Feingold KR. Role of cholesterol sulfate in epidermal structure and function: lessons from X-linked ichthyosis. *Biochim Biophys Acta* 2014;**1841**:353–61.
127. Motta S, Sesana S, Ghidoni R, Monti M. Content of the different lipid classes in psoriatic scale. *Arch Dermatol Res* 1995;**287**:691–4.
128. Robson KJ, Stewart ME, Michelsen S, Lazo ND, Downing DT. 6-Hydroxy-4-sphingenine in human epidermal ceramides. *J Lipid Res* 1994;**35**:2060–8.

CHAPTER

# 42

# Structural Aspects of Stratum Corneum

*I. Hatta*

**Nagoya Industrial Science Research Institute, Nagoya, Japan**

## 42.1 INTRODUCTION

In this chapter, I will focus my attention on microscopic structures formed in stratum corneum (SC). X-ray diffraction technique is a powerful tool to obtain structural evidence at the molecular level when we consider the function of stratum corneum. Generally, when an X-ray beam impinges on an object, part of the beam called a direct beam is transmitted through the object and part is scattered by the object. An object with periodic structure can give rise to diffraction at certain angles; at other scattered angles destructive interference causes the X-ray waves to cancel. In an object with a three-dimensional periodic crystal structure, the atoms or molecules are arranged in parallel layers or crystal planes that reflect X-ray beams as a mirror reflects light. Positive interference between X-rays reflected from the parallel layers or crystal planes occurs at angles, satisfying Bragg's law:

$$2d \sin(2\theta_B/2) = n\lambda \tag{42.1}$$

where $2\theta_B$ is the angle between the incident and the reflected X-ray beams called the Bragg angle, i.e., $\theta_B$ is the angle between the incident X-ray beam and the parallel layers or crystal planes, $d$ is the perpendicular spacing between the parallel layers or crystal planes, $\lambda$ is the wavelength of X-ray, and $n$ is an integer. The wavelength of X-rays is around 0.1 nm. Therefore, according to Bragg's law the spacing $d$ that is more than 0.2 nm can be detected by X-ray diffraction.

We can observe X-ray diffraction when periodic structures take place in SC. Periodic structures formed in intercellular lipids of SC are characterized in terms of two orthogonal lattice spacings: one is the lamellar repeat distances and another is the lattice spacings of the hydrocarbon-chain packing structure (so-called "subcell structure"). From X-ray diffraction for the lamellar structure of hairless mouse SC that exhibits one of the typical X-ray diffraction in mammalian SC, the long lamellar structure with the repeat distance of 13.6 nm and the short lamellar structure with the repeat distance of about 6 nm have been obtained as illustrated schematically in Fig. 42.1A and B, respectively.[1] The illustrations show only the presumable molecular arrangement of ceramides, free fatty acids, and cholesterol in SC. But there are a lot of arguments for the molecular arrangements. To solve them it is important to perform the detailed structural study at the molecular level not only on SC but also on SC lipid model system in which the constituent molecules are known. Based upon the structural study on an SC lipid model system, it has been pointed out that in the formation of the long lamellar structure a long ceramide molecule such as CER(EOS) is one of the key elements.[2] For the short lamellar structure it is worthwhile pointing out that water molecules are incorporated into the short lamellar structure and therefore that a water layer between the successive lipid bilayers in the short lamellar structure takes place as shown in Fig. 42.1B.[3–5]

On the other hand, for the lateral packing of the lipids there are hexagonal and orthorhombic hydrocarbon-chain packing structures with the lattice constant of 0.42 nm and with the lattice constants of 0.42 and 0.37 nm, respectively, at room temperature as illustrated schematically in Fig. 42.2A and B.[1] Here the periodic crystal planes are shown by straight lines, where centers of electron-density distribution in a hydrocarbon chain are connected with straight lines. It should be noted that the lattice constant is not the distance between the neighboring hydrocarbon chains but the spacing between the neighboring crystal planes. We have to pay attention to one more important result that based upon the wide-angle X-ray diffraction in the hydrocarbon-chain packing structures Doucet et al.[6] have estimated the proportion of liquid-crystalline state that exhibits a diffraction pattern of a diffuse ring

*Cosmetic Science and Technology: Theoretical Principles and Applications*
http://dx.doi.org/10.1016/B978-0-12-802005-0.00042-2



Copyright © 2017 Elsevier Inc. All rights reserved.

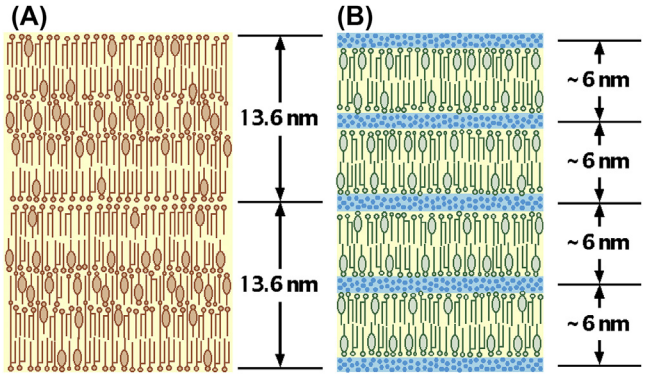



FIGURE 42.1 Schematic view for (A) long lamellar structure with lamellar repeat distance 13.6 nm and (B) short lamellar structure with about 6 nm. Both structures are composed of ceramides, free fatty acid, cholesterol, etc. In short lamellar structure water layers appear, where water molecules are indicated by *blue dots* (Gray in print versions).

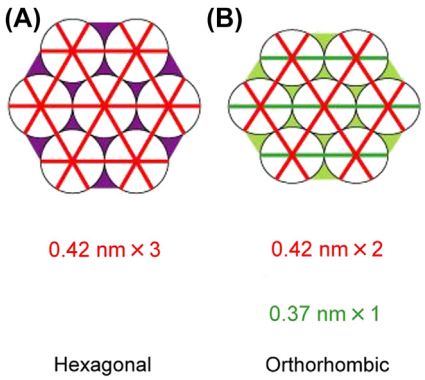



FIGURE 42.2 Hydrocarbon-chain packing structures: (A) Hexagonal where lattice constant is 0.42 nm, (B) Orthorhombic where lattice constants are 0.37 and 0.42 nm.

near 4.6 nm and as a result the proportion of liquid-crystalline state reaches about 80%. This fact might be important in considering barrier function and penetration pathway in SC.

It should be pointed out that the structure formed by soft keratin is one of the key factors in considering the behavior of water in SC.[5] Soft keratin in corneocytes show a diffraction pattern of two very diffuse rings of 4.6 and 1 nm. However, the diffuse ring near 4.6 nm superposes on the diffuse ring due to the liquid-crystalline hydrocarbon-chain packing structure. Therefore it is generally hard to discriminate two broad peaks.[6] From this viewpoint the X-ray diffraction measurement for 1 nm diffuse ring is promising in studying behavior of soft keratin.

In addition, a variety of structural studies on SC, such as electron microscopy, electron spin resonance, infrared spectroscopy, Raman spectroscopy, atomic force microscopy, etc., have been performed. Here I will focus my attention on in vitro X-ray diffraction measurement in SC, since the basic structural knowledge obtained from X-ray diffraction is indispensable in structural study on SC at the molecular level.

## 42.2 X-RAY DIFFRACTION STUDY ON STRATUM CORNEUM

The X-ray impinges on an SC sample and the X-ray diffraction pattern is recorded on a detector as shown in Fig. 42.3. The scattering vector is given by

$$S = \frac{2}{\lambda}\sin\left(\frac{2\theta}{2}\right) \tag{42.2}$$

where $2\theta$ is the scattering angle. Scattering angle is obtained from the distance ($x$) from the center of the detector and the sample-to-detector distance ($z$) as given by $\tan 2\theta = x/z$. Here I will briefly remark that the definition of scattering vector $S$ is a little different from the usual definition for scattering vector $q$ or $Q$, which is equal to $2\pi S$. Generally,

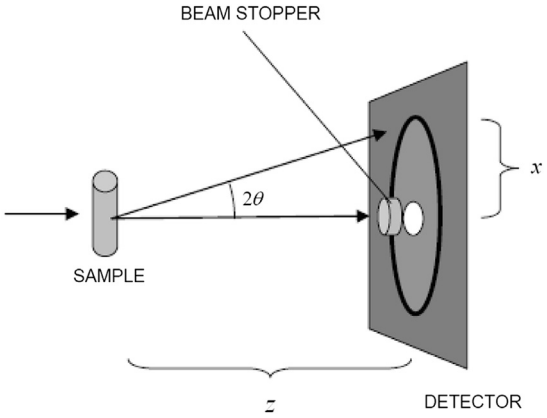



**FIGURE 42.3** X-ray diffraction measurement system. X-ray beam impinges on a sample, X-ray is diffracted by the sample, and the diffracted X-ray beams are detected by a detector; where $z$ is camera length and $2\theta$ is scattering angle.

when there is a periodic electron-density distribution with periodicity of $d$, the X-ray diffraction peak takes place due to Bragg's law. From Eqs. (42.1). and (42.2) the $n$-th order diffraction peak appears at the scattering vector:

$$S_{n\text{th}} = \frac{2}{\lambda}\sin\left(\frac{2\theta_B}{2}\right) = \left(\frac{n}{d}\right) \tag{42.3}$$

When the electron density in an SC sample is modulated periodically in the vertical direction as given in Fig. 42.1A and B, the diffraction peaks take place along the meridional axis. When the images shown in Fig. 42.1A and B are rotated by 90°, the diffraction peaks take place along the equatorial axis. Therefore when the crystal planes of a periodic structure distribute uniformly or randomly around 360° we can observe diffraction rings that are called Debye−Scherrer rings as shown in Fig. 42.3 schematically. The diffraction rings are circular averaged to obtain a radial intensity profile. In SC, in the small-angle diffraction region the diffraction peaks appear at $S = 1/13.6, 2/13.6, 3/13.6,\ldots$ nm-1 for the long lamellar structure and at $S \sim 1/6, 2/6,\ldots 1/6$ for the short lamellar structure. On the other hand, in the wide-angle diffraction region the peaks appear at $S = 1/0.42$ and $1/0.37\ \text{nm}^{-1}$ for the orthorhombic hydrocarbon-chain packing structure and at $S = 1/0.42\ \text{nm}^{-1}$ for the hexagonal hydrocarbon-chain packing structure.

## 42.3 HIGHLY SENSITIVE DETECTION OF MINUTE STRUCTURAL CHANGE ON APPLYING CHEMICAL AGENTS

Frequently when solution with chemical agents, such as cosmetics and drugs, is applied on SC, we encounter a case to clarify the percutaneous route at the molecular level. For this purpose a sample cell that was used for X-ray diffraction measurement in SC was developed as schematically shown in Fig. 42.4.[7] A stratum corneum sample was embedded in a central hollow surrounded by filter paper that was used to sustain the sample. The front and the rear surfaces of the cell were sealed by a pair of polymer thin films. Therefore when solution was applied to a stratum corneum sample, it was always exposed in sufficient solution. The incident X-ray beam impinged through the front surface. As mentioned previously, to obtain the total structural modification on applying solution with chemical agents in SC it is important to observe X-ray diffraction from small- to wide-angle region.

It has been pointed out that there exist two potential penetration pathways: one is an intercellular route in which the penetration of chemical agents takes place via the intercellular lipid matrix lying between the corneocytes, and the other is a transcellular route in which the penetration takes place across both the corneocytes and the intercellular lipid matrix.[8] However, whether the former is the dominant pathway or they both are equivalently important in the penetration is still controversial. Therefore, it is highly desirable to make clear the structural evidence at the molecular level when the chemical agents are applied to SC. In order to consider this problem further, we performed X-ray diffraction measurement in two kinds of the percutaneous penetration enhancers, hydrophilic and hydrophobic ones.

Ethanol is one of the hydrophilic penetration enhancers.[9–11] It has been pointed out that ethanol may extract some lipids from SC when it is used for prolonged times.[12,13] On the other hand, terpene, for instance D-limonene, is well-known as a hydrophobic penetration enhancer.[11,14–16] So far the effects of penetration enhancers have been studied

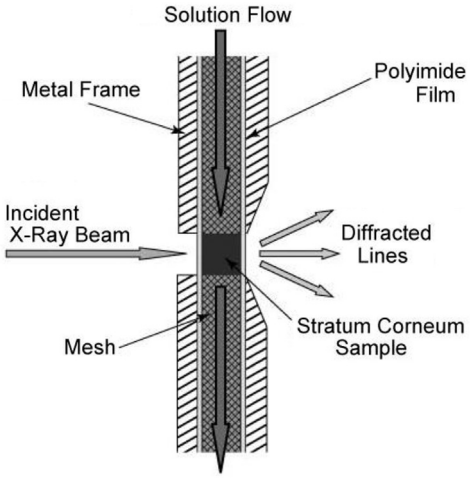



FIGURE 42.4 Sample cell for X-ray diffraction measurement to track structural change of a sample after applying solution. Using this method minute change of the diffraction profiles with time can be detected with high resolution.

by small-angle X-ray diffraction (SAXD) and wide-angle X-ray diffraction (WAXD). Cornwell et al.[15] have carried out WAXD in SC to study the effects of terpene such as D-limonene, nerolidol, and 1,8-cineole and found that after 12-h treatment WAXD intensities for the hexagonal and the orthorhombic hydrocarbon-chain packing structures do not change significantly, and on the other hand a broad intensity hump caused by liquid terpenes incorporated into SC takes place. Cornwell et al.[16] have performed SAXD in human SC to investigate the effects of D-limonene and 1,8-cineole and found that the intensity for the long lamellar structure decreases but the intensity for the short lamellar structure remains as a shoulder. The same behavior has also been pointed out by Cornwell et al.[15] in human SC. By X-ray diffraction the effects of hydrophilic penetration enhancers on SC have been studied for acetone,[16] ethanol,[7] ethanol and water mixture,[17] and also water.[3,5]

Generally when solution is applied to SC, the structure changes gradually with time. From the detection of the successive X-ray diffraction change we can obtain very minute modification of the structure. From the differences between the successive X-ray diffraction patterns we can distinguish only small changes of the structure. Furthermore, we can overcome problems of the individual differences among SCs since the change of the structure can be detected more or less by this method if any small structural change takes place. Based upon the result obtained from this method, we can get the effect of solutions at the molecular level. In the following discussion I will show typical results for hydrophilic ethanol and hydrophobic D-limonene on applying to SC.

## 42.4 PENETRATION ROUTE OF HYDROPHILIC MOLECULES IN STRATUM CORNEUM

Ethanol is commonly used as one of the transdermal formulations. It is well known that ethanol with water permeates rapidly through skin with a steady-state flux.[10] Here we have examined only the effects of pure ethanol. After application of ethanol to SC, as shown in Fig. 42.5A the X-ray diffraction intensity profiles change successively from *red* (0 s) to *blue* (7500 s) curves with time in the broad-angle region of $S = 0.05{-}3.0\ \mathrm{nm}^{-1}$. In this figure a *black curve* indicates the X-ray scattering profile for ethanol in arbitral scale. For the SAXD of $S = 0.05{-}0.4\ \mathrm{nm}^{-1}$ the intensity profiles are shown in Fig. 42.5B. In the middle angle X-ray diffraction of $S = 0.5{-}1.5\ \mathrm{nm}^{-1}$ the intensity difference, which was obtained from the intensity profiles subtracted by the initial intensity profile successively, is shown in Fig. 42.5C. The analysis to use the intensity difference is a predominant point of the present method by which we are able to obtain very small structural modification on applying solution to a single SC sample.

In SAXD, the peaks for the long lamellar structure take place at $S = 0.074$, 0.148, 0.222, and $0.296\ \mathrm{nm}^{-1}$ for first-, second-, third-, and fourth-order reflection, respectively, where the repeat distance of the lamellar structure is 13.6 nm. The repeat distance does not change with time. But the intensities decrease with time in superposition on a bigger scattering intensity slope in the smaller angle that increases with time. The growth of this smaller-angle scattering intensity might be related to the incorporation of hydrophilic ethanol into corneocytes, since similar behavior has been observed when water is applied to SC.[18,19] It is an important point that, although in Fig. 42.5B the peak for the short lamellar structure is weak, the swelling of the short lamellar structure must

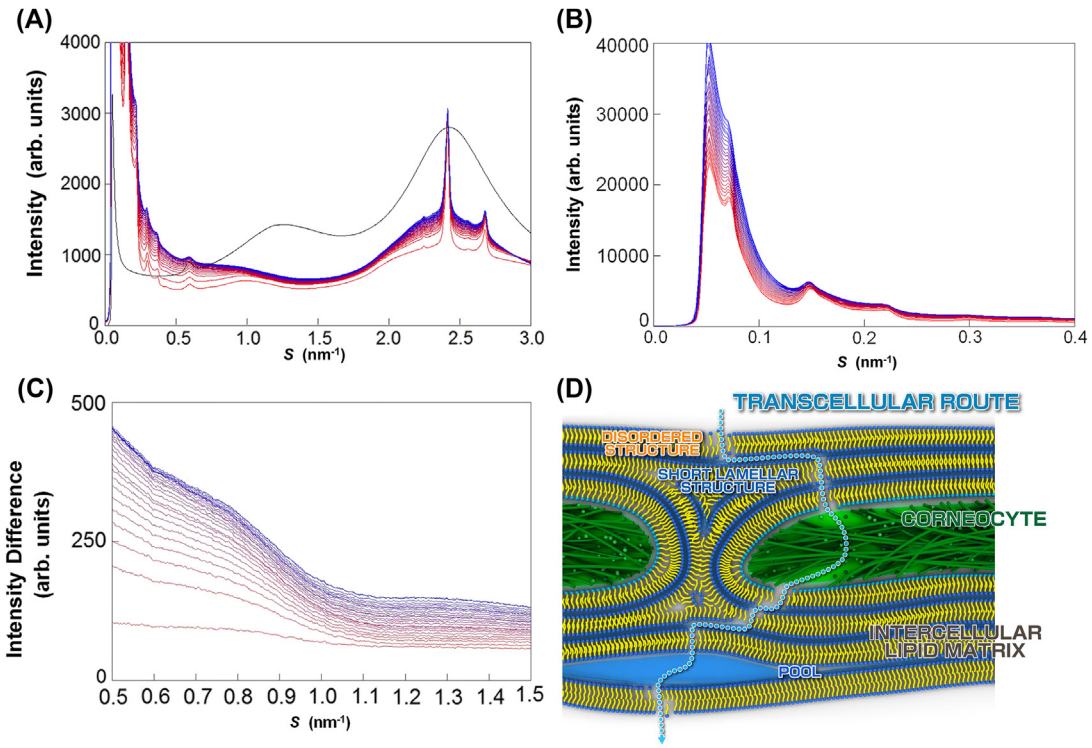



**FIGURE 42.5** After applying ethanol on stratum corneum, (A) in the broad-angle region the X-ray diffraction profiles change with time from *red* (Light gray in print versions) *to blue curves* (Dark gray in print versions), (B) in the small-angle region the intensities change as illustrated in the same manner, (C) in the middle-angle region the intensity differences change as illustrated in the same manner, and (D) schematic view of transcellular route of hydrophilic molecules predicted based upon the above results.

take place. Because of the X-ray diffraction measurement for application of hydrophilic ethanol and water mixture,[17] the peak shift of the short lamellar structure is clearly observable in contrast to unchanged behavior of the long lamellar structure. Furthermore, it is well known that uptake of water in SC yields swelling behavior of the short lamellar structure due to expansion of water layers.[3–5]

In medium angle X-ray diffraction, the diffraction peak around 1 $nm^{-1}$ (i.e., the lattice spacing: 1 nm) due to soft keratin decreases by applying ethanol as seen in Fig. 42.5A. The intensity difference is derived as in Fig. 42.5C. First of all, prior to consideration of soft keratin I will discuss the baseline, which has nothing to do with anomalous behavior of soft keratin. The baseline is composed of upward shift of an almost-flat curve and growth of the slope in the low-angle side. The former behavior seems to be due to taking up ethanol into SC and the latter due to a part of the slope observed in the SAXD.[18,19] By taking into account the contribution of the baselines, we can deduce that the intensity difference for soft keratin exhibits a shallow dip, deepens with time, and slightly shifts low angle, that is, the peak intensity at about 1 $nm^{-1}$ decreases with time and the peak position shifts slightly low angle. This fact indicates that as a result of penetration of ethanol into corneocytes, ethanol partially disrupts the structure of soft keratin in corneocytes.

In WAXD, the intensity peaks at 2.42 $nm^{-1}$ (lattice constant: 0.41 nm) and 2.67 $nm^{-1}$ (lattice constant: 0.37 nm), which appear in superposition on a broad diffraction peak around 2.4 $nm^{-1}$ (lattice constant: 0.42 nm), taking place as seen in Fig. 42.5A. The peak positions for the hydrocarbon-chain packing structures do not change with time, but the intensities decrease by a small amount. This might be due to either slight extraction or partial melting of lipids in intercellular matrix. Rise of the broad peak around 2.4 $nm^{-1}$ seems to be caused by uptake of ethanol in SC, because in pure ethanol we could observe a broad diffraction peak of ethanol around 2.4 $nm^{-1}$ as seen in Fig. 42.5A. This might be partly due to formation of pools composed of either ethanol or ethanol and water mixture.

Based upon the previous results, it is proposed that when hydrophilic molecules are applied to SC they penetrate via a transcellular route, as shown schematically in Fig. 42.5D. Namely, hydrophilic molecules can penetrate into water layers of the short lamellar structure in intercellular lipid matrix, go partly through corneocytes, and make pools of either hydrophilic molecule or mixtures of water and hydrophilic molecule.

## 42.5 PENETRATION ROUTE OF HYDROPHOBIC MOLECULES IN STRATUM CORNEUM

Terpene, D-limonene, is a penetration enhancer.[11,15,16] After application of D-limonene to the SC, the X-ray diffraction intensity profiles change successively from *red* (0 s) to *blue* (7500 s) curves with time as shown in Fig. 42.6A in the broad-angle range of $S = 0.05{-}3.0\ \text{nm}^{-1}$. In this figure a *black curve* indicates the X-ray scattering profile for D-limonene in arbitral scale. As seen in Fig. 42.6A, a broad hump near $S = 2.0\ \text{nm}^{-1}$ increases with time due to take-up of D-limonene in SC. This behavior indicates formation of pools composed of D-limonene in SC. For the SAXD of $S = 0.05{-}0.4\ \text{nm}^{-1}$, the intensity profiles are shown in Fig. 42.6B. For the middle-angle X-ray diffraction of $S = 0.5{-}1.5\ \text{nm}^{-1}$, the difference intensities that were obtained from the intensity profiles subtracted by the initial intensity profile successively are shown with high sensitivity in Fig. 42.6C.

On applying D-limonene to SC, the diffraction peak positions for the long lamellar structure in the SAXD shifts toward the lower angle as seen in Fig. 42.6B, that is, the swelling of the long lamellar structure takes place. In this figure, the repeat distance of the long lamellar structure expands from 13.5 nm and saturates near 14.5 nm with a relaxation time of 5000 s. This behavior is consistent with the fact that the hydrophobic molecules penetrate through the narrow band of the long lamellar structure with hydrophobic character during the percutaneous absorption as proposed by Bouwstra and Ponec.[20]

In the middle-angle X-ray diffraction the diffraction peak around $1\ \text{nm}^{-1}$ due to soft keratin does not change with application of D-limonene as seen in Fig. 42.6A. Namely in the intensity difference shown in Fig. 42.6C, except for growth of the slope above $1\ \text{nm}^{-1}$ is due to take-up of D-limonene in SC and the intensity difference for soft keratin is unchanged. This fact indicates that hydrophobic D-limonene does not penetrate into corneocytes.

On applying D-limonene to SC, the peak positions of the hydrocarbon-chain packing structures do not change with time, but as seen in the WAXD region of Fig. 42.6A the peak intensities decrease and therefore the hydrocarbon-chain packing structures are slightly disrupted, that is, hydrophobic chemicals such as D-limonene are compatible with the hydrophobic and disordered region in intercellular lipid matrix.

Based upon the previous results, it is proposed that when hydrophobic molecules such as D-limonene are applied to SC they penetrate via an intercellular route, as shown schematically in Fig. 42.6D. Namely, hydrophobic molecules

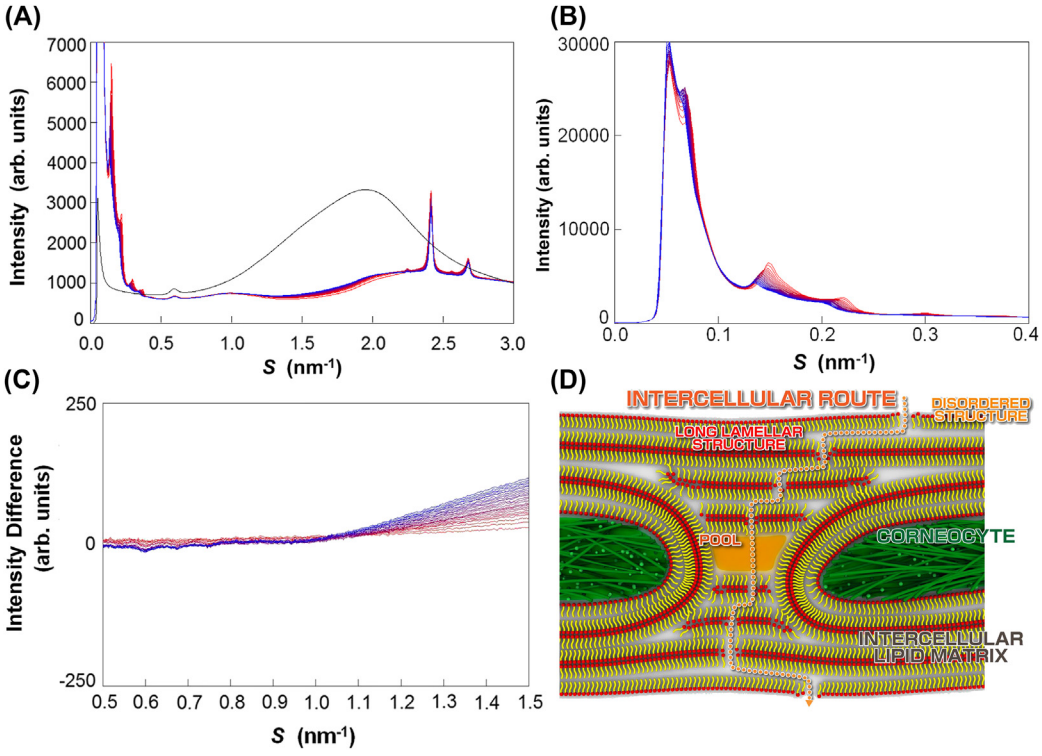



FIGURE 42.6 After applying D-limonene on stratum corneum, (A) in the broad-angle region the X-ray diffraction profiles change with time from *red* (Light gray in print versions) *to blue curves* (Dark gray in print versions), (B) in the small-angle region the intensities change as illustrated by a similar manner, (C) in the middle-angle region the intensity differences change as illustrated by a similar manner, and (D) schematic view of intercellular route of hydrophobic molecules predicted based upon the above results.

can penetrate into disordered layers of the long lamellar structure in intercellular lipid matrix and make pools composed of hydrophobic molecules.

## 42.6 BEHAVIOR OF WATER IN STRATUM CORNEUM

The role of water in SC is an important subject and a variety of studies have been performed. Transepidermal water loss and the water concentration gradient are useful indices to characterize the condition of SC. In principle to SC water is supplied from the body constantly and in the normal condition the same amount of water evaporates from the surface of skin. This fact means that the steady-state water permeation in SC occurs in nonequilibrium condition and then the water concentration results in gradient. By in vivo confocal Raman microscopy the water content in SC has been measured as a function of distance from skin surface.[21] The water content near the skin surface is estimated to be about 25 wt% and continuously increases with the depth down to viable cell where the water content reaches to about 65 wt%.[22] It is of interest to know the water behavior within SC when SC is instantaneously exposed to humid or dry conditions. Egawa and Kajikawa[22] have performed in vivo confocal Raman microscopy as follows: When water is applied to skin surface the water distribution near the surface of the SC increases markedly; after a while it returns almost to the original distribution. This fact indicates that under the normal condition the water content of about 25 wt% is kept near the surface of SC, that is, despite varying circumstances, the water content near the skin surface is regulated to be kept in a normal condition. In connection with this fact, it is worthwhile to pay attention to the results obtained by in vitro differential scanning calorimetric measurement (DSC) for various hydrated SC. From DSC the nonfreezing water has been estimated to be about 25 wt%,[23,24] where weight% is given by (weight of water incorporated into dried SC) $\times$ 100/(sum of weights of water and dried SC). These water molecules exist as bound water within SC and might play an important role in keeping the normal water condition in SC. These facts indicate that, needless to say, although in vivo study is very important to know what goes on in a living state, performing in vitro X-ray diffraction study is indispensable since it is possible to make clear the fundamental hydration mechanism at the molecular level.

## 42.7 WATER REGULATION MECHANISM IN STRATUM CORNEUM AT THE MOLECULAR LEVEL

We have carried out a detailed study on the SAXD in hairless mouse SC as a function of water content.[7] The SAXD profiles are shown in Fig. 42.7 at water contents of 0, 12, 21, 35, 50, 70, and 80 wt%. The peaks denoted by an open arrow exhibit the first- to fifth-order diffraction peak for 13.6 nm lamellar spacing, and the peaks denoted by closed arrow exhibit the first- and the second-order diffraction peaks for about 6 nm lamellar spacing. As seen in Fig. 42.7,

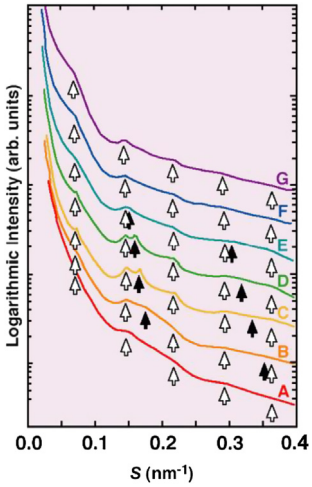



FIGURE 42.7 Small-angle X-ray diffraction of hairless mouse stratum corneum as a function of water content. The water contents are 0 wt% (A), 12 wt% (B), 21 wt% (C), 35 wt% (D), 50 wt% (E), 70 wt% (F), and 80 wt% (G).

with increasing water content the diffraction peak positions for the first- to fifth-order diffraction of 13.6 nm are almost unchanged, although the sharpness of these peaks depends on the water content. On the other hand, with increasing the water content the first- and second-order diffraction peaks for about 6 nm markedly shift toward lower angle, i.e., the short lamellar repeat distance becomes larger. This fact indicates the appearance of swelling due to the expansion of the water layers in the short lamellar structure. To elucidate the swelling effects further, we analyzed the shape of the diffraction profiles. For this purpose we focus our attention to the diffraction profile near $S \sim 0.15\ \mathrm{nm}^{-1}$, where the first-order diffraction peak of about 6 nm and the second-order diffraction peak of 13.6 nm lie. In Fig. 42.8, as a function of the water content the results on about 6 nm lamellar spacing are drawn together with the spacing of about 6.8 (=13.6/2) nm that is obtained from the second-order diffraction of the long lamellar structure with the repeat distance of 13.6 nm. The long lamellar spacing is almost unchanged with the water content. On the other hand, the short lamellar spacing grows from 5.8 to 6.6 nm as the water content increases from 12 to 50 wt%, and above 50 wt% the short lamellar diffraction peak becomes small and seems to merge into the second-order diffraction of the long lamellar structure with the spacing of 6.8 nm. In Fig. 42.8B, full width at half maximum of the diffraction profiles for the short and the long lamellar structures are shown as a function of the water content. At about 25 wt%, full width at half maximum becomes narrow not only in the spacing of about 6 nm but also in the spacing of 6.8 (=13.6/2) nm. To sum up, first, the behavior of the spacing of 6.8 nm for the second-order diffraction peak of the long lamellar structure is consistent with the results previously reported by Bouwstra et al.[25] Second, the swelling of the short lamellar structure occurs undoubtedly in our measurement.[3] Similar swelling behavior has been observed in the neutron diffraction on human SC.[4] Third, at the low water content, both full widths at half maximum broaden markedly, near 25 wt% both lamellar diffractions for the spacings of about 6 nm, and furthermore 6.8 (=13.6/2) nm become sharp, and at the higher water contents they become broad.

As discussed before, the long and the short lamellar structures coexist and therefore form domains. I will consider the correlation between the long and the short lamellar structures. The result of Fig. 42.8B indicates that at a water content of about 25 wt% both lamellar structures are well arranged and below and above the water content become disordered simultaneously. Generally, there is mismatch of the hydrophobic parts at the boundary of the two domains. In the case when there is boundary between hydrocarbon chains of lipid membrane and a hydrophobic part of a membrane protein, mechanical strain due to the mismatch is relaxed by disorder of hydrocarbon chains at the domain boundary.[26] If this is the case, I can propose that in intercellular lipids a domain composed of the long lamellar structure faces laterally a couple of the short lamellar structures where the domain boundary is constructed by a hydrophobic interface composed of hydrocarbon chains. At water contents lower than about 25 wt%, the hydrophobic part of the long lamellar structure is longer than twice the thickness of the short lamellar structure and therefore the distortion spreads over the both lamellar structures, i.e., the X-ray diffraction peaks for the long and the short lamellar spacings become broad simultaneously. At the water content of about 25 wt%, the distortion is relaxed and then both X-ray diffraction peaks become sharp. At the higher water content than about 25 wt%, distortion takes place again since the hydrophobic parts of the both lamellar structures cause mismatch, i.e., both X-ray diffraction peaks become broad again. The above aspect might be related to the existence of a disordered

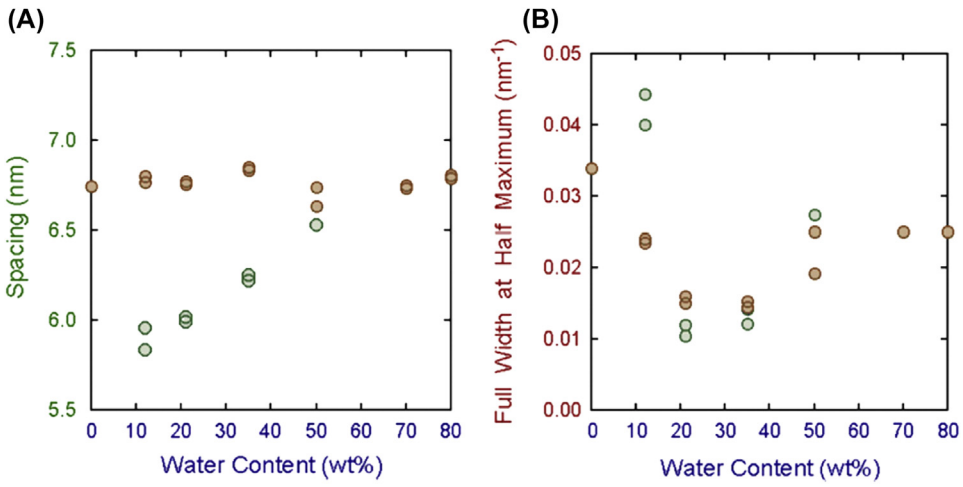



FIGURE 42.8 In hairless mouse stratum corneum, we have obtained (A) spacings of the short lamellar structure at the first-order diffraction peak and the long lamellar structure at the second-order diffraction peak and (B) full width at half maximum for both peaks.

intermediate region between the neighboring domains composed of the short and the long lamellar structures, although it is difficult to detect only by the X-ray diffraction measurement due to the irregular structures. Then as another role of the disordered region, Forslind[27] has proposed that in the domain mosaic model molecule permeation takes place via the disordered region.

The previous results indicate that the long and the short lamellar structures interact directly or indirectly with each other, the swelling of the short lamellar structure takes place, and as a result at a water content of about 25 wt% the lamellar structures are stabilized simultaneously. It should be pointed out that in SC almost all water is stored in corneocytes, so-called bricks, that become thick with increase of the water content in SC, but a small part of water comes out to the water layers of the short lamellar structure. Once the thickness of the water layer deviates from the steady-state water thickness, owing to the interaction between the neighboring domains a regulation mechanism to keep the water content of about 25 wt% in SC works so as to bring back to the steady-state thickness. Finally, the water content in the corneocytes is regulated to be kept at about 25 wt% in normal condition. In addition, in this regulation the bound water in corneocytes plays an important role subsidiarily.

It is highly desirable to study the short lamellar structure on human SC as a function of the water content. We have obtained the X-ray diffraction in human SC as shown in Fig. 42.9.[5] It has been confirmed that swelling of the short lamellar structure takes place and full width at the half maximum for this diffraction profile becomes narrow at the water content of about 25 wt% as shown in Fig. 42.10A and B, respectively, consistent with the results obtained from measurement on the hairless mouse SC.[3] Therefore generally the short lamellar structure exhibits the swelling behavior and becomes stable at the water content of about 25 wt%. Furthermore, in human stratum corneum it has been found that soft keratin within corneocytes changes near the water content of about 25 wt% as shown in Fig. 42.11. This fact indicates uptake of water molecules into corneocytes, and the interaction between water and soft keratin changes near 25 wt% is consistent with the fact that until the water content of 25 wt% water molecules form bound water within corneocytes and above 25 wt%, water molecules become free.

To sum up the behavior of water in SC is schematically shown in Fig. 42.12. Water molecules are supplied to SC always from viable cells and the same amount of water molecules is released continuously from skin surface.

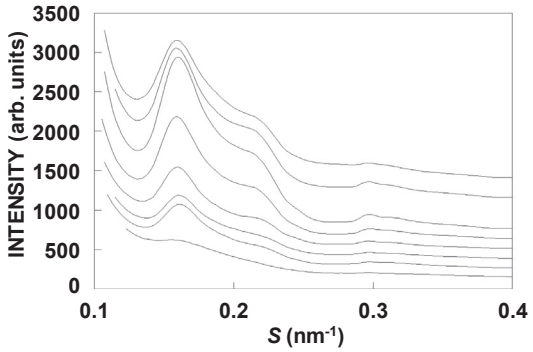



FIGURE 42.9 Small-angle diffraction profiles as a function of water content in human stratum corneum. The water content is 5, 10, 15, 20, 25, 30, 40, and 50 wt% from bottom to top in the profiles.

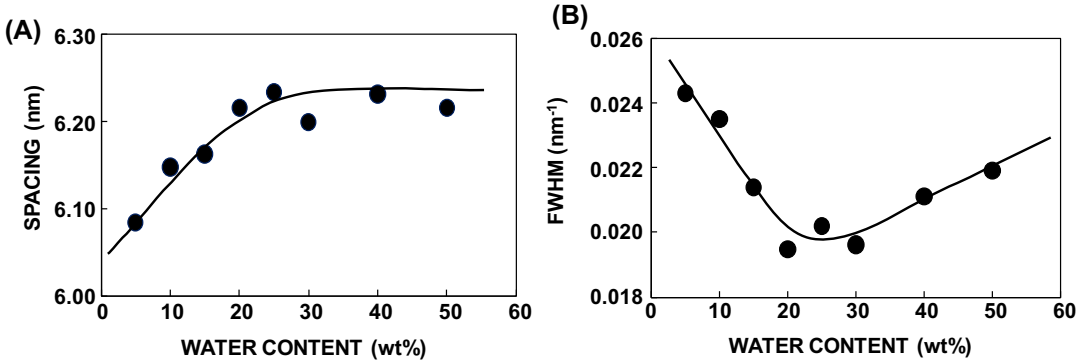



FIGURE 42.10 In human stratum corneum we have obtained (A) spacings of the short lamellar structure at the first-order diffraction peak and (B) full width at half maximum for this peak.

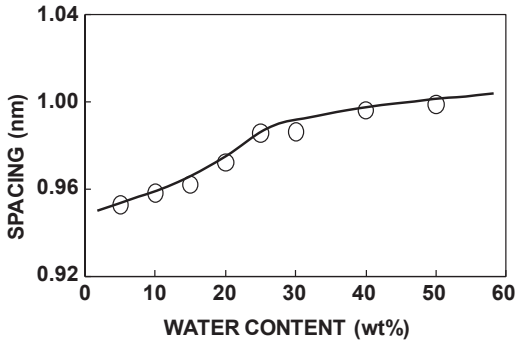



FIGURE 42.11 In human stratum corneum we have obtained spacing of soft keratin as a function of water content.

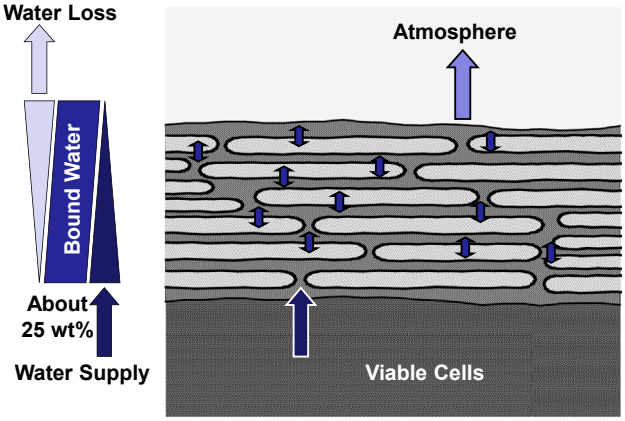



FIGURE 42.12 Schematic view of water behavior in stratum corneum at a stationary state.

Therefore SC lies in a stationary state against water. Within SC water molecules exist up to about 25 wt% as bound water, and a large amount of water molecules are in corneocytes. Near viable cell sides there are a lot of unbound water molecules, and the concentration of unbound water molecules decreases with approach to the skin surface. Beyond a water content of about 25 wt% the unbound water molecules seem to lie in corneocytes and also to form water pools in intercellular lipid matrix of SC. In this process permeation of water molecules takes place via a transcellular route as shown in Fig. 42.5D.

## References

1. Hatta I, Ohta N. *Photon factory activity report 2003 part A, highlights*. 2004. p. 49.
2. Groen D, Gooris GS, Bouwstra JA. *Biophys J* 2009;**97**:2242.
3. Ohta N, Ban S, Tanaka H, Nakata S, Hatta I. *Chem Phys Lipids* 2003;**123**:1.
4. Charalambopoulou GCh, Steriotis ThA, Hauss Th, Stubos AK, Kanellopoulos NK. *Physica B* 2004;**350**:e603.
5. Nakazawa H, Ohta N, Hatta I. *Chem Phys Lipids* 2012;**165**:238.
6. Doucet J, Potter A, Baltenneck C, Domanov Y. *J lipid Res* 2014;**55**:2380.
7. Hatta I, Nakazawa H, Obata Y, Ohta N, Inoue K, Yagi N. *Chem Phys Lipids* 2010;**163**:381.
8. Suhonen TM, Bouwstra JA, Urtti A. *J Control Rel* 1999;**59**:149.
9. Kurihara-Bergstrom T, Knutson K, DeNoble LJ, Goates CY. *Pharm Res* 1990;**7**:762.
10. Kai T, Mak VHW, Potts RO, Guy RH. *J Control Rel* 1990;**12**:103.
11. Williams AC, Barry BW. *Adv Drug Delivery Rev* 2004;**56**:603.
12. Golden GM, Guzek DB, Haris RR, McKie JE, Potts RO. *J Invest Dermatol* 1986;**86**:255.
13. Garson J-C, Doucet J, Leveque J-L, Tsoucaris G. *J Invest Dermatol* 1991;**96**:43.
14. Okabe H, Takayama K, Ogura A, Nagai T. *Drug Design Deliv* 1988;**4**:313.
15. Cornwell PA, Barry BW, Stoddart CP, Bouwstra JA. *J Pharm Pharmacol* 1944;**46**:938.
16. Cornwell PA, Barry BW, Bouwstra JA, Gooris GS. *Intern J Pharm* 1996;**127**:9.
17. Bouwstra JA, de Graaff A, Gooris GS, Wiechers JW, van Aelst AC. *J Invest Dermatol* 2003;**120**:750.
18. Charalambopoulou GCh, Steriotis TA, Mitropoulos ACh, Stefanopoulos KL, Ioffe A. *J Invest Dermatol* 1998;**110**:988.
19. Horita D, Hatta I, Yoshimoto M, Kitao Y, Todo H, Sugibayashi K. *Biochim Biophys Acta* 2015;**1848**:1196.

20. Bouwstra JA, Ponec M. *Biochim Biophys Acta* 2006;**1758**:2080.
21. Caspers PJ, Lucassen GW, A Carter E, Bruining HA, Puppels GJ. *J Invet Dermatol* 2001;**116**:434.
22. Egawa M, Kajikawa T. *Skin Res Tech* 2009;**15**:242.
23. Walkley K, Invet J. *Dermatol* 1972;**59**:225.
24. Inoue T, Tsujii K, Okamoto K, Toda K. *J Invet Dermatol* 1986;**86**:689.
25. Bouwstra JA, Gooris GS, van der Spek JA, Bras W. *J Invest Dermatol* 1991;**97**:1005.
26. Mouritsen OG, Bloom M. *Biophys J* 1984;**46**:141.
27. Forslind B. *Acta Derm Venereol* 1994;**74**:1.

CHAPTER

# 43

# Skin Aging

*S. Inoue*

**Cosmetic Health Science, Gifu Pharmaceutical University, Gifu, Japan**

Since the dawn of history, men have dreamed of attaining immortality, eternal youth, and beauty. There are many stories of people in power, such as the Chinese Emperor Shi Huangdi, Napoleon, and Countess Elizabeth Bathory, who eagerly searched for elixirs of life or beauty. Although the legends and fables of eternal youth are dream stories that lack scientific evidence, people today actually talk about and expect antisenescence and an extended lifespan due to remarkable advances in the medical and health fields as well as improvement in the social environment and lifestyle habits.

We have now entered the age of longevity and demand a high quality of life (QOL) with it. In other words, we expect a healthy, long life. In addition to having a sound body and mind, another important factor for a person's well-being is to be physically beautiful and attractive. Improvement of facial attractiveness has been shown to lead to positive changes in emotional and social dimensions of one's life.[1,2]

One common way to exude youth and beauty is to appear younger than one actually is, and maintain physiological functions of one's entire body including one's skin, at levels higher than those of other people of the same age. Perceived age, or the estimated age of a person, is widely used by clinicians as a general indication of a patient's health, suggesting a relationship between health and facial appearance associated with skin aging. Furthermore, perceived age is reported to be a reliable biomarker of aging that predicts survival among those over 70 years old and correlates with important functional and molecular aging characteristics.[3]

Seeking longevity means to extend one's lifespan as close to the biologically determined maximum age as possible. However, to prolong a healthy lifespan with improved health- and beauty-related QOL,[4] it is necessary to understand the phenomenon of senescence scientifically and develop antisenescent treatments to delay such senescence and suppress its symptoms.

This chapter does not necessarily address general characteristics of aging skin but highlights published studies to understand "senescence," focusing on senescence from the molecular level to the systemic level. Next, theoretical research strategies to develop antiaging cosmetics are discussed, taking into account age-associated decline and breakdown of homeostasis by the repair system against DNA and tissue damage, as well as cell senescence and chronic inflammation, which accelerates systemic senescence.

## 43.1 DIFFERENCE BETWEEN AGING AND SENESCENCE

The term *aging* refers to the passage of time from birth to death, which is unbiased and independent on the merits and demerits. *Senescence*, on the other hand, refers to the failure or unfavorable changes in physiological function after maturation, which eventually leads to death.

"Aging" is often used to describe negative changes in biological systems and functions. For example, "photoaging" refers to accelerated senescent characteristics on areas exposed to the sun, such as the face and neck. "Antiaging" conveys the idea of a negative phenotype. In this chapter, however, aging refers to the process itself, whether characteristics become visible or not, while senescence refers only to negative phenotypes. Hence, since aging itself cannot be physically stopped, nor the biologically determined maximum lifespan prolonged, antiaging means to delay age-dependent changes in the body as long as possible or to decrease the degree of such changes. On the other hand, "antisenescence" means to prevent the disadvantageous changes in the body or decrease the degree of damaging changes. These definitions should be helpful when discussing and understanding senescence scientifically.

*Cosmetic Science and Technology: Theoretical Principles and Applications*
http://dx.doi.org/10.1016/B978-0-12-802005-0.00043-4



Copyright © 2017 Elsevier Inc. All rights reserved.

## 43.2 SENESCENCE FROM THE MOLECULAR LEVEL TO THE SYSTEMIC LEVEL

Individual senescence has gradually been revealed to progress at a relatively mutual rate at the tissue, cellular, and molecular level, and is often difficult to recognize outwardly (Fig. 43.1).

### 43.2.1 Senescence of Biomolecules

Modification of intracellular DNA, proteins, and lipids as well as extracellular components is commonly known to occur at the molecular level during the aging process, through chemical oxidization by reactive oxygen species (ROS) or catalysis by oxidative enzymes, or through ultraviolet (UV) rays especially on the skin.

Of all the organs of the body, skin is the most easily affected by sunlight as an environmental risk factor, including UV rays such as UVB (290–320 nm) and UVA (320–400 nm). UVB is easily absorbed or scattered within the epidermis, resulting in an acute response. On the other hand, UVA is less intense but penetrates deeper into the skin, damaging the dermal matrix. UV energy is absorbed by chromophores in biomolecules leading to structural change, specifically UV-induced damage, and often generates ROS.

UV damages DNA in the two major forms, causing cyclobutane pyrimidine dimers and pyrimidine-pyrimidone 6–4 photoproducts, which are principally repaired by nucleotide excision repair (NER) system.[5] On the other hand, UV-induced or endogenously produced ROS cause various types of oxidative DNA damage, including well-known 8-hydroxydeoxyguanosine, and are primarily repaired by base excision repair (BER) system.[6] This damaged DNA is quickly repaired or removed from tissues via apoptotic cell death. However, unrepaired or misrepaired nucleotides gradually accumulate in cells as a person ages because DNA repair capacity by NER and BER systems declines with aging.[7–11] As mutations accumulate, cell function decreases, resulting in tissue senescence.

Collagen is the most abundant and stable protein in the dermis and has a slow turnover rate, which provides surrounding cells with the right conditions to maintain skin homeostasis. However, its long life makes collagen susceptible to the formation of aged proteins associated with cross-link structures, such as advanced glycation end products (AGEs) via reaction with reducing sugars[12] and histidinohydroxylysinonorleucine (HHL) residue via lysine oxidase activity.[13] Accumulation of modified collagen causes age-dependent reduction in elasticity, yellowing of the skin, and decrease in physiological functions, such as the migration or proliferation of surrounding keratinocytes and fibroblasts.[14,15] Furthermore, AGEs lead to an increase in oxidative stress, such as ROS generation, and negatively affects cells in contact.[16,17] In fact, such aged collagen with AGEs and HHL in the skin increase with age, and the accumulation of AGEs is exacerbated by diabetes or hyperglycemic conditions,[12,13] indicating that decreased collagen turnover with age and the concentration of glucose in tissue are environmental factors responsible for the senescence of collagen. Epidermal cytokeratin 10, a protein with a high turnover rate, is also reported to contain N(ε)-(Carboxymethyl) lysine (CML) residue, an AGE structure, but the relationship between the amount of CML-keratin and senescence of the skin remains unclear.[18]

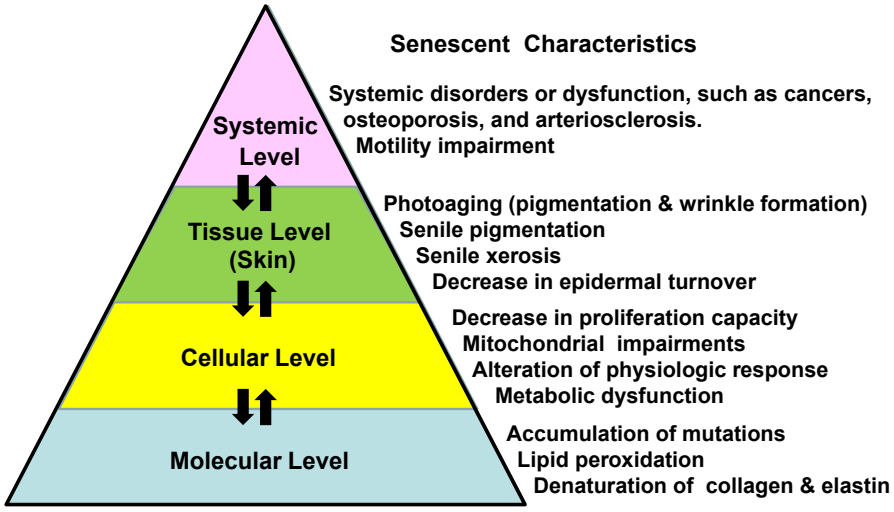



FIGURE 43.1 Senescence from the molecular level to the systemic level.

UV also damages the dermal elastic fibers causing solar elastosis, the most common histologic result of photoaged skin. Dermal elastic fibers are denatured and replaced with thickened and tangled amorphous elastotic materials with the progress of aging.[19,20]

An age-related example of lipid peroxidation is lipofuscin, highly autofluorescent granules of oxidized proteins and lipids in lysosomes. Lipofuscin accumulated in a wide range of cell and tissue types with increased age, and excess deposits, impair cell functions. In the skin, UVA-induced photo-oxidative stress is reported to lead to dermal photodamage by hindering lysosomal removal of lipofuscin.[21]

From the previous discussion, senescence of biomolecules is known to alter cellular functions and physical or physiological properties of tissue along with aging, and may affect the senescence of an individual (Fig. 43.1).

### 43.2.2 Senescence of Cells and Tissues (Skin)

A well-known example for senescence at the cellular level is the age-dependent reduction in telomere length, long sequences of nucleotides at the end of chromosomes that preserve genome stability and are involved in the proper division of a cell.[22,23] Telomeres become shorter with each cell division, and when they become too short, the cell is no longer able to divide, becoming "senescent."[24] When comparing cells among the same species, telomere length decreases with cell age,[23,25] and those with longer telomeres have a greater capacity to divide.[26] Telomeric oxidative damage induces cell senescence and cell death regardless of whether oxidative stress occurs elsewhere in the cell.[27]

Generally speaking, most biological functions of cells change with aging, including essential functions in cell viability and maintenance, and affect cell senescence. Mitochondrial impairments increase the production of ROS and the appearance of oxidative stress with aging. The age-dependent decrease in the repair capacity for various forms of damage results in the accumulation of dysfunctional molecules in cells and tissues, resulting in senescent phenotypes.

A decrease in keratinocyte proliferation along with aging is a predominant cause of age-dependent decrease in the rate of epidermal turnover and is involved in the accumulation of low-quality stratum corneum (SC), damaged or incompletely keratinized corneocytes, and cells containing melanin. These result in senescent characteristics such as senile xerosis, senile pigmentation, and fine wrinkles.[28,29]

The epidermis shows also senescent phenotypes, such as xerosis and delayed SC turnover, as proliferation of basal cells decreases under hyperglycemic diabetic conditions.[30,31] From this, lifestyle as an environmental factor is thought to be involved in skin senescence as shown by AGE formation of dermal collagen.

### 43.2.3 Systemic Senescence of an Individual

Individual senescence is seen as the result of senescence of each organ, such as the skin, skeleton, internal organs, and the brain. In particular, skin senescence is an important element in judgment of age since people often estimate the degree of individual senescence by one's appearance, in other words, perceived age.[32] Long-term UV exposure is considered to be an environmental factor that leads to increased pigmentation and fine wrinkles.

On the other hand, single mutation of several genes, such as *WRN*, *CS*, and *XP*, is known to cause progeria syndrome characterized by premature aging, where distinct features of individual senescence are observed.[33–35] These genes are known to contribute to genome stability and DNA repair, suggesting that a decrease in DNA maintenance capacity along with aging leads to cellular, tissue, and then individual senescence.

By identifying various genes related to lifespan and the aging process, senescence can be shown to be influenced by innate genetic factors. However, individuals of the same species show different rates of aging and varying degree of senescence that are not necessarily governed by the inherent lifespan of the species, despite the distinct and intrinsic lifespan of each species. These differences are due the effect of environmental factors, such as climate, nutrition, and lifestyle. This concept regarding individual senescence is strongly supported by findings that not only caloric restriction but rather a balance of various nutrients and their ratios play a crucial role in the regulation of the lifespan of mammals and simple model organisms.[36] For example twins over 70 years old show a different perceived age corresponding to their remaining lifespan.[3]

## 43.3 PROGRESS AND ISSUES IN SENESCENCE RESEARCH

Up to now, extensive research on senescence has been carried out. Man is deeply interested in why we age and eventually die, and how to stay healthy and young. In this section, important issues in research are briefly discussed in order to understand senescence, although this a small piece of the big picture.

### 43.3.1 Studies on Premature Aging and Longevity Caused by a Single Gene Mutation

Progeria syndrome is characterized by common senescent features such as cutaneous atrophy, juvenile alopecia or white hair, immunodeficiency, and infertility. It is also frequently associated with juvenile cataract formation, dyspigmentation, arteriosclerosis, osteoporosis, diabetes, and cancer. It may be extremely attractive to explain these phenotypes of individual senescence by the dysfunction of a single gene, and many studies have been carried out on human progeria syndrome caused by the mutation of a single gene. Various genes related to lifespan and individual senescence have been identified in humans.[33–35,37]

*WRN* is a causative gene for Werner syndrome. *WRN* encodes the RecQ helicase,[33] which is known to play a role in DNA replication and repair, transcription, and telomere maintenance.[37] *CS* and *XP* are causative genes of Cockayne syndrome and xeroderma pigmentosum, respectively, which are both involved in the NER system for repairing damaged DNA.[34,35] These findings suggest that DNA instability or damage in specific cells lead to individual senescence. In fact, NER as well as BER capacity have been reported to decrease along with aging in cultured human cells.[7–11] Whether WRN protein is related to physiological aging and lifespan in healthy human individuals is still unclear.

Many studies using mouse models have been carried out to identify specific genes that are strongly related to longevity. Many of these longevity genes are also reported to be related to trophic and anabolic activity, signaled through insulin/IGF-1-FOXO or the mTOR pathways, as can be seen in dysfunction of *SIRT1*,[38] *mTORC1*,[39] *S6K1*,[40] and *Klotho*[41] genes. Anabolic signaling is suggested to accelerate aging, and decreased nutrient signaling is thought to extend longevity.[42]

However, in some cases such as the *Klotho* gene, the effect of human homolog genes on longevity remains unclear.[43] but deficiency in the mouse *Klotho* gene is thought to promote senescence and its overexpression extends lifespan.[41,44] In contrast, mouse models with a deleted *Wrn* gene could not replicate accelerated aging characteristics, and the additional deletion of *Terc* (RNA component of telomerase) was needed to display for senescent phenotypes.[45] This discrepancy is thought to be due to the extremely long telomeres in laboratory mice and the residual level of telomerase in somatic tissue.

By combining the findings obtained from studies on human and mouse genes related to lifespan and individual senescence, data on understanding senescence can be obtained. However, how a gene is involved in the progress of senescence of a healthy human individual must be considered, and differences due to gene contribution in the senescence of humans, mice, and other simple organisms must be determined.

### 43.3.2 Studies on Senescence Using Wild-type Mice and Senescence-accelerated Mice Models

Analysis of the senescent process in a wild-type rodent is a popular method to determine characteristic variations and the mechanism of aging, where animals are bred for a long period of time under various conditions such as UV irradiation, dietary restriction, high-fat feeding, and drug administration. In the field of cosmetics, many studies on the formation of photoaged skin and the effects of active ingredients on the protection and improvement of wrinkles using UV-irradiated hairless mice and rats have been carried out. Reasonably, this procedure can be applied to the characterization of longevity genes such as *SIRT*. For example, the effect of polyphenol resveratrol on lifespan has been shown to be dependent on *SIRT1* in studies using wild-type and *SIRT1* knockout mice.[46,47]

Senescence accelerated mice (SAM) are obtained by continuous brother-sister breeding from original AKR mice with severe deterioration and are available for senescence research.[48,49] The SAM P series (SAMP) show juvenile loss of skin glossiness and increased coarseness, hair loss, periophthalmic lesions, increased lordokyphosis of the spine increasing in severity with advancing age, in other words acceleration of senescence. Whereas, the SAM R series (SAMR) show accelerated senescence resistance.

Information regarding age-associated changes in skin or photoaged skin can be obtained from these in vivo studies. This data is valuable in the understanding of senescence and the management of senescent symptoms. However, caution is needed. Due to the complexity of in vivo phenomena, which often include various causes and consequences simultaneously, an increase of something in photoaged skin can be misunderstood as detrimental and causing photoaging, and which should be inhibited or suppressed. For example, increased molecules in the skin due to UV exposure include both those necessary for tissue repair and those that cause tissue damage. Moreover, there is also species variation between humans and animals.

### 43.3.3 In Vitro Studies on Cell Senescence Using Cultured Cells

Cultured cells were mistakenly viewed as infinitely reproducible, in other words, free from senescence, since they are free from individual restriction. However, Hayflick and Moorhead demonstrated that human fetal fibroblasts

degenerated after about 50 subcultivations and one year in culture. This phenomenon was attributed to intrinsic factors that are expressed as senescence at the cellular level.[50] From this, in vitro studies to characterize senescent cells under the condition of in vitro aging became possible. The correlation between the longevity of mammalian species and the lifespan of normal fibroblasts in vitro and erythrocytes in vivo indicate that the lifespan of proliferative cells reflects the lifespan of the individual.[51]

However, loss of cellular proliferative ability in vivo is not necessarily the same as loss of organ or tissue function seen in brain and cardiac muscle cells. Lifespan of cell division during in vitro aging is not a suitable parameter of senescence because lifespan is a biological phenomenon that differs from senescence.

### 43.3.4 Studies to Understand Individual Senescence Based on Cell Senescence

Long-term observation during the aging process is needed to study human individual senescence. As the use of animal models becomes increasingly difficult, especially in the field of cosmetics, from the viewpoint of animal protection and welfare, in vitro culture system or artificial skin models have become indispensable in the study of skin senescence of humans. By comparing the in vitro characteristics of cells obtained from various aged individuals with the in vivo skin phenotypes, it is possible to deduce individual skin senescence from findings obtained on cell senescence. For example, studies on telomeres can be mentioned as a representative example of this methodology—the length of a telomere decreases with age,[23,25] a longer telomere has greater potential for a longer lifespan of cell division,[26] and NER as well as BER capacity decreases along with aging.[23,25] These findings are obtained from isolated cells but are very helpful in the practical understanding of individual senescence.

However, this kind of approach (cross-sectional study) has limitations regarding the precise interpretation of results since the obtained data is considered to be the mean value of every age of the population. A longitudinal study to examine how the same individual changes with age is essential but requires a long period of time to complete.

## 43.4 CHRONIC INFLAMMATION AND SENESCENCE

Recently, new approaches in research have been proposed, such as linking cell senescence with individual senescence. This approach suggests the process where cell senescence leads to chronic inflammation, then tissue damage (disease), and finally individual senescence. This is an attractive hypothesis that opens the way to the development of new antisenescent drugs and cosmetics.

### 43.4.1 What is Chronic Inflammation?

Inflammation is vital protective and repair function, which maintains local and systemic homeostasis of the organisms by excluding invading xenobiotics or intrinsic dead cells. Acute inflammation as an emergent response gradually decreases within several months. Chronic inflammation accompanied with a weak inflammatory reaction may unknowingly occur repeatedly and without signs such as swelling, fever, flare, and aches. Recent research has shown that chronic inflammation does not necessarily follow acute inflammation, and qualitatively differs from acute cases, which cause systemic or organ senescence. Chronic inflammation results in metabolic syndromes, malignant tumors, and autoimmune response, allergic, cardiovascular, and neurodegenerative diseases.[52]

Chronic inflammation is the constant inflammatory reaction propagated by the production of cytokines and migration of immune cells, which is induced by endogenous ligands (damage-associated molecular patterns; DAMPs) when cells are exposed to stress and damage. Chronic inflammation is also an inflammatory reaction due to extrinsic xenobiotics (pathogen-associated molecular patterns; PAMPs).[52–55]

### 43.4.2 Inflammaging-Senescence Induced by Chronic Inflammation

Constant and weak chronic inflammation is believed to promote individual senescence by systemic cell senescence and immunosenescence with age. This is called “inflammaging”[52–57] (Fig. 43.2).

Stress, such as UV and ROS, and the shortening and dysfunction of telomeres trigger DNA damage that is left unrepaired and activate tumor suppression genes p53 and p16. Usually p53, p16, and/or p21 lead damaged cells to apoptotic death. However, some cells escape apoptosis and cease to divide irreversibly. This condition is called “cell senescence.”[56,57] Senescent cells induce chronic systemic or organ inflammation by secreting senescence-

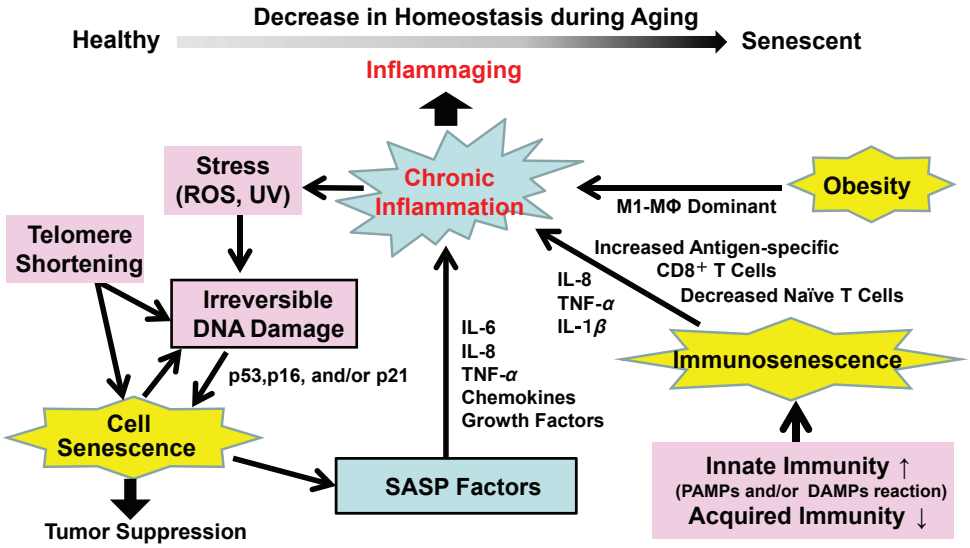



FIGURE 43.2 Chronic inflammation promotes "Inflammaging." *DAMPs*, damage-associated molecular patterns; *PAMPs*, pathogen-associated molecular patterns; *SASP*, senescence-associated secretory phenotype.

associated secretary phenotype (SASP) factors such as cytokines IL-6, IL-8, and TNFα, growth factors, and chemokines[58,59] (Fig. 43.2).

In the immune system, the ability of lymphocytes to differentiate declines along with aging, resulting in fewer naïve T cells that are not yet associated with a specific antigen. Consequently, chronic inflammation is accelerated as the natural immune system becomes more dominant than the acquired immune system, and cytokines, such as IL-6, IL-8, and TNFα, are supplied. In cases of lifestyle-related diseases such as obesity, inflammatory M1 macrophages infiltrate fat tissue and secrete proinflammatory cytokines, inducing chronic inflammation.[54] Furthermore, as shown in Fig. 43.3, senescent cells are thought to cause tissue and then individual senescence by inducing cell senescence of stem cells in individual organs, or by alteration and senescence of the extra cellular matrix (ECM) responsible for homeostasis in the cell environment.

Jurk et al. reported a mouse model with chronic and progressive low-grade inflammation induced by deficiency of a negatively regulating subunit (NF-κB1) in the transcription factor NF-κB.[53] These mice show premature aging

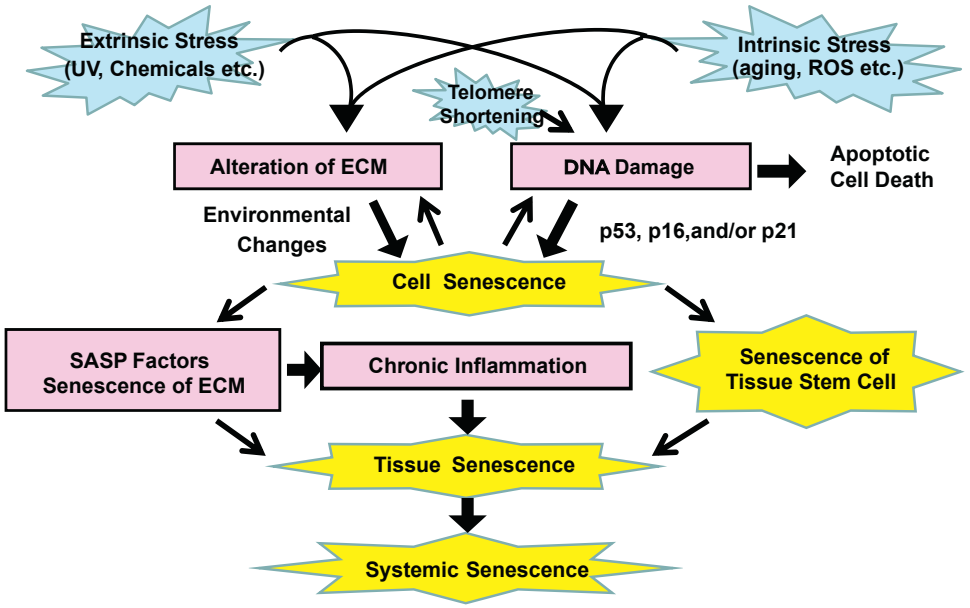



FIGURE 43.3 How can cell senescence cause systemic senescence?

and a shortened lifespan. Dysfunction of telomeres, stabilization of DNA damage, and accumulation of senescent cells were observed with an increase of plasma IL-6 concentration. Interestingly, preferential accumulation of telomere-dysfunctional senescent cells in tissue is blocked by antiinflammatory or antioxidant treatment in mice, and the regenerative potential of tissue can be regained. These findings indicate that systemic and chronic inflammation accelerates senescent phenotypes. However, antiinflammatory treatment could not extend mouse lifespan due to well-known, long-term side effects of nonsteroidal antiinflammatory drugs (NSAIDs).

A large-scale cohort study on human individual senescence was carried out targeting 1554 individuals including 684 centenarians and (semi-)supercentenarians, 167 pairs of centenarian offspring and their spouses, and 536 community-living very old (85–99 years).[60] Inflammation scores, such as plasma IL-6 and TNF-α levels, were lower in children of centenarians compared to age-matched controls, and centenarians and their children retained longer telomeres. However, telomere length was not a predictor of successful aging in centenarians and semisupercentenarians. Furthermore, centenarians in the group with lower inflammation scores were shown to have a longer wellness ability and cognitive function. These findings suggest that a lower inflammation level indicates healthier longevity, and chronic inflammation is an important variable driver of aging even in extreme old age in humans.[60]

From the previous discussion, the chronic inflammation theory for accelerated senescence can be considered in conjunction with other various theories, such as the program theory, molecular damage accumulation theory, and oxidative stress theory.[61]

In vitro research on cell senescence and regulation mechanisms of SASP will be valuable in the understanding of individual senescence and in proposing antiaging treatments in cosmetic fields.

## 43.5 SIRTUIN AND RESVERATROL

Kaeberlein et al. observed that overexpression of *Sir2* (Silent Information Regulator two; *Sirtuin 2*) prolonged the lifespan of budding yeast in 1999.[62] Sirtuin and resveratrol, a polyphenol present in red wine that activates sirtuin, have gained attention as elixirs of longevity. Important information of longevity and energy metabolism has been obtained from many studies on both molecules.

### 43.5.1 Sirtuin

Mammalian sirtuins, in seven isoforms of SIRT1-SIRT7 proteins, are homologs of yeast Sir2.[63] All sirtuins except for SIRT4 have catalytic activity of nicotinamide adenine dinucleotide ($NAD^+$)-dependent protein deacetylase. SIRT1 is most widely characterized and reported to extend the lifespan of mice by the overexpression of the *SIRT1* gene or activation of SIRT1, either by restricting calories or by pharmacological activity using resveratrol, and protects mice from age-related metabolic dysfunction, liver adiposis, neurodegeneration, cardiovascular disease, and various types of cancer.[63]

SIRT1 catalyzes the removal of the acetyl group of acetylated lysine residue of various substrate proteins while binding to the nicotinamide group from NAD, resulting in reaction products of deacetylated proteins, nicotinamide (NA), and acetyl-ADP-ribose (Fig. 43.4). Substrates include a number of important transcription factors, such as p53, NF-κB, KU70, peroxisome proliferator-activated receptor γ (PPARγ), PPARγ coactivator 1α (PGC-1α), and the forkhead box, subgroup O (FOXO) family, to drive DNA repair, apoptotic cell death, and metabolic responses, such as insulin secretion, gluconeogenesis, and fatty acid oxidation[63] (Fig. 43.5). The resulting deacetylated transcription factors activate the expression of target genes, such as *PGC-1α*, *KU70*, and *FOXO*, or in reverse suppress gene expression of *p53*, *PPAR-γ*, and *NF-κB* (Figs. 43.4 and 43.5). Expected relationships among SIRT1, p53, and cell senescence after DNA damage induced by UV or ROS are summarized in Fig. 43.6.

Beneficial effects in many physiological and pathological processes, such as cell survival and prolonged lifespan, attributed to calorie restriction (CR), have been shown to be the result of the catalytic activity of SIRT1.[64,65] In this regulation, interestingly, $NAD^+$ is a cofactor of SIRT1 and plays an important role in sensing various stresses, such as energy depletion due to CR and an oxidative stress. This can be seen by the increase in the $NAD^+/NADH^+$ ratio in the cells with increased ATP consumption and oxidative shift of the cellular redox state. This indicates that an increase in $NAD^+$ activates SIRT1 to respond to such stress (Fig. 43.5).

Most of *SIRT1* deficient (knockout) mouse strains survive to adulthood, and typically show a small, weak phenotype, and display a number of developmental defects.[66–68] However, a knockout mouse strain dies shortly after birth only in the 129/J inbred background.

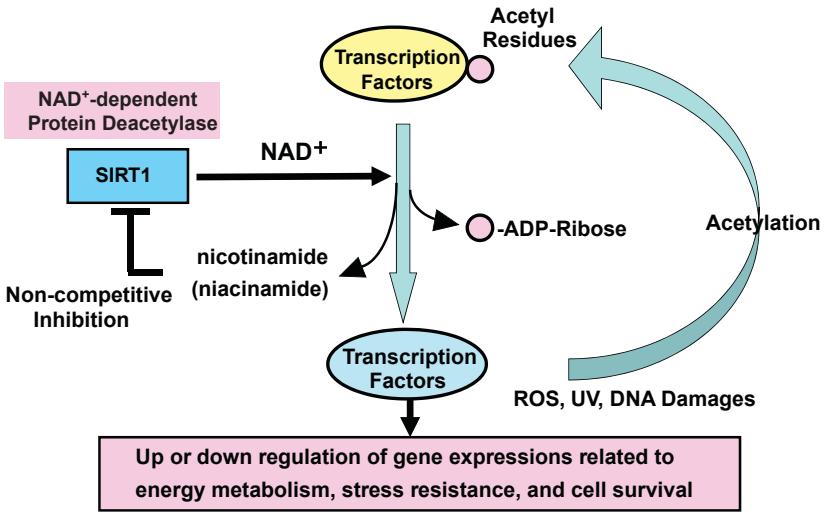



FIGURE 43.4 Enzymatic activity of SIRT1.

In consideration of the previous discussion, SIRT1 is suggested to play a crucial role in ensuring homeostasis in energy metabolism and restoring homeostasis during stress responses and inflammation. However, extending lifespan and processing senescence may vary depending on cell type, animal species, and physiological conditions. Much remains to be clarified regarding the biology of sirtuins. For example, the role of SIRT1 as well as other sirtuin homologs in human organs and individuals remains unclear.[63]

## 43.5.2 Resveratrol

Prolonged CR has been postulated as a nongenetic intervention that has consistently been found to extend both mean and maximal life span among a variety of species. In line with this, much attention has been given to the search for alternative approaches that can produce effects similar to CR without a reduction in caloric intake. Resveratrol is the most characterized and representative candidate for extending lifespan by activating SIRT1 (Fig. 43.5).

Resveratrol was identified as a potent activator of SIRT1 and has been confirmed to mimic CR in yeast by stimulating Sir2 with increased DNA stability and extended lifespan.[69] After extensive research using other simple organisms, the effect of resveratrol on lifespan in mammals was shown to be dependent on SIRT1 but not directly on

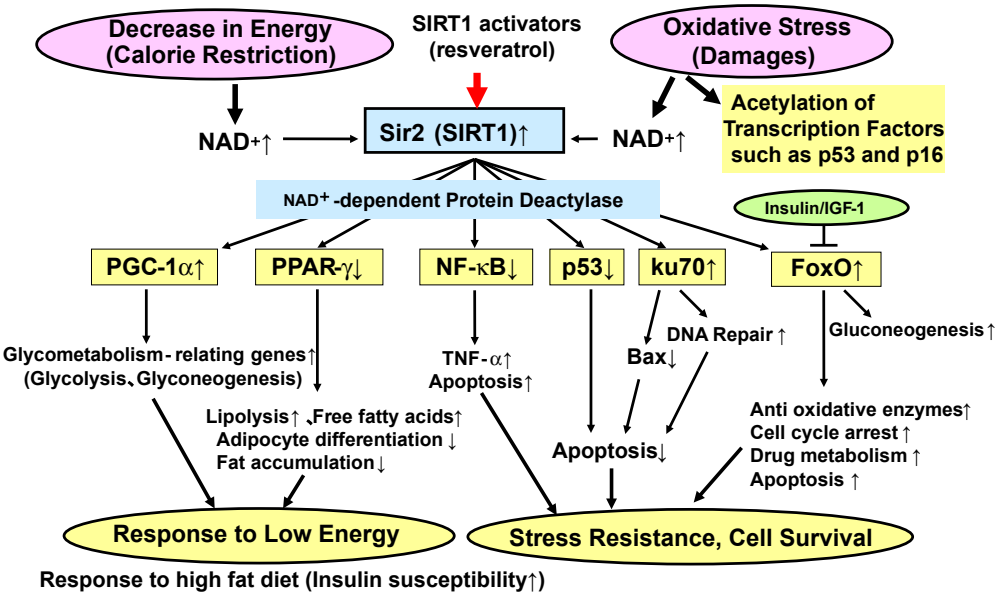



FIGURE 43.5 Roles of SIRT1 in response to low energy, stress resistance, and cell survival.

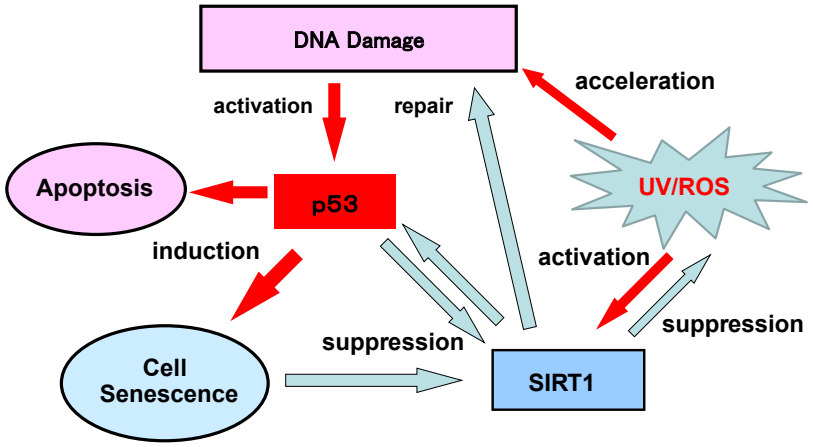



FIGURE 43.6 Relationship between SIRT1, p53, and cell senescence after DNA damage induced by UV or ROS.

antioxidant activity, because the effect was negated when *SIRT1* knockout mice were used instead of wild-type mice and were fed a high calorie diet ad libitum.[46,47,70] However, under conditions of a standard diet, resveratrol did not increase overall survival or maximum lifespan.[70] Interestingly, overall health improved under all dietary conditions, as reflected by the reduction of osteoporosis, cataracts, vascular dysfunction, and decline in motor coordination. From these results, resveratrol is suggested to extend lifespan by maintaining metabolic homeostasis under a disturbed condition. Recent studies on higher eukaryotes have shown the importance of nutrient balance in dietary regimens rather than simply a reduction of caloric intake. In addition, effect on longevity regulation by resveratrol suggests that not only CR but rather a balance of different nutrients and their ratios play a pivotal role in regulating lifespan.[36]

In studies on the skin, resveratrol has been reported to modulate a TGF-β/SMAD pathway, collagen deposition, and cellular proliferation in human skin fibroblasts in vitro.[71,72] In human keratinocytes, SIRT1 is known to promote differentiation of cultured normal keratinocytes.[73] Resveratrol has been reported to suppress cell proliferation or to show strong cytotoxicity,[74–76] while preventing cell damage by oxidative stress and chemicals.[77,78] In human melanocytes, resveratrol inhibits melanogenesis and promotes cytotoxicity.[79,80] Some effects of resveratrol are thought to be due to the activation of SIRT1,[73,75,76,78] however, its mechanism is not clear since resveratrol has other biological characteristics such as antioxidant activity.

As shown in Fig. 43.4, NA is a powerful feedback inhibitor of SIRT1. NA is reported to enhance concurrent production of ceramides, cholesterols, and free fatty acids, which are crucial for epidermal barrier function.[81] A topical application of NA improves dry skin by increasing ceramides in the cornified layer. As the concentration range of NA responsible for ceramide formation and SIRT1 inhibition is similar (in the order of μM),[82] the effects of NA on skin barrier may be due to SIRT1 inhibition.

From these findings, whether resveratrol or SIRT1 activators are suitable as a cosmetic ingredient for a treatment against skin aging is still unclear. SIRT1 and other SIRT homologs may deacetylate a different pattern of transcription factors specific to an organ or cells. Thus, when considering the function of SIRT1, the effects of SIRT1 activators and inhibitors on the skin may vary between target cells (keratinocytes, fibroblasts, or melanocytes), cell stage (proliferative or differentiated), and cell environment (stress, nutrient, or extracellular matrix). Further extensive studies are needed before resveratrol and SIRT activators can be advantageously applied to antisenescence cosmetics.

## 43.6 STRATEGIES IN RESEARCH ON SKIN AGING

Based on the previously mentioned findings on senescence research in recent years, this section highlights strategies in research to develop antisenescence cosmetics.

### 43.6.1 Genetic and Environmental Factors That Advance Skin Senescence

Skin is the body's protective barrier from the ambient environment. Skin senescence is associated with constant exposure to exogenous natural stimuli, such as UV, dryness, and temperature change, in addition to intrinsic genetic factors, and advances step by step. Skin is greatly affected by UV, followed by ROS generated by UV exposure of the

skin to UV and endogenous ROS generated by cellular energy production or skin inflammation. These environmental conditions produce an accelerated senescent phenotype called "photoaging," which is characterized by wrinkles, hyperpigmentation, telangiectasia, actinic keratosis, and a higher risk of skin cancer on sun-exposed areas such as the face and neck. Generally speaking, in the field of cosmetics, photoaging includes all nonpathological changes in sun-exposed skin with aging, slightly differing from the narrow clinical definition of photosenescence. While intrinsic aging affects unexposed areas, such as the buttocks and inner upper arm, and skin manifestations include dryness, laxity, and skin atrophy. Environmental factors definitely contribute to photoaging, but both extrinsic and intrinsic factors are responsible for the progression of photosenescence as the skin's response to UV varies by the individual and is regulated genetically. UV-induced phenomena in the skin is well reported, including morphological, histochemical, and biochemical changes, and various gene responses. However, details on their causal relationship and regulation system are still unclear.

Cosmetics cannot modify or reinforce the corresponding genes involved in protecting the skin from senescence caused by genetic factors, but they can influence environmental changes and regulate the gene expression and its related factors, which are responsible for disturbing homeostasis.

Strategies in research on antisenescence seek to (1) suppress processes that trigger senescence, (2) block processes that lead to senescent symptoms, and (3) improve senescent symptoms that occur with aging, by accumulating and considering scientific evidence on how environmental factors are involved in the occurrence and advance of senescent symptoms of the skin, and how biological changes in the skin are related to skin senescence and are regulated with aging. In other words, these strategies seek to maintain homeostasis that naturally exists in the skin.

### 43.6.2 Age-Associated Decline and Disintegration of Homeostasis for the Repair System Against DNA and Tissue Damage

Damage to DNA and tissue is a central issue in senescence, which is triggered by extrinsic and intrinsic stress such as UV and ROS, resulting in chronic inflammation. However, neither wrinkles nor pigmentation spots, typical signs of photoaging, appear in young people, even after exposed to UV for an entire day. Clearly, senescent signs develop over a long period of time as the skin strongly resists environmental stimuli and has a great capacity to repair cell and tissue damage (Fig. 43.7). When UV damages DNA, the body's repair system, including NER and BER, is activated. If the repair system fails to completely restore the DNA, then the host cells with the damaged DNA are removed by apoptosis.

Melanocytes accelerate melanin synthesis by stimulation from direct UV irradiation or via UV-induced cytokines released from the keratinocytes (Fig. 43.7). The resulting melanin pigment is transferred from the melanocytes to the surrounding keratinocytes and spreads across over the epidermis.[83] This is the skin's way of protecting itself against the next UV attack. Melanized keratinocytes stratify to form corneocytes through terminal differentiation and are desquamated from the body.

Another mechanism in the repair system targets the ECM (Fig. 43.7). UV and/or ROS attacks damage tissue and ECM, which become inflamed under some conditions. Dermal fibroblasts stimulated by UV or inflammatory cytokines produce ECM-degrading enzymes such as matrix metalloproteinases (MMPs), which include collagenases

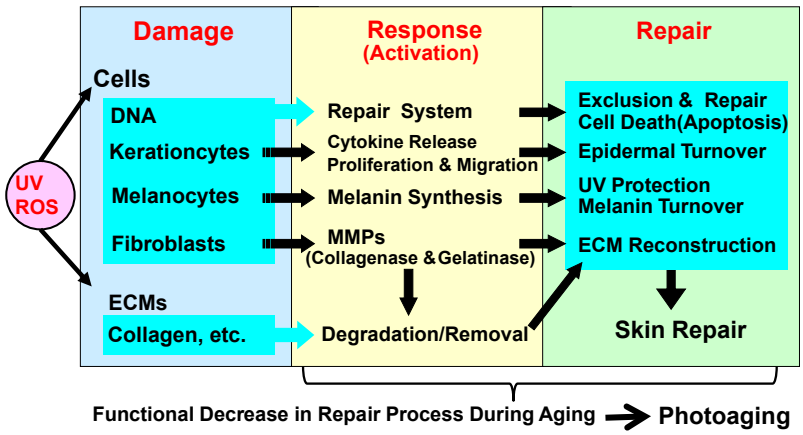



FIGURE 43.7 Age-associated changes in damage-induced skin repair process result in photoaging.

(MMP-1, MMP-3, and MMP-13) and gelatinases (MMP-2 and MMP-9).[84] MMPs degrade and remove damaged collagen in tissue, which is then replaced with newly synthesized collagen.

The skin maintains homeostasis by repeating the "damage, response (activation), and repair" cycle as aging progresses, so senescent signs such as wrinkles and pigmentation spots do not appear when young. However, typical senescent features are often observed early in cases of progeria, caused by malfunction of either the DNA repair system or the ROS resistance system. This observation strongly suggests that skin senescence progresses slowly as the "damage, response (activation), and repair" cycle functionally decreases with age (Fig. 43.7). Thus, an age-dependent decrease in the repair capacity results in the accumulation of dysfunctional molecules in cells and tissue and causes chronic inflammation. In turn, senescent characteristics gradually rise to the surface with aging.

### 43.6.3 Targets in the Research and Development for Antisenescence Cosmetics

From the previously mentioned findings, aging processes related to possible targets of research and development for antisenescence cosmetics are shown in Fig. 43.8:

1. Protect the skin from factors that induce damages along with aging.
   This approach is conventionally used when UV protection or antioxidative agents are added as cosmetic ingredients.
2. Upregulate the DNA repair system, which declines with aging.
   Recent studies have been carried out on a new class of DNA repair-activating chemopreventive agents that function by enhancing BER of oxidative DNA damage. Acetohexamide and benserazide have been found to enhance BER as well as decreased basal levels and $H_2O_2$-induced levels of oxidative DNA damage.[85] Acetohexamide and benserazide have already been through human trials and have been approved for clinical use in the United States for diabetes, and in the United Kingdom and Canada for Parkinson's disease, respectively. A parthenolide-depleted Feverfew extract is reported to inhibit oxidative damage by inducing DNA repair in human keratinocytes via a $PI_3$-kinase-dependent Nrf2/ARE pathway,[86] and a cat's claw extract is reported to enhance DNA repair in UV-irradiated skin organ cultures although the underlying mechanism is not clear.[87]
3. Upregulate the tissue repair system, which declines with aging.
   Possible involvement of gelatinases (MMP-2 and MMP-9) in basement membrane damage and wrinkle formation using a UVB-exposed hairless mouse model has been reported.[88] MMP-2 and MMP-9 activities, both of which are responsible for degrading type IV collagen in the basement membrane, were significantly higher in a sample of wrinkled skin. In this mouse model, repeated topical application of an MMP inhibitor inhibited basement membrane damage, epidermal hyperplasia, dermal collagen degradation, and wrinkle formation, although this induction of MMPs may be a physiological response to the removal and repair of the damaged basement membrane.[89]

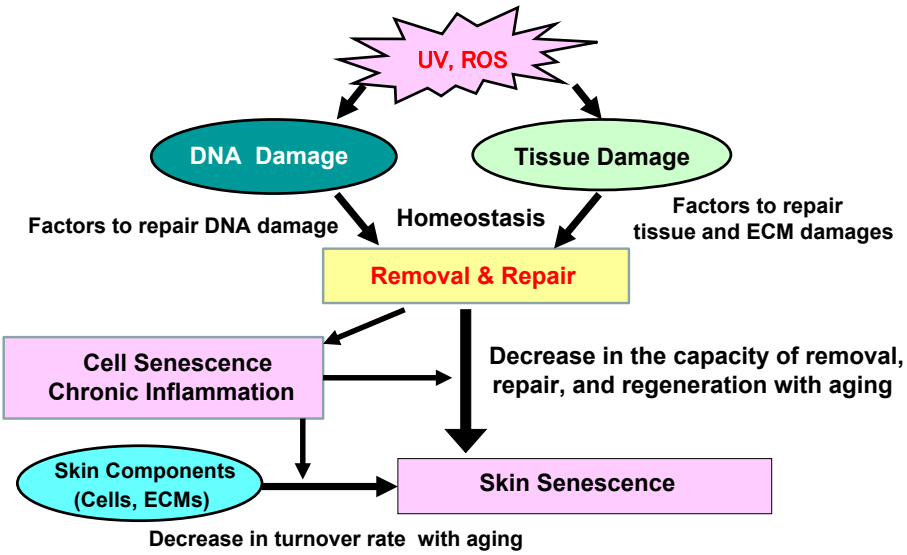



FIGURE 43.8 Cell senescence and chronic inflammation caused by unrepaired damages as well as a decrease in repair capacity and physiological turnover with aging accelerates skin senescence.

Oral application of *N*-methyl-ethanolamine, an MMP-1 production inducer of fibroblasts possibly via phospholipase D inhibition, has been reported to attenuate cardiac fibrosis and improve diastolic function in a hypertensive heart failure model.[90] The quality of collagen was maintained to ensure plasticity, suggesting that upregulation of MMP activity leading to collagen neogenesis may promote repair of tissue damage.[91]

4. Suppress cell senescence and downregulate secretion of senescence-associated secretory phenotype (SASP) factors from senescent cells.

   Simvastatin is an HMG-CoA reductase inhibitor and is known to attenuate inflammation and prevent certain cancers. It is also shown to decrease SASP in senescent human fibroblasts by decreasing Rac1 and Cdc42 activities, without affecting senescent growth arrest.[92] Similarly, the researchers reported that both corticosterone and cortisol decreased production and secretion of selected SASP components, including several proinflammatory cytokines, using normal human fibroblasts and a library of compounds that are approved for human use.[93] This approach indicates that application to develop effective anti-SASP cosmetics is possible, although understanding the complete SASP profile, its tissue and cell specificity, and the signaling pathways that regulate it is important.

   In addition, targets one and two are also possible since UV- or ROS-triggered DNA damage, which cannot be repaired and activate tumor suppression genes, such as p53 and p16, leads damaged cells to "cell senescence."[56,57]

5. Remove senescent cells from the skin.

   Senescent cells accumulate in various tissues and organs during aging, but details whether these cells influence health and lifespan and, if so, by what mechanism, remain unknown.[94] However, developing antisenescent cosmetics by specifically removing senescent cells in the skin appears to be an attractive approach.[95] Recently, removal of $p16^{Ink4a}$ positive senescent cells by injection of a synthetic FK506 analog AP20187 in a mouse model has been shown to delay tumorigenesis and attenuate age-related deterioration of several organs without overt side effects.[96] This finding suggests that therapeutic removal of senescent cells may be able to extend the healthy lifespan and improve senescent tissues including the skin.

6. Suppress chronic inflammation or neutralize proinflammatory cytokine activity.

   Pharmacological and genetic inhibition of inflammatory processes is considered to be an effective and proven antisenescent strategy.[97] NSAIDs prevent age-associated features and increase the lifespan of mice.[98] Senescent cells in tissue were blocked by antiinflammatory treatment in mice by short-term application of NSAIDs, although long-term administration was difficult due to side effects.[53]

   According to recent studies, NSAIDs have multiple activity in molecular targets, including cyclooxygenase inhibition, antioxidant effect, and NFκB inhibition.[99,100] Search and selection of a suitable agent with NASID-like activity but without toxicity is needed for cosmetic use. However, neutralizing proinflammatory cytokine activity may be less attractive due to low efficacy and low-cost performance.

7. Upregulate the turnover rate of cells and ECM, which reduce with aging.

   The following skin care program seeks to delay the decline in epidermal cell turnover rate with aging. First, keratinocyte differentiation is normalized in order to accelerate the formation of mature stratum corneum (SC) functions. Next, desquamation is accelerated to protect the SC from compaction. Finally, epidermal turnover is improved. To achieve this, the following candidates are considered, although few cosmetic ingredients have been scientifically proven to be effective.

   Retinoic acid (RA), a naturally occurring form of Vitamin A, is reported to have an antiaging effect, especially for photodamaged skin, and has been scientifically proven in clinical tests.[101,102] Short-term topical application promotes epidermal regeneration by keratinocyte hyperproliferation.[103] Long-term application exceeding four months is required before an effect is seen in the dermis.[104] Using RA to accelerate epidermal turnover rate is thought to improve melasma or hyperpigmented spots in photodamaged skin.[105] Retinol and its ester derivatives, which are safer and have a more moderate activity, are used in cosmetics.[106]

   Previously mentioned NA is a noncompetitive inhibitor of SIRT1 within the vitamin B class. Several studies have suggested that topical treatment with NA was effective for dry skin, photodamage, photoimmunosuppression, and hyperpigmentation.[81,107–110] In vivo and in vitro studies show that NA promotes mature SC functions by increasing biosynthesis of the SC intercellular lipids that are needed for the epidermal permeability barrier. [81] According to these findings, application of SIRT1 activators such as resveratrol for cosmetic use is questionable.

   Alpha hydroxy acids (AHAs), such as lactic acid and glycolic acid, are known to promote epidermal turnover by accelerating keratinocyte proliferation and SC desquamation.[111,112] Because its effect is dependent on the concentration of free acid,[113] acidity may be required for activation, taking into account the fact that cathepsin D, an important desquamation enzyme, is known to be activated in the low-pH range.[114] Polyhydroxy acids (PHAs) such as gluconolactone and lactobionic acid are suggested as replacements for AHAs because they are less

irritating.[115]

The accumulation of cross-linked collagen such as AGEs and HHL in the dermis along with age[12,13] suggests that collagen turnover decreases physiologically during aging. The receptor for AGEs (RAGE) detects AGEs, and induces cell apoptosis via both JNK and p38 mitogen-activated protein kinase in various cell types including stem cells.[116,117] Accordingly, AGEs may be involved in cell senescence or chronic inflammation via RAGE, promoting the maintenance of "quality" as well as quantity of collagen essential for antisenescent skin care.

Collagenases (MMP-1, MMP-8, and MMP-13), are specific key enzymes to degrade intact type I, II, and III collagens under physiologic conditions. Among these, MMP-1 is the most important enzyme to start normal collagen turnover, tissue reconstruction, and wound healing[91,116] although fibroblast-derived MMP-14 (also known as MT 1-MMP) was proposed recently as a main regulator of normal collagen homeostasis in adult skin.[118] Few ingredients promote MMP-1 production of fibroblasts, but MEA, an ethanolamine derivative, is one candidate.[90] MMP-1 action along with increase in de novo collagen synthesis is expected to play a crucial role in normal collagen turnover and response to ECM damage, as collagen synthesis decreases in both photo- and intrinsic aging.[119,120] Vitamin C (ascorbic acid) and its ester derivatives are well known to enhance collagen synthesis by upregulating and stabilizing mRNA,[121,122] and upregulation of type I and III collagen mRNAs has been confirmed by human skin biopsy after topical treatment of vitamin C.[123]

Another proposal suggests the cosmetic use involving the inhibition of MMPs and the suppression of MMP production. MMPs are thought to degrade and remove collagen in the tissue, resulting in the formation of wrinkles. The amount of mRNA and the protein level of MMP-1 in aged fibroblasts or after UV irradiation has been reported to be higher, and its upregulation is thought to be a main cause of wrinkle formation.[124] On the other hand, this may also be a physiological response to exclude damaged collagen. Consideration of suppression of excessive MMP-1 activity is also needed. MMP-13 also has been reported to enhance remodeling of three-dimensional collagen and to promote survival of human skin fibroblasts.[125]

## 43.7 ISSUES TO BE RESOLVED AND FUTURE CONSIDERATIONS

### 43.7.1 Methods to Quantify Senescence and Evaluate Anti-Senescence Efficacy

In this chapter research strategies and possible targets for developing antisenescence cosmetics were discussed. However, obtaining evidence of their antiaging efficacy is quite difficult. Very little scientific data exists, as has been reported, to support the claims of efficacy of the many vitamins, minerals, plant extracts, and other active ingredients widely used in antiaging cosmetics for the human skin, even from the many in vitro experiments and in vivo animal models.[126]

There are several reasons for such difficulty:

1. No quantitative and specific determination methods are available for skin senescence, which progresses in various cell types by different mechanisms. While senescence-associated β-galactosidase assay is the most widely used technique to identify senescent cells as well as to characterize skin tissue, it is an invasive procedure and is less quantitative. It has also been suggested that some of the identified activity is not causally related to senescent cell induction.[127,128]
2. Quantitative and noninvasive assessment of preventive antiaging effects, including improved DNA repair activity, collagen turnover rate, and activation of other repair enzymes, is considerably difficult, but evaluating the effects of candidate treatment on existing wrinkles or hyperpigmentation is possible. Serum levels of proinflammatory cytokines and SASP factors can be used as noninvasive systemic senescent markers to some extent, as well as skin characteristics.
3. Long-term examination over many years is required to observe changes in senescent features because aging proceeds slowly. A longitudinal study to examine how the same individual changes along with age is desirable, but the long time required to complete the study is a major obstacle,[60] whereas a cross-sectional study based on a mean value of every age of population is easier. However, a cross-sectional study often gives misleading results.

In consideration of this discussion, an evaluation system for human individuals should be based on (1) scientifically certified criteria corresponding to the phenomena and mechanisms of skin senescence, and (2) quantitative and noninvasive methods to determining changes in skin components. In the first item, new target proteins or genes responsible for intrinsic and/or photoaged skin should be sought and analyzed in relation to skin phenotype. The second item concerns quantitative and noninvasive evaluation methods, focusing on advanced optical technologies

such as confocal Raman microscopy, two-photon fluorescence microscopy, and optical coherence tomography (OCT), which have been applied to the evaluation of human skin. Noninvasive methodologies for observing phenomenon and changes in the skin are important in the understanding of how skin components change as they age, and to prove efficacy of the candidate ingredients on human skin after topical application.

For example, the gradient of amount of specific molecules such as water, lipids, amino acids, melanin, and drugs penetrating into the SC can be quantitatively determined using confocal Raman microscopy.[129] A polarization-sensitive spectra domain optical coherence tomography (PS-SD-OCT), a specialized PS-OCT, is a promising tool for noninvasive observation and imaging the intracutaneous state of a collagen structure.[130] Regularity of human dermal collagen structure as a degree of birefringence can be shown in 3D, and a decrease in regularity of the collagen structure just below the basement membrane around deeper wrinkles can be shown quantitatively compared to that around shallow wrinkles. Further advances of noninvasive determining technology will contribute to deeper understanding of age-associated changes in the skin of individuals.

### 43.7.2 Search for and Evaluation of Effective Ingredients for Cosmetic use Without Animal Testing

Scientific approach using a senescent animal model and a genetically modified mouse model is a favored method to search and evaluate antisenescent materials. However, use of animal testing in the development of effective materials for cosmetics should be avoided from the viewpoint of animal protection and welfare. Valid scientific logic obtained by theoretical approach at the cellular and/or molecular level, which can connect in vitro evidence with in vivo phenomena, is essential in animal-free research. In vitro research on cell senescence and regulation mechanisms of SASP can be of value if the relation between chronic inflammation and skin senescence can be clearly understood scientifically. Searching for effective antisenescent materials for cosmetic use from among chemical or natural ingredient sources that already have been evaluated for their pharmacological efficacy and safety may be an attractive strategy. In this way, safety and other biological actions can be predicted without animal testing.

In this chapter, theoretical research strategies in the development of antiaging cosmetics were discussed, focusing on age-associated decline and breakdown of homeostasis by the repair system against DNA and tissue damage while taking into account cell senescence and chronic inflammation. Systemic factors such as obesity, diabetes, and chronic inflammation, are related to health and lifestyle habits beyond the skin, and were shown to influence skin aging. These findings will accelerate holistic studies, which seek to understand the relation of beauty with health and heart, and thus lead to new proposals to fight skin aging. Life science and applied technology are also making steady progress, and will encourage the comprehensive understanding of senescence in the future, which will help predict and improve skin aging and enhance QOL.

## References


1. Paltzer GL. Improving self-esteem by improving physical attractiveness. *J Esthet Dent* 1997;**9**:44–6.
2. Sadick NS. The impact of cosmetic interventions on quality of life. *Dermatol Online J* 2008;**14**:2. http://dx.doi.org/10.1016/j.bips. 2007.01.071.
3. Christensen K, Thinggaard M, McGue M, Rexbye H, Hjelmborg JV, Aviv A, Gunn D, van der Ouderaa F, Vaupel JW. Perceived age as clinically useful biomarker of ageing: cohort study. *BMJ* 2009;**339**:b5262.
4. Beresniak A, de Linares Y, Krueger GG, Talarico S, Tsutani K, Duru G, Berger G. Validation of a new international quality-of-life instrument specific to cosmetics and physical appearance: BeautyQoL questionnaire. *Arch Dermatol* 2012;**148**:1275–82.
5. Cadet J, Anselmino C, Douki T, Voituriez L. Photochemistry of nucleic acids in cells. *J Photochem Photobiol B* 1992;**15**:277–98.
6. Dianov GL, Souza-Pinto N, Nyaga SG, Thybo T, Stevnsner T, Bohr VA. Base excision repair in nuclear and mitochondrial DNA. *Prog Nucleic Acid Res Mol Biol* 2001;**68**:285–97.
7. Moriwaki S, Ray S, Tarone RE, Kraemer KH, Grossman L. The effect of donor age on the processing of UV-damaged DNA by cultured human cells: reduced DNA repair capacity and increased DNA mutability. *Mutat Res* 1996;**364**:117–23.
8. Goukassian D, Gad F, Yaar M, Eller MS, Nehal US, Gilchrest BA. Mechanisms and implications of the age-associated decrease in DNA repair capacity. *FASEB J* 2000;**14**:1325–34.
9. Takahashi Y, Moriwaki S, Sugiyama Y, Endo Y, Yamazaki K, Mori T, Takigawa M, Inoue S. Decreased gene expression responsible for post-ultraviolet DNA repair synthesis in aging: a possible mechanism of age-related reduction in DNA repair capacity. *J Invest Dermatol* 2005;**124**: 435–42.
10. Chen SK, Hsieh WA, Tsai MH, Chen CC, Hong AI, Wei YH, Chang WP. Age-associated decrease of oxidative repair enzymes, human 8-oxoguanine DNA glycosylases (hOgg1), in human aging. *J Radiat Res (Tokyo)* 2003;**44**:31–5.
11. Sauvaigo S, Caillat S, Odin F, Nkengne A, Bertin C, Oddos T. Effect of aging on DNA excision/synthesis repair capacities of human skin fibroblasts. *J Invest Dermatol* 2010;**130**:1739–41.
12. Dyer DG, Dunn JA, Thorpe SR, Bailie KE, Lyons TJ, McCance DR, Baynes JW. Accumulation of Maillard reaction products in skin collagen in diabetes and aging. *J Clin Invest* 1993;**91**:2463–9.

13. Yamauchi M, London RE, Guenat C, Hashimoto F, Mechanic GL. Structure and formation of a stable histidine-based trifunctional cross-link in skin collagen. *J Biol Chem* 1987;**262**:11428–34.
14. Morita K, Urabe K, Moroi Y, Koga T, Nagai R, Horiuchi S, Furue M. Migration of keratinocytes is impaired on glycated collagen I. *Wound Repair Regen* 2005;**13**:93–101.
15. Kawano E, Takahashi S, Sakano Y, Fujimoto D. Nonenzymatic glycation alters properties of collagen as a substratum for cells. *Matrix* 1990;**10**: 300–5.
16. Alikhani Z, Alikhani M, Boyd CM, Nagao K, Trackman PC, Graves DT. Advanced glycation end products enhance expression of pro-apoptotic genes and stimulate fibroblast apoptosis through cytoplasmic and mitochondrial pathways. *J Biol Chem* 2005;**280**:12087–9.
17. Howard EW, Benton R, Ahern-Moore J, Tomasek TJ. Cellular contraction of collagen lattices is inhibited by nonenzymatic glycation. *Exp Cell Res* 1996;**228**:132–7.
18. Kawabata K, Yoshikawa H, Saruwatari K, Akazawa Y, Inoue T, Kuze T, Sayo T, Uchida N, Sugiyama Y. The presence of $N^{\varepsilon}$-(Carboxymethyl) lysine in the human epidermis. *Biochim Biophys Acta* 2011;**1814**:1246–52.
19. Montagna W, Kirchner S, Carlisle K. Histology of sun-damaged human skin. *J Am Acad Dermatol* 1989;**21**:907–18.
20. Sellheyer K. Pathogenesis of solar elastosis: synthesis or degradation? *J Cutan Pathol* 2003;**30**:123–7.
21. Lamore SD, Qiao S, Horn D, Wondrak GT. Proteomic identification of cathepsin B and nucleophosmin as novel UVA-targets in human skin fibroblasts. *Photochem Photobiol* 2010;**86**:1307–17.
22. Sfeir AJ, Chai W, Shay JW, Wright WE. Telomere-end processing: the terminal nucleotides of human chromosomes. *Mol Cell* 2005;**18**:131–8.
23. Baird DM, Kipling D. The extent and significance of telomere loss with age. *Ann N Y Acad Sci* 2004;**1019**:265–8.
24. Campisi J, d'Adda di Fagagna F. Cellular senescence: when bad things happen to good cells. *Nat Rev Mol Cell Biol* 2007;**8**:729–40.
25. Vaziri H, Schächter F, Uchida I, Wei L, Zhu X, Effros R, Cohen D, Harley CB. Loss of telomeric DNA during aging of normal and trisomy 21 human lymphocytes. *Am J Hum Genet* 1993;**52**:661–7.
26. Allsopp RC, Vaziri H, Patterson C, Goldstein S, Younglai EV, Futcher AB, Greider CW, Harley CB. Telomere length predicts replicative capacity of human fibroblasts. *Proc Natl Acad Sci USA* 1992;**89**:10114–8.
27. Sun L, Tan R, Xu J, LaFace J, Gao Y, Xiao Y, Attar M, Neumann C, Li GM, Su B, Liu Y, Nakajima S, Levine AS, Lan L. Targeted DNA damage at individual telomeres disrupts their integrity and triggers cell death. *Nucleic Acids Res* 2015;**43**:6334–47.
28. Grove GL, Kligman AM. Age-associated changes in human epidermal cell renewal. *J Gerontol* 1983;**38**:137–42.
29. Hara M, Kikuchi K, Watanabe M, Denda M, Koyama J, Nomura J, Horii I, Tagami H. Senile xerosis: functional, morphological, and biochemical studies. *J Geriatr Dermatol* 1993;**1**:111–20.
30. Sakai S, Kikuchi K, Satoh J, Tagami H, Inoue S. Functional properties of the stratum corneum in patients with diabetes mellitus: similarities to senile xerosis. *Br J Dermatol* 2005;**153**:319–23.
31. Sakai S, Endo Y, Ozawa N, Sugawara T, Kusaka A, Sayo T, Tagami H, Inoue S. Characteristics of the epidermis and stratum corneum of hairless mice with experimentally induced diabetes mellitus. *J Invest Dermatol* 2003;**120**:79–85.
32. Gunn DA, Rexbye H, Griffiths CE, Murray PG, Fereday A, Catt SD, Tomlin CC, Strongitharm BH, Perrett DI, Catt M, Mayes AE, Messenger AG, Green MR, van der Ouderaa F, Vaupel JW, Christensen K. Why some women look young for their age. *PLoS One* 2009;**4**: e8021. http://dx.doi.org/10.1371/journal.pone.0008021.
33. Crabbe L, Jauch A, Naeger CM, Holtgreve-Grez H, Karlseder J. Telomere dysfunction as a cause of genomic instability in Werner syndrome. *Proc Natl Acad Sci USA* 2007;**104**:2205–10.
34. Saijo M, Hirai T, Ogawa A, Kobayashi A, Kamiuchi S, Tanaka K. Functional TFIIH is required for UV-induced translocation of CSA to the nuclear matrix. *Mol Cell Biol* 2007;**27**:2538–47.
35. Moriwaki S, Kraemer KH. Xeroderma pigmentosum—bridging a gap between clinic and laboratory. *Photodermatol Photoimmunol Photomed* 2001;**17**:47–54.
36. Santos J, Leitão-Correia F, Sousa MJ, Leão C. Dietary restriction and nutrient balance in aging. *Oxid Med Cell Longev* 2016;**2016**, 4010357. http://dx.doi.org/10.1155/2016/4010357.
37. Rossi ML, Ghosh AK, Bohr VA. Roles of Werner syndrome protein in protection of genome integrity. *DNA Repair (Amst)* 2010;**9**:331–44.
38. Yao H, Chung S, Hwang JW, Rajendrasozhan S, Sundar IK, Dean DA, McBurney MW, Guarente L, Gu W, Rönty M, Kinnula VL, Rahman I. SIRT1 protects against emphysema via FOXO3-mediated reduction of premature senescence in mice. *J Clin Invest* 2012;**122**:2032–45.
39. Lamming DW, Ye L, Katajisto P, Goncalves MD, Saitoh M, Stevens DM, Davis JG, Salmon AB, Richardson A, Ahima RS, Guertin DA, Sabatini DM, Baur DA. Rapamycin-induced insulin resistance is mediated by mTORC2 loss and uncoupled from longevity. *Science* 2012; **335**:1638–43.
40. Selman C, Tullet JM, Wieser D, Irvine E, Lingard SJ, Choudhury AI, Claret M, Al-Qassab H, Carmignac D, Ramadani F, Woods A, Robinson IC, Schuster E, Batterham RL, Kozma SC, Thomas G, Carling D, Okkenhaug K, Thornton JM, Partridge L, Gems D, Withers DJ. Ribosomal protein S6 kinase 1 signaling regulates mammalian life span. *Science* 2009;**326**:140–4.
41. Kurosu H, Yamamoto M, Clark JD, Pastor JV, Nandi A, Gurnani P, McGuinness OP, Chikuda H, Yamaguchi M, Kawaguchi H, Shimomura I, Takayama Y, Herz J, Kahn CR, Rosenblatt KP, Kuro-o M. Suppression of aging in mice by the hormone Klotho. *Science* 2005;**309**:1829–33.
42. Fontana L, Partridge L, Longo VD. Extending healthy life span–from yeast to humans. *Science* 2010;**328**:321–6.
43. Arking DE, Krebsova A, Macek Sr M, Macek Jr M, Arking A, Mian IS, Fried L, Hamosh A, Dey S, McIntosh I, Dietz HC. Association of human aging with a functional variant of klotho. *Proc Natl Acad Sci USA* 2002;**99**:856–61.
44. Kuro-o M, Matsumura Y, Aizawa H, Kawaguchi H, Suga T, Utsugi T, Ohyama Y, Kurabayashi M, Kaname T, Kume E, Iwasaki H, Iida A, Shiraki-Iida T, Nishikawa S, Nagai R, Nabeshima YI. Mutation of the mouse klotho gene leads to a syndrome resembling ageing. *Nature* 1997;**390**:45–51.
45. Dreesen O, Stewart CL. Accelerated aging syndromes, are they relevant to normal human aging? *Aging* 2011;**3**:889–95.
46. Baur JA, Pearson KJ, Price NL, Jamieson HA, Lerin C, Kalra A, Prabhu VV, Allard JS, Lopez-Lluch G, Lewis K, Pistell PJ, Poosala S, Becker KG, Boss O, Gwinn D, Wang M, Ramaswamy S, Fishbein KW, Spencer RG, Lakatta EG, Le Couteur D, Shaw RJ, Navas P, Puigserver P, Ingram DK, de Cabo R, Sinclair DA. Resveratrol improves health and survival of mice on a high-calorie diet. *Nature* 2006; **444**(7117):337–42.

47. Lagouge M, Argmann C, Gerhart-Hines Z, Meziane H, Lerin C, Daussin F, Messadeq N, Milne J, Lambert P, Elliott P, Geny B, Laakso M, Puigserver P, Auwerx J. Resveratrol improves mitochondrial function and protects against metabolic disease by activating SIRT1 and PGC-1α. *Cell* 2006;**127**:1109–22.
48. Takeda T, Hosokawa M, Takeshita S, Irino M, Higuchi K, Matsushita T, Tomita Y, Yasuhira K, Hamamoto H, Shimizu K, Ishii M, Yamamuro T. A new murine model of accelerated senescence. *Mech Ageing Dev* 1981;**17**:183–94.
49. Chiba Y, Shimada A, Kumagai N, Yoshikawa K, Ishii S, Furukawa A, Takei S, Sakura M, Kawamura N, Hosokawa M. The senescence-accelerated mouse (SAM): a higher oxidative stress and age-dependent degenerative diseases model. *Neurochem Res* 2009;**34**:679–87.
50. Hayflick L, Moorhead PS. The serial cultivation of human diploid cell strains. *Exp Cell Res* 1961;**25**:585–621.
51. Röhme D. Evidence for a relationship between longevity of mammalian species and life spans of normal fibroblasts *in vitro* and erythrocytes *in vivo*. *Proc Natl Acad Sci USA* 1981;**78**:5009–13.
52. Franceschi C, Campisi J. Chronic inflammation (inflammaging) and its potential contribution to age-associated diseases. *J Gerontol A Biol Sci Med Sci* 2014;**69**(Suppl. 1):S4–9.
53. Jurk D, Wilson C, Passos JF, Oakley F, Correia-Melo C, Greaves L, Saretzki G, Fox C, Lawless C, Anderson R, Hewitt G, Pender SL, Fullard N, Nelson G, Mann J, van de Sluis B, Mann DA, von Zglinicki T. Chronic inflammation induces telomere dysfunction and accelerates ageing in mice. *Nat Commun* 2014;**2**:4172. http://dx.doi.org/10.1038/ncomms5172.
54. Franceschi C, Bonafè M, Valensin S, Olivieri F, De Luca M, Ottaviani E, De Benedictis G. Inflamm-aging. An evolutionary perspective on immunosenescence. *Ann N Y Acad Sci* 2000;**908**:244–54.
55. Zhuang Y, Lyga J. Inflammaging in skin and other tissues - the roles of complement system and macrophage. *Inflamm Allergy Drug Targets* 2014;**13**:153–61.
56. Serrano M, Lin AW, McCurrach ME, Beach D, Lowe SW. Oncogenic ras provokes premature cell senescence associated with accumulation of p53 and $p16^{INK4a}$. *Cell* 1997;**88**:593–602.
57. Sayama K, Shirakata Y, Midorikawa K, Hanakawa Y, Hashimoto K. Possible involvement of p21 but not of p16 or p53 in keratinocyte senescence. *J Cell Physiol* 1999;**179**:40–4.
58. Young ARJ, Narita M. SASP reflects senescence. *EMBO Rep* 2009;**10**:228–30.
59. Coppé JP, Patil CK, Rodier F, Sun Y, Muñoz DP, Goldstein J, Nelson PS, Desprez PY, Campisi J. Senescence-associated secretory phenotypes reveal cell-nonautonomous functions of oncogenic RAS and the p53 tumor suppressor. *PLoS Biol* 2008;**6**:2853–68.
60. Arai Y, Martin-Ruiz CM, Takayama M, Abe Y, Takebayashi T, Koyasu S, Suematsu M, Hirose N, von Zglinicki T. Inflammation, but not telomere length, predicts successful ageing at extreme old age: a longitudinal study of semi-supercentenarians. *EBioMedicine* 2015;**2**:1549–58. http://dx.doi.org/10.1016/j.ebiom.2015.07.029.
61. Zimniak P. What is the proximal cause of aging? *Front Genet* 2012;**3**:189. http://dx.doi.org/10.3389/fgene.2012.00189.
62. Kaeberlein M, McVey M, Guarente L. The *SIR2/3/4* complex and *SIR2* alone promote longevity in *Saccharomyces cerevisiae* by two different mechanisms. *Genes Dev* 1999;**13**:2570–80.
63. Haigis MC, Sinclair DA. Mammalian sirtuins: biological insights and disease relevance. *Annu Rev Pathol* 2010;**5**:253–95.
64. Cohen HY, Miller C, Bitterman KJ, Wall NR, Hekking B, Kessler B, Howitz KT, Gorospe M, de Cabo R, Sinclair DA. Calorie restriction promotes mammalian cell survival by inducing the SIRT1 deacetylase. *Science* 2004b;**305**:390–2.
65. Boily G, Seifert EL, Bevilacqua L, He XH, Sabourin G, Estey C, Moffat C, Crawford S, Saliba S, Jardine K, Xuan J, Evans M, Harper ME, McBurney MW. SirT1 regulates energy metabolism and response to caloric restriction in mice. *PLoS One* 2008;**3**:e1759.
66. McBurney MW, Yang X, Jardine K, Hixon M, Boekelheide K, Webb JR, Lansdorp PM, Lemieux M. The mammalian SIR2alpha protein has a role in embryogenesis and gametogenesis. *Mol Cell Biol* 2003;**23**:38–54.
67. Cheng HL, Mostoslavsky R, Saito S, Manis JP, Gu Y, Patel P, Bronson R, Appella E, Alt FW, Chua KF. Developmental defects and p53 hyperacetylation in Sir2 homolog (SIRT1)-deficient mice. *Proc Natl Acad Sci USA* 2003;**100**:10794–9.
68. Li H, Rajendran GK, Liu N, Ware C, Rubin BP, Gu Y. SirT1 modulates the estrogen-insulin-like growth factor-1 signaling for postnatal development of mammary gland in mice. *Breast Cancer Res* 2007;**9**:R1.
69. Howitz KT, Bitterman KJ, Cohen HY, Lamming DW, Lavu S, Wood JG, Zipkin RE, Chung P, Kisielewski A, Zhang LL, Scherer B, Sinclair DA. Small molecule activators of sirtuins extend *Saccharomyces cerevisiae* lifespan. *Nature* 2003;**425**(6954):191–6.
70. Pearson KJ, Baur JA, Lewis KN, Peshkin L, Price NL, Labinskyy N, Swindell WR, Kamara D, Minor RK, Perez E, Jamieson HA, Zhang Y, Dunn SR, Sharma K, Pleshko N, Woollett LA, Csiszar A, Ikeno Y, Le Couteur D, Elliott PJ, Becker KG, Navas P, Ingram DK, Wolf NS, Ungvari Z, Sinclair DA, de Cabo R. Resveratrol delays age-related deterioration and mimics transcriptional aspects of dietary restriction without extending life span. *Cell Metab* 2008;**8**:157–68.
71. Kim KH, Back JH, Zhu Y, Arbesman J, Athar M, Kopelovich L, Kim AL, Bickers DR. Resveratrol targets transforming growth factor-β2 signaling to block UV-induced tumor progression. *J Invest Dermatol* 2011;**131**:195–202.
72. Ikeda K, Torigoe T, Matsumoto Y, Fujita T, Sato N, Yotsuyanagi T. Resveratrol inhibits fibrogenesis and induces apoptosis in keloid fibroblasts. *Wound Repair Regen* 2013;**21**:616–23.
73. Blander G, Bhimavarapu A, Mammone T, Maes D, Elliston K, Reich C, Matsui MS, Guarente L, Loureiro JJ. SIRT1 promotes differentiation of normal human keratinocytes. *J Invest Dermatol* 2009;**129**:41–9.
74. Holian O, Walter RJ. Resveratrol inhibits the proliferation of normal human keratinocytes in vitro. *J Cell Biochem Suppl* 2001;(Suppl. 36):55–62.
75. Lee JH, Kim JS, Park SY, Lee YJ. Resveratrol induces human keratinocyte damage via the activation of class III histone deacetylase, Sirt1. *Oncol Rep* 2016;**35**:524–9.
76. Wu Z, Uchi H, Morino-Koga S, Shi W, Furue M. Resveratrol inhibition of human keratinocyte proliferation via SIRT1/ARNT/ERK dependent downregulation of aquaporin 3. *J Dermatol Sci* 2014;**75**:16–23.
77. Adhami VM, Afaq F, Ahmad N. Suppression of ultraviolet B exposure-mediated activation of NF-kappaB in normal human keratinocytes by resveratrol. *Neoplasia* 2003;**5**:74–82.
78. Ido Y, Duranton A, Lan F, Weikel KA, Breton L, Ruderman NB. Resveratrol prevents oxidative stress-induced senescence and proliferative dysfunction by activating the AMPK-FOXO3 cascade in cultured primary human keratinocytes. *PLoS One* 2015;**10**:e0115341. http://dx.doi.org/10.1371/journal.pone.0115341.

79. Newton RA, Cook AL, Roberts DW, Leonard JH, Sturm RA. Post-transcriptional regulation of melanin biosynthetic enzymes by cAMP and resveratrol in human melanocytes. *J Invest Dermatol* 2007;**127**:2216–27.
80. Okura M, Yamashita T, Ishii-Osai Y, Yoshikawa M, Sumikawa Y, Wakamatsu K, Ito S. Effects of rhododendrol and its metabolic products on melanocytic cell growth. *J Dermatol Sci* 2015;**80**:142–9.
81. Tanno O, Ota Y, Kitamura N, Katsube T, Inoue S. Nicotinamide increases biosynthesis of ceramides as well as other stratum corneum lipids to improve the epidermal permeability barrier. *Br J Dermatol* 2000;**143**:524–31.
82. Bitterman KJ, Anderson RM, Cohen HY, Latorre-Esteves M, Sinclair DA. Inhibition of silencing and accelerated aging by nicotinamide, a putative negative regulator of yeast sir2 and human SIRT1. *J Biol Chem* 2002;**277**:45099–107.
83. Yamamoto O, Bhawan J. Three modes of melanosome transfers in Caucasian facial skin: hypothesis based on an ultrastructural study. *Pigment Cell Res* 1994;**7**:158–69.
84. Fisher GJ, Datta SC, Talwar HS, Wang ZQ, Varani J, Kang S, Voorhees JJ. Molecular basis of sun-induced premature skin ageing and retinoid antagonism. *Nature* 1996;**379**:335–9.
85. Alli E, Solow-Cordero D, Casey SC, Ford JM. Therapeutic targeting of BRCA1-mutated breast cancers with agents that activate DNA repair. *Cancer Res* 2014;**74**:6205–15.
86. Rodriguez KJ, Wong HK, Oddos T, Southall M, Frei B, Kaur S. A purified Feverfew extract protects from oxidative damage by inducing DNA repair in skin cells via a PI3-kinase-dependent Nrf2/ARE pathway. *J Dermatol Sci* 2013;**72**:304–10.
87. Mammone T, Akesson C, Gan D, Giampapa V, Pero RW. A water soluble extract from *Uncaria tomentosa* (Cat's Claw) is a potent enhancer of DNA repair in primary organ cultures of human skin. *Phytother Res* 2006;**20**:178–83.
88. Inomata S, Matsunaga Y, Amano S, Takada K, Kobayashi K, Tsunenaga M, Nishiyama T, Kohno Y, ukuda M. Possible involvement of gelatinases in basement membrane damage and wrinkle formation in chronically ultraviolet B-exposed hairless mouse. *J Invest Dermatol* 2003;**120**: 128–34.
89. Amano S, Ogura Y, Akutsu N, Matsunaga Y, Kadoya K, Adachi E, Nishiyama T. Protective effect of matrix metalloproteinase inhibitors against epidermal basement membrane damage: skin equivalents partially mimic photoageing process. *Br J Dermatol* 2005;**153**(Suppl. 2): 37–46.
90. Yamamoto K, Takahashi Y, Mano T, Sakata Y, Nishikawa N, Yoshida J, Oishi Y, Hori M, Miwa T, Inoue S, Masuyama T. *N*-methylethanolamine attenuates cardiac fibrosis and improves diastolic function: inhibition of phospholipase D as a possible mechanism. *Eur Heart J* 2004;**25**: 1221–9.
91. Stamenkovic I. Extracellular matrix remodelling: the role of matrix metalloproteinases. *J Pathol* 2003;**200**:448–64.
92. Liu S, Uppal H, Demaria M, Desprez PY, Campisi J, Kapahi P. Simvastatin suppresses breast cancer cell proliferation induced by senescent cells. *Sci Rep* 2015;**5**:17895. http://dx.doi.org/10.1038/srep17895.
93. Laberge RM, Zhou L, Sarantos MR, Rodier F, Freund A, de Keizer PLJ, Liu S, Demaria M, Cong YS, Kapahi P, Desprez PY, Hughes RE, Campisi J. Glucocorticoids suppress selected components of the senescence-associated secretory phenotype. *Aging Cell* 2012;**11**:569–78.
94. Dimri GP, Lee X, Basile G, Acosta M, Scott G, Roskelley C, Medrano EE, Linskens M, Rubelj I, Pereira-Smith O. A biomarker that identifies senescent human cells in culture and in aging skin *in vivo*. *Proc Natl Acad Sci USA* 1995;**92**:9363–7.
95. Naylor RM, Baker DJ, van Deursen JM. Senescent cells: a novel therapeutic target for aging and age-related diseases. *Clin Pharmacol Ther* 2013; **93**:105–16.
96. Baker DJ, Childs BG, Durik M, Wijers ME, Sieben CJ, Zhong J, Saltness RA, Jeganathan KB, Verzosa GC, Pezeshki A, Khazaie K, Miller JD, van Deursen JM. Naturally occurring $p16^{Ink4a}$-positive cells shorten healthy lifespan. *Nature* 2016;**530**(7589):184–9.
97. López-Otín C, Blasco MA, Partridge L, Serrano M, Kroemer G. The hallmarks of aging. *Cell* 2013;**153**:1194–217.
98. Lee ME, Kim SR, Lee S, Jung YJ, Choi SS, Kim WJ, Han JA. Cyclooxygenase-2 inhibitors modulate skin aging in a catalytic activity-independent manner. *Exp Mol Med* 2012;**44**:536–44.
99. Orhan H, Doğruer DS, Cakir B, Sahin G, Sahin M. The *in vitro* effects of new non-steroidal antiinflammatory compounds on antioxidant system of human erythrocytes. *Exp Toxicol Pathol* 1999;**51**:397–402.
100. Poole JC, Thain A, Perkins ND, Roninson IB. Induction of transcription by $p21^{Waf1/Cip1/Sdi1}$: role of NFkappaB and effect of non-steroidal anti-inflammatory drugs. *Cell Cycle* 2004;**3**:931–40.
101. Weinstein GD, Nigra TP, Pochi PE, Savin RC, Allan A, Benik K, Jeffes E, Lufrano L, Thorne EG. Topical tretinoin for treatment of photodamaged skin. A multicenter study. *Arch Dermatol* 1991;**127**:659–65.
102. Griffiths GE, Kang S, Ellis CN, Kim KJ, Finkel LJ, Ortiz-Ferrer LC, White GM, Rhein TA, Hamilton F, Voorhees JJ. Two concentrations of topical tretinoin (retinoic acid) cause similar improvement of photoaging but different degrees of irritation. A double-blind, vehicle-controlled comparison of 0.1% and 0.025% tretinoin creams. *Arch Dermatol* 1995;**131**:1037–44.
103. Lundin A, Berne B, Michaelsson G. Topical retinoic acid treatment of photoaged skin: its effects on hyaluronan distribution in epidermis and on hyaluronan and retinoic acid in suction blister fluid. *Acta Derm Venereol* 1992;**72**:423–7.
104. Kligman AM, Dogadkina D, Lavker RM. Effects of topical tretinoin on non-sun-exposed protected skin of the elderly. *J Am Acad Dermatol* 1993;**29**:25–33.
105. Rafal ES, Griffiths CE, Ditre CM, Finkel LJ, Hamilton TA, Ellis CN, Voorhees JJ. Topical tretinoin (retinoic acid) treatment for liver spots associated with photodamage. *N Engl J Med* 1992;**326**:368–74.
106. Kang S, Duell EA, Fisher GJ, Datta SC, Wang ZQ, Reddy AP, Tavakkol A, Yi JY, Griffiths CE, Elder JT, Voorhees JJ. Application of retinol to human skin *in vivo* induces epidermal hyperplasia and cellular retinoid binding proteins characteristic of retinoic acid but without measurable retinoic acid levels or irritation. *J Invest Dermatol* 1995;**105**:549–56.
107. Damian DL, Patterson CT, Stapelberg M, Park J, Barnetson RS, Halliday GM. UV radiation-induced immunosuppression is greater in men and prevented by topical nicotinamide. *J Invest Dermatol* 2008;**128**:447–54.
108. Kawada A, Konishi N, Oiso N, Kawara S, Date A. Evaluation of anti-wrinkle effects of a novel cosmetic containing niacinamide. *J Dermatol* 2008;**35**:637–42.
109. Bissett DL, Oblong JE, Berge CA. Niacinamide: A B vitamin that improves aging facial skin appearance. *Derm Surg* 2005;**31**:860–5. discussion 865.

110. Hakozaki T, Minwalla L, Zhuang J, Chhoa M, Matsubara A, Miyamoto K, Greatens A, Hillebrand GG, Bissett DL, Boissy RE. The effect of niacinamide on reducing cutaneous pigmentation and suppression of melanosome transfer. *Br J Dermatol* 2002;**147**:20–31.
111. Ditre CM, Griffin TD, Murphy GF, Sueki H, Telegan B, Johnson WC, Yu RJ, van Scott EJ. Effects of alpha-hydroxy acids on photoaged skin: a pilot clinical, histologic, and ultrastructural study. *J Am Acad Dermatol* 1996;**34**:187–95.
112. Smith WP. Epidermal and dermal effects of topical lactic acid. *J Am Acad Dermatol* 1996;**35**:388–91.
113. Thueson DO, Chan EK, Oechsli LM, Hahn GS. The roles of pH and concentration in lactic acid-induced stimulation of epidermal turnover. *Derm Surg* 1998;**24**:641–5.
114. Horikoshi T, Matsumoto M, Usuki A, Igarashi S, Hikima R, Uchiwa H, Hayashi S, Brysk MM, Ichihashi M, Funasaka Y. Effects of glycolic acid on desquamation-regulating proteinases in human stratum corneum. *Exp Dermatol* 2005;**14**:34–40.
115. Rendl M, Mayer C, Weninger W, Tschachler E. Topically applied lactic acid increases spontaneous secretion of vascular endothelial growth factor by human reconstructed epidermis. *Br J Dermatol* 2001;**145**:3–9.
116. Xue J, Rai V, Singer D, Chabierski S, Xie J, Reverdatto S, Burz DS, Schmidt AM, Hoffmann R, Shekhtman A. Advanced glycation end product recognition by the receptor for AGEs. *Structure* 2011;**19**:722–32.
117. Wang Z, Li H, Zhang D, Liu X, Zhao F, Pang X, Wang Q. Effect of advanced glycosylation end products on apoptosis in human adipose tissue-derived stem cells *in vitro*. *Cell Biosci* 2015;**5**:3. http://dx.doi.org/10.1186/2045-3701-5-3.
118. Zigrino P, Brinckmann J, Niehoff A, Lu Y, Giebeler N, Eckes B, Kadler KE, Mauch C. Fibroblast-derived MMP-14 regulates collagen homeostasis in adult skin. *J Invest Dermatol* 2016;**136**:1575–83.
119. Phillips CL, Combs SB, Pinnell SR. Effects of ascorbic acid on proliferation and collagen synthesis in relation to the donor age of human dermal fibroblasts. *J Invest Dermatol* 1994;**103**:228–32.
120. Talwar HS, Griffiths CE, Fisher GJ, Hamilton TA, Voorhees JJ. Reduced type I and type III procollagens in photodamaged adult human skin. *J Invest Dermatol* 1995;**105**:285–90.
121. Geesin JC, Darr D, Kaufman R, Murad S, Pinnell SR. Ascorbic acid specifically increases type I and type III procollagen messenger RNA levels in human skin fibroblast. *J Invest Dermatol* 1988;**90**:420–4.
122. Phillips CL, Tajima S, Pinnell SR. Ascorbic acid and transforming growth factor-beta 1 increase collagen biosynthesis via different mechanisms: coordinate regulation of pro alpha 1(I) and pro alpha 1(III) collagens. *Arch Biochem Biophys* 1992;**295**:397–403.
123. Nusgens BV, Humbert P, Rougier A, Colige AC, Haftek M, Lambert CA, Richard A, Creidi P, Lapiere CM. Topically applied vitamin C enhances the mRNA level of collagens I and III, their processing enzymes and tissue inhibitor of matrix metalloproteinase1 in the human dermis. *J Invest Dermatol* 2001;**116**:853–9.
124. Brennan M, Bhatti H, Nerusu KC, Bhagavathula N, Kang S, Fisher GJ, Varani J, Voorhees JJ. Matrix metalloproteinase-1 is the major collagenolytic enzyme responsible for collagen damage in UV-irradiated human skin. *Photochem Photobiol* 2003;**78**:43–8.
125. Toriseva MJ, Ala-aho R, Karvinen J, Baker AH, Marjomaki VS, Heino J, Kahari VM. Collagenase-3 (MMP-13) enhances remodeling of three-dimensional collagen and promotes survival of human skin fibroblasts. *J Invest Dermatol* 2007;**127**:49–59.
126. Chiu A, Kimball AB. Topical vitamins, minerals and botanical ingredients as modulators of environmental and chronological skin damage. *Br J Dermatol* 2003;**149**:681–91.
127. Itahana K, Campisi J, Dimri GP. Methods to detect biomarkers of cellular senescence: the senescence-associated beta-galactosidase assay. *Methods Mol Biol* 2007;**371**:21–31.
128. Severino J, Allen RG, Balin S, Balin A, Cristofalo VJ. Is beta-galactosidase staining a marker of senescence *in vitro* and *in vivo*? *Exp Cell Res* 2000;**257**:162–71.
129. Franzen L, Windbergs M. Applications of Raman spectroscopy in skin research–from skin physiology and diagnosis up to risk assessment and dermal drug delivery. *Adv Drug Deliv Rev* 2015;**89**:91–104.
130. Sakai S, Yamanari M, Miyazawa A, Matsumoto M, Nakagawa N, Sugawara T, Kawabata K, Yatagai T, Yasuno Y. *In vivo* three-dimensional birefringence analysis shows collagen differences between young and old photo-aged human skin. *J Invest Dermatol* 2008;**128**:1641–7.

CHAPTER

# 44

# Melanogenesis

*H. Ando*

**Okayama University of Science, Okayama, Japan**

## 44.1 INTRODUCTION

Solar ultraviolet (UV)-B radiation (290−320 nm) is absorbed by DNA in the epidermis while UV-A radiation (320−400 nm) generates reactive oxygen species in the dermis. Both types of UV radiation damage DNA directly or indirectly, which can lead to the formation of mutations, which can in turn result in UV-induced skin cancers. In the basal layer of the epidermis, there are specialized cells, named melanocytes, that produce melanins. The role of melanins is to prevent UV-induced skin cancers by absorbing the UV energy and thus protecting against nuclear DNA damage. Melanin synthesis in the skin, hair, and eyes is ultimately regulated by tyrosinase, the critical rate-limiting enzyme produced by melanocytes within those tissues. Following the translation and subsequent processing of tyrosinase in the endoplasmic reticulum (ER) and Golgi apparatus, it is trafficked to specialized organelles, termed melanosomes, wherein melanin is synthesized and deposited. In the skin and hair, melanosomes are transferred from melanocytes to neighboring keratinocytes and are distributed in those tissues to produce visible color.

Although melanin is important for photoprotection from UV radiation, excess melanin production and/or its abnormal distribution can cause irregular hyperpigmentation of the skin, such as occurs in melasma and in age spots. In order to develop therapies or prophylactics that improve or prevent hyperpigmentary disorders, disruption of tyrosinase activity has usually been targeted. To date, many approaches that can inhibit tyrosinase activity and thus decrease melanin production have been reported, for example, the inhibition of tyrosinase mRNA transcription, the disruption of tyrosinase glycosylation, the competitive or noncompetitive inhibition of tyrosinase catalytic activity, or the acceleration of tyrosinase degradation, all of which would reduce melanin synthesis and deposition.[1]

## 44.2 INSTANCES OF SKIN-LIGHTENING QDS DEVELOPED IN JAPAN

To date, various quasi-drugs (QDs) that prevent or improve hyperpigmentary disorders have been developed and officially approved by the Ministry of Health, Labor and Welfare (MHLW) of Japan (Table 44.1). The major target of those QDs is tyrosinase in melanocytes, while some QDs work on keratinocytes or on epidermal metabolism. Among the melanocyte-targeted QDs, the inhibitory mechanism targeting tyrosinase activity can be divided into two groups, i.e., the inhibition of tyrosinase catalytic activity, such as antioxidation, chelating copper atoms in its active site, and competitive inhibition, while the other is to decrease tyrosinase protein levels that also leads to the inhibition of tyrosinase activity, such as accelerating tyrosinase degradation or inhibiting tyrosinase maturation that eventually forwards immature tyrosinase to the ER-associated protein degradation pathway.[2]

On the other hand, the keratinocyte-targeted QDs inhibit the activation of melanocytes by blocking or reducing UVB-induced inflammatory cytokines, and melanocyte quiescence eventually leads to decreased tyrosinase activity. In addition, the epidermis-targeted QDs elicit excretion of melanin from the epidermis that leads to the recovery of hyperpigmentary disorders, and this is a special skin lightening strategy that is substantially independent from melanocyte function.

Until the late 1980s, ascorbic acid (also termed Vitamin C) and placental extracts had been used as traditional skin-lightening QDs in Japan. Since then, starting with the approval of kojic acid by the MHLW, many companies have begun to develop their own original QDs.

*Cosmetic Science and Technology: Theoretical Principles and Applications*
http://dx.doi.org/10.1016/B978-0-12-802005-0.00044-6



Copyright © 2017 Elsevier Inc. All rights reserved.

**TABLE 44.1** Mechanistic Classification of Quasi-Drugs Approved by the MHLW of Japan

| *Target* | *Mechanism* | *Detail* | *Hypopigmenting QD* |
|---|---|---|---|
| Melanocyte | Inhibition of tyrosinase activity | Anti-oxidation | Ascorbic acid / derivatives |
| | | Chelating copper atoms | Kojic acid Ellagic acid |
| | | Competitive inhibition | Arbutin Rucinol 4MSK Rododendrol |
| | Decrease of tyrosinase protein level | Acceleration of Tyr degradation | Linoleic acid |
| | | Inhibition of Tyr maturation | Magnolignan |
| Keratinocyte | Inhibition of KC-MC signaling | Inhibition of UV inflammation | Chamomilla extract Tranexamic acid / derivative |
| Melanocyte & Keratinocyte | Inhibition of melanosome transfer | Inhibition of melanin dispersion | Niacinamide |
| Epidermis | Acceleration of epidermal turnover | Desquamation of melanin | Placental extract Adenosine mono-phosphate |

*KC*, keratinocyte, *MC*, melanocyte, *Tyr*, tyrosinase, *UV*, ultraviolet light.

### 44.2.1 Ascorbic Acid (Vitamin C) and Its Derivatives

Melanin synthesis is regulated by the rate-limiting enzyme tyrosinase, a membrane-bound copper-containing glycoprotein, which initiates the biosynthetic pathway of melanin by catalyzing the hydroxylation of tyrosine to DOPA (L-3,4-dihydroxyphenylalanine). Since subsequent reactions in the melanin synthetic pathway, e.g., the conversion of DOPA to DOPAquinone, as well as other nonenzymatic reactions, are oxidative reactions, antioxidants such as ascorbic acid are effective inhibitors of melanin synthesis. Ascorbic acid and its derivatives are the most popular skin lightening QDs that have ever been used in Japan.

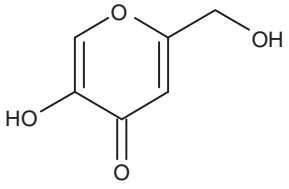
Examples of ascorbic acid derivatives are magnesium L-ascorbic acid 2-phosphate, sodium L-ascorbic acid 2-phosphate, L-ascorbic acid 2-glucoside and L-ascorbic acid ethyl ester. Although the inhibitory mechanism of skin lightening by L-ascorbic acid ethyl ester is to prevent the immediate pigment darkening of the skin induced by ultraviolet light A (UV-A) (320–400 nm)[3], the inhibitory mechanisms of melanin synthesis by ascorbic acid and its other derivatives are mainly antioxidant in nature.

As for clinical trials, a 10% magnesium L-ascorbic acid 2-phosphate-containing formulation was shown to be effective for treating hyperpigmentary disorders, such as melasma and age spots.[4] A 2% L-ascorbic acid 2-glucoside-containing cream was shown to decrease ultraviolet light B (UV-B) (280–320 nm)-induced hyperpigmentation of the skin.[5]

### 44.2.2 Placental Extract

Placental extracts have long been used as an active ingredient for skin lightening QDs, together with ascorbic acid and its derivatives. Previously, a bovine-derived placental extract was mainly used, however, swine-derived placental extracts are now more often used because of the incidence of mad cow disease. Various kinds of amino acids and minerals are enriched in placental extracts and the efficient inhibition of melanin synthesis and the enhancement of melanin excretion from the skin due to increased epidermal turnover have been reported, but much of the regulatory mechanisms underlying the effects of placental extracts are still unknown.

### 44.2.3 Kojic Acid

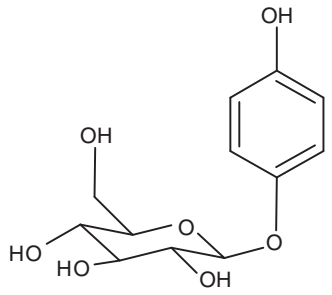


The approval of kojic acid as a QD was obtained by Sansho Seiyaku Co., Ltd. in 1988. Kojic acid, a pyrone derivative obtained from the fermentation process of Japanese liquor, has been known to have an antibacterial activity. Kojic acid was shown to inhibit the activity of tyrosinase by chelating copper atoms in its active site.[6]

As for clinical trials, a 1% kojic acid–containing formulation was shown to be effective for treating hyperpigmentary disorders, such as melasma, postinflammatory hyperpigmentation, age spots, and freckles.[7]

Manufacturers of kojic acid received notification from the MHLW in March 2003 to delay manufacture or import because of concern about possible carcinogenic effects. However, after revaluation in November 2005, kojic acid is now accepted to be safe as a cosmetic ingredient and continues to be used as a skin-lightening QD.[8]

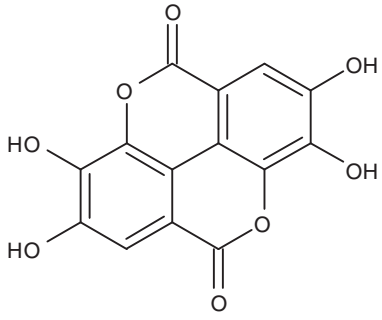
### 44.2.4 Arbutin




The approval of arbutin as a QD was obtained by Shiseido Co., Ltd. in 1989. Arbutin, a naturally occurring β-D-glucopyranoside derivative of hydroquinone, is found in cowberry leaves; it inhibits tyrosinase activity competitively but at noncytotoxic concentrations in cultured melanocytes.[9]

As for clinical trials, a 3% arbutin-containing formulation was shown to be effective for treating hyperpigmentary disorders, such as melasma.[10]

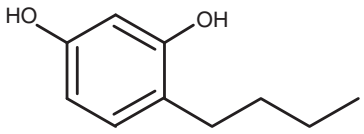
### 44.2.5 Ellagic Acid




The approval of ellagic acid as a QD was obtained by the Lion Corporation in 1996. Ellagic acid is a naturally occurring polyphenol, found in a variety of plants such as strawberries, geraniums, and green tea. The inhibitory effect of ellagic acid on melanin synthesis is similar to kojic acid, i.e., ellagic acid inhibits tyrosinase activity by chelating copper atoms in its active site.[11]

As for clinical trials, a 0.5% ellagic acid-containing cream was shown to be effective for treating UVB-induced hyperpigmentation of the skin.[12]

### 44.2.6 Rucinol (4-n-Butylresorcinol)



The approval of Rucinol (4-n-butylresorcinol) as a QD was obtained by POLA in 1998. Rucinol was selected by screening synthetic resorcinol derivatives that can elicit strong competitive inhibition of tyrosinase activity. Melanin synthesis is catalyzed by tyrosinase, together with tyrosinase-related proteins (TRPs) −1 and −2, and Rucinol has been shown to inhibit melanin synthesis in cultured mouse melanocytes via direct inhibition not only of tyrosinase activity[13] but also of TRP-1 activity.[14]

As for clinical trials, a 0.3% Rucinol-containing lotion was shown to be effective for treating hyperpigmentary disorders, such as melasma.[14]

### 44.2.7 Chamomilla Extract

The approval of chamomilla extract as a QD was obtained by the Kao Corporation in 1998. Chamomilla extract has been used as a traditional antiinflammatory agent, and is the only one so far that has been approved as a skin-lightening QD in Japan from botanical extracts. It has been shown that keratinocytes secrete endothelin-1, a type of inflammatory cytokine, which activates melanocytes when UV is irradiated on the epidermis.[15] Chamomilla extracts have been shown to act as an antagonist for endothelin-receptor binding, which mediates cell-to-cell signaling between keratinocytes and melanocytes and leads to the inhibition of melanin synthesis in melanocytes.[16] All earlier skin-lightening QDs had been developed to inhibit tyrosinase activity, whereas the chamomilla extract was a unique QD focusing on affecting keratinocytes that surround melanocytes.

As for clinical trials, a 0.5% chamomilla extract−containing cream was shown to be effective for treating UVB-induced hyperpigmentation of the skin.[17]

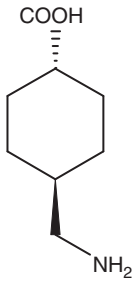
### 44.2.8 Linoleic Acid




The approval of linoleic acid as a QD was obtained by Sunstar Inc. in 2001. Linoleic acid is an unsaturated fatty acid (C18:2) derived from hydrolyzed botanical oils, such as safflower, and is a major component of biological cell membranes. Tyrosinase is degraded endogenously in melanocytes, and linoleic acid has been shown to accelerate tyrosinase degradation and to decrease tyrosinase levels, which leads to downregulation of melanin synthesis.[18]

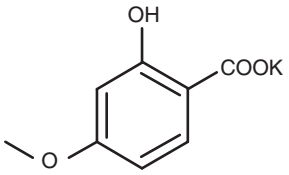
As for clinical trials, topical application of a 0.1% linoleic acid-containing liposomal formulation has been shown to be effective for treating melasma[19] and to lighten UVB-induced hyperpigmentation of the skin.[20]

### 44.2.9 Tranexamic Acid (Trans-aminomethylcyclohexanecarboxylic Acid)



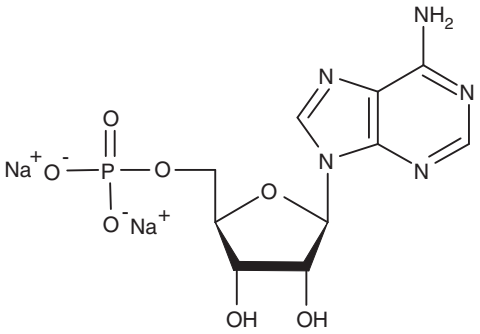

The approval of tranexamic acid (trans-aminomethylcyclohexanecarboxylic acid) as a QD was obtained by Shiseido Co., Ltd. in 2002. Tranexamic acid has been used as a traditional hemostatic medicine and is known as an oral medicine for treating melasma. Plasmin, a kind of protease in the blood serum, functions to enhance the intracellular release of arachidonic acid[21], a precursor of prostanoid, which can activate melanin synthesis by melanocytes. Therefore, the antiplasmin activity of tranexamic acid is thought to play a role in its topical effectiveness for treating melasma.

### 44.2.10 4MSK (4-Methoxy Potassium Salicylate)




The approval of 4MSK (4-methoxy potassium salicylate) as a QD was obtained by Shiseido Co., Ltd. in 2003. The inhibitory mechanism of 4MSK on melanin synthesis was shown to be competitive inhibition of tyrosinase activity, which is similar to the mechanisms of arbutin and Rucinol.

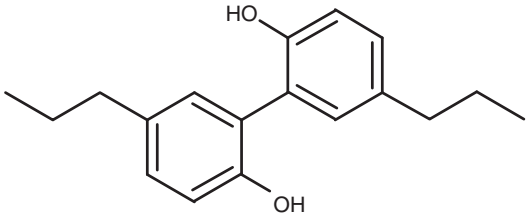
### 44.2.11 Adenosine Monophosphate Disodium Salt




The approval of adenosine monophosphate disodium salt as a QD was obtained by Otsuka Pharmaceutical Co., Ltd. in 2004. Adenosine monophosphate has a potency to increase the amount of intracellular glucose uptake that is necessary for the biosynthesis of adenosine tri-phosphate, a source of intracellular energy. Therefore, adenosine mono-phosphate disodium salt accelerates epidermal turnover due to the elevated intracellular energy metabolism that leads to the excretion of melanin from the skin, i.e., adenosine monophosphate prevents the accumulation of melanin in the skin.

As for clinical trials, a 3% adenosine monophosphate disodium salt—containing formulation was shown to be effective for treating hyperpigmentary disorders, such as melasma.[22]

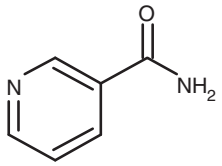
### 44.2.12 Magnolignan (5,5′-Dipropyl-biphenyl-2,2′-diol)




The approval of Magnolignan (5,5′-dipropyl-biphenyl-2,2′-diol) as a QD was obtained by Kanebo Cosmetics Inc. in 2005. Magnolignan is a biphenyl compound and a kind of polyphenol that has a structure similar to magnolol and honokiol involved in *Magnolia obovata*. Tyrosinase is known to mature due to its glycosylation in the ER and Golgi apparatus, and Magnolignan inhibits the maturation of tyrosinase that leads to decreased melanin synthesis.[23]

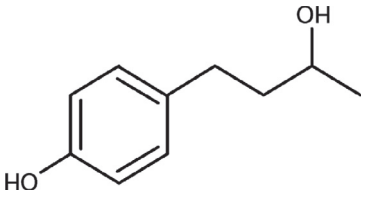
As for clinical trials, a 0.5% Magnolignan-containing formulation was shown to be effective for treating UV-B-induced hyperpigmentation of the skin[24] and also is effective in treating hyperpigmentary disorders, such as melasma and senile lentigo.[25]

### 44.2.13 Niacinamide



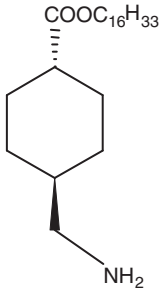

Niacinamide (also termed nicotinamide), a derivative of vitamin $B_3$, has been shown to act as an antiinflammatory agent in acne.[26] Niacinamide had no effect on the tyrosinase activity and melanin synthesis of cultured normal human melanocytes, however, it was found that niacinamide significantly decreased hyperpigmentation, such as melasma and solar lentigines, via inhibition of melanosome transfer from melanocytes to keratinocytes.[27]

### 44.2.14 Rhododendrol (4-(4-Hydroxyphenyl)-2-butanol)




The approval of rhododendrol (4-(4-hydroxyphenyl)-2-butanol) as a QD was obtained by Kanebo Cosmetics Inc. in 2007. Rhododendrol is a phenol compound found in extracts of white birch and Nikko maple. The inhibitory mechanism of rhododendrol on melanin synthesis was shown to be due to its competitive inhibition of tyrosinase activity. In 2013, rhododendrol-induced leukoderma (skin depigmentation) was reported in about 2% of consumers using rhododendrol-containing skin-lightening cosmetics.[28] It was suggested that one of the reasons for rhododendrol-induced leukoderma was due to the cytotoxicity in melanocytes by rhododendrol-cyclic catechol, an oxidative metabolite of rhododendrol catalyzed by tyrosinase.[29]

### 44.2.15 Tranexamic Acid Cetyl Ester Hydrochloride




The approval of tranexamic acid cetyl ester hydrochloride as a QD was obtained by CHANEL.KK in 2009. The effect of tranexamic acid cetyl ester hydrochloride to treat hyperpigmentary disorders is due to the inhibition of

UV-B-induced inflammation that leads to the quiescence of active melanocytes, a mechanism similar to chamomilla extract and tranexamic acid.

## 44.3 CONCLUSIONS

Nowadays, many of the hyperpigmentary disorders of the skin can be remedied by some types of laser therapies. Moreover, the chemical peeling of horny layers using α-hydroxy acids, such as glycolic acid[30] and lactic acid[31], has also been shown to be effective for treating hyperpigmentary disorders, such as melasma, due to the desquamation of melanin from the epidermis. In addition, hydroquinone, the traditional topical drug for treating hyperpigmentary disorders, had been used only as an ethical drug in Japan because its side effects, such as bleaching or white spots, had been of concern for the Japanese moderately pigmented skin, however, a change of Japanese Pharmaceutical Law in 2001 allowed the use of hydroquinone as an ingredient of cosmetic formulations and it is now used at relatively low and safe concentrations. Thus, there are many ways other than skin-lightening QDs to prevent or improve hyperpigmentary disorders. However, those QDs remain popular, especially in Asian cosmetic markets, as a convenient and self-choosing means to prevent hyperpigmentary disorders of the skin.

To date, various skin-lightening QDs have been developed based on a variety of functional mechanisms. Those developments will be continued, simultaneously launching with different strategies from previous theories for QDs. As a matter of course, novel skin-lightening QDs based on new approaches would be desirable. Multifunctional topical formulations that combine existing skin-lightening QDs, including not only inhibition of melanin synthesis but also inhibition of inflammation and/or acceleration of epidermal turnover, may increase their efficacy to treat hyperpigmentary disorders and contribute to the healthy pigmentation of the skin.

## References


1. Ando H, Kondoh H, Ichihashi M, Hearing VJ. Approaches to identify inhibitors of melanin biosynthesis via the quality control of tyrosinase. *J Invest Dermatol* 2007;**127**:751–61.
2. Ando H, Ichihashi M, Hearing VJ. Role of the ubiquitin proteasome system in regulating skin pigmentation. *Int J Mol Sci* 2009;**10**:4428–34.
3. Maeda K, Hatao M. Involvement of photooxidation of melanogenic precursors in prolonged pigmentation induced by ultraviolet A. *J Invest Dermatol* 2004;**122**:503–9.
4. Kameyama K, Sakai C, Kondoh S, Yonemoto K, Nishiyama S, Tagawa M, Murata T, Ohnuma T, Quigley J, Dorsky A, Ducks D, Blanock K. Inhibitory effect of magnesium L-ascorbyl-2-phosphate (VC-PMG) on melanogenesis in vitro and in vivo. *J Am Acad Dermatol* 1996;**34**:29–33.
5. Miyai E, Yamamoto I, Akiyama J, Yanagida M. Inhibitory effect of ascorbic acid 2-*O*-α-glucoside on the pigmentation of skin by exposure to ultraviolet light. *Nishinihon J Dermatol* 1990;**6**:105–8.
6. Mishima Y, Hatta S, Ohyama Y, Inazu M. Induction of melanogenesis suppression: cellular pharmacology and mode of differential action. *Pigment Cell Res* 1988;**1**:367–74.
7. Mishima Y, Ohyama Y, Shibata T, Seto H, Hatae S. Inhibitory action of kojic acid on melanogenesis and its therapeutic effect for various human hyper-pigmentation disorders. *Skin Res (Hifu)* 1994;**36**:134–50.
8. Higa Y, Kawabe M, Nabae K, Toda Y, Kitamoto S, Hara T, Tanaka N, Kariya K, Takahashi M. Kojic acid—Absence of tumor-initiating activity in rat liver, and of carcinogenic and photo-genotoxic potential in mouse skin. *J Toxicol Sci* 2007;**32**:143–59.
9. Maeda K, Fukuda M. Arbutin: Mechanism of its depigmenting action in human melanocyte culture. *J Pharm Exp Ther* 1996;**276**:765–9.
10. Sugai T. Clinical effects of arbutin in patients with chloasma. *Skin Res (Hifu)* 1992;**34**:522–9.
11. Shimogaki H, Tanaka Y, Tamai H, Masuda M. In vitro and in vivo evaluation of ellagic acid on melanogenesis inhibition. *Int J Cosmet Sci* 2000; **22**:291–303.
12. Kamide R, Arase S, Takiwaki H, Watanabe S, Watanabe Y, Kageyama S. Clinical effects of XSC-29 formulation on UV-induced pigmentation. *Nishinihon J Dermatol* 1995;**57**:136–42.
13. Kim DS, Kim SY, Park SH, Choi YG, Kwon SB, Kim MK, Na JI, Youn SW, Park KC. Inhibitory effects of 4-n-butylresorcinol on tyrosinase activity and melanin synthesis. *Biol Pharm Bull* 2005;**28**:2216–9.
14. Katagiri T, Okubo T, Oyobikawa M, Futaki K, Shaku M, Kawai M, Takenouchi M. Inhibitory action of 4-n-butylresorcinol (Rucinol®) on melanogenesis and its skin whitening effects. *J Cosmet Chem Jpn* 2001;**35**:42–9.
15. Imokawa G, Yada Y, Miyagishi M. Endothelins secreted from human keratinocytes are intrinsic mitogens for human melanocytes. *J Biol Chem* 1992;**267**:24675–80.
16. Imokawa G, Kobayashi T, Miyagishi M, Higashi K, Yada Y. The role of endothelin-1 in epidermal hyperpigmentation and signaling mechanisms of mitogenesis and melanogenesis. *Pigment Cell Res* 1997;**10**:218–28.
17. Ichihashi M, Kobayashi A, Okuda M, Imokawa G. Effect of chamomilla extracts application on UV-induced pigmentation. *Skin Res (Hifu)* 1999; **41**:475–80.
18. Ando H, Watabe H, Valencia JC, Yasumoto K, Furumura M, Funasaka Y, Oka M, Ichihashi M, Hearing VJ. *J Biol Chem* 2004;**279**:15427–33.
19. Clinical trial group for linoleic acid-containing gel. Clinical trial for liver spots using a linoleic acid-containing gel. *Nishinihon J Dermatol* 1998; **60**:537–42.
20. Ando H, Ryu A, Hashimoto A, Oka M, Ichihashi M. Linoleic acid and α-linolenic acid lightens ultraviolet-induced hyperpigmentation of the skin. *Arch Dermatol Res* 1998;**290**:375–81.

21. Chung WC, Shi GY, Chow YH, Chang LC, Hau JS, Lin MT, Jen CJ, Wing LY, Wu HL. Human plasmin induces a receptor-mediated arachidonate release coupled with G proteins in endothelial cells. *Am J Physiol* 1993;**264**:C271–81.
22. Kawashima M, Mizuno A, Murata Y. Improvement of hyperpigmentation based on accelerated epidermal turnover: Clinical effects of disodium adenosine monophosphate in patients with melasma. *Jpn J Clin Dermatol* 2008;**62**:250–7.
23. Nakamura K, Yoshida M, Uchiwa H, Kawa Y, Mizoguchi M. Down-regulation of melanin synthesis by a biphenyl derivative and its mechanism. *Pigment Cell Res* 2003;**16**:494–500.
24. Takeda K, Yokota T, Ikemoto T, Kakishima H, Matsuo T. Inhibitory effect of a formuloation containing 0.5% Magnolignan® (5, 5′-dipropyl-biphenyl-2, 2′-diol) on UV-induced skin pigmentation. *Nishinihon J Dermatol* 2006;**68**:288–92.
25. Takeda K, Arase S, Sagawa Y, Shikata Y, Okada H, Watanabe S, Yokota T, Ikemoto T, Kakishima H, Matsuo T. Clinical evaluation of the topical application of Magnolignan® (5, 5′-dipropyl-biphenyl-2, 2′-diol) for hyperpigmentation on the face. *Nishinihon J Dermatol* 2006;**68**:293–8.
26. Shalita AR, Smith JG, Parish LH, Sofman MS, Chalker DK. Topical nicotinamide compared with clindamycin gel in the treatment of inflammatory acne vulgaris. *Int J Dermatol* 1995;**34**:434–7.
27. Hakozaki T, Minwalla L, Zhuang J, Chhoa M, Matsubara A, Miyamoto K, Greatens A, Hillebrand GG, Bissett DL, Boissy RE. The effect of niacinamide on reducing cutaneous pigmentation and suppression of melanosome transfer. *Br J Dermatol* 2002;**147**:20–31.
28. Abe Y, Okamura K, Kawaguchi M, Hozumi Y, Aoki H, Kunisada T, Ito S, Wakamatsu K, Matsunaga K, Suzuki T. Rhododenol-induced leukoderma in a mouse model mimicking Japanese skin. *J Dermatol Sci* 2016;**81**:35–43.
29. Okura M, Yamashita T, Ishii-Osai Y, Yoshikawa M, Sumikawa Y, Wakamatsu K, Ito S. Effects of rhododendrol and its metabolic products on melanocytic cell growth. *J Dermatol Sci* 2015;**80**:142–9.
30. Javaheri SM, Handa S, Kaur I, Kumar B. Safety and efficacy of glycolic acid facial peel in Indian women with melasma. *Int J Dermatol* 2001;**40**:354–7.
31. Sharquie KE, Al-Tikreety MM, Al-Mashhadani SA. Lactic acid as a new therapeutic peeling agent in melasma. *Dermatol Surg* 2005;**31**:149–54.

CHAPTER

# 45

# Sensitive Skin

*E. Berardesca*

**San Gallicano Dermatological Institute, IRCCS, Rome, Italy**

## 45.1 INTRODUCTION

Subjects with sensitive skin report exaggerated reactions when their skin is in contact with cosmetics, soaps, and sunscreens, and they often report worsening after exposure to a dry and cold climate. Epidemiological studies have been carried out to assess whether there is a correlation with sex, age, skin type, or race and are described elsewhere in this book.

Subjects with sensitive skin may have a thinner stratum corneum with a reduced corneocyte area causing a higher transcutaneous penetration of water soluble chemicals.[1] Frosch and Kligman,[2] by testing different irritants, showed a 14% incidence of sensitive skin in the normal population, likely correlated to a thin permeable stratum corneum which make these subjects more susceptible to chemical irritation.

Moreover, deceased barrier function in sensitive skin has been reported as the result of an imbalance of intercellular lipids of the stratum corneum.[3] Although impaired barrier function is easily understood as a mechanism of sensitive skin, other factors are also possible, such as changes in the nerve system and/or the structure of the epidermis. In one study,[4] detailed characteristics of sensitive skin were investigated using noninvasive methods. Sensitive skin has been classified into three different types based on their physiological parameters. Type I has been defined as the low−barrier function group. Type II has been defined as the inflammation group with normal barrier function and inflammatory changes. Type III has been specified as the pseudo healthy group in terms of normal barrier function and no inflammatory changes. In all types, a high content of nerve growth factor has been observed in the stratum corneum, relative to that of nonsensitive skin. In both type II and type III, the sensitivity to electrical stimuli was high.[4] These data suggest that the hypersensitive reaction of sensitive skin is closely related to nerve fibers innervating the epidermis. Yamasaki and Gallo[5] proposed recently that the innate immune system triggers an abnormal inflammatory reaction that mediates the symptoms of rosacea and sensitive skin. If so, flushing, blushing erythema may be due to chronic inflammation. In particular, cathelicidin may play a role in inducing the cytokine cascade. Indeed, some forms of cathelicidin peptides were known to have a unique capacity to be both vasoactive and proinflammatory.[5]

Direct connections were observed between unmyelinated nerve fibers and mast cells; stress in animal models induces substance P (SP) in unmyelinated nerve fibers, which triggers mast cell degranulation with subsequent histamine release.[6] Stress is commonly reported as a trigger for sensitive skin, and mast cell degranulation is supported by the finding that sensitive skin sufferers had a greater density of mast cells and size of lymphatic microvasculature.[7] Neurogenic inflammation probably results from release of neurotransmitters such as SP, calcitonin gene−related peptide (CGRP), and vasoactive intestinal peptide, which induce vasodilatation and mast cell degranulation. Nonspecific inflammation may also be associated with the release of interleukins. Indeed, sensitive skin could be the result of an inflammatory process resulting from the abnormal penetration in the skin of potentially irritating substances because of skin barrier dysfunction.[8] In addition, the presence of a nonspecific reaction has been related to cutaneous sensory innervation in the establishment of skin sensitivity.[9,10] Neuropeptides released from cutaneous nerves and skin resident cells such as SP, CGRP, and proopiomelanocortin (POMC) peptides (e.g., β-endorphin and encephalin) are mandatory for fine-tuned regulation of cutaneous immune responses and tissue maintenance and repair.[11,12] In response to noxious stimuli, SP and CGRP lead to vasodilatation and mast cell degranulation, originating a process called "neurogenic inflammation." Classic pathways are then activated,

*Cosmetic Science and Technology: Theoretical Principles and Applications*
http://dx.doi.org/10.1016/B978-0-12-802005-0.00045-8



Copyright © 2017 Elsevier Inc. All rights reserved.

causing a nonspecific inflammation of released cytokines and eicosanoids such as interleukin (IL)-1α, tumor necrosis factor-α, prostaglandin E2, and prostaglandin F2.[13] On the other hand, POMC activities include antagonism and downregulation of adhesion molecules and reduced inflammation by modulation of IL-10 production, which contributes to the amelioration of the subjective neurosensory forms of discomfort.

Recent research studies, however, are investigating the molecular basis for sensory hyperreactivity. Transient receptor potential vanilloid family 1 (TRPV1) is a nonreceptive, thermosensitive ion channel that reacts to noxious stimuli, most notably noxious heat and low pH. TRPV1 is expressed on fibroblasts, mast cells, and endothelial cells; activation results in pain or pruritus with a burning component. TRPV1 is also dramatically upregulated by inflammatory mediators,[14] as well as by heat and capsaicin. It has been hypothesized that the development of sensitive skin may be related to the dysregulation of muscle contraction and relaxation process[15]; actin-bound myosin cross-bridges in sensitive skin had a more compacted shape than did those in nonsensitive skin, indicating more contracted cross-bridge state in sensitive skin tissues. This could be also linked to altered ATP metabolism and response of skin pH. These data demonstrated that subjects with sensitive skin showed impaired pH homeostasis after lactic acid stimulation and increase of detection ability for pH on internal or external stimuli such as lactic acid.[15] Enhanced acidity might induce pain via stimulation of TRPV1, ASIC3, and CGRP in the human sensitive skin. Stratum corneum microbiome has been also investigated in subjects affected by sensitive skin, and no differences versus normal controls have been reported.[16]

The existing overlap between atopic population and subjects affected by sensitive skin is well documented. Using transepidermal water loss (TEWL) modeling, statistically significant differences have been detected in the parameters obtained in the sensitive skin group, which supports the thesis that individuals with increased skin susceptibility have impaired barrier function.[17] However, few studies have investigated stratum corneum lipid composition in subjects affected by sensitive skin. Cho and coworkers[18] compared the average amount of ceramides in the stratum corneum on various parts of the body (right cheek, forearm, thigh, leg, back, palm) between the sensitive group and the nonsensitive group. The results indicated that the mean values of the amount of ceramides in the parts of the body surface other than the face were lower in the sensitive group than in the nonsensitive group, but the difference was not statistically significant. However, on the face, the sensitive group showed a statistically significant decrease in the mean value of the amount of ceramides compared with the nonsensitive group, indicating that the amount of ceramides in the stratum corneum on the facial skin has a correlation with skin sensitivity.

Changes in stratum corneum thickness and, therefore, of transcutaneous penetration may explain regional differences or specialized areas of sensitive skin. The face has been demonstrated to be the most common site of skin sensitivity, predictable physiologically due to the larger and multiple number of products used on the face (particularly in women), a thinner barrier in facial skin, and a greater density of nerve endings.[19] The nasolabial fold was reported to be the most sensitive region of the facial area, followed by the malar eminence, chin, forehead, and upper lip.[20,21] Saint-Martory et al. found that hand, scalp, feet, neck, torso, and back sensitivity followed facial sensitivity, in descending order of prevalence.[22] Significant numbers of individuals experience sensitivity of the scalp.[23,24] One-third of the population interviewed reported sensitive scalp, with higher levels in woman than in men. Interestingly, the prevalence who declared sensitive scalp increased with age. The authors explain this could be due to alterations of nerve endings as a result of the aging process or increased proclivity to irritation as a consequence of chronic exposure to surfactants contained in shampoos.

The genital area is another site frequently affected with sensitive skin. In a study of 1039 men and women, 56.2% reported sensitivity of genital skin,[2] an area of particular interest because it is formed partially from embryonic endoderm and therefore differs from skin at other body sites.[25] A surprising 56.2% of responders claimed sensitive genital skin, with significantly more African Americans than whites (66.4%, $p < .0001$) claiming sensitivity of this area. Rough fabrics were found to be the most common offender for sensitive skin in the genital area.[26]

## 45.2 ASSESSMENT OF SENSITIVE SKIN

The stinging test has been used as a method for the assessment of skin neurosensitivity. Stinging seems to be a variant of pain that develops rapidly and fades quickly whenever the appropriate sensory nerve is stimulated. The test relies on the intensity of stinging sensation induced by chemicals applied onto the nasolabial fold.[27] Procedures differ depending on the chemical used. It is still uncertain how it relates to the identification of sensitive skin, as a high variation in results is observed with these tests.

### 45.2.1 Lactic Acid

After a 5- to 10-min facial sauna, an aqueous lactic acid solution (5% or 10% according to different methods) is rubbed with a cotton swab onto the test site while an inert control substance, such as saline solution, is applied to the contralateral test site. After application, within a few minutes, a moderate to severe stinging sensation occurs for the "stingers group." Subjects are then asked to describe the intensity of the sensation by using a point scale. Hyperreactors, particularly those with a positive dermatological history, have higher scores. Using this screening procedure, 20% of the subjects exposed to 5% lactic acid in a hot, humid environment were found to develop a stinging response.[27] Lammintausta et al. confirmed these observations,[28] identifying in his study 18% of subjects as stingers. In addition, stingers were found to develop stronger reactions to materials causing nonimmunological contact urticarial and to have increased TEWL and blood flow velocimetry values after the application of an irritant under a patch test.

### 45.2.2 Capsaicin

An alternative test involves the application of capsaicin. A new procedure assessed by Jourdain and coworkers[29] appears to be accurate and reliable for the diagnosis of sensitive skin. After a facial cleansing, five increasing capsaicin concentrations in 10% ethanol aqueous solution are applied onto the nasolabial folds. The formulation of capsaicin in hydroalcoholic solution accelerates the action of capsaicin on the face in comparison with the previously used 0.075% capsaicin emulsion, without being associated with painful sensation.

The capsaicin detection thresholds are more strongly linked to self-declared sensitive skin than is the lactic acid stinging test.[29]

### 45.2.3 Dimethylsulfoxide

The alternative application of 90% aqueous dimethylsulfoxide does not have the same efficacy as the lactic acid or capsaicin stinging test. After application, intense burning, tender wheal, and persistent erythema often occur in stingers.

## 45.3 CONCLUSIONS

Sensitive skin can be considered a complex syndrome characterized by the association between subjective and objective symptoms triggered both by a combination of structural barrier problems and by altered neurogenic and vascular responses.[30,31]

## References


1. Berardesca E, Cespa M, Farinelli N, Rabbiosi G, Maibach HI. In vivo transcutaneous penetration of nicotinates and sensitive skin. *Contact Dermatitis* 1991;**25**:35–8.
2. Frosch PJ, Kligman AM. A method for appraising the stinging capacity of topically applied substances. *J Soc Cosmet Chem* 1977;**28**:197–209.
3. Ohta M, Hikima R, Ogawa T. Physiological characteristics of sensitive skin classified by stinging test. *J Cosmet Sci Soc Jpn* 2000;**23**:163–7.
4. Yokota T, Matsumoto M, Sakamaki T, et al. Classification of sensitive skin and development of a treatment system appropriate for each group. *IFSCC Mag* 2003;**6**:303–7.
5. Yamasaki K, Gallo RL. The molecular pathology of rosacea. *J Dermatol Sci* 2009;**55**:77–81.
6. Kumagai M, Nagano M, Suzuki H, Kawana S. Effects of stress memory by fear conditioning on nerve-mast cell circuit in skin. *J Dermatol* 2011; **38**:553–61.
7. Quatresooz P, Piérard-Franchimont C, Piérard GE. Vulnerability of reactive skin to electric current perception–a pilot study implicating mast cells and the lymphatic microvasculature. *J Cosmet Dermatol* 2009;**8**:186–9.
8. Yosipovitch G, Yarnitzky D. Quantitative sensory testing. In: Maibach HI, Marzulli FN, editors. *Dermatotoxicology methods: the Laboratory worker's vade mecum*. New York: Taylor & Francis; 1997. p. 120–35.
9. Primavera G, Berardesca E. Sensitive skin: mechanisms and diagnosis. *Int J Cosmet Sci* 2005;**27**:1–10.
10. Misery L, Myon E, Martin N, et al. Sensitive skin: psychological effects and seasonal changes. *J Eur Acad Dermatol Venereol* 2007;**21**:620–8.
11. Peters EMJ, Ericson ME, Hosoi J, et al. Neuropeptide control mechanisms in cutaneous biology: physiological and clinical significance. *J Invest Dermatol* 2006;**126**:1937–47.
12. Luger TA, Lotti T. Neuropeptides: role in inflammatory skin diseases. *J Eur Acad Dermatol Venereol* 1998;**10**:207–11.
13. Luger TA. Neuromediators – a crucial component of the skin immune system. *J Dermatol Sci* 2002;**30**:87–93.
14. Kueper T, Krohn M, Haustedt LO, Hatt H, et al. Inhibition of TRPV1 for the treatment of sensitive skin. *Exp Dermatol* 2010;**19**:980–6.

15. Kim EJ, Lee DH, Kim YK, Kim M-K, Kim JY, Lee MJ, Chung JH. Decreased ATP synthesis and lower pH may lead to abnormal muscle contraction and skin sensitivity in human skin. *J Dermatol Sci* 2014;**76**(3):214–21.
16. Hillion M, Mijouin L, Jaouen T, Barreau M, Meunier P, Lefeuvre L, Feuilloley MGJ. Comparative study of normal and sensitive skin aerobic bacterial populations. *MicrobiologyOpen* 2013;**2**(6):953–61.
17. Pinto P, Rosado C, Parreirão C, Rodrigues LM. Is there any barrier impairment in sensitive skin?: a quantitative analysis of sensitive skin by mathematical modeling of transepidermal water loss desorption curves. *Skin Res Technol* 2011;**17**(2):181–5.
18. Cho HJ, Chung BY, Lee HB, Kim HO, Park CW, Lee CH. Quantitative study of stratum corneum ceramides contents in patients with sensitive skin. *J Dermatol* 2012;**39**(3):295–300.
19. Chew A, Maibach H. Sensitive skin. In: Loden M, Maibach H, editors. *Dry skin and moisturizers: chemistry and function*. Boca Raton: CRC Press; 2000. p. 429–40.
20. Marriott M, Holmes J, Peters L, Cooper K, et al. The complex problem of sensitive skin. *Contact Dermatitis* 2005;**53**:93–9.
21. Distante F, Bonfigli A, Rigano L, D'Agostino R, Berardesca E. Intra- and inter-individual differences in facial skin biophysical properties. *Cosmet Toiletries* 2002;**7**:149–58.
22. Saint-Martory C, Roguedas-Contios AM, Sibaud V, Degouy A, et al. Sensitive skin is not limited to the face. *Br J Dermatol* 2008;**158**:130–3.
23. Misery L, Sibaud V, Ambronati M, Macy G, et al. Sensitive scalp: does this condition exist? An epidemiological study. *Contact Dermatitis* 2008; **58**:234–8.
24. Misery L, Rahhali N, Ambonati M, Black D, et al. Evaluation of sensitive scalp severity and symptomatology by using a new score. *J Eur Acad Dermatol Venereol* 2011;**25**:1295–8.
25. Farage M, Maibach HI. The vulvar epithelium differs from the skin: implications for cutaneous testing to address topical vulvar exposures. *Contact Dermatitis* 2004;**51**:201–9.
26. Farage MA. Perceptions of sensitive skin of the genital area. *Curr Probl Dermatol* 2011;**40**:142–54.
27. Frosch PJ, Kligman AM. A method for appraising the stinging capacity of topically applied substances. *J Soc Cosmet Chem* 1977;**28**:197–9.
28. Lammintausta K, Maibach HI, Wilson D. Mechanisms of subjective (sensory ) irritation: propensity of non immunologic contact urticaria and objective irritation in stingers. *Derm Beruf Umwelt* 1988;**36**:45–9.
29. Jourdain R, Bastien P, de Lacharrière O, Rubinstenn G. Detection threshold of capsaicin: a new test to assess facial skin neurosensitivity. *J Cosmet Sci* 2005;**56**:153–5.
30. Berardesca E, Fluhr JW, Maibach H, editors. *Sensitive skin syndrome*. New York: Taylor and Francis; 2006.
31. Berardesca E, Farage M, Maibach H. Sensitive skin: an overview. *Int J Cosmet Sci* 2013;**35**:2–8.

CHAPTER

# 46

# Skin Penetration

A.C.H.R. Machado[1], P.S. Lopes[1], C.P. Raffier[2], I.N. Haridass[2], M. Roberts[2], J. Grice[2], V.R. Leite-Silva[1]

[1]Universidade Federal de São Paulo, UNIFESP-Diadema SP, Brasil; [2]The University of Queensland, Woolloongabba, QLD, Australia

## 46.1 INTRODUCTION

The cosmetics industry continues to expand worldwide with the cosmetic market growing by around 3–5.5% per year in recent years. The market has demonstrated an ability to achieve this strong growth consistently while remaining resilient to unfavorable economic conditions.[1,2]

The claims described on a cosmetic product label or in promotional material must be substantiated with scientific data or clinical studies, ensuring that the product actually has the promised effect. For example, if the product is claimed to reduce cellulite or wrinkles, validated data must be submitted to support that claim.

Many cosmetics, like moisturizers and sunscreens, are designed to exert their effects while remaining on the skin surface. On the other hand, some cosmetic substances can only be effective when they cross the skin barrier and act in deeper skin layers such as the dermis (e.g., antioxidants) or hypodermis (e.g., fat reducers).[3,4] Generally, however, all cosmetics are expected to be excluded from the systemic circulation. Developing cosmetic formulations that will allow an active substance to penetrate the skin barrier and yet not reach the bloodstream remains a significant challenge.

Cosmetics must be safe to use over the long term, so safety assurance is critical. Testing the skin penetration of cosmetic actives and excipients is one example of the safety measures that are required. Because of intersubject variability and variability in conditions under which cosmetics are used, it is not possible to ensure the safety of a cosmetic with 100% certainty. However, the knowledge gained by studying cosmetic formulations and skin interactions may help to alleviate some of the variability and uncertainty.[5,6]

In the past, many animals were used for cosmetic safety tests, but in 1959, British scientists William M. S. Russell and Rex L. Burch wrote "The Principles of Humane Experimental Technique" where they introduced the principle of the 3Rs (refinement, reduction, and replacement). The aim of the 3Rs was to always look for ways to minimize or even eliminate the use of animals for product testing, and it led to a concerted effort to look for alternative methods of testing. However, the largest movement in the cosmetic area occurred in the 2000s, peaking around 2013 with the prohibition of animal testing for cosmetic evaluation in Europe. Following this watershed decision, product safety has had to be assessed by in vitro methods or in vivo human studies.[7,8] This has led to a new set of challenges to find and validate in vitro techniques that reliably predict in vivo human responses.

## 46.2 A LITTLE BIT ABOUT HISTORY

For thousands of years, humans have painted their bodies with natural products for adornment or religious purposes, and the practice of applying substances to the skin to cause specific responses dates back at least to the 16th century BC.[9] However, it is only in the last 100 years or so that there have been significant advances in understanding the mechanism of absorption through the skin. This, as we know, can be a crucial factor in determining the efficacy and safety of a cosmetic product whose target lies below the surface of the skin. Rapid scientific progress

*Cosmetic Science and Technology: Theoretical Principles and Applications*
http://dx.doi.org/10.1016/B978-0-12-802005-0.00046-X



Copyright © 2017 Elsevier Inc. All rights reserved.

began at the end of the 19th century, and the first important findings demonstrating the passage of lipophilic and nonelectrolyte components through the skin were reported in 1904.[10]

The existence of the skin barrier was first proposed in the mid-19th century, but its location, now taken for granted to reside in the stratum corneum (SC), was a subject of speculation for many years. In 1877, Fleisher[11] proposed that the skin of humans and some animals was impermeable to all types of substances, although this was soon disproved. But it was only in the late 1960s that definitive work by one of the pioneers in scientific skin permeation, Robert Scheuplein, showed that the entire stratum corneum contributed to the barrier.[12] As we shall see later, the unique structure of the stratum corneum, most simply described as a series of layers of flattened corneocytes surrounded by a lipid envelope, is largely responsible for the skin barrier. And as we have already noted, the first essential requirement for a cosmetic substance that targets regions below the skin surface is to breach this stratum corneum layer.

These ideas were developed in following years and many models and mechanisms have been proposed to understand how some compounds can, and others can't, cross the stratum corneum barrier. In the 1960s, Dale Wurster used pharmacokinetics to quantitatively describe percutaneous absorption.[13] Around the same time, Takeru Higuchi proposed different thermodynamic and diffusion principles for skin penetration.[14]

An important development in experimental design was the introduction of apparatus such as the static diffusion cells developed by Tom Franz[15,16] and the flow-through system of Bob Bronaugh.[17] These allowed in vitro skin permeation to be assessed much more reproducibly than previously. More recently, a modified diffusion cell was developed by the Saarbrücken group.[18] In their Saarbrücken Penetration Model (SB-M), the skin is placed on a filter paper rather than over a buffer solution, in order to avoid what the authors believed to be nonphysiological hydration of the skin that occurs in the Franz diffusion cell. Penetration into the skin is assessed by tape stripping, followed by cutting the deeper layers parallel to the surface with a cryomicrotome.

From the 1970s on there has been an acceleration in understanding of the way in which products interact with the stratum corneum barrier. Application of this knowledge remains a priority in the pharmaceutical and cosmetic sciences.

## 46.3 SKIN STRUCTURE/PROPERTIES

The skin is the largest human organ (Fig. 46.1) and acts as the main interface between the body and its environment, being responsible for the physical interactions (sensation, defense, regulation) and psychological responses (interpersonal, intrapersonal, social) to the world. It has the essential function of protecting the body from the

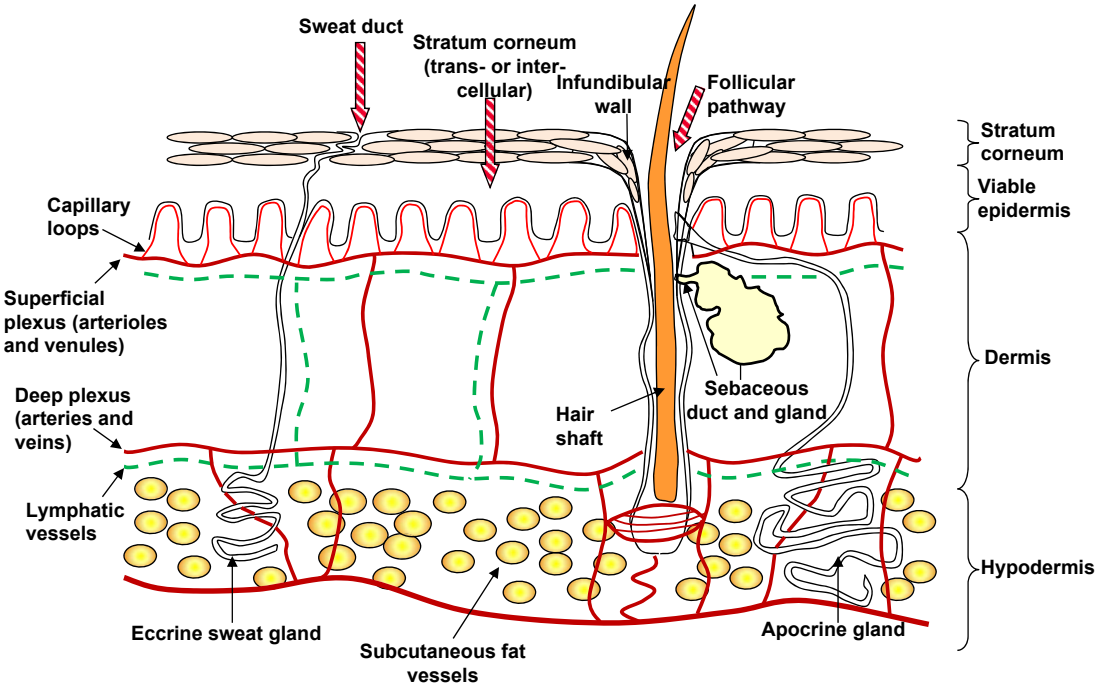



FIGURE 46.1 Skin diagram.

surrounding environment, providing an efficient permeation barrier to exogenous molecules and microorganisms[19] and maintaining homeostasis by preventing excessive loss of water.

It is now understood that a complex set of structures and mechanisms combine to create the skin barrier, and an understanding of how these mechanisms work can allow products to be designed to overcome it. We have already seen that cosmetics can have multifunctional roles, providing benefits not just at the skin surface but in deeper layers. One of the goals of the cosmetic formulator is to apply knowledge about the skin barrier to design products that can reach and act at specific target sites to achieve aesthetic responses, such as treating the effects of aging.

The epidermis is the outermost layer of the skin and has the primary responsibility for protection against the environment and to maintain the skin's barrier function. The epidermis is being constantly renewed, as new keratinocytes are formed in the stratum basale and undergo maturation, moving upward through the spinous, granular, lucid, and corneal layers, to eventually lose their nucleus and other organelles and become corneocytes in the stratum corneum, or horny layer. The corneocytes are eventually sloughed off, to be replaced by other keratinized cells resulting from continual maturation. The entire process from keratinocyte formation to corneocyte loss occurs over approximately 14 days.

Apart from the corneocytes, the stratum corneum features an array of intercellular lipids, with desmosomes acting to adhere the cells. The corneocytes lack a nucleus and are composed of keratin and lipids in a cornified cell envelope, which when absent, alter the skin's barrier function. The principal intercellular lipids of the stratum corneum are ceramides, cholesterol, cholesteryl esters, fatty acids, and a small fraction of cholesterol sulfate.[20]

## 46.4 FACTORS AFFECTING THE SKIN BARRIER

**Age** The properties of the skin may be dependent on its age. Waller (2005) reported that aged skin generally shows reduced blood perfusion, decreased epidermal thickness, and a significant increase in stratum corneum pH after about 70 years of age.[21] However, no significant change in stratum corneum thickness, morphology, and composition as a result of advancing age was observed. Studies also show that there is a decrease in transepidermal water loss (TEWL) with age (in adults), although this does not significantly affect the permeation of compounds such as caffeine, nicotinates, or water.[6]

Instrumental evaluation of TEWL, skin water content by capacitance, and pH at two different anatomical sites shows that in comparison to adults, the skin of children aged 8–24 months are more functionally immature. This may potentially result in an increased permeability and a reduced ability to defend against chemical and microbial attack.[22]

In 2016, Mack et al. evaluated 397 children (3–49 months) and 117 adults (average age 31 years) of different ethnicities in the cities of Beijing (China), Skillman (New Jersey, USA), and Mumbai (India). Analysis of TEWL, conductance, and digital images failed to identify significant differences among adults of different ethnicities. Among children, the authors noticed a constant decrease in TEWL between the ages of 3 months and 4 years, presumably due to improving water-retention ability of the skin. Differences in skin barrier function were therefore concluded to be due to age and independent of ethnicity and geographical location of the subject.[23]

**Ethnicity, gender, and anatomical site** It is generally accepted that skin barrier function is not related to ethnicity. In 1988, Wilson et al. compared inner thigh TEWL values of African American and American white males and found no significant differences.[24] Later, Voegeli et al. used a color-mapping approach to analyze skin hydration and facial barrier properties of four ethnic groups (Caucasian, Indian, Chinese, and black Africans) in South Africa. While skin pigmentation was found to have an effect on facial skin hydration, with higher skin hydration in the black African and Indian volunteers compared to those of Chinese and Caucasian origin, there were no differences in barrier properties measured by TEWL. The African and Indian volunteers were found to have higher skin hydration than the Chinese and Caucasian volunteers.[25] The Maibach group, in collaboration with L'Oréal, investigated the effect of ethnicity on the permeation of three model compounds: benzoic acid, caffeine, and acetylsalicylic acid.[26] They reported that in vivo, there were no differences in the percutaneous absorption of these three compounds in black, Asian, and Caucasian volunteers. These findings have also been confirmed by other studies.[27,28]

A significant amount of research has been conducted to investigate the effect of anatomical sites on skin permeation. The stratum corneum has been reported to vary in thickness at different sites on the body, irrespective of volunteer age and gender. The genital area has the thinnest stratum corneum layer, whereas the acral regions, such as the palm, sole, and heel, were found to have the thickest stratum corneum layers.[29] Undoubtedly, stratum corneum thickness is thought to influence the barrier function of the skin and its sensitivity to topically applied products.

Rougier et al. reported the forehead to be most permeable to benzoic acid penetration, followed by the abdomen, thigh, and arm. The back was found to be least permeable.[30] These findings can be partly explained by the stratum

corneum thickness at these sites, expressed in the number of cell layers. The forehead was found to have $9 \pm 1$ cell layers, whereas the thigh has $16 \pm 4$ layers.[29] The stratum corneum absorption and retention of benzophenone-3, octyl salicylate, and homosalate, three topically applied UV filters that are designed to be retained in the upper layers of the stratum corneum for optimal sunscreen efficacy, was significantly higher on the face than the back.[31] However, these differences can also be perceived to be dependent on the compound that is being administered to the skin. Highly lipophilic drugs, such as fentanyl and sufentanil, were found to have comparable permeation through human skin obtained from different anatomical sites in vitro.[32] The lipophilic nature of these actives favor their partitioning into the stratum corneum.

**Skin Disorders** The skin surface has a pH of approximately 4–6. Disturbances in the acid mantle resulting in elevated skin surface pH may be contributing factors to the occurrence of topical diseases such as contact dermatitis, ichthyosis, psoriasis, and atopic dermatitis. The acid mantle confers an antimicrobial function to the skin, as well as supporting its physical defense.[33]

Occupational skin diseases (OSD) are the second most commonly occurring occupational diseases worldwide, with occupational contact dermatitis the most reported of these OSDs.[34] Irritant contact dermatitis, allergic contact dermatitis, contact urticaria, and protein contact dermatitis are all considered types of contact dermatitis. Among the external factors that contribute to the development of the disease is the continuous exposure to chemicals and allergens that affect the structure and composition of the stratum corneum, causing a dysfunction in the skin barrier. Among the professionals most affected by OSDs are health care professionals, hairdressers, and construction workers. These professionals may have a more permeable skin as a result of the perturbed barrier.

Topically applied cosmetic products can alter skin permeability through skin moisturization, depolarization of the active, and through the use of detergents and other permeation-enhancing agents.[35]

## 46.5 ASSESSING THE SKIN BARRIER

The stratum corneum is the skin's main barrier to penetration and therefore the disruption of this barrier is the target of a great number of topical formulations. Nevertheless, skin appendages, such as hair follicles, sweat glands, and sebaceous glands, which reach the deep dermis from the skin surface, are important target sites for the delivery of actives.

A key noninvasive technique for the analysis of skin integrity and skin barrier efficacy is the evaluation of the TEWL. This technique relies on the diffusion of water through the skin surface. The stratum corneum, composed layers of 10–15 layers keratinized cells, regulates transepidermal water loss and prevents the entry of potentially harmful substances and microorganisms. The relationship between the stratum corneum and the water loss from the skin was demonstrated in 1944 by Winsor and Burch.[36]

There are many commercially available instruments that have been proven to efficiently evaluate TEWL and skin barrier function, by extension. The measure of TEWL comprises of evaluating water evaporation from the skin surface in grams (g) of water per meter squared ($m^2$) per hour (h) ($g/m^2/h$).[37] The barrier function, characterized by TEWL, has been shown to be related to the total content of stratum corneum lipids, particularly sphingolipids and free sterols.[38]

## 46.6 OVERCOMING THE SKIN BARRIER

**The vehicle** It is important to consider the vehicle as it will be responsible for the transport of the compound through the skin. It comes into contact and may interact with the stratum corneum and therefore has the potential to modify it.[6,39,40]

Among the cosmetic formulations used as vehicles, the most common are gels, especially hydrophilic gels, and emulsions. Many types of emulsions can be formulated for cosmetic purposes, such as oil-in-water, water-in-oil, water-in-oil-in-water, and oil-in-water-in-oil. Therefore, the choice of vehicle depends on the active it features, as this aspect is crucial to the delivery of the active to its target site.[41]

Viscous formulations generally reduce the diffusion coefficient of the molecule in the vehicle, thus retarding or eliminating its skin partitioning and absorption.[42] However, this may not always be the case, and careful examination of the experimental conditions is necessary if false interpretations of the data are to be avoided.[6]

The final charge of the emulsion is generally influenced by the charge of the primary surfactant. Surfactants may be ionic, nonionic, or amphoteric. Nonionic surfactants are generally better tolerated by the skin compared to ionic surfactants, and only in a very few specific cases are amphoteric surfactants used.[43] Several studies have shown that

the use of cationic surfactants results in improved skin penetration of actives,[44] however, others have failed to demonstrate this relationship, while implicating other variables, such as the solvents used.[45,46]

**The size and shape of the permeant** will influence its diffusivity within the stratum corneum. It has been shown that there is an inverse relationship between permeant size and skin permeation.[47] Several studies have reported that nanoproducts applied to the skin only penetrate through follicular openings and skin pores, with minimal amounts of the product being found below the stratum corneum.[48]

Nanomaterial-based delivery of actives to the skin is a very dynamic field and has progressed tremendously.[49] In the cosmetic field, it involves encapsulating the active of interest in a nanovehicle, such as a liposome, to enhance its delivery to the skin. To further improve the efficiency of liposomes, novel particles such as niosomes, ethosomes, and transfersomes were subsequently developed.

Liposomes are composed of mixtures of phospholipids, with or without cholesterol, which form a single or multiple lipid bilayers that enclose an aqueous environment.[50] Niosomes are made of mixtures of nonionic surfactants, cholesterol, and, in some cases, small amounts of phospholipids. These nanoparticles are reported to be more stable than liposomes.[51] Ethosomes may contain between 20% and 45% of ethanol, and were designed to improve skin penetration by increasing the elasticity of the lipid vesicle.[52] Transfersomes are made of phospholipids supplemented with surfactants that act as edge activators to provide vesicle elasticity and deformability.[42,53] SECosomes, composed of surfactants, ethanol, and cholesterol, have been reported to form stable and ultradeformable nano-sized vesicles with the capacity to improve topical active delivery when compared with nonflexible liposomes.[54] The increased flexibility in these particles greatly enhances their ability to deliver their payload to targeted cells.

## 46.7 SKIN PENETRATION

Cosmetic industries as well as governmental institutions share a common interest in skin investigation such as bioavailability studies, risk assessment of products, and consumer protection among others.[55]

The extent of skin penetration of a substance may depend on the route of absorption. There are three pathways that can be involved in the transdermal permeation of compounds: (1) the skin appendages; (2) the intercellular lipid domains in SC; and (3) the corneocytes[19,56] (Fig. 46.2).

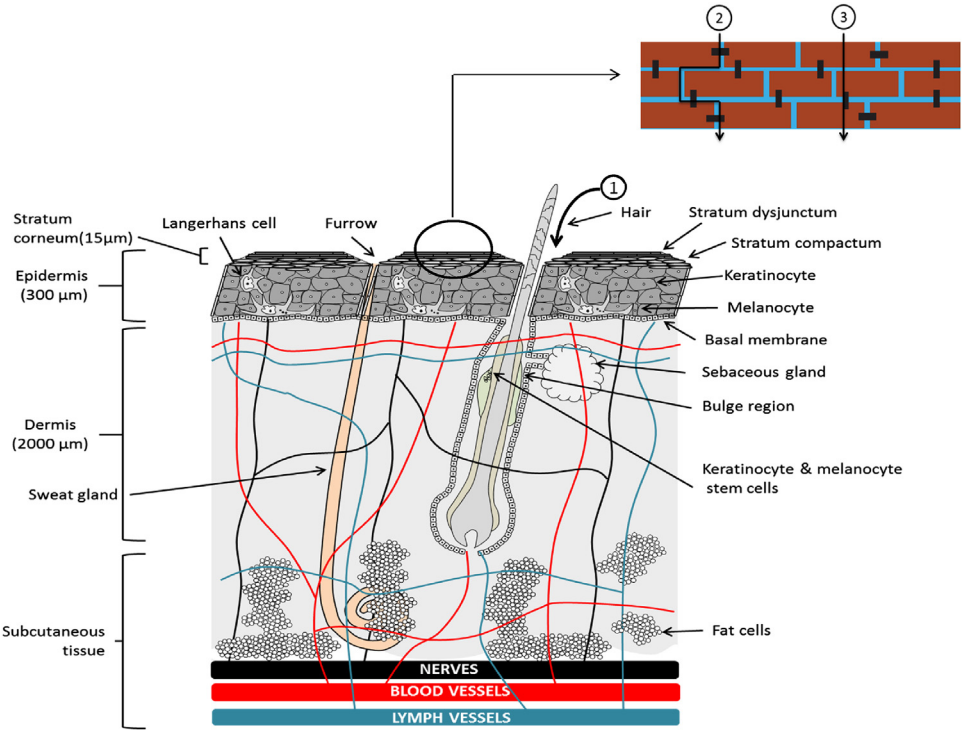



FIGURE 46.2 Skin structure and pathways that can be involved in the transdermal permeation of chemicals.

The number of substances that can cross the stratum corneum under passive conditions is very much limited, and therefore penetration enhancers are employed to promote active penetration. These can be chemicals or substances that have the ability to alter the properties of the skin. The mechanisms for such changes include: (1) disruption of the lipid bilayer structure; (2) extraction of the stratum corneum lipids; (3) increasing the active solubility and partitioning in the stratum corneum; (4) changing stratum corneum hydration; and (5) interaction with keratin of corneocytes.[57]

Skin penetration can also be enhanced by physical, mechanical, and electrical approaches. There are numerous techniques known to cosmeticians or beauty therapists to increase the penetration of an active that can be performed before or after application of the product on the skin. Mechanical methods such as tape stripping or dermal abrasion can reduce the thickness of the stratum corneum, while massaging generally weakens the barrier and can favor follicular transport.[58] The use of microneedles and jet propulsion overcome the stratum corneum by either creating microchannels in the epidermis or by propelling the active through the skin at high velocities.[59,60] The external application of energy in the form of thermal energy, ultrasound, and radio frequency has also been shown to create pores or to reduce skin resistance.

The assessment of percutaneous absorption of molecules is one of the most important steps in evaluating the safety and/or efficacy of cosmetics. Percutaneous absorption is usually assessed in silico, in vitro, ex vivo, and in vivo in animal models and humans. In practice, a combination of these methods is used to evaluate cosmetic products. For example, a product may be evaluated in vitro using a model membrane and in vivo with human volunteers.[19] This prevents the reliance on a single method to provide information on the safety and efficacy of the product. One of the main challenges of this process is correlating the absorption data obtained in vitro with the data obtained in vivo as both techniques are necessary to be able to draw a conclusion.[19]

## 46.8 EVALUATION OF SKIN PENETRATION

### 46.8.1 In vitro/Ex Vivo Studies

In vitro models are currently widely used for skin penetration/permeation studies. Indeed, they present numerous advantages and are relatively easy to carry out. The process is well known and reproducible compared to in vivo studies. In vitro methods can provide information about the interactions and mechanisms of drug permeation/penetration through the skin. However, to get relevant and exploitable results when using in vitro studies in predicting topical/transdermal delivery of drugs, a correlation between in vitro and vivo studies must be established. The in-vitro in-vivo correlation (IVIVC) was introduced in 1997 by the US Food and Drug Administration (FDA) and is defined according to a "predictive mathematical model describing the relationship between an in-vitro property of a dosage form and an in-vivo response." Good IVIVCs have generally been found, provided the in vitro and in vivo studies are well harmonized.[61–66]

Despite limitations, the in vitro skin penetration/permeation studies, under controlled conditions, have enabled rapid and easy screening and selection of drugs, delivery systems, and penetration enhancers that are most appropriate for an intended purpose.

The Franz diffusion cell is one of the most widely used systems for in vitro skin permeation studies (Fig. 46.3). First described by Franz in 1978, this cell has an upper donor compartment and a lower and receptor compartment.

The compartments are separated by a permeable membrane and the sample is applied to the membrane surface in the donor compartment. Material passes through the membrane into the receptor compartment which contains a buffer which is continuously stirred; samples are taken from the receptor at predetermined time intervals through a side opening.[67,68]

In this original design, the cell was static and had a single unstoppered sampling port. A number of modifications have been subsequently made to the original design by Franz. The central part of the receptor chamber can be enclosed in a water jacket for temperature control; a second sidearm has been added to permit flow-through operation, the donor compartment can be sealed, and it can be made in a variety of active surface area diameters.[69]

Inadequate mixing in the receptor chamber of Franz cells, particularly in the region of the sidearm, was detected by dye dispersion experiments.[69] Thus, some improvements were made in this model[70] including a more efficient magnetic stirring system.[71]

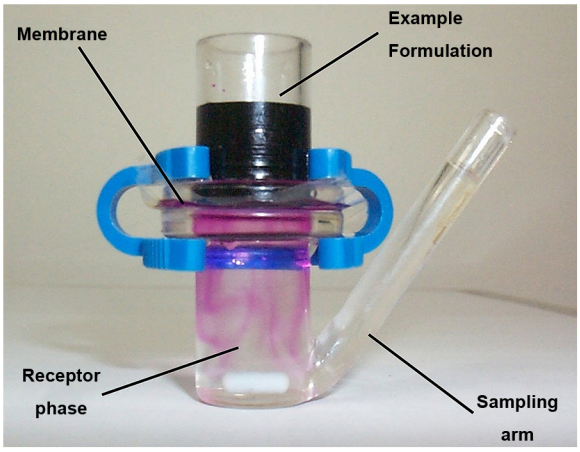



FIGURE 46.3 Franz-type horizontal diffusion cells (Author's picture).

These in vitro models use biological or artificial membranes and are useful as procedures for determination of skin permeation parameters such as flux, partition coefficients, and diffusion coefficients.[72–74]

#### *46.8.1.1 Membranes*

While studying in vitro topical/transdermal delivery, different kinds of membranes (artificial, reconstructed, and biological) have been used.

Table 46.1 summarizes the range of membranes used over the years and currently, as well as some advantages and disadvantages. This list is not exhaustive, however, as some studies carried out with animal membranes such as rabbit skin showed much greater permeability than human skin and were considered to be of little relevance.[75,76]

### 46.8.2 In Vivo Studies

As mentioned before, the European Union signed an agreement in 2013 to eliminate cosmetic testing on animals, giving priority to study in humans, especially tests that can be done noninvasively. In vivo studies with human skin are preferred to evaluate skin penetration, however, in initial development of a new active, generally this is not feasible.[19]

Specimens of human skin of sufficient size and quality for penetration experiments are not readily available to most investigators or only available in limited amounts.[81] Human volunteer studies are often difficult to justify, particularly if the product (active ingredient or a component of the formulation) has toxic or irritant properties.[102]

### 46.8.3 In Vivo Imaging

For these noninvasive studies in humans, imaging technologies such as confocal microscopy or multiphoton laser scanning tomography (MPT) have been used to visualize the penetration of fluorescent materials. They can provide morphological and biochemical information about the skin through the skin autofluorescence detection with little damage to tissue.[103–105] This method uses the different "lifetimes," the average fluorescence time (photon emission) for a molecule from an excitation light–induced excited state to its ground state.

Fluorescent lifetime imaging (FLIM) is the resolution of lifetimes for different molecules in space (x, y, z) and time. FLIM can also be combined with spectral imaging, a process that has been called multispectral FLIM (SLIM) detection. Thus, FLIM and SLIM can be used to produce a spatial image showing the differences in the fluorescence lifetime between several fluorophores, and can therefore distinguish compounds with a similar emission spectrum. MPT differs from traditional confocal fluorescence microscopy by using two or more photons of low energy, rather than one high-energy photon, to excite fluorophores within the sample. Deeper tissues can be imaged, due to the greater penetration of infrared radiation.[106]

**TABLE 46.1** Advantages and Drawbacks of Different Types of Membranes Used in Skin Permeability Studies

| Type of Membrane | | Advantages | | Disadvantages | References |
|---|---|---|---|---|---|
| Human skin | Full thickness<br>Split thickness dermatomed skin<br>Epidermis + SC<br>SC (Stratum corneum) | • Most relevant model<br>• Metabolically competent<br>• In vitro results close with in vivo conditions | | • Limited availability (surgery, cadavers, amputations.)<br>• High costs and<br>• Donor variability<br>• Limited acceptance (ex: USA) | 73,77,78 |
| Animal | Pig | • The ear showed anatomical similarities to human skin: SC and epidermal thickness, follicular structure and the hair density.<br>• Permeability is close to human skin | • Wild availability<br>• Metabolically competent<br>• Economic, simple, reproducible<br>• High number of experiments can be run simultaneously | • Species extrapolation necessary<br>• Differences permeability between animal species and human skin (ex: rat)<br>• Generally more permeable than human skin (rat, rabbit) | 64,79–81 |
| | Guinea pig | No fur | | | 82–84 |
| | Shed snake | • Similarities between shed snake skin and human skin<br>• Ease of storage and handling<br>• Low cost | | | 85–87 |
| | Mouse | • Fairly easily handled and is relatively inexpensive | | | |
| | Hairless rat/mouse | No fur | | | 76,83,85,88 |
| | Rat | • Close anatomical similarity to human skin | | | 76,89–91 |
| | Monkey | • Percutaneous absorption compares well to human skin | | | 76,92 |
| Artificial | Lipid based: PAMPA<br>PVPA | • Biomimetic system: contains components similar to real human stratum corneum<br>• Adjustment of lipid composition possible | • High-throughput screening model economic, simple, reproducible<br>• Easily standardized<br>• Primary prediction of skin permeability of drugs | • Exclude other factors that can be present in real conditions: no metabolism<br>• Restriction of the studied drugs: Only aqueous solutions | 74,93–95 |
| | Nonlipid based: Ex: Polymers | • Studies of lipophilic compounds | | • Could not be used for the hydrophilic compound | 73,95,96 |
| Reconstructed Tissues | Reconstruct skin cell culture Episkin, SkinEthic | • Easily available, standardized, reproducible<br>• Large range of reconstructed tissues available (full thickness, epidermis…)<br>• Metabolically competent (results close to in vivo conditions)<br>• Screenings and prediction of permeability of numerous components<br>• Mimic the morphological, biochemical, and physiological properties of the human epidermis: interspecies extrapolation is avoided | | • High cost<br>• Weak barrier: Over predicts absorption<br>• Lack of vascularization, sweat glands and hair<br>• Technical limitations (low stability) | 97–101 |

### 46.8.4 In Vivo Tape Stripping

Tape stripping is a simple, minimally invasive method that can be used for a range of experimentations. In the case of topically applied skin products, essential information, such as the drug concentration and the fraction of drug that is able to across the stratum corneum can be obtained.[20] Thus, thanks to this tool, bioavailability and bioequivalence studies can be carried out. As we have seen, the stratum corneum is the main rate-limiting barrier to percutaneous drug transport, which is why the assessment of drugs within the skin is a vital step for efficient topical and transdermal delivery development.[107]

The principle of tape stripping is based on the removal of layers of stratum corneum cells. The formulation is first applied on the skin, and after its permeation the cell layers of the stratum corneum are successively removed from the same skin area with an adhesive tape. During this procedure, not only the corneocytes embedded in their lipid matrix but also compounds bound to the latter, such as a drug, will be removed.[108] This method can be coupled with an analytical method, for instance high performance liquid chromathography, to determine the amount of drug in each adhesive tape. To extract the drug from the tape, an additional step of chemical extraction or sonification is required.[109] If the amount of drug is determined and the thickness of the stratum corneum is known, from the Fick equation we can calculate the diffusivity of the drug in the stratum corneum and the partition coefficient vehicle/stratum corneum. These parameters provide essential information for dermatopharmacokinetic (DPK) studies, allowing the estimation of the fficiency of a drug by determining the rate of drug that is able to across the stratum corneum.

In the DPK approach, the drug levels in the stratum corneum (SC) are measured as a function of time post-application and post-removal of the drug, providing a measure of drug uptake. After the skin area is exposed to the formulation for a defined period of time and then cleaned of excess formulation, tape stripping is performed after a defined latency time.[110–112] The extent of stratum corneum uptake is obtained from the area under the curve given by concentration as a function of time (AUC), and the maximum concentration of drug in the stratum corneum ($C_{max}$) measures the product of rate and extent, as well the corresponding time at which the value is at maximum concentration, $T_{max}$.[110,113]

Although this technique is a promising method to determine DPK parameters, it has some weakness. The amount of stratum corneum removed may be variable from one tape to another. Different factors can influence the quantity of stratum corneum removed by each tape, such as skin hydration, vehicle, cohesion between corneocytes, the selected anatomical site, age of the patient, pressure applied when stripping, and duration of the application, etc.[107,108,114–116] Therefore, instead of estimating the quantity of stratum corneum removed with each tape, different methods were used to quantify the stratum corneum, including gravimetric, microscopic, and spectrophotometric methods.[108,114,117,118]

N'Dri-Stempfer used a streamlined approach with only one uptake time and one clearance time at two treatment sites to analyse literature DPK data for tretinoin gel products and show bioequivalence. Results showed better efficiency with reduction of variability and improved reproducibility compared to the original analysis.[113]

Tape stripping was first used mostly on human skin in vivo, but over the years researchers extended its use to animals and excised human skin. Recently, studies were carried out comparing tape stripping in human in vitro and skin in vivo after exposure to emulsions containing aspartic acid or finite doses of microemulsions or hydrogels containing curcumin or fluorescein sodium. Results showed good correlations between the in vitro and in vivo models.[119,120] Further studies led by Saeheng et al. (2013) compared DPK between in vitro tape pig ear skin and in vivo human skin using terbinafine hydrochloride 1% topical cream. Results displayed a nonsignificant difference between the human/pig ear, suggesting that in vitro animal studies can be used as surrogates to estimate in vivo human skin absorption.[121]

In a nutshell, tape stripping is a useful tool to estimate the DKP of a topically applied compound in vivo as well as in vitro, but it's necessary to consider all factors that can influence the measures.

### 46.8.5 In Vivo Skin Blanching/Vasoconstrictor Assay

The skin blanching test or vasoconstrictor assay, first described by McKenzie and Stoughton in 1962,[122] is suitable for the determination of the activity of topical corticosteroids. Among corticosteroids, topical glucocorticoids are well known to be responsible for an antiinflammatory effect for skin diseases. They usually induce an antiproliferation effect, apoptosis, and vasoconstriction, thus leading to a decrease in inflammation. However, all glucocorticoids don't have the same efficiency and potency, which is why it is relevant to determine their bioavailability.[123]

The exact mechanism of the production of blanching of the skin is still not fully understood, and the measurement of this blanching was based on a visual scoring performed by the human eye using a scale such as the Olsen vasoconstriction scale, but this method was questioned because of the lack of objectivity.[124] To obtain more objective results, a colorimetry technique was proposed, but the use of handheld probes can lead to variability between measurements. Although the chromametric method was standardized by Elsner[125] and approved by the FDA, it presents some gaps. To overcome the problem of subjectivity, Zhai developed in 2009 a complementary technique based on tissue viability imaging to obtain an objective assessment.[126] This method uses a digital cross-polarization spectroscopic technology to deliver color maps of dermal red blood cell concentrations which can be captured non-invasively. The integrated image processing features allow the captured images to be converted automatically into quantitative data of erythema and blanching enabling objective and operator-independent results. This method remains one of the most advanced because it permits elimination of all the disadvantages of handheld probes to obtain objective results.

### 46.8.6 In Vivo Microdialysis

Microdialysis is a technique that is able to measure concentrations of the free, active drug or endogenous compounds in almost all human tissues and organs. Because it is a semi-invasive technique, it is not the first choice for cosmetic measurement. It is currently being used for diagnostic and therapeutic decisions in medical practice and is still generally based on blood concentrations of drugs or cosmetics (determination of whiteners for instance).[127,128] The principle of microdialysis is to mime the passive function of a small blood vessel by inserting a tubular semipermeable dialysis membrane implanted in the tissue.[129] The probe is implanted in the dermis of the skin using a guide cannula and the microdialysis fiber is perfused with a tissue compatible fluid (the perfusate). The fiber is connected with a tube at a micropump at the afferent side, and the efferent side is connecting to a sampling tube, which permits the collection of dialysate, which can then be analyzed.

The exchange of molecules across the membrane occurs by passive diffusion driven by the concentration gradient according to the Fick's law, until reaching the physiological medium. The microdialysis probes have specific pore sizes, which set upper limits (cutoff value) for the molecules that can be sampled, but also exclude larger molecules and proteins from entering the sampling fluid.[130] However, it's important to note that such a technique also has its limits—it's not suitable for the analysis of high-lipophilic compounds and its reproducibility needs to be improved.[131]

One of the reasons for limited use in cosmetic investigations is the associated skin trauma inflicted when inserting the probe/catheter horizontally in the dermis. Skin blood flow was increased and erythema and inflammation were apparent after insertion of the microdialysis probe. Probe depth in the dermis was not related to the effects of trauma.[132]

### 46.8.7 In Silico Models

Mathematical modeling to predict skin permeation is considered a potential alternative to in vivo investigations, especially considering the ethical and economical questions surrounding human and animal experimentation.[55]

In silico approaches aiming to derive simple predictive relationships between complex effects and structural properties are ambitious and may not account for the subtlety in the mechanisms, such as time dependence and receptor-binding effects.

In addition to models to predict skin permeation, considerable interest is shown in developing in silico models for toxicological responses to cosmetic products. Progress has been hampered by the considerable complexity of the systems being studied and the variability of in-use application procedures.[133]

One of the most important parameters is the permeability coefficient ($k_p$), which was used to determine quantitative structure−permeation relationships (QSPRs) based on mathematical models developed by Abraham in 1999. This is a linear-free energy relationship[134] that takes into account physicochemical and/or structural properties of the penetrating molecule. Methods such as these generally allow reasonable predictions of skin absorption, an important step for cosmetic development.[135]

As discussed previously, the vehicle has an influence on skin permeation and, as a consequence, on the delivery and absorption of the applied topical component. Consequently, different mathematical models have been developed to predict the results of the interaction between the vehicle and the solute.[136]

Riviere and Brooks (2005) proposed a mixture factor that takes into account the physicochemical properties of the vehicle/mixture components. The resultant model was analyzed using 16 solutes (atrazine, chlorpyrifos, ethylparathion, fenthion, methylparathion, nonylphenol, p-nitrophenol, pentachlorophenol, phenol, propazine, simazine, triazine, DEET, SDS, permethrin andricinoleic acid) in a combination of vehicles (water, ethanol, propylene glycol) and additives (sodium lauryl sulfate, methyl nicotinate), resulting in 344 treatment combinations. The resulting model, incorporating a mixture factor related to the physicochemical properties of mixture refractive index, polarizability, and log (1/Henry's law constant) into Abraham's QSPR model leads to a significant improvement in predictability of skin permeability coefficients.[137]

Various other mathematical models have been developed as predictive tools in the design stage of topical/transdermal drug delivery systems. They can be useful to screen the potential of drugs and delivery systems in relation to skin penetration/permeation. However, their application beyond this remains limited, considering that most models are: (1) applicable mainly to simple systems such as solute/water (with complex mixtures being little explored); (2) are useful for a limited range of polarities and sizes of solutes; and (3) are often limited to solutes of similar classes.[138,139]

## 46.9 FUTURE DIRECTIONS

While recognizing the enormous importance of safety testing, the efficacy of the products is still the greatest concern of the cosmetic consumer. It is therefore crucial that consumers become better informed about the products they use. One way for them to do this is by acquiring the habit of reading product labels carefully. However, the elegant bottles and seductive labels and package inserts will not necessarily provide specific information about the active ingredients or the tests done on the products by the manufacturer. This information needs to be made readily available to consumers so they can make informed choices about the products they buy. To help the consumer, the law is clear—it is the total responsibility of companies to do the tests that prove the effectiveness of their products.

Despite major advances, there is still significant progress required to define cellular targets in the skin, to direct active ingredients specifically to those targets, and to standardize the quantification of cosmetic responses. This needs to be done while taking into account the important sensorial properties of the cosmetic formulation at the same time.

## References


1. Łopaciuk A, Łoboda M. Zadar, Croatia. In: *Knowledge management & innovation 1079–1087*; 2013.
2. Hassali MA. Malaysian cosmetic market: current and future prospects. *Pharm Regul Aff* 2015.
3. Farris P, Krol Y. Under persistent assault: understanding the factors that deteriorate human skin and clinical efficacy of topical antioxidants in treating aging skin. *Cosmetics* 2015;**2**:355.
4. Herman A, Herman AP. Caffeine's mechanisms of action and its cosmetic use. *Skin Pharmacol Physiol* 2013;**26**:8–14.
5. Inomata S. Safety assurance of cosmetics in Japan: current situation and future prospects. *J Oleo Sci* 2014;**63**:1–6.
6. Leite-Silva VR, Almeida MM, Fradin A, Grice EJ, Roberts MS. Delivery of drugs applied topically to the skin. *Expert Rev Dermatol* 2012: 383–97. http://dx.doi.org/10.1586/edm.12.32.
7. Burden N, Sewell F, Chapman K. Testing chemical safety: what is needed to ensure the widespread application of non-animal approaches? *PLoS Biol* 2015;**13**:e1002156,. http://dx.doi.org/10.1371/journal.pbio.1002156.
8. Goldberg AM, Zurlo J, Rudacille D. The three Rs and biomedical research. *Science* 1996;**272**:1403. http://dx.doi.org/10.1126/science.272.5267.1403.
9. Mez-Mangold L. *A history of drugs*. F. Hoffmann-La Roche; 1971.
10. Schwenkenbecher. Das Absorptionsvermögen der Haut. *Archiv für Physiologie* 1904;**121–165**(1/2).
11. Fleischer R. *Untersuchungen über das Resorptionsvermögen der menschlichen Haut*. E. Besold; 1877.
12. Scheuplein RJ. Analysis of permeability data for the case of parallel diffusion pathways. *Biophys J* 1966;**6**:1–17. http://dx.doi.org/10.1016/S0006-3495(66)86636-5.
13. Wurster DE, Kramer SF. Investigation of some factors influencing percutaneous absorption. *J Pharm Sci* 1961;**50**:288–93.
14. Higuchi T. Physical chemical analysis of percutaneous absorption process from creams and ointments. *J Soc Cosmet Chem* January 1960;**11**: 85–97.
15. Franz TJ. Percutaneous absorption on the relevance of in vitro data. *J Invest Dermatol* 1975;**64**:190–5.
16. Franz TJ, Lehman PA, Raney SG. Use of excised human skin to assess the bioequivalence of topical products. *Skin Pharmacol Physiol* 2009;**22**: 276–86. http://dx.doi.org/10.1159/000235828.
17. Bronaugh RL, Stewart RF. Methods for in vitro percutaneous absorption studies IV: The flow-through diffusion cell. *J Pharm Sci* 1985;**74**:64–7.
18. Wagner H, Kostka KH, Lehr CM, Schaefer UF. Drug distribution in human skin using two different in vitro test systems: comparison with in vivo data. *Pharm Res* 2000;**17**:1475–81.

19. Godin B, Touitou E. Transdermal skin delivery: predictions for humans from in vivo, ex vivo and animal models. *Adv Drug Deliv Rev* 2007;**59**:1152–61. http://dx.doi.org/10.1016/j.addr.2007.07.004.
20. Moser K, Kriwet K, Naik A, Kalia YN, Guy RH. Passive skin penetration enhancement and its quantification in vitro. *Eur J Pharm Biopharm* 2001;**52**(2):103–12.
21. Waller JM, Maibach HI. Age and skin structure and function, a quantitative approach (I): blood flow, pH, thickness, and ultrasound echogenicity. *Skin Res Technol* 2005;**11**:221–35. http://dx.doi.org/10.1111/j.0909-725X.2005.00151.x.
22. Giusti F, Martella A, Bertoni L, Seidenari S. Skin barrier, hydration, and pH of the skin of infants under 2 years of age. *Pediatr Dermatol* 2001;**18**:93–6.
23. Mack MC, et al. Water-holding and transport properties of skin stratum corneum of infants and toddlers are different from those of adults: studies in three geographical regions and four ethnic groups. *Pediatr Dermatol* 2016. http://dx.doi.org/10.1111/pde.12798.
24. Wilson D, Berardesca E, Maibach HI. In vitro transepidermal water loss: differences between black and white human skin. *Br J Dermatol* 1988;**119**:647–52.
25. Voegeli R, Rawlings AV, Seroul P, Summers B. A novel continuous colour mapping approach for visualization of facial skin hydration and transepidermal water loss for four ethnic groups. *Int J Cosmet Sci* 2015;**37**:595–605. http://dx.doi.org/10.1111/ics.12265.
26. Lotte C, Wester RC, Rougier A, Maibach HI. Racial differences in the in vivo percutaneous absorption of some organic compounds: a comparison between black, Caucasian and Asian subjects. *Arch Dermatol Res* 1993;**284**:456–9.
27. Sinha AJW, Shaw SR, Weber DJ. Percutaneous absorption and excretion of tritium-labeled diflorasone diacetate, a new topical corticosteroid in the rat, monkey and man. *J Invest Dermatol* 1978;**71**:372–7.
28. Wedig JH, Maibach HI. Percutaneous penetration of dipyrithione in man: effect of skin color (race). *J Am Acad Dermatol* 1981;**5**:433–8.
29. Ya-Xian Z, Suetake T, Tagami H. Number of cell layers of the stratum corneum in normal skin – relationship to the anatomical location on the body, age, sex and physical parameters. *Arch Dermatol Res* 1999;**291**:555–9.
30. Rougier A, et al. Regional variation in percutaneous absorption in man: measurement by the stripping method. *Arch Dermatol Res* 1986;**278**:465–9.
31. Benson HA, Sarveiya V, Risk S, Roberts MS. Influence of anatomical site and topical formulation on skin penetration of sunscreens. *Ther Clin Risk Manag* 2005;**1**:209–18.
32. Roy SD, Flynn GL. Transdermal delivery of narcotic analgesics: pH, anatomical, and subject influences on cutaneous permeability of fentanyl and sufentanil. *Pharm Res* 1990;**7**:842–7.
33. Proksch E, Brandner JM, Jensen JM. The skin: an indispensable barrier. *Exp Dermatol* 2008;**17**:1063–72.
34. *The National Institute for Occupational Safety and Health, Skin exposures and effects*. 2012. http://www.cdc.gov/niosh/topics/skin/.
35. Landriscina A, Rosen J, Friedman J. Nanotechnology, inflammation and the skin barrier: innovative approaches for skin health and Cosmesis. *Cosmetics* 2015:177–86. http://dx.doi.org/10.3390/cosmetics2020177.
36. Winsor T, Burch GE. Differential roles of layers of human epigastric skin on diffusion rate of water. *Arch Intern Med* 1944;**74**:428–36.
37. Fluhr JW, Feingold KR, Elias PM. Transepidermal water loss reflects permeability barrier status: validation in human and rodent in vivo and ex vivo models. *Exp Dermatol* 2006;**15**:483–92. http://dx.doi.org/10.1111/j.1600-0625.2006.00437.x.
38. Blank IH. Further observations on factors which influence the water content of the stratum corneum. *J Invest Dermatol* 1953;**21**:259–71. http://dx.doi.org/10.1038/Jid.1953.100.
39. Winckle G, Anissimov YG, Cross SE, Wise G, Roberts MS. An integrated pharmacokinetic and imaging evaluation of vehicle effects on solute human epidermal flux and, retention characteristics. *Pharm Res* 2008;**25**:158–66. http://dx.doi.org/10.1007/s11095-007-9416-z.
40. Barry B. In: *Topical drug bioavailability, bioequivalence, and penetration*. Springer; 1993. p. 261–76.
41. Grice JE, et al. Relative uptake of minoxidil into appendages and stratum corneum and permeation through human skin in vitro. *J Pharm Sci* 2010;**99**:712–8. http://dx.doi.org/10.1002/jps.21856.
42. Baroli B. Penetration of nanoparticles and nanomaterials in the skin: fiction or reality? *J Pharm Sci* 2010;**99**:21–50. http://dx.doi.org/10.1002/jps.21817.
43. Kumar KS, et al. A new three-component reaction: green synthesis of novel isoindolo[2,1-a]quinazoline derivatives as potent inhibitors of TNF-alpha. *Chem Commun* 2011;**47**:5010–2. http://dx.doi.org/10.1039/c1cc10715a.
44. Klang S, Abdulrazik M, Benita S. Influence of emulsion droplet surface charge on indomethacin ocular tissue distribution. *Pharm Dev Technol* 2000;**5**:521–32. http://dx.doi.org/10.1081/PDT-100102035.
45. Kitagawa S, Kasamaki M. Enhancement effects of double-chained cationic surfactants of n-dimethyldialkylammoniums on permeability of salicylate through guinea pig dorsal skin. *Chem Pharm Bull* 2002;**50**:1370–2. http://dx.doi.org/10.1248/Cpb.50.1370.
46. Javadzadeh Y, Shokri J, Hallaj-Nezhadi S, Hamishehkar H, Nokhodchi A. Enhancement of percutaneous absorption of finasteride by cosolvents, cosurfactant and surfactants. *Pharm Dev Technol* 2010;**15**:619–25.
47. Benson HAE. In: *Topical and transdermal drug delivery*. John Wiley & Sons, Inc.; 2012. p. 1–22.
48. Lohani A, Verma A, Joshi H, Yadav N, Karki N. Nanotechnology-based cosmeceuticals. *ISRN Dermatol* 2014;**2014**:843687. http://dx.doi.org/10.1155/2014/843687.
49. Prow TW, et al. Nanoparticles and microparticles for skin drug delivery. *Adv Drug Deliv Rev* 2011;**63**:470–91. http://dx.doi.org/10.1016/j.addr.2011.01.012. S0169-409X(11)00016-0 [pii].
50. El Maghraby GM, Williams AC, Barry BW. Can drug-bearing liposomes penetrate intact skin? *J Pharm Pharmacol* 2006;**58**:415–29. http://dx.doi.org/10.1211/jpp.58.4.0001.
51. Choi MJ, Maibach HI. Liposomes and niosomes as topical drug delivery systems. *Skin Pharmacol Physiol* 2005;**18**:209–19. http://dx.doi.org/10.1159/000086666.
52. Godin B, Touitou E. Ethosomes: new prospects in transdermal delivery. *Crit Rev Ther Drug Carrier Syst* 2003;**20**:63–102.
53. Benson HA. Transfersomes for transdermal drug delivery. *Expert Opin Drug Deliv* 2006;**3**:727–37. http://dx.doi.org/10.1517/17425247.3.6.727.
54. Geusens B, et al. Flexible nanosomes (SECosomes) enable efficient siRNA delivery in cultured primary skin cells and in the viable epidermis of ex vivo human skin. *Adv Funct Mater* 2010;**20**:4077–90. http://dx.doi.org/10.1002/adfm.201000484.
55. Hansen S, et al. In-silico model of skin penetration based on experimentally determined input parameters. Part I: Experimental determination of partition and diffusion coefficients. *Eur J Pharm Biopharm* 2008;**68**:352–67. http://dx.doi.org/10.1016/j.ejpb.2007.05.012.

56. Albery WJ, Hadgraft J. Percutaneous absorption: in vivo experiments. *J Pharm Pharmacol* 1979;**31**:140–7.
57. Benson HA. Transdermal drug delivery: penetration enhancement techniques. *Curr Drug Deliv* 2005;**2**:23–33.
58. Trauer S, et al. Influence of massage and occlusion on the ex vivo skin penetration of rigid liposomes and invasomes. *Eur J Pharm Biopharm* 2014;**86**:301–6. http://dx.doi.org/10.1016/j.ejpb.2013.11.004.
59. Mohammed YH, et al. Microneedle enhanced delivery of cosmeceutically relevant peptides in human skin. *PLoS One* 2014;**9**:e101956,. http://dx.doi.org/10.1371/journal.pone.0101956.
60. Yan L, et al. Nanocomposite-strengthened dissolving microneedles for improved transdermal delivery to human skin. *Adv Healthcare Mater* 2014;**3**:555–64. http://dx.doi.org/10.1002/adhm.201300312.
61. Emami J. In vitro − in vivo correlation: from theory to applications. *J Pharm Pharm Sci* 2006;**9**:169–89.
62. Reijnders CM, et al. Development of a full-thickness human skin equivalent in vitro model derived from TERT-immortalized keratinocytes and fibroblasts. *Tissue Eng Part A* 2015;**21**:2448–59. http://dx.doi.org/10.1089/ten.TEA.2015.0139.
63. Lehman PA, Raney SG, Franz TJ. Percutaneous absorption in man: in vitro-in vivo correlation. *Skin Pharmacol Physiol* 2011;**24**:224–30. http://dx.doi.org/10.1159/000324884.
64. Herkenne C, Naik A, Kalia YN, Hadgraft J, Guy RH. Pig ear skin ex vivo as a model for in vivo dermatopharmacokinetic studies in man. *Pharm Res* 2006;**23**:1850–6. http://dx.doi.org/10.1007/s11095-006-9011-8.
65. Wagner H, Kostka KH, Lehr CM, Schaefer UF. Human skin penetration of flufenamic acid: in vivo/in vitro correlation (deeper skin layers) for skin samples from the same subject. *J Invest Dermatol* 2002;**118**:540–4. http://dx.doi.org/10.1046/j.0022-202x.2001.01688.x.
66. Mohammed D, Matts PJ, Hadgraft J, Lane ME. In vitro-in vivo correlation in skin permeation. *Pharm Res* 2014;**31**:394–400. http://dx.doi.org/10.1007/s11095-013-1169-2.
67. Collier SW, Storm JE, Bronaugh RL. Reduction of azo dyes during in vitro percutaneous absorption. *Toxicol Appl Pharmacol* 1993;**118**:73–9. http://dx.doi.org/10.1006/taap.1993.1011.
68. Ng S-F, Rouse JJ, Sanderson FD, Meidan V, Eccleston GM. Validation of a static Franz diffusion cell system for in vitro permeation studies. *AAPS PharmSciTech* 2010;**11**:1432–41. http://dx.doi.org/10.1208/s12249-010-9522-9.
69. Friend DR. In vitro skin permeation techniques. *J Controll Release* 1992;**18**:235–48. http://dx.doi.org/10.1016/0168-3659(92)90169-R.
70. Wester RC, Maibach HI. Animal models for percutaneous absorption. *Models Dermatol* 1985;**2**:159–69.
71. Hawkins GS, Reifenrath WG. Influence of skin source, penetration cell fluid, and partition coefficient on in vitro skin penetration. *J Pharm Sci* 1986;**75**:378–81.
72. Barry BW. *Dermatological formulations: percutaneous absorption*. Taylor & Francis; 1983.
73. Haigh JM, Smith EW. The selection and use of natural and synthetic membranes for in-vitro diffusion experiments. *Eur J Pharm Sci* 1994;**2**:311–30. http://dx.doi.org/10.1016/0928-0987(94)90032-9.
74. Sinko B, et al. Skin-PAMPA: a new method for fast prediction of skin penetration. *Eur J Pharm Sci* 2012;**45**:698–707. http://dx.doi.org/10.1016/j.ejps.2012.01.011.
75. Hirvonen J, Rytting JH, Paronen P, Urtti A. Dodecyl N,N-dimethylamino acetate and azone enhance drug penetration across human, snake, and rabbit skin. *Pharm Res* 1991;**8**:933–7. http://dx.doi.org/10.1023/A:1015824100788.
76. Maibach HI. Online service. In: Shah VP, Maibach HI, John Jenner, editors. *Topical drug bioavailability, bioequivalence, and penetration*, **XIII**. SpringerLink; 2014. 402 p. 464 illus., 416 illus. in color.
77. Rochefort A, Druot P, Leduc M, Vassalet R, Agache P. A new technique for the evaluation of cosmetics effect on mechanical properties of stratum corneum and epidermis in vitro. *Int J Cosmet Sci* 1986;**8**:27–36. http://dx.doi.org/10.1111/j.1467-2494.1986.tb00427.x.
78. Cross SE, Roberts MS. Use of in vitro human skin membranes to model and predict the effect of changing blood flow on the flux and retention of topically applied solutes. *J Pharm Sci* 2008;**97**:3442–50. http://dx.doi.org/10.1002/jps.21253.
79. Cilurzo F, Minghetti P, Sinico C. Newborn pig skin as model membrane in in vitro drug permeation studies: a technical note. *AAPS PharmSciTech* 2007;**8**:E94. http://dx.doi.org/10.1208/pt0804094.
80. Jacobi U, et al. Porcine ear skin: an in vitro model for human skin. *Skin Res Technol* 2007;**13**:19–24. http://dx.doi.org/10.1111/j.1600-0846.2006.00179.x.
81. Schmook FP, Meingassner JG, Billich A. Comparison of human skin or epidermis models with human and animal skin in in-vitro percutaneous absorption. *Int J Pharm* 2001;**205**:51–6. http://dx.doi.org/10.1016/S0378-5173(00)00665-7.
82. Barbero AM, Frasch HF. Pig and guinea pig skin as surrogates for human in vitro penetration studies: a quantitative review. *Toxicol In Vitro* 2009;**23**:1–13. http://dx.doi.org/10.1016/j.tiv.2008.10.008.
83. Reifenrath WG, Chellquist EM, Shipwash EA, Jederberg WW. Evaluation of animal models for predicting skin penetration in man. *Fundam Appl Toxicol* 1984;**4**:S224–30.
84. Bogen KT, Colston Jr BW, Machicao LK. Dermal absorption of dilute aqueous chloroform, trichloroethylene, and tetrachloroethylene in hairless guinea pigs. *Fundam Appl Toxicol* 1992;**18**:30–9.
85. Rigg PC, Barry BW. Shed snake skin and hairless mouse skin as model membranes for human skin during permeation studies. *J Invest Dermatol* 1990;**94**:235–40.
86. Itoh T, Xia J, Magavi R, Nishihata T, Rytting JH. Use of shed snake skin as a model membrane for in vitro percutaneous penetration studies: comparison with human skin. *Pharm Res* 1990;**7**:1042–7.
87. Kumpugdee-Vollrath M, Subongkot T, Ngawhirunpat T. *Model membrane from shed snake skins*. 2003.
88. Rougier A, Lotte C, Maibach HI. The hairless rat: a relevant animal model to predict in vivo percutaneous absorption in humans? *J Invest Dermatol* 1987;**88**:577–81.
89. Takeuchi H, et al. Usefulness of rat skin as a substitute for human skin in the in vitro skin permeation study. *Exp Anim* 2011;**60**:373–84.
90. van Ravenzwaay B, Leibold E. A comparison between in vitro rat and human and in vivo rat skin absorption studies. *Hum Exp Toxicol* 2004;**23**:421–30.
91. Poet TS, et al. Utility of real time breath analysis and physiologically based pharmacokinetic modeling to determine the percutaneous absorption of methyl chloroform in rats and humans. *Toxicol Sci* 2000;**54**:42–51.
92. Wester RC, Maibach HI. Percutaneous absorption in the rhesus monkey compared to man. *Toxicol Appl Pharmacol* 1975;**32**:394–8.

93. Dobricic V, et al. 17beta-carboxamide steroids—in vitro prediction of human skin permeability and retention using PAMPA technique. *Eur J Pharm Sci* 2014;**52**:95—108. http://dx.doi.org/10.1016/j.ejps.2013.10.017.
94. Markovic BD, Vladimirov SM, Cudina OA, Odovic JV, Karljikovic-Rajic KDA. PAMPA assay as fast predictive model of passive human skin permeability of new synthesized corticosteroid C-21 esters. *Molecules* 2012;**17**:480—91. http://dx.doi.org/10.3390/molecules17010480.
95. Flaten GE, et al. In vitro skin models as a tool in optimization of drug formulation. *Eur J Pharm Sci* 2015;**75**:10—24. http://dx.doi.org/10.1016/j.ejps.2015.02.018.
96. Miki R, et al. Development of a membrane impregnated with a poly(dimethylsiloxane)/poly(ethylene glycol) copolymer for a high-throughput screening of the permeability of drugs, cosmetics, and other chemicals across the human skin. *Eur J Pharm Sci* 2014;**66C**:41—9. http://dx.doi.org/10.1016/j.ejps.2014.09.024.
97. Li L, Fukunaga-Kalabis M, Herlyn M. The three-dimensional human skin reconstruct model: a tool to study normal skin and melanoma progression. *J Vis Exp* 2011. http://dx.doi.org/10.3791/2937.
98. Zghoul N, Fuchs R, Lehr CM, Schaefer UF. Reconstructed skin equivalents for assessing percutaneous drug absorption from pharmaceutical formulations. *ALTEX* 2001;**18**:103—6.
99. Schäfer-Korting M, et al. The use of reconstructed human epidermis for skin absorption testing: Results of the validation study. *Altern Lab Anim* 2008;**36**:161—87.
100. Netzlaff F, Lehr CM, Wertz PW, Schaefer UF. The human epidermis models EpiSkin, SkinEthic and EpiDerm: an evaluation of morphology and their suitability for testing phototoxicity, irritancy, corrosivity, and substance transport. *Eur J Pharm Biopharm* 2005;**60**:167—78. http://dx.doi.org/10.1016/j.ejpb.2005.03.004.
101. Abou-Elwafa Abdallah M, Pawar G, Harrad S. Evaluation of 3D-human skin equivalents for assessment of human dermal absorption of some brominated flame retardants. *Environ Int* 2015;**84**:64—70. http://dx.doi.org/10.1016/j.envint.2015.07.015.
102. Dick IP, Scott RC. Pig ear skin as an in-vitro model for human skin permeability. *J Pharm Pharm* 1992;**44**:640—5. http://dx.doi.org/10.1111/j.2042-7158.1992.tb05485.x.
103. Alvarez-Roman R, Naik A, Kalia YN, Guy RH, Fessi H. Enhancement of topical delivery from biodegradable nanoparticles. *Pharm Res* 2004;**21**:1818—25.
104. Tsai TH, Jee SH, Dong CY, Lin SJ. Multiphoton microscopy in dermatological imaging. *J Dermatol Sci* 2009;**56**:1—8. http://dx.doi.org/10.1016/j.jdermsci.2009.06.008.
105. Tsai TH, et al. Visualizing laser-skin interaction in vivo by multiphoton microscopy. *J Biomed Opt* 2009;**14**:024034. http://dx.doi.org/10.1117/1.3116711.
106. Leite-Silva VR, et al. The effect of formulation on the penetration of coated and uncoated zinc oxide nanoparticles into the viable epidermis of human skin in vivo. *Eur J Pharm Biopharm* 2013;**84**:297—308. http://dx.doi.org/10.1016/j.ejpb.2013.01.020.
107. Escobar-Chavez JJ, et al. The tape-stripping technique as a method for drug quantification in skin. *J Pharm Pharm Sci* 2008;**11**:104—30.
108. Lademann J, Jacobi U, Surber C, Weigmann H, Fluhr JW. The tape stripping procedure – evaluation of some critical parameters. *Eur J Pharm Biopharm* 2009;**72**:317—23. http://dx.doi.org/10.1016/j.ejpb.2008.08.008.
109. Rogers J, Harding C, Mayo A, Banks J, Rawlings A. Stratum corneum lipids: the effect of ageing and the seasons. *Arch Dermatol Res* 1996;**288**:765—70.
110. Navidi W, Hutchinson A, N'Dri-Stempfer B, Bunge A. Determining bioequivalence of topical dermatological drug products by tape-stripping. *J Pharmacokinet Pharmacodyn* 2008;**35**:337—48. http://dx.doi.org/10.1007/s10928-008-9091-7.
111. Shashi P. Skin kinetics and dermal clearance. *Int Res J Pharm* 2012;**3**:14—21.
112. Herkenne C, Alberti I, Naik A, Kalia YN, Guy RH. In vivo methods for the assessment of topical drug bioavailability. *Pharm Res* 2008;**25**. http://dx.doi.org/10.1007/s11095-007-9429-7.
113. N'Dri-Stempfer B, Navidi WC, Guy RH, Bunge AL. Optimizing metrics for the assessment of bioequivalence between topical drug products. *Pharm Res* 2008;**25**:1621—30. http://dx.doi.org/10.1007/s11095-008-9577-4.
114. Wen P, Paturi J, Sun Y. *Impact of formula structure to skin delivery in Handbook of cosmetic science and technology.* 4th ed. 2014. p. 609—19.
115. Bashir SJ, Chew AL, Anigbogu A, Dreher F, Maibach HI. Physical and physiological effects of stratum corneum tape stripping. *Skin Res Technol* 2001;**7**:40—8.
116. Loffler H, Dreher F, Maibach H. Stratum corneum adhesive tape stripping: influence of anatomical site, application pressure, duration and removal. *Br J Dermatol* 2004;**151**:746—52.
117. Nagelreiter C, Mahrhauser D, Wiatschka K, Skipiol S, Valenta C. Importance of a suitable working protocol for tape stripping experiments on porcine ear skin: Influence of lipophilic formulations and strip adhesion impairment. *Int J Pharm* 2015;**491**:162—9. http://dx.doi.org/10.1016/j.ijpharm.2015.06.031.
118. Mohammed D, et al. Comparison of gravimetric and spectroscopic approaches to quantify stratum corneum removed by tape-stripping. *Eur J Pharm Biopharm* 2012;**82**:171—4. http://dx.doi.org/10.1016/j.ejpb.2012.05.018.
119. Duracher L, Mavon A. In vitro and in vivo dermal absorption assessment of acetyl aspartic acid: a compartmental study. *Int J Cosmet Sci* 2015;**37**:34—40. http://dx.doi.org/10.1111/ics.12255.
120. Klang V, et al. In vitro vs. in vivo tape stripping: validation of the porcine ear model and penetration assessment of novel sucrose stearate emulsions. *Eur J Pharm Biopharm* 2012;**80**:604—14. http://dx.doi.org/10.1016/j.ejpb.2011.11.009.
121. Saeheng S, Nosoongnoen W, Varothai S. In vitro – in vivo correlation study for the dermatopharmacokinetics of terbinafine hydrochloride topical cream. *Drug Dev Ind Pharm* 2013;**39**:1372—7. http://dx.doi.org/10.3109/03639045.2012.718786.
122. Mc KA, Stoughton RB. Method for comparing percutaneous absorption of steroids. *Arch Dermatol* 1962;**86**:608—10. http://dx.doi.org/10.1001/archderm.1962.01590110044005.
123. Schäfer-Korting M, Kleuser B, Ahmed M, Höltje HD, Korting HC. Glucocorticoids for human skin: new aspects of the mechanism of action. *Skin Pharmacol Physiol* 2005;**18**:103—14.
124. Haigh JM, Meyer E, Smith EW, Kanfer I. The human skin blanching assay for in vivo topical corticosteroid assessment: I. Reproducibility of the assay. *Int J Pharm* 1997;**152**:179—83. http://dx.doi.org/10.1016/S0378-5173(97)00078-1.

125. Elsner P. *Chromametry: hardware, measuring principles, and standardization of measurements. Bioengineering of the skin: cutaneous blood flow and erythema*. Boca Raton: CRC Press, Inc.; 1995. p. 247–52.
126. Zhai H, Chan HP, Farahmand S, Nilsson GE, Maibach HI. Comparison of tissue viability imaging and colorimetry: skin blanching. *Skin Res Technol* 2009;**15**:20–3. http://dx.doi.org/10.1111/j.1600-0846.2008.00346.x.
127. Azeredo FJ, Dalla Costa T, Derendorf H. Role of microdialysis in pharmacokinetics and pharmacodynamics: current status and future directions. *Clin Pharmacokinet* 2014;**53**:205–12. http://dx.doi.org/10.1007/s40262-014-0131-8.
128. Chen R-X, Wang L, Wang J, Xu F-Q. Determination of whiteners in cosmetics by microdialysis and high-performance liquid chromatography. *Anal Lett* 2015;**48**:2159–71.
129. Ungerstedt U. Microdialysis–principles and applications for studies in animals and man. *J Intern Med* 1991;**230**:365–73.
130. Holmgaard R, Benfeldt E, Nielsen JB. Percutaneous penetration–methodological considerations. *Basic Clin Pharmacol Toxicol* 2014;**115**:101–9. http://dx.doi.org/10.1111/bcpt.12188.
131. Kreilgaard M. Assessment of cutaneous drug delivery using microdialysis. *Adv Drug Deliv Rev* 2002;**54**(Suppl. 1):S99–121.
132. Groth L, Serup J. Cutaneous microdialysis in man: effects of needle insertion trauma and anaesthesia on skin perfusion, erythema and skin thickness. *Acta Derm Venereol* 1998;**78**:5–9.
133. Adler S, et al. Alternative (non-animal) methods for cosmetics testing: current status and future prospects-2010. *Arch Toxicol* 2011;**85**:367–485. http://dx.doi.org/10.1007/s00204-011-0693-2.
134. Karadzovska D, Brooks JD, Monteiro-Riviere NA, Riviere JE. Predicting skin permeability from complex vehicles. *Adv Drug Deliv Rev* 2013; **65**:265–77.
135. Todo H, Oshizaka T, Kadhum WR, Sugibayashi K. Mathematical model to predict skin concentration after topical application of drugs. *Pharmaceutics* 2013;**5**:634–51. http://dx.doi.org/10.3390/pharmaceutics5040634.
136. Riviere JE, Brooks JD. Predicting skin permeability from complex chemical mixtures: dependency of quantitative structure permeation relationships on biology of skin model used. *Toxicol Sci* 2011;**119**:224–32. http://dx.doi.org/10.1093/toxsci/kfq317.
137. Riviere JE, Brooks JD. Predicting skin permeability from complex chemical mixtures. *Toxicol Appl Pharmacol* 2005;**208**:99–110. http://dx.doi.org/10.1016/j.taap.2005.02.016.
138. Mitragotri S, et al. Mathematical models of skin permeability: an overview. *Int J Pharm* 2011;**418**:115–29. http://dx.doi.org/10.1016/j.ijpharm.2011.02.023.
139. Geinoz S, Guy RH, Testa B, Carrupt PA. Quantitative Structure-Permeation Relationships (QSPeRs) to predict skin permeation: a critical evaluation. *Pharm Res* 2004;**21**:83–92. http://dx.doi.org/10.1023/B: PHAM.0000012155.27488.2b.

CHAPTER

# 47

# Effects of Air Pollution on Skin: Dermatologic Options

*A. Ghofranian, H.I. Maibach*

**University of California, San Francisco, CA, United States**

## 47.1 INTRODUCTION

Air pollution is a serious problem worldwide, especially in well-developed and industrialized countries. Much evidence exists on the relationship between air pollution and the development or exacerbation of cardiovascular and respiratory diseases; however, fewer studies concern the impact of air pollution and particulate matter on skin integrity. This overview highlights key evidence on the disruption of the skin barrier in association with the size and content of particulate matter and proposes potential options for skin care to minimize skin damage.

## 47.2 MATERIALS AND METHODS

A literature review was performed using ClinicalKey, Google Scholar, OvidMedline, and PubMed using combinations of the following words: air pollution, skin, stratum corneum, indoor pollution, outdoor pollution, particulate matter, sensitive skin, nitrogen dioxide, ozone, eczema, psoriasis, atopic dermatitis, acne, skin cancer, and tobacco smoke. Key findings were collected from the most recently published original articles.

## 47.3 RESULTS

### 47.3.1 Disturbed Skin Barrier

Pan et al. demonstrated that urban dusts with an average diameter of 11 μm composed of polycyclic aromatic hydrocarbons (PAHs), polychlorinated biphenyl congeners, pesticides, and dioxins significantly disturbed stratum corneum (SC) and tight junctions (TJs) by diminishing proteins essential to barrier function leading to a subsequent increase in transepidermal water loss (TEWL). Particulate matter (PM) with soluble heavy metal content had negligible effects on SC and TJs. Although other studies have associated ultrafine particles (UFPs) with being more dangerous to human health than larger particles,[6] Pan et al. attribute the more significant damage of larger particles in their study to particle content rather than size. Another significant finding was that in PM-treated skin, ascorbic acid and tretinoin absorption were significantly increased, presumably related to disrupted skin barrier. The potential danger in this is the possibility of overabsorption of substances applied via topical administration; therefore, caution should be taken in the long-term use of products containing these acids.

### 47.3.2 Development or Exacerbation of Atopic Dermatitis

Two studies found atopic dermatitis (AD) symptoms were present when concentrations of small-particle air pollutants such as $PM_{2.5}$, $PM_{10}$, $NO_2$, heavy metals, and total volatile organic compounds (TVOCs) were higher in ambient air.[24,22] Additionally, indoor air pollution was associated with AD symptom aggravation.[23] Song et al.

*Cosmetic Science and Technology: Theoretical Principles and Applications*
http://dx.doi.org/10.1016/B978-0-12-802005-0.00047-1



Copyright © 2017 Elsevier Inc. All rights reserved.

observed a cohort of children with AD and found AD symptoms positively associated with ambient UFP levels and itch symptoms positively associated with the previous days UFP levels but not with larger particles or other gaseous pollutants.[49] This suggests the ability of UFPs to penetrate skin. A study limitation was that the symptoms were documented by parents instead of by a physician. Huss-Marp et al. observed the effect of exposure to airborne volatile compounds and house dust mite (HDM) on barrier function and dermal blood flow in AD patients compared to controls. TEWL was significantly increased post exposure to volatile organic compounds (VOCs), indicating disruption to barrier function. Note that there was a 48 h delay, which can be attributed to the time it takes for significant amounts of VOCs to penetrate skin and exert an effect. In patients with AD, dermal blood flow was increased after combined exposure to VOCs and HDM. Also, AD patients showed a significant increase in skin reaction to an atopy patch test with HDM after exposure to VOCs, compared to controls.[20] This suggests that exposure to air pollution impairs barrier function and may allow aeroallergens to penetrate the skin more readily, making the skin more vulnerable to the observed AD skin reactions. $NO_2$ and formaldehyde, common indoor air pollutants, were used to evaluate the effects of polluted air on barrier function by analyzing TEWL and skin roughness. Eberlein-Konig et al. found that all subjects had increased TEWL after exposure to $NO_2$ but only AD patients had significantly increased TEWL after formaldehyde exposure. Control subjects had significantly increased roughness after $NO_2$ exposure.[12] Additionally, traffic-related air pollution and environmental tobacco smoke have been significantly associated with AD prevalence.[30,47]

### 47.3.3 Development of Psoriasis

Ozden et al. evaluated risk factors associated with development of pediatric psoriasis and observed more frequent reports of tobacco smoke exposure in the year preceding diagnosis when compared to controls.[41]

### 47.3.4 Oxidative Stress

Skin is a major target organ of environmental oxidative stress because it is constantly in contact with substances that interact with the barrier to form reactive oxygen species (ROS). Lefebvre et al. evaluated the quality of skin in people in two cities of Mexico, Mexico City, considered highly polluted, and Cuernavaca, considered free of pollution. Mexico City subjects had dryer skin, significantly lower Vitamin E and squalene concentrations, and higher lactic acid and oxidized protein levels, while Cuernavaca subjects had higher chymotrypsin-like activity and interleukin-1α levels. Additionally, Mexico City subjects had higher levels of dermatographism and urticarial antecedents.[31] The higher levels of interleukin-1α in the Cuernavaca population deserves further investigation because other studies suggest exposure to air pollutants increases these levels.[7,34,53] Thiele et al. observed impact of ozone exposure on Vitamin E and lipid peroxidation levels. In a dose-dependent matter, ozone reduced α- and γ-tocopherol levels (parameters of Vitamin E concentration) and increased malondialdehyde (MDA, parameter of lipid peroxidation). Interestingly, repeated exposure to the lowest level of ozone exerted cumulative stress effects as shown by α- and γ-tocopherol depletion and MDA increase.[50] Although this experiment was performed in murine SC, the latter findings are important because they more accurately reflect human exposure to pollutants in day-to-day life. Vitamin E depletion and MDA increase are evidence of oxidative stress. Another study also demonstrated oxidative damage in skin tissue models by exposing it to concentrated air particles (CAPs). Increased levels of $F_2$-α isoprostanes (marker of oxidative damage), increased phospholipid oxidation, and increased intracellular ROS production were observed.[35]

### 47.3.5 Inflammation

Choi et al. observed the relationship between Asian dust storm particles (ADSPs), including pollutants from urban and industrial emissions, and inflammation. There was a significant increase in gene transcription of cytokines IL-6, IL-8, and GM-CSF, which are involved in the proinflammatory response.[7] Diesel exhaust particles (DEPs) also increased in IL-8 levels. Related to this, increased activation of transcription factor NF-κB, a moderator of a variety of proinflammatory cytokines including IL-8, was observed after exposure to nontoxic concentrations of DEP, representing effects of day-to-day exposure.[34] Additionally, tobacco smoke increased expression of inflammatory cytokines IL-1α, IL-8, as well as Egr-1, a regulator of the inflammatory response.[21,52,56]

### 47.3.6 Skin Aging

Huls et al. found in two cohorts, Chinese women and German women, that they had facial lentigines partially associated with exposure to $NO_2$, a toxic gas found in traffic-related air pollution. This is significant because these

populations are largely ethnically diverse but presented similarly.[19] In addition, Vierkotter et al. observed that higher levels of soot, traffic-related air pollution, as well as PM were associated with more pigment spots on the face and more pronounced nasolabial folds.[54] Note that air pollution does not solely originate from outdoor sources but can also manifest indoors from particulates associated with cooking. In two Chinese populations, Li et al. observed that cooking with solid fuels was highly associated with a more-wrinkled appearance on the face and dorsal hands, particularly.[33] A study limitation, as reported by the authors, was the use of questionnaire-based data to assess indoor air pollution exposure. A more reliable method of indoor air pollution measurement and air composition analysis would be preferred. Composition of solid fuels for cooking or heating include PM, PAH, CO, nitrogen oxides, e.g. $NO_2$, and sulfur dioxide.[15] Additionally, in vitro and in vivo studies have observed a decrease in new collagen synthesis, increase in tropoelastin, and matrix metalloproteinases (MMPs) after exposure to tobacco smoke, suggesting its role in premature skin aging.[57,29]

## 47.4 DISCUSSION

Air pollution comes from many sources, including traffic emissions, factories, and human activities, and contains compounds including PM, ozone, $NO_2$, and volatile organic compounds, and each component has its own proposed mechanism of interaction with the skin barrier.

PM, ranging in size from $PM_{2.5}$ to $PM_{10}$, is composed of metals, minerals, and organic and biological compounds surrounding a carbon core. PMs come from crustal material, motor vehicle exhaust, as well as factory emissions.[28] They generate ROS in the lungs,[11] however, it is not known if they have the same effect upon interacting with skin. PMs, however, contain PAH, a potent ligand for the aryl hydrocarbon receptor (AhR). Activation of AhR is involved in gene expression in keratinocytes and melanocytes that contribute to wrinkle formation and pigment spot formation, known markers of skin aging. It has been suggested that activation of AhR can lead to the production of ROS.[27a] Some PMs carry heavy metals such as Cu, Mn, Ni, Pb, and Ti,[55] which can also cause the production of ROS.[35] UFPs are more concerning, however, because of their potential to penetrate skin and directly incorporate into the vascular system. Gulson et al. applied sunscreen to human volunteers twice daily for five days and found small amounts of Zn tracer in the subjects' blood, suggesting that long-term retention of UFPs on the skin can be absorbed and enter blood circulation.[18a] These substances presumably penetrate SC by the transepidermal route or via pore transport. The transepidermal route includes the transcellular or intercellular route and via pore transport includes the transglandular or transfollicular route.[5,51a]

Ozone can normally be found in the troposphere, but it is also produced at ground level from the combustion of fossil fuels, vehicle emissions, and when ozone precursors react with sunlight (UVR), $NO_x$, and VOCs. Ozone is a strong oxidant so it reacts quickly with biological targets, depleting antioxidants and damaging biomolecules.[42,51] When ozone interacts with murine skin, Vitamin E levels are depleted and MDA levels are increased, as shown by Thiele et al.[50] Possible mechanisms of Vitamin E's action against ozone include reacting with it directly to destroy it or scavenging for PUFA-derived radicals (polyunsaturated fatty acids that form free radicals with ozone).[50] Depletion in Vitamin E levels indicates an effort by the body to buffer the creation of ROS.

$NO_2$, an air pollutant that mainly comes from vehicle emissions and combustion of fossil fuels, causes generation of free radicals that can oxidize amino acids in tissue proteins or initiate lipid peroxidation of polyunsaturated fatty acids in pulmonary cell membranes.[12] This mechanism of action may also take place when $NO_2$ interacts with SC.

Volatile organic compounds come from motor vehicles, gasoline evaporation, industrial plants, but also household items such as wood-based products, paints, and floor finishes.[9,40] Ushio et al. showed keratinocytes exposed to VOCs increased cytokine levels, which could lead to an inflammatory response and exacerbate inflammatory conditions such as atopic dermatitis, psoriasis, and acne.[53]

Tobacco and secondary tobacco smoke are associated with cardiovascular and respiratory disease and cancer. Tobacco smoke is composed of thousands of different compounds including carcinogens such as benzo[a]pyrene and 4-(methylnitrosoamino)-1-(3-pyridyl)-1-butanone as well as oxygen radical-forming substances such as catechol and hydroquinone.[16] Upon interaction with skin, chemicals in tobacco smoke collectively induce an inflammatory response, oxidative stress, TEWL, and tumor cell generation. This suggests their role in the development of inflammatory diseases such as atopic dermatitis, psoriasis, and acne, as well as basal and squamous cell carcinomas.[32]

### 47.4.1 Relationship to Sensitive Skin

Sensitive skin is a condition that involves hyperreactivity of the skin to stimuli such as environmental factors and cosmetic products that are otherwise well tolerated.[1] Sensitive skin can present with visible irritation such as

erythema and scaling or subjective responses such as itching, stinging, and burning.[26] The prevalence of sensitive skin has been an important concern, particularly in industrialized countries. It has been reported that 44.6% of a representative sample of the American population consider themselves to have sensitive skin.[37] In Europe, 38.4% of subjects reported sensitive skin, as well as 39.46% of students in Beijing colleges and universities.[36,39] Because certain air pollutants disrupt SC, deregulate barrier function, increase TEWL, and are associated with skin pigmentation, it is plausible that air pollution is an indirect cause of sensitive skin.[13]

## 47.4.2 Relationship to Inflammatory Diseases: Atopic Dermatitis, Psoriasis, and Acne

### *47.4.2.1 Atopic Dermatitis*

Atopic dermatitis is a chronic inflammatory skin condition caused by environmental as well as genetic factors and involves a disruption of the skin barrier and the immune system.[38,2] According to the international study of asthma and allergies in childhood, AD prevalence continues to increase in children in developed and developing countries, and air pollutants are significantly associated with AD development as well as exacerbation of symptoms.[54a] More specifically, VOC, airborne nitrogen, formaldehyde, particulate matter, and UFPs significantly worsen AD symptoms in AD patients. These findings suggest that while healthy skin can also be affected by air pollution, diseased skin is generally more vulnerable to further damage.

### *47.4.2.2 Psoriasis*

Psoriasis is a chronic inflammatory skin disease affecting 2% of people in Europe and North America.[8] The most common form is chronic plaque psoriasis, accounting for 90% of cases and presenting with monomorphic lesions that are erythematous and scaly.[3] In psoriatic skin, Th17 cells and IL-17 play a predominant role in pathogenesis.[25] PM increases Th17 differentiation and, as mentioned previously, an inflammatory response. Therefore, air pollutants that enhance the differentiation of Th17 cells and production of proinflammatory cytokines such as particulate matter, tobacco smoke, diesel exhaust particles, and urban and industrial emissions may play a role in the exacerbation of psoriasis.

### *47.4.2.3 Acne*

Acne vulgaris, another chronic inflammatory disorder involving sebaceous glands, ducts, and hair follicles, is caused by a combination of genetic, environmental, and hormonal factors. Acne affects mostly children and adolescents, and these patients will typically present with comedones, papules, pustules, and cysts.[17] In accordance with this inflammatory disorder, cytokines play a role in lesion formation and patients have increased interleukin levels.[17] Because air pollutants and tobacco smoke induce an inflammatory response upon skin interaction, this suggests the role of air pollutants in acne vulgaris exacerbation.

## 47.4.3 Relationship to Skin Cancer

Melanoma and nonmelanoma (basal and squamous cell carcinoma) skin cancers are the most common types of cancer in white populations, and the incidence is increasing rapidly.[10] Recent studies have shown a relationship between air pollutants and incidence. Environmental exposure to tobacco smoke and high-PAH levels are associated with increased incidence and production of basal and squamous cell carcinomas.[45,4,48,46] Tobacco smoke causes the generation of ROS and proinflammatory cytokines, which may lead to DNA damage, DNA repair system damage, as well as an upregulation of cell proliferation. Additionally, PAH is a potent ligand for AhR, a transcription factor. Excessive PAH binding to AhR can promote skin cancer development.

## 47.4.4 Proposals for Skin Care

Among the many air pollutants, PAHs, heavy metals, CAPS, ozone, and tobacco smoke produce ROS upon interaction with skin. Topical application of antioxidants can help buffer the generation of ROS. The antioxidant network maintains an equilibrium between pro- and antioxidants by intervening at different stages of the oxidation process via free radical and lipid peroxyl radical binding, metal ion binding, and removing damaged biomolecules.[50] Ozone specifically depletes Vitamin E levels and increases MDA levels. Therefore, topical tocopherol application can slow or prevent this process via its antiinflammatory action.[14] Topical application of tocopherol has also been shown to reduce incidence of skin tumors caused by UV radiation,[14] suggesting it could also be used to combat the

carcinogenic effects of tobacco smoke and PAH. Topical application of a single antioxidant such as Vitamin E or C as well as combinations of antioxidants show photoprotective effects, suggesting that they may play a similar role is protection against air pollutants.[51] Interestingly, melatonin has strong antioxidant properties and strongly suppresses ROS as well as UV-induced erythema.[51] Again, this suggests melatonin can be used in the prevention of oxidative damage caused by air pollution. The two main routes of tocopherol uptake are via direct percutaneous uptake and hair follicles to reach the dermis.[14]

PM can carry PAH, a potent ligand for the AhR receptor involved in pigment spot formation, wrinkle formation, and the generation of ROS. Therefore, topical application of an AhR antagonist can inhibit these processes. Multiple air pollutants have also be shown to weaken the skin barrier, therefore the application of topical agents to enhance the skin barrier could protect the skin from this kind of damage. Industrial air pollutants, traffic-related air pollutants, and tobacco smoke are associated with an inflammatory response, so antiinflammatories may protect against these substances. Finally, topical application for retinoids was proven to present and repair clinical features of photoaging, suggesting it may produce a similar effect on skin exposed to air pollution.[18]

## 47.5 CONCLUSIONS AND FUTURE CONSIDERATIONS

In conclusion, air pollutants such as tobacco smoke, CAPS, VOCs, ozone, and $NO_2$ are significantly associated with an inflammatory response, weakened barrier function, and oxidative stress, which can lead to the development or exacerbation of inflammatory skin diseases, skin aging, as well as skin cancer. Our challenge rests in decreasing the effects of air pollution on skin and identifying evidence-based interventions that will decrease damage when removal is not practical or delayed. Further studies should be conducted on the mechanism of action of these pollutants as well as the possible preventive effects of topical antiinflammatories, receptor antagonists, and barrier enhancers.

**Original Articles and Key Findings**

| Title | Reference Number | Key Findings | Notes |
|---|---|---|---|
| Impact of urban particulate pollution on skin barrier function and subsequent drug absorption.[43] | PMID: 25680853 | 1649b tx:<br>• Diminished cytokeratin, filaggrin, E-cadherin<br>• Increased TEWL<br>• More skin furrows<br>• Upregulation of TIM, annexin A2, MDH<br>• Increased skin absorption of ascorbic acid and tretinoin<br><br>1649a tx:<br>• Negligible role in damaging SC and TJ<br>• Composition but not size was primary factor governing PM-induced skin toxicity | • Performed on pig<br>• PM concentration may not reflect day-to-day exposure |
| Influence of short-term exposure to airborne Der p 1 and volatile organics on barrier function and dermal blood flow in AD and healthy individuals.[20] | PMID: 16499645 | • Short-term exposure to mixture of VOCs lead to significantly increased TEWL<br>• AD and healthy individuals reacted similarly with impairment of skin barrier toward exposure with VOCs<br>• Increased skin blood flow after combined exposure to VOCs and Der p 1 in AD<br>• TEWL (all subjects) and skin blood flow (AE patients) significantly increased 48 h after exposure<br>• After VOC exposure, applied APT with HDM significantly enhanced in AE patients compared with control (filtered air alone) | • Performed on human |

**Original Articles and Key Findings**

| Title | Reference Number | Key Findings | Notes |
|---|---|---|---|
| Ozone exposure depletes vitamin E and induces lipid peroxidation in murine stratum corneum.[50] | PMID: 9129228 | • $O_3$ depletes vitamin E (significantly decreased levels of alpha and gamma tocopherol) in dose-dependent fashion and induced lipid peroxidation (significantly increased MDA concentrations) in SC<br>• Repeated exposures to lowest tested $O_3$ level (1 ppm) exerts cumulative oxidative stress effects (significant vitamin E depletion and MDA increase)<br>• α-Tocopherol more readily depleted than γ-tocopherol | • Performed on hairless mice |
| Epidemiological evidence that indoor air pollution from cooking with solid fuels accelerates skin aging in Chinese women.[33] | PMID: 26055797 | • Cooking with solid fuels significantly associated with a 5–8% more severe wrinkle appearance on face and a 74% increased risk of fine wrinkles on dorsal hands in both studies combined | • Cross-sectional study<br>• Composition of indoor air pollution may vary geographically<br>• Used questionnaire-based data |
| Influence of airborne $NO_2$ or FA on skin function and cellular activation in AD and control subjects.[12] | PMID: 9449520 | • AD and control subjects showed significantly increased TEWL after $NO_2$ exposure<br>• AD patients showed significantly increased TEWL after FA exposure<br>• Control subjects showed significantly increased roughness after $NO_2$ exposure | • Performed on human |
| Evaluation of impact of urban pollution skin quality: multicenter study in Mexico.[31] | PMID: 25655908 | • Skin moisture significantly higher in Cuernavaca and indicating a dryer skin in Mexico City<br>• Significantly lower Vitamin E and squalene concentrations and significantly higher lactic acid concentrations in Mexico City<br>• Significantly higher chymotrypsin-like activity in Cuernavaca<br>• Higher oxidized protein levels in Mexico City<br>• Significantly higher IL-1α levels in Cuernavaca<br>• More dermographism and urticarial antecedents in Mexico City | • Clinical evaluation by dermatologist<br>• Multicenter clinical study |
| Acute health effects of urban fine and ultrafine particles (UFP) on AD children.[49] | PMID: 21367405 | • Positive association between ambient UFPs and symptom exacerbation in AD children<br>• Itch symptoms positively affected by previous day's UFPs<br>• Significant effect of temperature on AD symptoms | • Don't show any temperature data<br>• Subjective measurements<br>• Exposure data from fixed sites rather than personal monitoring |
| TRAP contributes to facial lentigines development: epidemiological evidence from Caucasians and Asians.[19] | PMID: 26868871 | • Exposure to $NO_2$ significantly associated with more lentigines on the cheeks in both cohorts | • Lentigines evaluated by skilled personnel<br>• Analysis of SALIA population and Chinese Taizhou cohort |
| Skin damage mechanisms related to airborne particulate matter exposure.[35] | PMID: 26507108 | • CAPS exposure significantly increased LDH release, increased $F_2$-α isoprostane levels (oxidative damage), increased phospholipid oxidation, increased intracellular ROS production, increased IL-1α levels, presented TUNEL positive nuclei (DNA fragmentation), PM present in upper and deeper cell layers | • Performed on RHE tissue and immortalized human keratinocyte HaCaT cell line |

**Original Articles and Key Findings**

| Title | Reference Number | Key Findings | Notes |
|---|---|---|---|
| AD symptoms influenced by outdoor air pollution.[24] | PMID: 23763977 | • Spring: AD symptoms presented when temperature was lower and styrene was higher<br>• Summer: AD symptoms presented when $NO_2$ and toluene were higher<br>• Autumn: AD symptoms presented when temperature and TVOC were higher<br>• Winter: AD symptoms presented when $PM_{2.5}$ and TVOC were higher<br>• Throughout study: AD symptoms presented when outdoor $PM_{10}$, $PM_{2.5}$, toluene and TVOC were higher | • Subjective measurements<br>• Exposure data from fixed sites rather than personal monitoring<br>• Small cohort |
| Airborne particle exposure and extrinsic skin aging.[54] | PMID: 20664556 | • Significant association between TRAP and pigment spots, nasolabial fold<br>• Increase in soot, TRAP, and $PM_{10}$ associated with more pronounced nasolabial folds | • SALIA study cohort |
| Environmental tobacco smoke and AD symptom risk among school children in South Africa: a cross-sectional study.[47] | PMID: 26310401 | • Environmental exposure to tobacco smoke at school and home significantly associated with ever having AD and AD symptoms | • Questionnaire-based data could be subjective |
| Traffic-related air pollution, climate, and prevalence of eczema in Taiwanese school children.[30] | PMID: 18449213 | • TRAP's $NO_x$ and CO associated with AD | • Exposure data from fixed sites rather than personal monitoring<br>• Parental reports of children |
| AD, respiratory allergies, and TRAP in birth cohorts from small-town areas.[27] | PMID: 19713084 | • AD prevalence at age 6 significantly higher in children residing in areas with higher TRAP | • Questionnaire based data<br>• Parental reports of children |
| Association between small particle air pollution, climate, and childhood AD prevalence and severity: a US population-based study.[22] | PMID: 26842875 | • AD associated with higher mean annual $NO_2$, $SO_2$, $SO_3$, As, Ni, Pb, V, Zn<br>• Moderate-severe AD associated with higher mean annual $NO_3$, OC, $PM_{2.5}$, Cu, Pb, Zn | |
| Environmental risk factors in pediatric psoriasis: a multicenter case control study.[41] | PMID: 21615473 | • Exposure to tobacco smoke associated with development of pediatric psoriasis | • Etrospective data collection<br>• Questionnaire based data |
| Indoor air pollution aggravates AD symptoms in children.[23] | PMID: 25781186 | • Indoor air pollution increased risk of aggravated AD symptoms in children<br>• Itch symptoms correlated with toluene levels | • Exposure data from fixed sites rather than personal monitoring |
| Effect of environmental pollutants on production of proinflammatory cytokines by normal human dermal keratinocytes (hKC).[53] | PMID: 10092052 | • DEP and FA associated with stimulation of IL-1β production by hKCs | • Performed on normal hKCs |
| Activation of NF-κB by DEP in mouse epidermal cells through phosphatidylinositol 3-kinase/Akt signaling pathway.[34] | PMID: 15130773 | • DEP significantly stimulated NF-κB activity | • Performed on JB6 $P^+$ mouse epidermal cell line (CI 41) |
| Asian dust storm particles (ADSP) induce broad toxicological transcriptional program in HEK.[7] | PMID: 21056094 | • ADSPs significantly increase mRNA levels of cytochrome P450 enzymes CYP1A1, CYP1A2, CYP1B1<br>• ADSPs increased transcription of IL-1β, IL-6, IL-8, GM-CSF, CASP14 | • Performed on HEK |

**Original Articles and Key Findings**

| Title | Reference Number | Key Findings | Notes |
|---|---|---|---|
| Cigarette smoke-induced IL-1α involved in pathogenesis of adult acne.[56] | PMID: 24648681 | • Smokers significantly associated with higher IL-1α and LPO in comedones | • Sampled comedone content in acne patients |
| Benzo(a)pyrene, induces oxidative stress-mediated IL-8 production in human keratinocytes via AhR signaling pathway.[52] | PMID: 21316925 | • BaP induced nuclear translocation of AhR from cytoplasm<br>• AhR activation subsequently induced CYP1A1 mRNA and protein expression<br>• BaP induced IL-8 production in dose-dependent manner<br>• BaP induced ROS production | • Performed on NHEKs |
| Upregulation of TNF-α secretion by cigarette smoke is mediated by Egr-1 in HaCaT human keratinocytes.[21] | PMID: 20653771 | • Over 20% CSE concentration significantly reduced HaCaT keratinocyte viability<br>• CSE increased Egr-1 protein expression in dose-dependent manner<br>• CSE increased ERK1/2, JNK1/2, and p38kinase phosphorylation in time-dependent manner<br>• CSE increased TNF-α secretion in dose-dependent manner | • Performed on HaCaT human keratinocyte cell line |
| Alterations of ECM induced by tobacco smoke extract (TSE).[57] | PMID: 10836612 | • TSE induces MMP-1/3 mRNA expression<br>• TSE induces MMP-1 protein<br>• TSE inhibits type I/III procollagen production<br>• TSE decreases collagen biosynthesis | • Performed on cultured skin fibroblasts from nonsmokers |
| MMP-1 and skin aging in smokers.[29] | PMID: 11289356 | • Significantly more MMP-1 mRNA in skin of smokers compared to controls | • Skin biopsy samples from human subjects |

*AD*, Atopic dermatitis; *AE*, atopic eczema; *APT*, atopy patch test; *CAPS*, concentrated ambient particles; *CSE*, cigarette smoke extract; *DEP*, diesel exhaust particles; *ECM*, extracellular matrix; *FA*, formaldehyde; *HDM*, house dust mites; *HEK*, human epidermal keratinocytes; *LDH*, lactate dehydrogenase; *LPO*, lipid peroxide; *MDA*, malondialdehyde; *MDH*, malate dehydrogenase; *NHEK*, normal human epidermal keratinocytes; *PM*, particulate matter; *RHE*, reconstructed human epidermis; *ROS*, reactive oxygen species; *SC*, stratum corneum; *TEWL*, transepidermal water loss; *TIM*, triosephosphate isomerase; *TJ*, tight junctions; *TRAP*, traffic related air pollution; *TUNEL*, terminal deoxynucleotidyl transferase-mediated deoxyuridine triphosphate nick end labeling; *TVOC*, total volatile organic compound; *tx*, treatment; *UFP*, ultrafine particles; *VOC*, volatile organic compounds.

**Proposals for Skin Care**

| Air Pollutant | Potential Treatment |
|---|---|
| PM, UFP, PAH | Topical application of skin barrier enhancer |
| PM, $NO_2$, VOC, UFP, FA, TRAP, tobacco smoke | Topical application of antiinflammatory |
| Ozone, CAPS, PAH, tobacco smoke, heavy metals | Topical application of antioxidants (Vitamins E, C and melatonin) |
| $NO_2$, soot, TRAP, solid fuels | Topical application of retinoids |

*CAPS*, Concentrated ambient particles; *FA*, formaldehyde; *PAH*, polycyclic aromatic hydrocarbons; *PM*, particulate matter; *TRAP*, traffic related air pollution; *UFP*, ultrafine particle; *VOC*, volatile organic compounds.

## References

1. Berardesca E, Farage M, Maibach H. Sensitive skin: an overview. *Int J Cosmet Sci* 2013;**35**(1):2–8.
2. Bieber T. Atopic dermatitis. *N Engl J Med* 2008;**358**(14):1383–94.
3. Boehncke W-H, Schön MP. *Psoriasis***386**. England: Elsevier B.V.; 2015. http://dx.doi.org/10.1016/S0140−6736(14)61909-7.

4. Boffetta P, Jourenkova N, Gustavsson P. Cancer risk from occupational and environmental exposure to polycyclic aromatic hydrocarbons. *Cancer Causes Control* 1997;**8**(3):444–72.
5. Bunge AL, Cleek RL. A new method for estimating dermal absorption from chemical exposure: 2. Effect of molecular weight and octanol-water partitioning. *Pharmaceutical research* 1995;**12.1**:88–95.
6. Chen R, et al. Beyond PM 2.5: the role of ultrafine particles on adverse health effects of air pollution. *Biochim Biophys Acta Gen Sub* 2016;**1860**(12).
7. Choi H, et al. Asian dust storm particles induce a broad toxicological transcriptional program in human epidermal keratinocytes. *Toxicol Lett* 2011;**200**(1):92–9.
8. Christophers E. Psoriasis – epidemiology and clinical spectrum. *Clin Exp Dermatol* 2001;**26**(4):314–20.
9. Dales R, et al. Quality of indoor residential air and health. *Can Med Assoc J* 2008;**179**(2):147–52.
10. Diepgen TL, Mahler V. The epidemiology of skin cancer. *Br J Dermatol* 2002;**146**(s61):1–6.
11. Donaldson K, et al. Role of inflammation in cardiopulmonary health effects of PM. *Toxicol Appl Pharmacol* 2005;**207**(2):483–8.
12. Eberlein-König B, et al. Influence of airborne nitrogen dioxide or formaldehyde on parameters of skin function and cellular activation in patients with atopic eczema and control subjects. *J Allergy Clin Immunol* 1998;**101**(1):141–3.
13. Farage MA, Maibach HI. Sensitive skin: closing in on a physiological cause. *Contact Dermatitis* 2010;**62**(3):137–49.
14. Fuchs J, editor. *Oxidative stress in dermatology,* vol. 8. Marcel Dekker; 1993.
15. Ge S, et al. Emissions of air pollutants from household stoves: honeycomb coal versus coal cake. *Environ Sci Technol* 2004;**38**(17):4612–8.
16. Gopalakrishna R, Chen Z-H, Gundimeda U. Tobacco smoke tumor promoters, catechol and hydroquinone, induce oxidative regulation of protein kinase C and influence invasion and metastasis of lung carcinoma cells. *Proc Natl Acad Sci* 1994;**91**(25):12233–7.
17. Greydanus DE. *Acne*vol. 8. Hauppauge: Nova Science Publishers, Inc; 2015. *In J Child Health Human Dev.*
18. Griffiths CEM. The role of retinoids in the prevention and repair of aged and photoaged skin. *Clin Exp Dermatol* 2001;**26**(7):613–8;

18a. Gulson B, et al. Small amounts of zinc from zinc oxide particles in sunscreens applied outdoors are absorbed through human skin. *Toxicological Sciences* 2010. kfq243.

19. Hüls A, et al. Traffic-related air pollution contributes to development of facial lentigines: further epidemiological evidence from Caucasians and Asians. *J Invest Dermatol* 2016;**136**(5):1053–6.
20. Huss-Marp J, et al. Influence of short-term exposure to airborne Der p 1 and volatile organic compounds on skin barrier function and dermal blood flow in patients with atopic eczema and healthy individuals. *Clin Exp Allergy* 2006;**36**(3):338–45.
21. Jeong SH, et al. Up-regulation of TNF-alpha secretion by cigarette smoke is mediated by Egr-1 in HaCaT human keratinocytes. *Exp Dermatol* 2010;**19**(8):e206–12.
22. Kathuria P, Silverberg JI. Association between small particle air pollution, climate and childhood eczema prevalence and severity: a US population-based study. *Pediatr Allergy Immunol* 2016;**27**(5).
23. Kim E-H, et al. Indoor air pollution aggravates symptoms of atopic dermatitis in children. *PLoS One* 2015;**10**(3):e0119501.
24. Kim J, et al. Symptoms of atopic dermatitis are influenced by outdoor air pollution. *J Allergy Clin Immunol* 2013;**132**(2):495–8.
25. Kim KE, Cho D, Park HJ. Air pollution and skin diseases: adverse effects of airborne particulate matter on various skin diseases. *Life Sci* 2016; **152**:126–34.
26. Kligman AM, et al. Experimental studies on the nature of sensitive skin. *Skin Res Technol* 2006;**12**(4):217–22.
27. Krämer U, et al. Eczema, respiratory allergies, and traffic-related air pollution in birth cohorts from small-town areas. *J Dermatol Sci* 2009;**56**(2): 99–105;

27a. Krutmann Jean, et al. Pollution and skin: from epidemiological and mechanistic studies to clinical implications. *Journal of dermatological science* 2014;**76**(3):163–8.

28. Laden F, et al. Association of fine particulate matter from different sources with daily mortality in six US cities. *Environ Health Perspect* 2000; **108**(10):941.
29. Lahmann C, et al. Matrix metalloproteinase-1 and skin ageing in smokers. *Lancet* 2001;**357**(9260):935–6.
30. Lee Y-L, et al. Traffic-related air pollution, climate, and prevalence of eczema in Taiwanese school children. *J Invest Dermatol* 2008;**128**(10): 2412–20.
31. Lefebvre M-A, et al. Evaluation of the impact of urban pollution on the quality of skin: a multicentre study in Mexico. *Int J Cosmet Sci* 2015; **37**(3):329–38.
32. Leow Y-H, Maibach HI. Cigarette smoking, cutaneous vasculature and tissue oxygen: an overview. *Skin Res Technol* February 1998;**4**(1):1–8.
33. Li M, et al. Epidemiological evidence that indoor air pollution from cooking with solid fuels accelerates skin aging in Chinese women. *J Dermatol Sci* 2015;**79**(2):148–54.
34. Ma C, Wang J, Luo J. Activation of nuclear factor kappa B by diesel exhaust particles in mouse epidermal cells through phosphatidylinositol 3-kinase/Akt signaling pathway. *Biochem Pharmacol* 2004;**67**(10):1975–83.
35. Magnani ND, et al. Skin damage mechanisms related to airborne particulate matter exposure. *Toxicol Sci* 2016;**149**(1):227–36.
36. Misery L, et al. Sensitive skin in Europe. *J Eur Acad Dermatol Venereol* 2009;**23**(4):376–81.
37. Misery L, et al. Sensitive skin in the American population: prevalence, clinical data, and role of the dermatologist. *Int J Dermatol* 2011;**50**(8): 961–7.
38. National Institute of Arthritis and Musculoskeletal and Skin Diseases (U.S.). *Atopic dermatitis: A type of eczema*. Bethesda, Md: National Institutes of Health, National Institute of Arthritis and Musculoskeletal and Skin Diseases; 1998.
39. Nong L, et al. Epidemiological survey on sensitive skin of college students in Beijing. In: *Proceedings of the 2nd congress of Chinese Medical Women's Association*; 2013.
40. Okada Y, et al. Environmental risk assessment and concentration trend of atmospheric volatile organic compounds in Hyogo Prefecture, Japan. *Environ Sci Pollut Res* 2012;**19**(1):201–13.
41. Özden MG, et al. Environmental risk factors in pediatric psoriasis: a multicenter case–control study. *Pediatr Dermatol* 2011;**28**(3):306–12.
42. Packer L, Sies H. *Singlet Oxygen, UV-A, and Ozone*. San Diego, Calif: Academic Press; 2000. Print.
43. Pan T-L, et al. The impact of urban particulate pollution on skin barrier function and the subsequent drug absorption. *J Dermatol Sci* 2015;**78**(1): 51–60.
44. Deleted in review.

45. Pavlou P, et al. In-vivo data on the influence of tobacco smoke and UV light on murine skin. *Toxicol Indust Health* 2009;**25**(4–5):231–9.
46. Puntoni R, et al. Occupational exposure to carbon black and risk of cancer. *Cancer Causes Control* 2004;**15**(5):511–6.
47. Shirinde J, Wichmann J, Voyi K. Environmental tobacco smoke and the risk of eczema symptoms among school children in South Africa: a cross-sectional study. *BMJ Open* 2015;**5**(8):e008234.
48. Siddens LK, et al. Polycyclic aromatic hydrocarbons as skin carcinogens: comparison of benzo[a]pyrene, dibenzo[def, p]chrysene and three environmental mixtures in the FVB/N mouse. *Toxicol Appl Pharmacol* 2012;**264**(3):377–86.
49. Song S, et al. Acute health effects of urban fine and ultrafine particles on children with atopic dermatitis. *Environ Res* 2011;**111**(3):394–9.
50. Thiele JJ, et al. Ozone-exposure depletes vitamin E and induces lipid peroxidation in murine stratum corneum. *J Invest Dermatol* 1997;**108**(5): 753–7.
51. Thiele J, Elsner P, editors. *Oxidants and antioxidants in cutaneous biology*, vol. 29. Karger Medical and Scientific Publishers; 2001;
51a. Trommer H, Neubert RHH. Overcoming the stratum corneum: the modulation of skin penetration. *Skin pharmacology and physiology* 2006;**19**(2): 106–21.
52. Tsuji G, et al. An environmental contaminant, benzo (a) pyrene, induces oxidative stress-mediated interleukin-8 production in human keratinocytes via the aryl hydrocarbon receptor signaling pathway. *J Dermatol Sci* 2011;**62**(1):42–9.
53. Ushio H, Nohara K, Fujimaki H. Effect of environmental pollutants on the production of pro-inflammatory cytokines by normal human dermal keratinocytes. *Toxicol Lett* 1999;**105**(1):17–24.
54. Vierkötter A, et al. Airborne particle exposure and extrinsic skin aging. *J Invest Dermatol* 2010;**130**(12):2719–26;
54a. Williams H, et al. Is eczema really on the increase worldwide? *Journal of Allergy and Clinical Immunology* 2008;**121.4**:947–54.
55. Wise SA, et al. Standard reference materials (SRMs) for determination of organic contaminants in environmental samples. *Anal Bioanal Chem* 2006;**386**(4):1153–90.
56. Yang YS, et al. Cigarette smoke-induced interleukin-1 alpha may be involved in the pathogenesis of adult acne. *Ann Dermatol* 2014;**26**(1):11–6.
57. Yin L, Morita A, Tsuji T. Alterations of extracellular matrix induced by tobacco smoke extract. *Arch Dermatol Res* 2000;**292**(4):188–94.

CHAPTER

# 48

# Hair Physiology (Hair Growth, Alopecia, Scalp Treatment, etc.)

*J. Kishimoto, Y. Nakazawa*

**Shiseido Global Innovation Center, Yokohama, Kanagawa, Japan**

## 48.1 INTRODUCTION

The tissue responsible for human hair growth is the hair follicle, which is a skin appendage found inside the dermis. As a unique miniature organ that self-regenerates throughout almost the entire lifetime, the hair follicle has been frequently used as a research model not only in dermatology but also in developmental biology, molecular biology, and genetics, and a significant number of research reports on the physiology of the hair follicle have been published in top journals, such as *Nature*, *Science*, and *Cell*. We will let other reviews explain the entire aspect of the hair follicle; in this chapter, we will review its role mainly from a cosmetics or cosmeceutical point of view. We will cover sufficient basic knowledge and provide a concise overview of the history of research of the structure and function of the hair follicle and factors that affect its functions. Although we will not consider serious intractable hair diseases in dermatology, the scope of this chapter is hair thinning/hair loss with aging. We will introduce methods and challenges that should be overcome, mainly in the field of cosmetics/cosmeceutics, as well as updates on the latest treatments including cosmetic surgery and cell-based therapy, and we will conclude with a vision of what awaits us in the future.

## 48.2 BASIC CONCEPTS, HAIR BIOLOGY, CAUSE OF HAIR LOSS, AND TREATMENTS

### 48.2.1 Hair Follicle Structure and Hair Cycle

Many reviews and books have summarized the structure and functions of the hair follicle. By the 1990–2000s, most of the basic structure and functions of the hair follicle and mechanisms of the hair cycle had been revealed. However, rapid progress in molecular biology and genome-associated gene manipulation and analysis have led to the revelation of even more details about factors and mechanisms that are related to hair follicle formation and dynamics of the hair cycle.

The structure of the hair follicle can be roughly classified into the hair shaft (the hair fiber) that is exposed from the stratum corneum of the skin and the "hair follicle" structures that are found inside the dermis. The hair shaft is composed of the cortex, medulla, and cuticle structure and is made of terminally differentiated cornified cells that lack nuclei but have abundant keratin fibers, which are visually perceived as "hair." However, each "hair" is actually produced from a hair follicle, which is made of dermal sheath (DS) cells, the inner and outer root sheath (IRS, ORS), hair matrix cells, and dermal papilla (DP) cells that actively grow (proliferate). Hair follicles are also classified in the epithelial or dermal component based on their embryology into ectodermal origin, including hair matrix cells, IRS, ORS, and cells of mesodermal origin known as mesenchymal cells, such as DP and DS cells. Active cell components are concentrated within the bottom of the hair follicle, called the hair bulb, which is shaped in a bulbar structure like an "onion" (Fig. 48.1). Ultimately, the cornified epithelial tissue becomes the hair shaft that functions as "hair" so the hair epithelium is important, but the inner dermal components, DP cells, are the actual "control towers" that send out commands to balance the growth (proliferation) and division (differentiation), namely the cornification degree, of hair epithelial cells. Further, the hair follicle sends interactive signaling factors between the mesenchymal cells (DP and DS

*Cosmetic Science and Technology: Theoretical Principles and Applications*
http://dx.doi.org/10.1016/B978-0-12-802005-0.00048-3



Copyright © 2017 Elsevier Inc. All rights reserved.

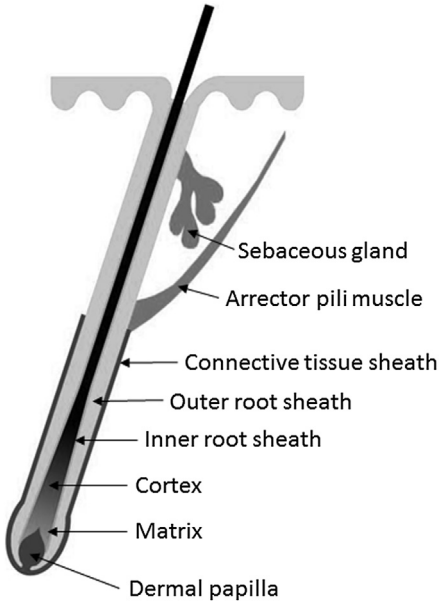



**FIGURE 48.1** Structure of the hair follicle.

cells) and the hair follicle epithelial tissue, known as the epithelial−mesenchymal interaction (EMI). Through EMI, the origin of hair follicles (hair germ) forms at embryogenesis, and postnatally they continue the hair cycle for nearly the entire lifetime. EMI is not only a concept important in hair follicle development but also a clinically important mechanism that is common to the formation of many other organs, such as the heart, liver, kidney, and lungs.

The hair cycle has three physiological and morphological stages: growing, transitional, and dormant phases, called anagen, catagen, and telogen, respectively (Fig. 48.2). With certain stimulatory factors, many of which are still unknown, they re-enter the anagen phase, initiating active EMI between hair stem cells and DP cells, resulting in the induction of matrix cell proliferation. There are approximately 100,000 hairs in the human scalp, and although there are ethnic differences, the density is approximately 100−200 hairs/cm$^2$. The human hair cycle has a long 3- to 7-year cycle with 90% in the active anagen phase. Recent gene profiling analysis has revealed that each hair cycle has a unique genetic expression pattern.[19,34] Further, in addition to the classic three phases noted earlier, an extra phase has been proposed, namely an "exogen phase," in the telogen phase where the hair shaft sheds (hair shedding).[50]

As for seasonal changes, autumn shows the largest change in hair shedding, and spring shows a similar change in shedding, although it is smaller than that for autumn.

## 48.2.2 Target Cells and Tissues in the Hair Follicle

### *48.2.2.1 Secondary Hair Germ*

Hair matrix cells are the original source of the hair shafts that become hair, and are actively growing epithelial cells found in the hair bulb at the base of each hair follicle. Since these cells start to grow after an early embryogenetic stage, they are also known as "secondary hair germs." Hair matrix cells grow and differentiate into the ORS, IRS, cortex, and medulla, which compose the multiple layers of the hair shaft and the hair follicle epithelium. As such, the hair matrix cells are the "mother" of hair and are believed to function as a switch for growth (proliferation) and differentiation, so most topical agents and cosmetic hair growth promoting reagents aim to work on the hair matrix cells in the hair follicle either directly or indirectly.

### *48.2.2.2 Hair Follicle Stem Cells*

Many of the organs and tissues in the human body, including the brain and neurons, are known to have somatic stem cells, but the hair follicle is one of the first tissues in the body where stem cells were experimentally identified. In 1990, a historical article by Cotsarelis and Lavker clearly proved that stem cells of the hair epithelium were found in vivo and in vitro in an area called the bulge, an area in the upper one-third of the hair follicle where the arrector pili muscle associates.[7] Many biomarkers of hair follicle stem cells, such as keratin15 (K15[35]) and LRG5,[33] have been

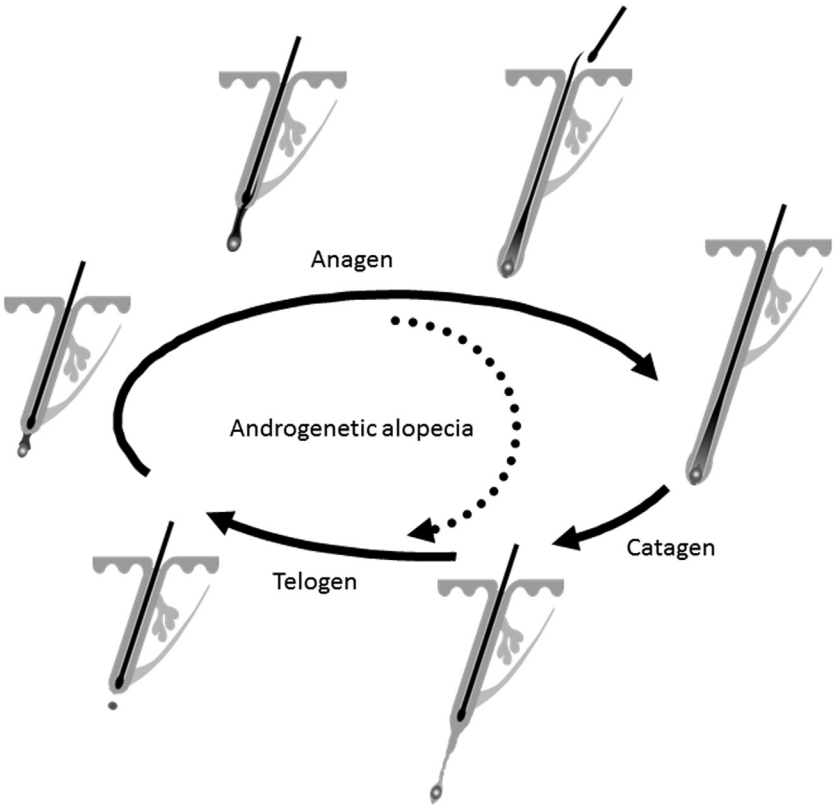



**FIGURE 48.2** Human hair follicle growth cycle.

identified, and there are studies that have isolated stem cells by using those specific markers. Although hair stem cells define their stemness as their multipotency to differentiate into different cell types, they are also defined by their quiescent (or dormant) nature. Therefore, the concept of the simple activation of stem cells by external compounds does not always cause a positive biological and physiological effect on hair growth, and this makes applications in the field of cosmetics more difficult, as well as more complicated.

#### *48.2.2.3 Dermal Papilla Cells*

Dermal Papilla (DP) cells are found at the base of each hair bulb and are some of the few mesenchymal cells described in the hair follicle. Embryologically, the DP results in dermal condensations or compact structures of mesenchymal cells of the fetal dermis and are believed to be specifically differentiated fibroblasts that show different properties compared to normal dermal fibroblasts. Many studies have shown that they interact with the epithelium and work as the "control tower" through EMI to work reciprocally on the hair matrix to secrete tropic hair growth factors, and DP cells have been repeatedly claimed as the most important cell type in the hair follicle. Stimulating DP cells to initiate the release of tropic factors is regarded an effective approach to regulate hair growth, so DP cells have been targeted in cosmeticpproaches and many hair growth−promoting reagents claim to work on DP cells as well as on matrix cells.

Some reports have implied that the number of DP cells defines the size of the hair follicle (i.e., they contribute to the hair thickness[9]). Moreover, Chi et al. provided more direct evidence where the number of DP cells, rather than the size of individual cell volumes, contributes to the size of the DP and the resultant hair follicle size.[5] Since DP cells are known to grow slowly relative to dermal fibroblasts, and they do not seem to actively divide in vivo, many hair growth−promoting reagents aim to induce DP cell growth.

#### *48.2.2.4 Dermal Sheath Cells*

Until recently, DP cells were the main focus with mesenchymal hair follicle cells and DS cells being considered as only minor components without significant functions, but in the past decade, their roles have gradually been revealed to be more important than previously thought.[38] The DS, also called the connective tissue sheath, is the outermost layer of the hair follicle and is the border between the hair follicle and the interfollicular dermis. The

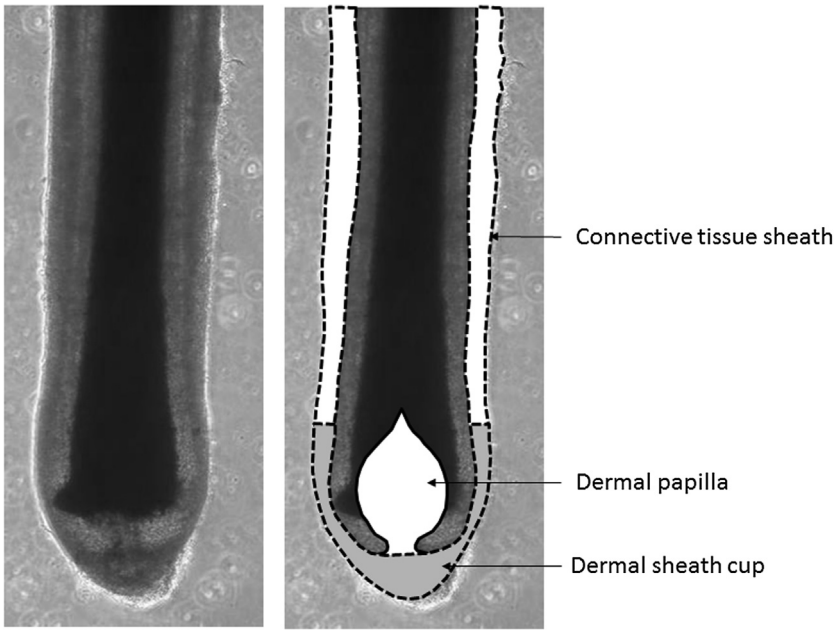



FIGURE 48.3 Dermal sheath cup.

DS is thought to be composed of fibroblast-like mesenchymal cells but includes blood vessels (pericytes) and nerves as well as collagen and elastic fibers.

DS cup (DSC) cells are DS cells located at the bottom of the hair bulb and have been found to have an especially high hair follicle induction potential (Fig. 48.3). For example, Reynolds et al. isolated DP cells and DSC cells, transplanted them individually to the upper arm, and reported that hair growth was seen only with the DSC cell transplants.[47] Additionally, recent reports have indicated that by using lineage analysis with genetically engineered mice, DSC cells are actually the precursor (or reservoir) of the DP.[46] DSC cells have gained much interest since their activation can be an alternative effective approach for hair growth from cosmetics.

#### *48.2.2.5 Microvasculature/Vascular Endothelial Cells Surrounding the Hair Follicle*

Capillaries associated with each hair follicle carry the nutrients that are required for hair follicle growth, and based on this concept, the circulatory system has always been suggested as a vital factor for hair growth. However, research on the relationship between skin/hair follicles and blood vessels was not significant until appropriate blood vessel markers were found. After 2000, many unique factors were found in the circulatory system, and this has led to many discoveries and reports on blood vessels around the hair follicle and their functions, proving the importance of the circulatory system. According to Yano et al., VEGF-1, a vascular endothelial growth factor, and its inhibitory factor, TSP-1, complementarily adjust the renewal of blood vessels around the hair follicle.[59,60] Blood vessels are one of the main targets for hair growth–promoting reagents, and indeed, there are two major such compounds, one a medical drug (minoxidil) and the other a quasi-drug (adenosine), that focus their proof of concept on the vasodilation of the microvasculature surrounding the hair follicle. However, it is important to remember that hair growth is ultimately caused by EMI between the DP and hair matrix cells through these vessel networks. Recent progress in image analysis technology has revealed that the capillary plexus is more complex than originally predicted, and it is also organized and spreads out around each hair follicle (Fig. 48.4).

### 48.2.3 Trophic Factors That Affect Hair Growth

Many protein nutrient factors and growth factors have been reported to play a role in regulating hair growth and the hair cycle. Many of those factors also play essential roles in the developmental phase of the hair follicle (folliculogenesis). Whenever possible, cosmetics should try to use chemical agents that have an effect only on the hair cycle and do not affect the initial hair development. However, in general, factors that work only on the hair cycle seem to be theoretically rare since hair development and the hair cycle share a similar mechanism of EMI. Table 48.1 shows potential factors categorized by mesenchymal and epithelial origin.[4] We consider in this section prominent growth

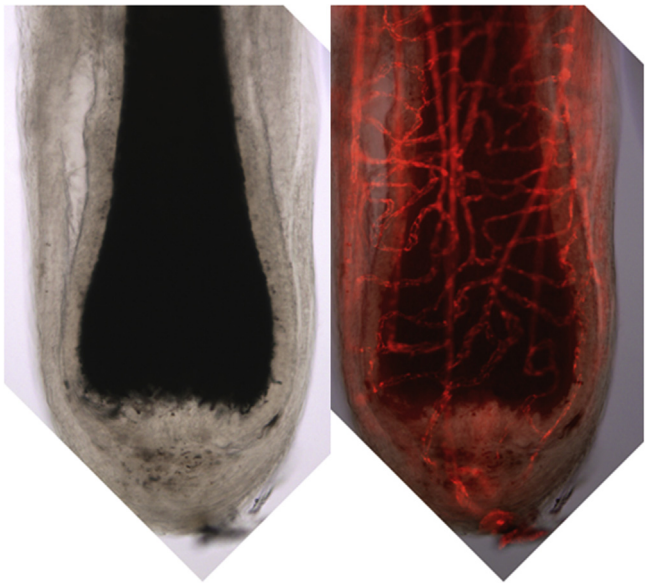


**FIGURE 48.4** Capillary plexus around the hair follicle.

**TABLE 48.1** List of Modulators Potential to Affect Hair Growth

| Modulators | Origin |
|---|---|
| BMP2/BMP4/Noggin | Epithelium/Mesenchyme |
| EGF | Epithelium |
| Edar | Epithelium |
| FGF5/FGF18 | Epithelium |
| FGF7 | Mesenchyme |
| HGF | Mesenchyme |
| IGF-I | Mesenchyme |
| Shh | Epithelium |
| Wnt3a/Wnt7/Wnt10b | Epithelium |
| Wnt5 | Mesenchyme |

and tropic factors that are expected to be used as cosmetics along with their mechanisms of action and application approaches.

#### *48.2.3.1 Fibroblast Growth Factor*

Fibroblast growth factor (FGF) is a family of growth factors that have various functions such as in cell growth and in wound healing. In the hair follicle, FGF-7 [also known as KGF (keratinocyte growth factor)] has been reported to have a hair growth mechanism where it is produced by DP cells during the anagen phase of the hair cycle and helps DP cell growth through FGF receptors.[58] Adenosine is thought to induce hair growth via this mechanism.[18] FGF-5 increases during the latter half of the hair follicle anagen phase, and mice with an FGF-5 gene mutation have long hair and are called Angola.[51] Because the hair of FGF-5 knockout mice does not have a catagen phase and the mice have long hair, FGF-5 is believed to be a factor that stimulates the transition from anagen to catagen phase.[14] A plant extract from "Burnet" has an inhibitory activity on FGF-5 and is claimed to improve hair loss by extending the anagen phase.[37] Likewise, FGF-18 was found to be a factor that maintains the telogen phase of the hair cycle in studies using knockout mice.[29] Additionally, a factor called FGF-5s is another known factor that inhibits FGF-5 activity and induces hair growth.[23] The degree of efficacy among these FGF family members (FGF-5, FGF-5s, and FGF-18) has not

yet been clarified. Because FGF is a factor that works on DP cells and other mesenchymal cells, it is expected to be useful to extend the anagen phase through its effects.

#### 48.2.3.2 Epidermal Growth Factor

Epidermal growth factor (EGF) is a factor that modulates cell growth through EGF receptors. Mice with knocked-out EGF receptor genes in their epithelial cells showed that hair follicle formation was relatively normal during development, but those hair follicles remained in anagen phase and did not transition to the catagen stage, indicating that EGF has an effect to induce the transition from the telogen phase to anagen phase and extends the anagen phase.[26] There is a substantial literature regarding EGF/EGF receptor and hair growth promotion. Most of those studies used mice, and although the compounds show an inhibitory effect on EGF receptors and have been developed as anticancer and anti-inflammatory drugs, there has been no hair-promoting reagent developed to date that affects EGF/EGF receptor activity.

#### 48.2.3.3 Insulin-Like Growth Factor

Insulin-like growth factor (IGF) is a polypeptide that has a similar structure to that of insulin and is produced in the liver and genital organs. IGF is believed to be vital for folliculogenesis during the fetal period and for maintaining the anagen phase. Among members of the IGF family, IGF-1 is produced by DP cells during the anagen phase and is widely known as a hair growth induction factor from its lengthening induction action on hair follicles in cultured organs.[57] With hair follicle tissues that are stimulated by male hormones, such as facial hair, IGF-1 shows autocrine-like effects with receptors in DP cells, and it has been reported that they induce hair matrix cell growth and inhibit the catagen phase.[21]

#### 48.2.3.4 Wnt

Wnt is a molecule that plays one of the most important roles in the development, proliferation, differentiation, and regeneration of hair follicles. Wnt is a family of glycoproteins with 350–400 amino acids, and they are secreted by cells and interact with the extracellular matrix to work on neighboring cells through their unique and highly sophisticated signaling pathways. The details of the Wnt signaling pathway have already been revealed, but, ultimately, Wnt targets an intracellular factor called beta-catenin that is normally located in the cytosol, but which then moves into the nucleus and works on the transcriptional control of its target genes. Although it may be difficult to directly use factors that modify the Wnt pathway, they have potential applications in methods such as screening procedures to search for compounds and extracts that modify the effects of Wnt on DP cells or hair epithelium cells. Wnt3a, Wnt7, and Wnt10b are subtypes that are known to form a family and have effects on the hair follicle. Wnt5 seems have inhibitory properties. Additionally, a group in China has recently reported that Wnt1 also has physiological effects similar to other inducing Wnt family members.[8]

#### 48.2.3.5 Shh

Shh is a unique factor named after "Sonic the Hedgehog," a video game character that was popular when the factor was found, but around 2000, Shh became a popular research subject along with Wnt due to its relationship with the hair cycle. Sato et al. reported that Shh works by switching the telogen phase to anagen phase.[48] Shh was reported not to be vital in the early folliculogenetic stage,[6] and as mentioned earlier, it has attracted much attention since it may be a factor that does not affect the formation of the hair follicle and only works on hair growth. However, due to safety concerns with Shh-related compound agonists (pseudo-compounds that bind to Shh receptors), it appears that development of hair growth–promoting reagents using Shh has been discontinued. Although not related to hair growth effects, there are also reports that Shh is related to the mechanism of hair flow, or direction of hair.[44,48]

#### 48.2.3.6 Bone Morphogenic Protein

Bone morphogenic protein (BMP) is known to be expressed and to function not only during bone development but also with other organs. Botchkarev et al. reported that BMP is an important factor in hair follicle development and in hair cycling.[3] BMP is thought to work with a competitive inhibition factor, Noggin, to control folliculogenesis. In cosmetic research, BMP has been studied through its relationship with a BMP-related substance called ephrin and has been reported to be related to blood vessel formation.[40] The application of BMP signal–related factors and extracts is actively being developed in cosmetic research, and it is expected that BMP will be a highly potent factor to promote hair growth. (See also "cytopurine" in Section 48.3.4.)

#### *48.2.3.7 Edar*

Edar is a factor that was recently discovered and has attracted much attention. Edar is a receptor protein molecule that mainly works specifically on the epidermis in the early stage of folliculogenesis. There are reports that Edar may have a direct causal relationship with heredity and hair loss.[10,31] Because Edar is a factor that works during early developmental stages, reagents that modulate Edar may be difficult to use as hair growth–promoting reagents.

### 48.2.4 Hair Loss Diseases and Their Causes

Serious hair thinning and hair loss are skin appendage disorders, and patients with those disorders should consult with a dermatologist. These disorders include patterned hair loss, alopecia areata, and telogen alopecia. In this chapter, we will focus on patterned hair loss, which is seen most frequently and is the disorder most often treated and can be prevented from worsening cosmeceutically as well as pharmaceutically. Patterned hair loss is thought to be caused both by inherited and by physiological backgrounds, in addition to yet undiscovered causes. Patterned hair loss gradually proceeds following a specific pattern in front and on top of the scalp. With males, hair shedding often begins after puberty due to the effect of the male hormone, androgen, and is named male pattern baldness, also known as androgenetic alopecia (AGA). The major cause of AGA in humans is thought to be as follows. The human hair follicle follows a cycle of a relatively long-lasting anagen phase and relatively short catagen and telogen phases. Each hair follicle is replaced with a revitalized newly generated hair (Fig. 48.2), but when AGA occurs, the anagen phase becomes shorter and the hair follicle does not fully grow and enter the next hair cycle, which results in increasing amounts of short and thin hairs (miniaturized hairs), and eventually the temporal or forehead scalp surface skin becomes visible.[20] Recently, the number of female patients with patterned hair loss has increased, and this disorder is sometimes called female AGA or female pattern hair loss (FPHL), but it is believed to be substantially the same disorder as male pattern hair loss.[2] FPHL proceeds independently of male hormones, and its pattern is characterized where the forehead hair line is maintained but all hair on the head becomes thinner with decreased numbers of hairs and thinning of each hair.[36,52,61]

## 48.3 HAIR GROWTH–PROMOTING COMPOUNDS

### 48.3.1 General View

The recent challenging competition for functional cosmetics has made the boundary between cosmetics and pharmaceuticals a thin line. However, even under such situations, the boundary between pharmaceuticals and cosmetics is clearer in the category of hair growth–promoting reagents compared with other fields in cosmetics, such as skin aging (antiwrinkle formation) or antipigmentation (whitening). Although the situation varies depending on each country, it seems that the development of hair growth ingredients in cosmetics has become discreet, especially in Europe and North America, since the first hair growth–promoting reagent was approved as a pharmaceutical drug by regulatory authorities (i.e., U.S. Food and Drug Administration [FDA] in the United States). Of course, many ingredients can be found online that claim to be effective, but there are only a few evidence-based hair growth–promoting ingredients that are proved to be effective based on fair scientific and clinical data. In this section, we will review hair growth–promoting ingredients that have been reported to be effective based on evidence from scientific publications with peer review.

### 48.3.2 Guidelines for the Management of Androgenetic Alopecia (2010)

Approved hair growth chemical agents include minoxidil, a topical agent that was approved in Canada in 1986, in 1988 in the United States, and in 1999 in Japan, and finasteride, an oral drug that was approved in 1997 in the United States and in 2005 in Japan. Medical products with those two reagents have been sold as hair growth–promoting products and have been widely accepted by consumers, thus widening the gap between previous hair growth–promoting cosmetic products and medical drugs. Thus, it has become difficult to objectively outline hair growth–promoting reagents other than those two chemical agents in the cosmetics field. In such situations, an important opinion and criteria were announced by the Japanese Dermatological Association in 2010, namely the Guidelines for the Management of Androgenetic Alopecia (Tsuboi 2010). In those guidelines, several products approved by the Ministry of Health, Labor, and Welfare of Japan as quasi-drugs were listed as suggested hair growth–promoting reagents along with minoxidil and finasteride. Although quasi-drugs are a standard by the

regulatory unique to Japan, clinical data that show the safety, effectiveness and effective mechanism must be substantially submitted for approval. Thus, they have a certain degree of credibility as scientifically tested evidence-based chemical agents. The guidelines do not classify whether the agents are approved as medical drugs or as quasi-drugs as a specific standard; rather, the standard is based on whether there is sufficient clinical data reported on the agents. In this section, we will briefly introduce minoxidil and finasteride and will focus on other chemical agents, mainly quasi-drugs.

## 48.3.3 Approved Drugs

### *48.3.3.1 Minoxidil*

Minoxidil was first used as an oral drug to treat high blood pressure, but it was found to have hair growth–promoting effects and was then developed as a topical hair growth–promoting reagent. Minoxidil is transformed into minoxidil sulfate in the hair follicle, and works on the sulfonylurea receptor (SUR) to release adenosine triphosphate (ATP) from the cells. The released ATP is decomposed into adenosine by ATPase and works on adenosine receptors in DP cells to make them produce VEGF (vascular endothelial cells), which is the proven hair growth mechanism of minoxidil.[32] There have been numerous clinical tests with 1–5% minoxidil on both male and female patterned hair loss patients in many countries, and its safety and efficacy have been established. However, this does not mean that minoxidil is effective with all patients, and continuous use is required to maintain significant improvement.[27]

### *48.3.3.2 Finasteride*

Finasteride is an antiandrogen agent (male hormone) that was developed as a drug for prostatitis. By inhibiting the enzyme 5α-reductase, finasteride blocks male hormone testosterone from transforming into dihydrotestosterone (DHT), a hormone that shows a much stronger activity than testosterone. 5α-Reductase is classified into type I and type II depending on the originating organ or optimal pH, but finasteride selectively blocks the type II 5α-reductase that is expressed by the prostate. Since type II 5α-reductase is expressed by DP cells in male pattern baldness,[22] finasteride was developed as an oral hair growth–promoting reagent. There have been numerous clinical tests in many countries that show the efficacy of finasteride, but like minoxidil, continuous use is required and hair loss may proceed again if intake is discontinued.[28] Since there are concerns with potential effects on fetuses, its use is limited to males. Finasteride is a prescription drug that must be used with strict management under medical consultation.

### *48.3.3.3 Dutasteride*

Like finasteride, dutasteride is a drug that was used for prostatitis but was diverted as a hair growth–promoting reagent. Unlike finasteride, which blocks only type II 5α-reductase, dutasteride shows a stronger blocking action against both type I and type II 5α-reductase and is expected to be used for more effective treatment for male pattern baldness. International joint clinical trials have shown that dutasteride is superior to a placebo and is not inferior to finasteride.[12] Dutasteride has been approved in South Korea in 2009 and in Japan in 2015. This drug was not listed in the AGA Management Guidelines (2010 Edition).

## 48.3.4 Quasi-Drugs

Quasi-drugs such as adenosine, t-flavanone, citopurine, pentadecane, and the pharmaceutical drug carpronium chloride, are categorized as Suggested Rate C1 (use may be considered) in the guidelines and provide an alternative option to FDA-approved drugs for mild hair loss symptoms with reduced undesired side effects (Fig. 48.5).

### *48.3.4.1 Carpronium Chloride*

Carpronium chloride was synthesized as a γ-amino acid derivative and was approved as a pharmaceutical ingredient in Japan in 1968. Carpronium chloride shows hair growth–promoting activity through its vasodilatory effect on local blood vessels and stimulates the transition from telogen phase to anagen phase. With both male and female subjects with patterned hair loss, carpronium chloride mixed with other herbal medicine ingredients reportedly showed some efficacy as a hair growth–promoting reagent.[13]

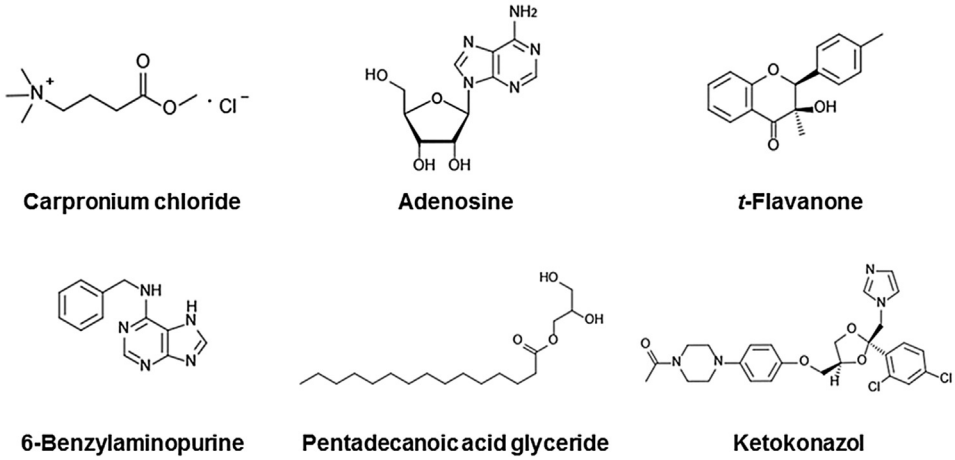



FIGURE 48.5 Chemical structures of hair growth quasi-drug.

#### 48.3.4.2 *Adenosine*

Adenosine is known as a part of ribonucleotide (RNA) or ATP and shows various physiological effects. In the hair follicle, it has been reported that adenosine works through A2b receptors on DP cells and increases cyclic adenosine monophosphate levels, resulting in the transcriptional activation on fibroblast growth factor-7 (FGF-7), which is weakened in patterned hair loss.[18] The hair growth mechanism of minoxidil has also been reported to induce the production of adenosine via SUR,[32] so adenosine potentially has a more direct effect on DP cells than minoxidil. It is believed that the FGF-7 produced by DP cells promotes hair growth by inducing cell proliferation through FGF receptors in hair matrix cells (Li 2001). In a 6-month double-blind clinical test of 102 Japanese male subjects with patterned hair loss, it was found that the adenosine-added hair growth–promoting reagent group showed a significant improvement based on global assessment by physicians compared with the control group. The improvement rate was 32.0% in the control group and 80.4% in the adenosine-treated group. Local evaluation using a phototrichogram also showed that the percentage of thick hair (with a hair radius larger than 60 μm) in the adenosine-treated group was significantly higher than that in the placebo-treated group.[56] In a double-blind clinical test of 30 female subjects with patterned hair loss, the visual improvement after 12 months was significantly higher compared with the placebo-treated group, and the hair growth rate of the anagen phase and the rate of thick hair (with a hair diameter larger than 80 μm) also increased.[45] Additionally, in a 6-month test of 40 white male subjects, the results showed a significant increase in the percentage of thick hair (with a hair diameter larger than 60 μm).[25] These results show that adenosine is effective for thickening hair regardless of ethnicity or sex and suggest that it is effective for improving patterned hair loss.

#### 48.3.4.3 *t-Flavanone*

t-Flavanone is a chemical compound that induces the growth of cultured hair epithelium cells and dermal fibroblasts. t-Flavanone is synthesized from taxifolin which is astilbin analog. Astilbin was initially identified as a derivative of the active component of *Hypericum perforatum*, which was identified in a screen of compounds that promote the proliferation of hair epithelial cells from more than 2000 products in a natural crude extract library. t-Flavanone promotes hair growth by inhibiting transforming growth factor-β (TGF-β), a signaling molecule that transits anagen hair to the catagen phase, and by inducing the growth of hair matrix cells in the hair bulb. Paired testing of t-flavanone and a placebo on 14 subjects showed that after 6 months of topical application, the hair diameter increased, especially with new-grown hair. A 6-month application test of 197 male subjects with patterned hair loss using t-flavanone, a placebo, and market hair growth–promoting reagents, with global assessment by doctors, revealed an improvement rate above slight improvement with t-flavanone being significantly higher than the placebo and increased firm hair (with a diameter larger than 40 μm). The overall improvement, including the amount of firm hair, was 19.4% and 75.0% with the placebo and t-flavanone agents, respectively.[16]

#### 48.3.4.4 *Cytopurine*

Cytopurine (6-benzylaminopurine) is expected to inhibit hair loss due to its effects on increasing bone morphogenetic protein and ephrin in DP cells, which reportedly decreases with hair loss and inducing ORS cell growth.

Cytopurine has been found to have a significantly higher improvement compared with placebo-treated subjects in an efficacy test of patterned hair loss subjects.[42]

#### 48.3.4.5 Pentadecan

Pentadecan is known to improve the energy metabolism of the hair follicle, such as by inducing ATP growth, and has been found to have a significantly higher improvement compared with placebo-treated subjects in an efficacy test of male subjects with patterned hair loss.[54]

#### 48.3.4.6 Ketoconazole

Ketoconazole is a synthetic antifungal drug used for the treatment of ringworm and seborrheic eczema, but it has also been reported to show a 5α-reductase–blocking activity.[17] Ketoconazole has been reported to be an effective material for treating patterned hair loss as a topical agent and as a shampoo, and it is categorized as C1 in the guidelines.

#### 48.3.4.7 Cepharanthine

Alkaloids (organic compounds) extracted from the root of a plant called *Stephania cepharantha hayata* are generally called cepharanthine and are categorized as natural ingredients. As a pharmaceutical component, they have been reported to show effects and functions on alopecia areata and on alopecia pityroides, but since there are not enough reports on their effectiveness on patterned hair loss, it is categorized as C2 (use not suggested).

### 48.3.5 Other Chemical Compounds

First, we will consider chemical agents that have a history as active components of quasi-drug hair growth–promoting reagents in Japan. β-Glycyrrhetinic acid is derived by the hydrolysis of an extract of glycyrrhizin in the legume family and has been expected to promote hair growth with its anti-inflammatory activity and 5α-reductase inhibitory action. Nicotinamide, vitamin E derivatives, and pantothenyl ethyl ether have been formulated in many hair growth products with expectations to promote hair growth from their cell activator action and blood circulation–promoting activity.[24]

Stemoxydine has an effect to maintain a hypoxic local environment to optimize the functionality of hair follicle stem cells, and it has shown an effect to increase hair density in a 3-month clinical test.

An amino acid, 5-aminolevulinic acid, has an enhancement action on the cytochromes of mitochondria and has been reported to show hair growth–promoting actions on animals and humans (Orokuma 2008). Development of 5-aminolevulinic acid in hair growth–promoting reagents is now being considered.

Epimorphin is a membrane protein found on the surface of mesenchyme cells and is known as an organ formation factor. Epimorphin has been expected to be used as a hair growth–promoting reagent due to its growth inducing action on hair, but its development was reportedly discontinued due to safety concerns.[15]

### 48.3.6 Natural Plant Extracts

Many plant extracts have been known to have hair growth–promoting activities from traditional folk therapies such as Chinese medicine and from advanced screening methods, and they are used in hair growth–promoting products mainly as cell activators. Here, we review the functions of prominent natural plant extracts. Ginseng extract is a long-used herbal medicine known to have an immunostimulatory action. A *Sophora* extract, extracted from the root of *Sophora*, has growth-inhibiting effects on cultured hair epithelium cells and hair lengthening effects on organ-cultured hair follicles. The *Sophora* extract has been found to be effective on human hair[53] and is used widely in Japan and in South Korea. Coriander is a commonly used spice, but coriander fruit extract has growth-stimulating effects on cultured hair epithelium cells and is used in hair growth products.[55] Mulberry root bark extract has an action to shorten the telogen phase and extend the anagen phase of hair and has been found effective on human hair.[30] A Cuachalalate extract from the bark of a tree that originated in Mexico inhibits the hair follicle's transition to catagen. The Cuachalalate extract has a three-step action: inhibiting DHT production with a 5α-reductase–blocking action,[43] inhibiting the activity of TGF-β2, a catagen-inhibiting factor that increases with DHT, and blocking caspase that causes apoptosis.[49] A hydrolyzed yeast extract has been reported to have a mechanism of inducing hair growth by growing the primary cilium on the surface of DP cells to promote various cell growth signals.[41]

The following methods require operations at medical institutions, but since some procedures of cosmetic surgery have overlapped the line between cosmetics and cosmetic surgery, relatively safe methods operated in medical clinics are becoming alternatives to cosmetics to consumers. As such, we will review some of these operations in this section of the chapter.

## 48.4 LIGHT-EMITTING DIODES, LASERS, AND OTHER COSMETIC SURGERIES

Laser surgery has been widely used in cosmetic surgery for hair removal. However, light-emitting diodes (LEDs) with a specific spectrum, also called low-level laser therapy (LLLT), have been reported to be effective in stimulating hair growth. Inui et al. studied hair growth promotion by activating hair matrix cells with a specific-spectrum red LED,[11] and Avci et al. reported the results of their tests in clinical research.[1]

## 48.5 GROWTH FACTOR COCKTAIL, CELL CULTURE MEDIA INJECTION, AND PLATELET-RICH PLASMA

Injecting biologically derived components directly into the scalp is an operation that has been actively performed in recent years. Platelet-rich plasma (PRP) therapy is a method that uses autologous components, whereas so-called HARG therapy and culture supernatant injection therapy use nonautologous, allogenic components. PRP therapy is a method used in clinics where the patient's platelets are isolated from their blood and are injected into their scalp to promote hair growth. Reports have shown that PRP therapy has a certain effect. To improve those effects, there is a method called W-PRP, where the components are modified with additional factors, such as including leukocytes. Although they do not have nuclei, platelets are perceived as "cells," and in Japan they are subject to new medical regulations for regenerative medicine. On the other hand, HARG therapy is an operation that uses a nutrient cocktail extracted from adipose tissues, which is believed to include stem cells. Although some medical institutions claim that HARG therapy has a substantial efficacy, it seems that objective clinical data are still insufficient. Further, the potential risks of injecting components derived from other persons cannot be ruled out. Culture supernatant therapy is a method that injects the supernatant from fibroblasts cultured under low-oxygen conditions into the scalp and has been reported to induce hair growth.[62]

## 48.6 HAIR TRANSPLANTATION

Various surgical treatments for male pattern baldness have been developed, such as the flap method, scalp resection, and hair transplantation, but the most common method seen globally now is hair transplantation of autologous hair follicles. Since symptoms of male pattern baldness start from the forehead or temporal area and do not usually occur at the side or occipital areas, this method takes advantage of this characteristic and uses donor hair follicles (whole hair follicles including the hair bulbs) from the occipital area and transplants them to the balding areas. Since this method requires a surgical operation, it must be done at a medical institution so it is a method that is contrary to cosmetics. In Europe and in the United States, hair transplantation has grown into a market larger than hair growth–promoting reagents and new operation methods such as follicular transplant units (FTUs) have been developed, and currently the invasiveness and stability of FTU are being improved. Further, automated grafting transplantation using robots has reached a practical level. This is a surgical method with conclusive results and has been widely adopted mainly due to the high engraftment rate and because of transplanting their own, autologous hair follicle tissues. Additionally, hair transplantation has an advantage over other surgical methods where the hair line and hair style can be designed according to the patient's preference.

## 48.7 FUTURE TREATMENT IN COSMETICS: REGENERATION OF HAIR FOLLICLES BY AUTOLOGOUS CELL-BASED THERAPY FOR HAIR LOSS

The technology of regenerative medicine, as well as the development of related legal regulations, is accelerating. Under such social and environmental circumstances, it is assumed that the category of regenerative medicine treatment is considered safe, such as the injection of autologous, differentiated somatic cells to specific areas locally with

homologous use, and will overlap with the field of cosmetics. When applying cells to humans, choosing between autologous or allogenic cells is an issue, but in the hair transplantation method introduced earlier, there have been issues during the development process where intense inflammatory reactions or rejection reactions occurred with allogenic hair follicles, which did not engraft and new hair did not grow. Based on these experiences with hair transplantation, autologous cells are planned to be used with clinical research in cell transplantation therapy.

### 48.7.1 Autologous Cell-Based Therapy for Hair Loss Treatment

Clinical trials on hair loss treatment with the injection of autologous hair follicle derived cells is advancing mainly in Europe and in North America and two ventures based in the United Kingdom and in the United States have passed their safety issue in phase 1 studies. They were proceeding to phase 2 trials for efficacy and safety with small patient groups. Although details for the specification of cells and the preparation procedures, including cell culture conditions, were not disclosed, they seem to use either DP cells or dermal fibroblasts together with epithelial components, and some trophic factors as well. However, these trials were discontinued in phase 2, and the final results have not been announced.

Although DP cells are a common primary target for hair growth promotion in the search for compounds and natural extracts, for cell-based therapy more premature cells may be appropriate such as DSC cells, which are thought to be precursors of DP cells. McElwee et al.[39] used hair follicles from the whiskers of mice to isolate DP cells, DSC cells, and nonhair bulb DS cells. After a few passages of cultivation, they were each injected into the auricle ear of immunodeficient mice to test the hair growth−induction effects. These preclinical tests showed that areas injected with DP cells or DSC cells had longer hair shafts compared with the noninjected areas after 4 weeks. DS cell−injected areas did not show any change. The DSC cell−injected areas showed an especially natural hair distribution and direction (angle) compared with the DP cell−injected areas, and observation using florescent-labeled cells showed that the DSC cells were incorporated into the DP. Further, there have been studies on humans, where DSC cells and DP cells were taken from male donors and transplanted to the inner forearm of female subjects. The results showed that the DSC cells had hair growth with male Y chromosomes, but hair regeneration was not found with DP cells.[47] These studies indicate that DSC cells work as precursor cells of DP cells and have the potential to derive hair follicles and induce hair growth. A clinical trial conducted in Europe with cultured autologous human DSC cells showed that in its phase 1 safety test, they have been confirmed to be safe as well as to show a certain degree of efficacy. These challenging and exciting approaches with cell-based therapies may take time to develop and be ready to use for hair loss patients, but very promising new treatments are being developed to be widely used together with cosmetic pretreatments and posttreatments.

## 48.8 SUMMARY AND FUTURE DIRECTIONS

In this chapter, we have considered hair, mainly from the viewpoint of hair growth promotion, including pharmaceutical, cosmeceutical, and some cosmetic surgery methods. We also looked at the future possibilities of hair growth with cell-based therapies and regenerative medicine. Hair strongly influences the esthetics of an individual and is undoubtedly important to improve our quality of life. Regardless of gender, there are desires or dissatisfaction with our hair, especially with women. Depending on the culture, the range of social acceptance is smaller in women compared with in men, and the desires and distress tend to be more serious. We hope that new and improved approaches can help meet such wishes. Further, as a long-time researcher in this field, there seems to be a large potential need for areas other than hair growth, such as the prevention and/or improvement of gray hair or fundamentally fixing curled hair. There have been some interesting studies on gray hair and curled hair. Most of those studies are fundamental studies using genetics or mouse models, and none of them propose solutions comparable to the studies on hair growth. We hope that in the future, the continued use of cosmetic/cosmeceutical products, clinical methods such as cell-based therapy, and the development of safe genetic manipulations can be combined to offer various effective options for users to choose from, and that people will be able to live more actively with vivid hair throughout their lifetime.

## References

1. Avci P, Gupta GK, et al. Low-level laser (light) therapy (LLLT) for treatment of hair loss. *Lasers Surg Med* 2014;**46**(2):144−51.
2. Blumeyer A, Tosti A, et al. Evidence-based (S3) guideline for the treatment of androgenetic alopecia in women and in men. *J Dtsch Dermatol Ges* 2011;**9**(Suppl. 6):S1−57.

3. Botchkarev VA, Sharov AA. BMP signaling in the control of skin development and hair follicle growth. *Differentiation* 2004;**72**(9−10):512−26.
4. Botchkarev VA, Kishimoto J. Molecular control of epithelial-mesenchymal interactions during hair follicle cycling. *J Investig Dermatol Symp Proc* 2003;**8**(1):46−55.
5. Chi W, Wu E, et al. Dermal papilla cell number specifies hair size, shape and cycling and its reduction causes follicular decline. *Development* 2013;**140**(8):1676−83.
6. Chiang C, Swan RZ, et al. Essential role for sonic hedgehog during hair follicle morphogenesis. *Dev Biol* 1999;**205**(1):1−9.
7. Cotsarelis G, Sun TT, et al. Label-retaining cells reside in the bulge area of pilosebaceous unit: implications for follicular stem cells, hair cycle, and skin carcinogenesis. *Cell* 1990;**61**(7):1329−37.
8. Dong L, Hao H, et al. Wnt1a maintains characteristics of dermal papilla cells that induce mouse hair regeneration in a 3D preculture system. *J Tissue Eng Regen Med* 2015.
9. Elliott K, Stephenson TJ, et al. Differences in hair follicle dermal papilla volume are due to extracellular matrix volume and cell number: implications for the control of hair follicle size and androgen responses. *J Invest Dermatol* 1999;**113**(6):873−7.
10. Fessing MY, Sharova TY, et al. Involvement of the Edar signaling in the control of hair follicle involution (catagen). *Am J Pathol* 2006;**169**(6): 2075−84.
11. Fushimi T, Inui S, et al. Narrow-band red LED light promotes mouse hair growth through paracrine growth factors from dermal papilla. *J Dermatol Sci* 2011;**64**(3):246−8.
12. Gubelin Harcha W, Barboza Martinez J, et al. A randomized, active- and placebo-controlled study of the efficacy and safety of different doses of dutasteride versus placebo and finasteride in the treatment of male subjects with androgenetic alopecia. *J Am Acad Dermatol* 2013;**70**(3): 489−498 e3.
13. Harada S, Nakayama J, et al. Clinical evaluation of DH-3923 in the treatment of male pattern baldness and other alopecias − A multi-center open trial. *J Clin Ther Med* 2004;**20**:351−76 (Rinsho-Iyaku in Japanese).
14. Hebert JM, Rosenquist T, et al. FGF5 as a regulator of the hair growth cycle: evidence from targeted and spontaneous mutations. *Cell* 1994;**78**(6): 1017−25.
15. Hirai Y, Takebe K, et al. Epimorphin: a mesenchymal protein essential for epithelial morphogenesis. *Cell* 1992;**69**(3):471−81.
16. Hotta M, I G. Effect of t-flavanone on hair growth. *Fragr J* 2013;**31**(2):33−40.
17. Hugo Perez BS. Ketocazole as an adjunct to finasteride in the treatment of androgenetic alopecia in men. *Med Hypotheses* 2004;**62**(1): 112−5.
18. Iino M, Ehama R, et al. Adenosine stimulates fibroblast growth factor-7 gene expression via adenosine A2b receptor signaling in dermal papilla cells. *J Invest Dermatol* 2007;**127**(6):1318−25.
19. Ishimatsu-Tsuji Y, Moro O, et al. Expression profiling and cellular localization of genes associated with the hair cycle induced by wax depilation. *J Invest Dermatol* 2005;**125**(3):410−20.
20. Ishino A, Takahashi T, et al. Contribution of hair density and hair diameter to the appearance and progression of androgenetic alopecia in Japanese men. *Br J Dermatol* 2014;**171**(5):1052−9.
21. Itami S, Inui S. Role of androgen in mesenchymal epithelial interactions in human hair follicle. *J Investig Dermatol Symp Proc* 2005;**10**(3):209−11.
22. Itami S, Kurata S, et al. Characterization of 5 alpha-reductase in cultured human dermal papilla cells from beard and occipital scalp hair. *J Invest Dermatol* 1991;**96**(1):57−60.
23. Ito C, Saitoh Y, et al. Decapeptide with fibroblast growth factor (FGF)-5 partial sequence inhibits hair growth suppressing activity of FGF-5. *J Cell Physiol* 2003;**197**(2):272−83.
24. Iwabuchi T. Recent trend and issue in the research for hair growth accelerators. *Fragr J* 2009;**37**(10):21−6.
25. Iwabuchi T, Ideta R, et al. Topical adenosine increases the proportion of thick hair in Caucasian men with androgenetic alopecia. *J Dermatol* 2015.
26. Jindo T, Tsuboi R, et al. Hepatocyte growth factor/scatter factor stimulates hair growth of mouse vibrissae in organ culture. *J Invest Dermatol* 1994;**103**(3):306−9.
27. Katz HI, Hien NT, et al. Long-term efficacy of topical minoxidil in male pattern baldness. *J Am Acad Dermatol* 1987;**16**(3 Pt 2):711−8.
28. Kaufman KD, Olsen EA, et al. Finasteride in the treatment of men with androgenetic alopecia. Finasteride Male Pattern Hair Loss Study Group. *J Am Acad Dermatol* 1998;**39**(4 Pt 1):578−89.
29. Kawano M, Komi-Kuramochi A, et al. Comprehensive analysis of FGF and FGFR expression in skin: FGF18 is highly expressed in hair follicles and capable of inducing anagen from telogen stage hair follicles. *J Invest Dermatol* 2005;**124**(5):877−85.
30. Kuwana R, M M, Date A, Sawamura Y, Aki O, Arase S. The effect of souhakuhi-extract on the hair cycle of New Zealand white rabbits and its topical therapy in male pattern baldness. *Nishinihon J Dermatol* 1996;**58**(4):619−24.
31. Laurikkala J, Pispa J, et al. Regulation of hair follicle development by the TNF signal ectodysplasin and its receptor Edar. *Development* 2002; **129**(10):2541−53.
32. Li M, Marubayashi A, et al. Minoxidil-induced hair growth is mediated by adenosine in cultured dermal papilla cells: possible involvement of sulfonylurea receptor 2B as a target of minoxidil. *J Invest Dermatol* 2001;**117**(6):1594−600.
33. Lin KK, Andersen B. Have hair follicle stem cells shed their tranquil image? *Cell Stem Cell* 2008;**3**(6):581−2.
34. Lin KK, Chudova D, et al. Identification of hair cycle-associated genes from time-course gene expression profile data by using replicate variance. *Proc Natl Acad Sci USA* 2004;**101**(45):15955−60.
35. Liu Y, Lyle S, et al. Keratin 15 promoter targets putative epithelial stem cells in the hair follicle bulge. *J Invest Dermatol* 2003;**121**(5):963−8.
36. Ludwig E. Classification of the types of androgenetic alopecia (common baldness) occurring in the female sex. *Br J Dermatol* 1977;**97**(3):247−54.
37. Maeda T, Y T, Ishikawa Y, Ito N, Arase S. *Sanguisorba officinalis* root extract has FGF-5 inhibitory activity and reduces hair loss by causing prolongation of the anagen period. *Nishinihon J Dermatol* 2007;**69**(1):81−6.
38. Matsuzaki T. In: Maeda K, editor. *Advanced technology of hair follicle regeneration*. Tokyo: CMC Publishing; 2013. p. 93−100.
39. McElwee KJ, Kissling S, et al. Cultured peribulbar dermal sheath cells can induce hair follicle development and contribute to the dermal sheath and dermal papilla. *J Invest Dermatol* 2003;**121**(6):1267−75.
40. Midorikawa T, Chikazawa T, et al. Different gene expression profile observed in dermal papilla cells related to androgenic alopecia by DNA macroarray analysis. *J Dermatol Sci* 2004;**36**(1):25−32.

41. Mifude C, Kaseda K. PDGF-AA-induced filamentous mitochondria benefit dermal papilla cells in cellular migration. *Int J Cosmet Sci* 2015; **37**(3):266–71.
42. Mishima Y, T S, Nakayama H, Ishii A, Kawano H, Ohkubo A, Hatae S. Effect of 6-benzylaminopurine (CTP) on the growth of human scalp hairs. *Skin Res* 1998;**40**:407–14.
43. Nakazawa Y, M T, Arai T, Ota M, Tajima M, Mogi T, Makino M, Fujimoto Y, Ithinohe Y. Inhibitory effects of the triterpene derived from Mexican plant Juliania adstringens on the steroid 5 alpha-reductase activity. In: *118th annual meeting of pharmaceutical society of Japan*, **2**; 1998. p. 155.
44. Oro AE, Higgins K. Hair cycle regulation of Hedgehog signal reception. *Dev Biol* 2003;**255**(2):238–48.
45. Oura H, Iino M, et al. Adenosine increases anagen hair growth and thick hairs in Japanese women with female pattern hair loss: a pilot, double-blind, randomized, placebo-controlled trial. *J Dermatol* 2008;**35**(12):763–7.
46. Rahmani W, Abbasi S, et al. Hair follicle dermal stem cells regenerate the dermal sheath, repopulate the dermal papilla, and modulate hair type. *Dev Cell* 2014;**31**(5):543–58.
47. Reynolds AJ, Lawrence C, et al. Trans-gender induction of hair follicles. *Nature* 1999;**402**(6757):33–4.
48. Sato N, Leopold PL, et al. Induction of the hair growth phase in postnatal mice by localized transient expression of sonic hedgehog. *J Clin Invest* 1999;**104**(7):855–64.
49. Soma T, Tsuji Y, et al. Involvement of transforming growth factor-beta2 in catagen induction during the human hair cycle. *J Invest Dermatol* 2002;**118**(6):993–7.
50. Stenn K. Exogen is an active, separately controlled phase of the hair growth cycle. *J Am Acad Dermatol* 2005;**52**(2):374–5.
51. Sundberg JP, Rourk MH, et al. Angora mouse mutation: altered hair cycle, follicular dystrophy, phenotypic maintenance of skin grafts, and changes in keratin expression. *Vet Pathol* 1997;**34**(3):171–9.
52. Tajima M, Hamada C, et al. Characteristic features of Japanese women's hair with aging and with progressing hair loss. *J Dermatol Sci* 2007; **45**(2):93–103.
53. Takahashi T, Ishino A, et al. Improvement of androgenetic alopecia with topical *Sophora flavescens* aiton extract, and identification of the two active compounds in the extract that stimulate proliferation of human hair keratinocytes. *Clin Exp Dermatol* 2015.
54. Takeda K, Arase S, Watanabe S, Nagashima K, Watanabe Y, Sakuma A. Clinical evaluation test for male pattern alopecia of LHOP pharmaceuticals. *Nishinihon J Dermatol* 1993;**55**(4):727–34.
55. Takeoka E, N Y, Suzuki J, Hamada C, Iwabuchi T, Arai T, Tajima M, Nohara T. Hair follicle epithelial cell proliferation accelerating effect of coriander. In: *118th annual meeting of pharmaceutical society of Japan*, **2**; 1998. p. 136.
56. Watanabe Y, Nagashima T, et al. Topical adenosine increases thick hair ratio in Japanese men with androgenetic alopecia. *Int J Cosmet Sci* 2015; **37**(6):579–87.
57. Weger N, Schlake T. Igf-I signalling controls the hair growth cycle and the differentiation of hair shafts. *J Invest Dermatol* 2005;**125**(5):873–82.
58. Werner S, Smola H, et al. The function of KGF in morphogenesis of epithelium and reepithelialization of wounds. *Science* 1994;**266**(5186): 819–22.
59. Yano K, Brown LF, et al. Control of hair growth and follicle size by VEGF-mediated angiogenesis. *J Clin Invest* 2001;**107**(4):409–17.
60. Yano K, Brown LF, et al. Thrombospondin-1 plays a critical role in the induction of hair follicle involution and vascular regression during the catagen phase. *J Invest Dermatol* 2003;**120**(1):14–9.
61. Yip L, Rufaut N, et al. Role of genetics and sex steroid hormones in male androgenetic alopecia and female pattern hair loss: an update of what we now know. *Australas J Dermatol* 2011;**52**(2):81–8.
62. Zimber MP, Ziering C, et al. Hair regrowth following a Wnt- and follistatin containing treatment: safety and efficacy in a first-in-man phase 1 clinical trial. *J Drugs Dermatol* 2011;**10**(11):1308–12.

CHAPTER

# 49

# Clinical Evaluation and Instrumental Techniques in Dermatology

*E. Berardesca, M. Ardigò*

**San Gallicano Dermatological Institute, IRCCS, Rome, Italy**

The stratum corneum barrier is commonly described according to the "brick and mortar" model constituted respectively by corneocytes and intercellular lipids; the former are composed mainly of insoluble bundled keratins surrounded by a cell envelope stabilized by cross-linked proteins and covalently bound lipids. Polar structures, such as corneodesmosomes, interconnect corneocytes determining stratum corneum cohesion. Intercorneocytic lipids are primarily generated from exocytosis of lamellar bodies during the keratinocytes' terminal differentiation and secondarily generated by sebaceous output. Lipids are required for a competent skin barrier and homeostatic control of transcutaneous penetration.[1]

The stratum corneum barrier is a dynamic structure resulting from the cornification process and the desquamation, which are intimately connected. The control of stratum corneum formation in response to barrier perturbation is directly pertinent to the etiology of several skin diseases; the development of new therapeutic strategies for skin disease treatment and barrier reinforcement is also strictly dependent on the preservation of skin barrier function.

The maturation of keratinocytes into corneocytes requires a time period between 2 and 4 weeks during which keratin filaments undergo transformation as revealed by the expression of different markers; indeed, keratin K5 and K4 synthesis, characteristic of the basal layer, is replaced by K1 and K10 in the suprabasal region. In the upper epidermal layers, keratins are bundled with profilaggrin that is degraded in, the stratum corneum, into amino acids and other molecules; this process influences stratum corneum hydration and water-holding capacity causing skin dryness. In stratum corneum, lipids are covalently bound to the cornified envelopes. Lipids are mainly ceramides derived from glucosylceramides present in lamellar bodies. The role of the covering lipids has been hypothesized to be relevant for stratum corneum cohesion, organization of the intercellular lipids, and preservation of corneocytes' permeability properties. Consequently, intercellular lipids (cholesterol, ceramides, essential, and nonessential fatty acids) play a major role in maintaining and modulating barrier efficiency, and a defective maturation of the cornified envelope may explain impairment of barrier function in some inflammatory skin disorders.

Psoriasis is a chronic skin disease characterized by hyperproliferation of the epidermis and inflammatory reactions in the dermis and epidermis. Psoriatic skin is characterized by an elevated turnover rate of keratinocytes and a shortened cell cycle, and as well, the desquamation process is altered. Scaling marks the clinical feature associated by hyperkeratosis, pruritus, inflammation, and stratum corneum dryness. Microscopically, immature cornified envelopes are present in psoriasis and are associated with parakeratosis, and inflammation in psoriasis lesion is characterized by the release of specific pattern of cytokines. In psoriasis, the amount of the covalently bound lipids is the same as in normal subjects, but the level of ceramide 2 is reduced whereas the level of free fatty acids and omega-hydroxyacids is increased. An emollient-based mild psoriasis treatment induced normalization of several proliferation and differentiation markers, whereas the clinical response showed few changes after 2 weeks.[2] Good correlation between skin capacitance and transepidermal water loss (TEWL) with visual assessment of skin dryness has been demonstrated. Both TEWL and capacitance values improved in the psoriatic lesions in a 6-week trial during treatment.[3] Patients' acceptance of emollients is generally excellent. An additional advantage of emollient therapies is their relatively low cost, however, in many countries no reimbursement is available for specific emollients in psoriasis. Controlled, randomized trials with a high grade of evidence will help in changing this lack of

*Cosmetic Science and Technology: Theoretical Principles and Applications*
http://dx.doi.org/10.1016/B978-0-12-802005-0.00049-5



Copyright © 2017 Elsevier Inc. All rights reserved.

reimbursement because patients with severe stratum corneum dryness might use more than 250 g of emollients per day. In particular, glycerol is widely used in cosmetic preparations; glycerol is a trihydroxy alcohol that has been included for many years in topical dermatological preparations. In addition, endogenous glycerol plays a role in skin hydration, cutaneous elasticity, and epidermal barrier repair. The aquaporin-3 transport channel and lipid metabolism in the pilosebaceous unit have been evidenced as potential pathways for endogenous delivery of glycerol and for its metabolism in the skin. Multiple effects of glycerol on the skin have been reported. The diverse actions of polyol glycerol on the epidermis include improvement of stratum corneum hydration, skin barrier function and skin mechanical properties, inhibition of the stratum corneum lipid phase transition, protection against irritating stimuli, enhancement of desmosomal degradation, and acceleration of wound-healing processes.

Ichthyoses are another condition characterized by skin dryness and barrier impairment. Recently, research into the pathomechanisms of these disorders has dramatically improved and led to the identification of several contributory genes and molecules underlying the genetic defects characterizing the ichthyoses group. In most types of ichthyosis, pathogenic mechanisms are associated with defects in skin barrier function. Three major components of the stratum corneum barrier are intercellular lipid layers, cornified cell envelope, and keratin-filaggrin degradation products. The causative molecules defining ichthyosis subtypes include ABCA12, lipoxygenase-3, 12R-lipoxygenase, CYP4F2 homolog, ichthyin, and steroid sulfatase; all of these are considered to be strictly related to the intercellular lipid layers. Transglutaminase 1 has a function in cornified cell envelope formation. Keratins 1, 2, and 10 are involved in the keratin network of suprabasal keratinocytes and filaggrin are essential for formation of keratohyalin granules. In fact, loss of ABCA12 function leads to a defective lipid barrier in the stratum corneum, resulting in the ichthyosiform phenotype as ABCA12 is a known keratinocyte lipid transporter associated with lipid transport in lamellar granules. Filaggrin gene mutations in ichthyosis vulgaris cause keratohyalin granule deficiency.

Atopic dermatitis is characterized by impaired barrier function, increased transepidermal water loss, and stratum corneum xerosis resulting from reduced levels of ceramides in the intercellular lipid domain.[4] Several biochemical "factors" can influence the derangement of skin barrier and stratum corneum lipids in atopic skin. Indeed, antigens and/or superantigens released by microbial flora can easily penetrate a deranged barrier and act as potent immunostimulatory molecules capable to activate IgE production. This can result in the formation of eczematous lesions and dermal inflammatory reaction. Studies have shown how experimentally induced stratum corneum damage by stripping can induce inflammation mediators release (interleukin-1 alpha, interleukin-1 beta, and TNF alpha).[5] Therefore, it appears how an inflammatory reaction involving immunological responses can be initiated only by external stimuli induced and mediated by stratum corneum damage.[6] Genetic associations have been found between atopic dermatitis and genes encoding proteins critical in skin barrier function, including serine protease inhibitor Kazal-type 5, stratum corneum chymotryptic enzyme, and filaggrin. Children with atopic dermatitis have abnormal skin barrier function in normal-appearing nonlesional skin, as assessed by TEWL. Moreover, TEWL correlates with atopic dermatitis disease severity. Thus it supports this alternative "outside-in" hypothesis that an intrinsic defect of barrier function is responsible for the pathogenesis of atopic dermatitis. In fact, it has been shown that barrier disruption in the skin results in the production of Th2 cytokines, including IL-4 and IL-5. In the context of underlying barrier dysfunction in atopic dermatitis, minimal exogenous skin trauma might be sufficient to activate epidermal cytokines and activate disease in clinically normal skin.[7]

Another condition characterized by barrier damage is irritant contact dermatitis that can be easily generated on a disrupted barrier, due both to enhanced transcutaneous penetration of aggressive chemicals and to xerosis and desquamation as a consequence of increased water loss from skin surface. From this point of view, irritant contact dermatitis can be considered as a preliminary step toward the development of a permanent sensitization. Potentially dangerous sensitizers can have easy access to living epidermal structures in irritated skin leading to permanent sensitization and skin damage.[8] Indeed, topical application of physiologic lipids has distinct effects from those of nonphysiologic lipids, like petrolatum. For example, it has been noted that topical application of only one or two of the three physiologic lipids to a disrupted hairless mouse skin impedes rather than facilitates barrier recovery, evidenced by changes in transepidermal water loss. However, if members of all three key lipid classes are applied together to barrier-disrupted skin, normalized rates of barrier repair are observed.[9]

It appears clear that any therapeutic approach that restores stratum corneum barrier function not only can improve the "cosmetic" appearance of the skin but can support the skin treatment as well, by reducing transcutaneous penetration of sensitizers and chemicals and decreasing the release of proinflammatory mediators induced by a disrupted barrier. Furthermore, in particular conditions, such as atopic eczema, the restoring of a functional barrier can prevent the interaction of superantigens with an abnormal immune system and thereby prevent the development of eczematous lesions.[10–12]

Noninvasive techniques and methods can help dermatologists or investigators in quantifying skin surface and skin condition, providing a more standardized and objective approach to skin investigation. These tools can help in monitoring barrier function, evaluate skin structure, or measure and quantify skin pathology. Therefore they can be useful in the clinical routine as well as in an experimental setup[13,14] and in the near future will be more and more popular. The possibility to send clinical pictures via media networks will increase the use of clinical teledermatology, promoting exchange of information between doctors and scientists as well as among patients, favoring communication between doctors and patients even in remote areas, contributing to early diagnosis and better health care.

## References


1. Schaefer H, Redelmeier TE, editors. *Skin barrier. Principles of percutaneous absorption*. Basel: Karger; 1966.
2. van Duijnhoven MW, Hagenberg R, Pasch MC, et al. Novel quantitative immunofluorescent technique reveals improvements in epidermal cell populations after mild treatment of psoriasis. *Acta Derm Venereol* 2005;**85**:311–7.
3. Rim JH, Jo SJ, Park JY, et al. Electrical measurement of moisturizing effect on skin hydration and barrier function in psoriasis patients. *Clin Exp Dermatol* 2005;**30**:409–13.
4. Murata Y, Ogata J, et al. Abnormal expression of sphingomyelin acylase in atopic dermatitis: an etiologic factor for ceramide deficiency? *J Invest Dermatol* 1996;**106**:1242–9.
5. Wood LC, Jackson SM, Elias PM, Grunfeld C, Feingold KR. Cutaneous barrier perturbation stimulates cytokine production in the epidermis of mice. *J Clin Invest* 1992;**90**:482–7.
6. Elias PM, Wood LC, et al. Epidermal pathogenesis of inflammatory dermatoses. *Am J Contact Dermat* 1999;**10**:119–26.
7. Fartasch M. Epidermal barrier in disorders of the skin. *Microscop Res Tech* 1997;**38**:361–72.
8. Berardesca E, Fideli D, Borroni G, Rabbiosi G, Maibach H. In vivo hydration and water retention capacity of stratum corneum in clinically uninvolved skin in atopic and psoriatic patients. *Acta Dermato Venereol (Stockholm)* 1990;**70**:400–4.
9. Mao-Qiang M, Elias PM, Feingold KR. Fatty acids are required for epidermal permeability barrier function. *J Clin Invest* 1993;**92**:791–8.
10. Mao-Qiang M, Brown BE, Wu-Pong S, Feingold KR, Elias PM. Exogenous nonphysiologic vs physiologic lipids. Divergent mechanisms for correction of permeability barrier dysfunction. *Arch Dermatol* 1995;**131**:809–16.
11. Thornfeldt C. Critical and optimal molar ratios of key lipids. In: Lodén M, Maibach HI, editors. *Dry skin and moisturizers*. Boca Raton: CRC Press; 2000. p. 337–47.
12. Berardesca E, Vignoli GP, Borroni G, Oresajo C, Rabbiosi G. Surfactant damaged skin: which treatment? In: Marks R, Plewig G, editors. *The Environmental threat to the skin*. London: Martin Duntiz; 1991. p. 283–5.
13. Wilhelm K, Elsner P, Berardesca E, Maibach H, editors. *Image analysis*. New York: Taylor and Francis; 2006.
14. Berardesca E, Maibach H, Wilhelm K, editors. *Non invasive diagnostic techniques in clinical dermatology*. Berlin: Springer; 2013.

CHAPTER

# 50

# Safety Evaluation

*M. Masuda*[1], *F. Harada*[2]

[1]Consultant, Ninomiya, Kanagawa, Japan; [2]Lion Corporation, Odawara, Kanagawa, Japan

## 50.1 INTRODUCTION

Cosmetics play a major role to enrich everyday life, such as contributing to the health maintenance and hygiene of the skin, hair, and teeth; cosmetic therapies; and psychological aromatic effects. From the average consumer's point of view, people use cosmetics over a long period of their lifespan, and cosmetics are considered to be safe and to have rarely been associated with serious health hazards. This view has been supported by predictive safety evaluation, which is designed to ensure as much as possible that new products can be used without harm to human health. Therefore, it is essential that attention be paid to potential toxicological hazards to consumers at an early stage in the development of cosmetics and that safety-in-use of products is verified before their launch.

## 50.2 WHAT IS SAFETY?

How is a safety evaluation of cosmetics conducted? First, we discuss the meaning of "safety" as the goal of evaluations.

"Safety" can be defined as freedom from danger or risk, but absolute safety does not exist. It is important to recognize the fact that all chemicals are potentially toxic at some level of dosage, therefore, safety is related to dose. Paracelsus (1492–1541), who is credited as the founder of toxicology, said, "What is there that is not poison? All things are poison and nothing is without poison. Solely the dose determines that a thing is not poison."[1] To summarize, safety is determined by the dosage.

In addition, Giovacchini[2] defined "safety" as follows:

> Safety is freedom from unreasonable risk of significant injury under reasonably foreseeable conditions of use. This definition recognizes that if the evidence from published and unpublished scientific and marketing information does not demonstrate or suggest reasonable grounds to suspect significant adverse reactions, the ingredient or product may be considered safe under the specified conditions of use. There are, of course, no absolutely harmless substances; but there are ways and means of using substances in a relatively harmless way. Thus, safety is defined in terms of the probability that the material will not produce significant damage under certain specified conditions.

## 50.3 HOW SHOULD WE CONSIDER THE SAFETY OF COSMETICS AND THEIR INGREDIENTS?

We decide to use an ingredient not only because there is no hazard but also because the ingredient could impart a variety of benefits and functions. It is acceptable if the dosage that could impart the benefit has no associated hazard. In the case of a dosage that poses both benefit and hazard, how could we reach decisions on the risk acceptability? The concept that risk acceptability is somehow related to the benefit derived from using an ingredient or a product has come to be generally recognized in some circumstances. This is the concept of risk-benefit balance, and the more realistic attitude of balancing conjectured risk with claimed benefits has come to the forefront.[3,4]

*Cosmetic Science and Technology: Theoretical Principles and Applications*
http://dx.doi.org/10.1016/B978-0-12-802005-0.00050-1



Copyright © 2017 Elsevier Inc. All rights reserved.

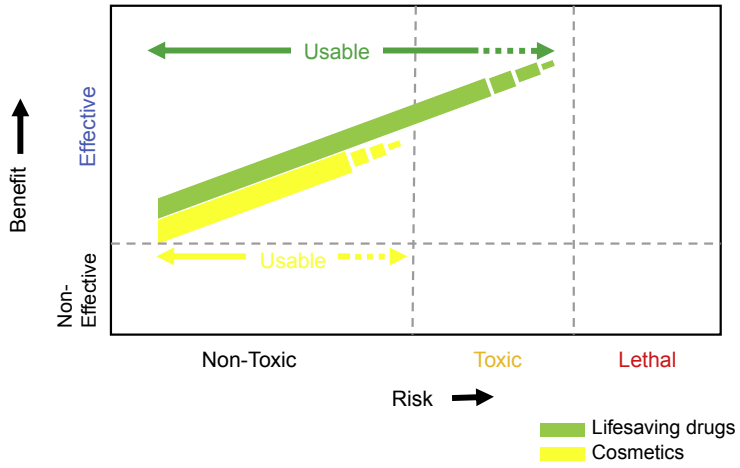



FIGURE 50.1 Risk-benefit balance between cosmetics and drugs.

Risk-benefit balance varies within categories of products (Fig. 50.1). A risk of serious side effects may have to be tolerated to gain the benefit of using lifesaving medicine, whereas the same level of risk in less desperate circumstances would not be countenanced. Suitability of a potent new medication is not likely to be challenged strongly when the issue at stake is a choice between the life and death of seriously ill patients. The case for risk-benefit analysis and the right approach to it are straightforward when applied to lifesaving benefits and life-threatening risks. The magnitude of benefit to be gained is sure to seem far more important than either the nature or frequency of harmful effects of, for example, cancer treatment medicines. Cosmetic products are valuable in our daily life, but such an unequivocal choice or balance between unquestionable benefit and risk cannot be expected for these products. "Nonessential" products like cosmetics must not have any risk. In particular, the use of cosmetics that provide no therapeutic benefit must have no risks. This is obviously unrealistic; there is no way to ensure zero capacity to cause harm. Every human activity involves some degree of risk; therefore, there is no logical reason to make an exception for cosmetics. It seems worth attempting to devise a mathematical form of expression for the benefit-risk for cosmetics. However, no one is likely to accept the proposition that a hair cream could justifiably be twice the irritant as another simply because it leaves the hair twice as glossy in appearance. The relationship between benefit and risk is not easily described in mathematical terms, mainly because benefits from using cosmetics are hard to quantify. Moreover, like cosmetics, further emphasis should be placed to ensure the safety of household products.

Human activities include some risk, and there is no exception even in cosmetics. However, there can be little doubt that the "type" and "severity" of any adverse effect should be regarded as the major considerations. Only one or two cases of irreversible loss of sight would show the need to withdraw a product, such as shampoo, from the market immediately, if the causal association was clear, regardless of how many people were known to have used the same product uneventfully. The occurrence of mild inflammation of the skin might not necessitate withdrawal but may suggest the need to develop a better-tolerated formulation for these sensitive populations. An approach to risk-benefit analysis entirely based on the incidence of adverse effects will never suffice: the qualitative nature of risk must always be taken into account. Attention to the severity of adverse effects rather than their numerical incidence is necessary when assessing risks associated with the use of cosmetics.

## 50.4 TO WHAT EXTENT WE SHOULD ASSURE THE SAFETY OF COSMETICS?

As described here, cosmetics represent a family of products that cannot afford to pose a risk that may result from their use. "Foolproof" is the ideal, but it is difficult in reality. Then, to what extent should we ensure the safety of cosmetics? The actual assessment should be made in connection with their use conditions.

Classification of the use conditions could broadly divided into the following four groups (Fig. 50.2): (1) intended use, (2) unintended but reasonably foreseeable use, (3) unintended and reasonably unforeseeable use, and (4) unforeseeable misuse, abnormal use, or unusual use. From the viewpoint of product liability, safety should be ensured

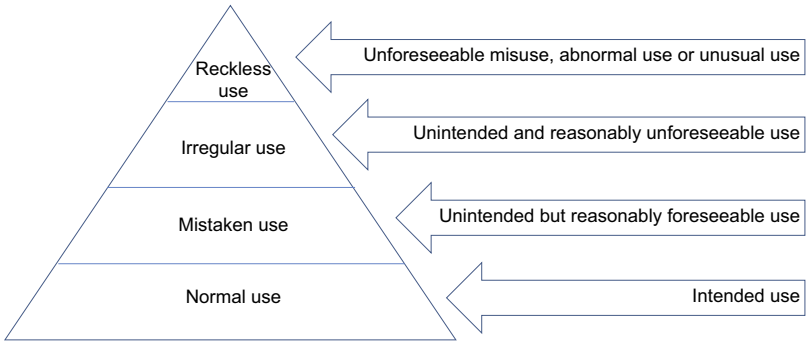



FIGURE 50.2 Use conditions of products.

under the former two use conditions ("intended use" and "unintended but reasonably foreseeable use").[5,6] In the case of a cosmetic product, adequate substantiation must be provided to ensure that the product cannot cause damage to human health under intended use and reasonably foreseeable conditions. Conditions for use differ in each product, and it is essential to investigate the conditions for safety assessment.

## 50.5 PROCESS OF SAFETY EVALUATION

The assessment for each ingredient should be initially performed to review whether it is suitable for use in cosmetic preparations. The next step is the evaluation for formulation composed of a plurality of components. Evaluation of a component alone is sometimes insufficient to ensure that there will be no adverse effects caused by an interaction of the components.

For components to be incorporated into the product, available related data and information are reviewed first. The following information will be needed: identity, structural formula, manufacturing process, chemical and physicochemical properties (purity, characterization of the impurities or accompanying contaminants, stability, analytical methods, etc.), and structure–activity relationships on structural alert for a toxic endpoint like carcinogenicity. For instance, a low-molecular-weight substance having a functional group that binds to cell surface proteins and chemicals capable of nucleophilic substitution reactions at saturated or unsaturated centers would raise a red flag regarding skin sensitization potential.[7]

Because of the frequent unavailability of chemically pure ingredients for cosmetic raw materials, it is required to ascertain not only the purity of an ingredient but also the presence of impurities and possible byproducts. In the case of the presence of a toxicologically relevant impurity, the maximum allowed concentration must be based on toxicological values. There are several examples, such as unreacted free amines, skin sensitizers in quaternary ammonium compounds, 1,4-dioxane, and carcinogenic substances in surfactants, that are produced through the polymerization of ethylene oxide. Methods should be devised for identification of chemical and physicochemical properties of an ingredient's components in order to check the chemical characterization and purity of the ingredient.

A recent health issue[8] shows the need to pay attention to methods of manufacturing. Several cases have been reported of contact urticaria provoked by soaps containing hydrolyzed wheat protein, followed by anaphylactic shock after the ingestion of food containing wheat proteins. The hydrolyzed wheat protein was prepared via partial hydrolysis of wheat gluten with an acid under heating conditions. It has been speculated that cross-reaction occurred with the antibody and wheat, after the absorption of these components from the skin and mucous membranes and the production of specific IgE antibodies to this component. The potential for sensitization depends on molecular weight; the Cosmetic Ingredient Review (CIR) Expert Panel reports in their final report that hydrolyzed wheat gluten and hydrolyzed wheat protein are safe for use in cosmetics when formulated to restrict peptides to a weight-average molecular weight of 3500 Da or less.[9]

The actual safety assessment procedures for ingredients and finished products will vary according to intended use of the product and consumer exposure conditions. Thus, before any safety evaluation and risk assessment, conditions such as degree and route of exposure must be studied. Table 50.1 shows the several factors[10] to be considered in exposure assessment on a product-by-product basis. One must also consider other exposed areas other than the

**TABLE 50.1** Information on Consumer Exposure for Cosmetics

- Class of cosmetic product(s) in which the substance may be used
- Method of application: rubbed-on, sprayed, applied and washed off, etc.
- Concentration of the substance in the finished cosmetic product
- Quantity of product used at each application
- Frequency of application
- Total area of skin contact
- Site of contact (e.g., mucous membrane, sunburnt skin)
- Duration of contact (e.g., rinse-off products)
- Foreseeable misuse that may increase exposure
- Consumer target group (e.g., children, people with "sensitive skin")
- Quantity likely to enter the body
- Application on skin areas exposed to sunlight

originally intended area for that product, like secondary exposure (e.g., inhalation with aerosol product use). In order to ensure the safety up to the aforementioned "use condition 2," exposure assessment should be conducted for the unintended but reasonably foreseeable use.

From all of the information, we determine what we need to focus on or what may be the issue or problem to be solved. From a literature review, human experience, unpublished data, and other considerations, the need for specific studies to ensure the safety of a particular ingredient can be delineated (Fig. 50.3).

If the literature and/or human experience provides sufficient information, studies to accumulate data in specific areas will be unnecessary. By collecting and reviewing the data, only those tests that are needed to fill gaps to complete a safety evaluation should be conducted. In recent years, information gathering has been much easier through the publications and disclosure of safety data, as described in Section 50.7. In cases where very little or no information is available on the biological potential of an ingredient, sufficient preclinical testing such as in vitro and in vivo studies may have to be conducted to elucidate the toxicity of a particular ingredient as a prelude to evaluating its safety-in-use.

General toxicological requirements for safety evaluation are shown in Table 50.2. The skin is an important barrier to prevent substances from penetrating the body; however, this barrier is not impermeable and substances do enter the body to produce adverse effects. When the data on dermal absorption indicate considerable penetration of the ingredient, further information (i.e., repeated-dose toxicity, reproductive and developmental toxicity) may be necessary, taking into account the toxicological profile of the substance and its chemical structure.

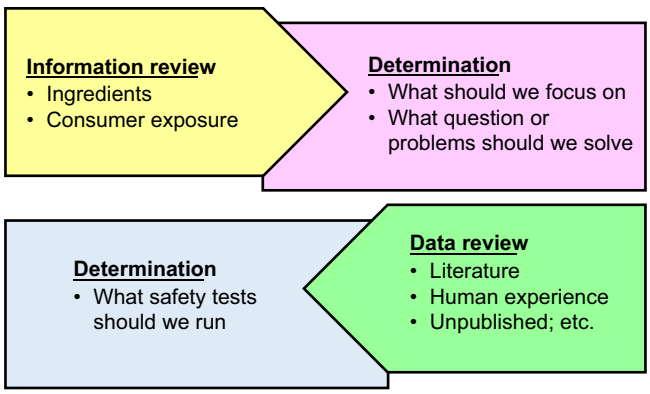



**FIGURE 50.3** Practical evaluation process.

**TABLE 50.2** General Endpoints for Safety Evaluation

- Acute toxicity
- Skin irritation
- Skin sensitization
- Phototoxicity and photosensitization
- Ocular irritation
- Genotoxicity
- Skin absorption

## 50.6 IMPLEMENTATION OF SAFETY TESTS

Type and methods of safety testing can vary considerably with different ingredients and category of the products that will be developed. There is no established testing standard, such as a textbook. An adequate series of toxicological studies should be performed with appropriate methods and test conditions for each cosmetic product in order to suit the purpose of the evaluation and to enable reliable conclusions.

The actual tests are divided along two lines: those aimed at observing potential "topical effects" and those aimed at studying the possibilities that "systemic effects" might occur. The contact or exposure that cosmetic products make with the human body is primarily cutaneous, and topical reactions should, therefore, be our main interest. These toxicity studies are also roughly divided into (1) qualitative evaluation and (2) quantitative evaluation, for purposes of evaluation.

1. Qualitative evaluation:
   Genotoxicity, reproductive toxicity, carcinogenicity, and sensitization are involved, and their related symptoms are severe and irreversible. As for such toxicity, it seems to be difficult to extrapolate to humans from the results of the test using safety margins. Thus, it is essential to check for the toxicological potential designed with high doses as much as possible.
2. Quantitative evaluation:
   Systemic toxicity and irritation are the target. For example, in the case of primary skin irritation, there are an absolute assessment and a comparative approach. As for an absolute assessment, when a maximum nonirritation concentration of the ingredient is higher than its human exposure level, the ingredient can be incorporated into the intended final product at that concentration (Fig. 50.4).

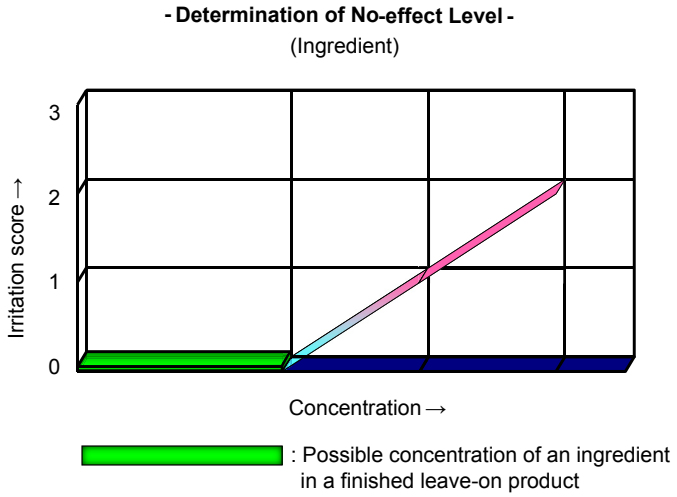



**FIGURE 50.4** Practical assessment of primary skin irritation.

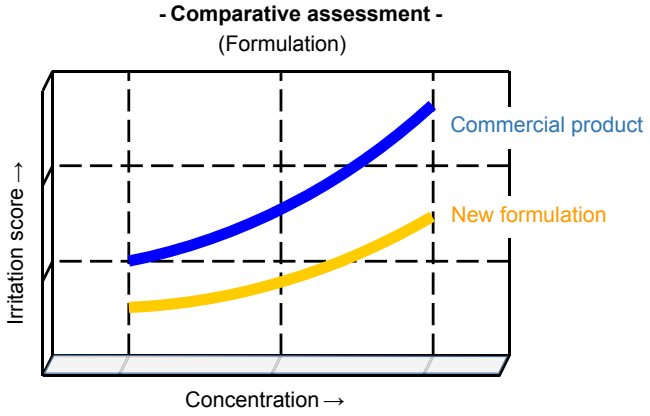



FIGURE 50.5 Comparative assessment on primary skin irritation.

Another possible assessment process is a comparative approach. This approach is to compare the safety aspects of a new preparation directly with those of an existing similar commercial product with known safety records under typical market conditions (Fig. 50.5). A target ingredient can be used as a cosmetic raw material, if its irritation potential is expected to be equivalent to or lower than a raw ingredient that has been already used in the similar applications. However, if the new formulation showed just a little more irritation than the reference, the basic assessment will be seriously weakened. Because the safety record under market conditions is known only for the reference product, the consequences of allowing a little more toxicity will be unpredictable.

It is also important to conduct safety-in-use studies in humans to ensure the predictive reliability of safety evaluation generated from the in vivo and/or in vitro laboratory investigations. It is self-evident that such a test can only be envisaged, provided that the toxicological profiles of the substances based on in vivo testing and/or in vitro methods are available and no concern among human volunteers is raised under the designed test condition. The objective of human use studies is to confirm the safety under the actual use conditions of products and conditions of the earlier-described normal intended use by the manufacturer and reasonably foreseeable exaggerated use should be incorporated into setting test design. In these studies, we would be able to detect the following by observation:

- Sensory irritation—a reaction that transiently occurs without an inflammatory symptom in the form of erythema or edema; involves stinging, burning, and itching sensation
- Comedo formation
- Subjective product attribute unrelated to safety, such as skin feel and, fragrance
- Subtle adverse effects that might have been missed in a previous evaluation

As a reference point in all tests, the expected use dose must be known or ascertained. Data and information on the actual circumstances of use and exposure to cosmetics are available in the Scientific Committee on Consumer Safety's note of guidance in the European Union[10] and "Consumer Product, Ingredient Safety−Exposure and Risk Screening Methods for Consumer Product Ingredients"[11] published by American Cleaning Institute. As shown in Fig. 50.6, detailed data about shampoos have also been reported. The data vary with various factors, such as age and individual habits of shampooing. The protocol for the human use test should be made taking into consideration the information on the target population and use conditions of the product.

Faced with the design of preclinical study, it is particularly essential to carry out the test method which is based on the best current scientific level. Taking the skin sensitization as an example, several experiences revealed that some impurities in chemical products have been identified as allergens. Contents of those impurities are usually so low in the ingredients that their sensitization potential would not be detected by test methods having poor sensitivity.

## 50.7 REEVALUATION AFTER LAUNCH

New cosmetic products will be introduced to the market after a certain predictive safety evaluation; follow-up activity is also essential to ensure product substantiation after the launch (Fig. 50.7). Science in toxicology and

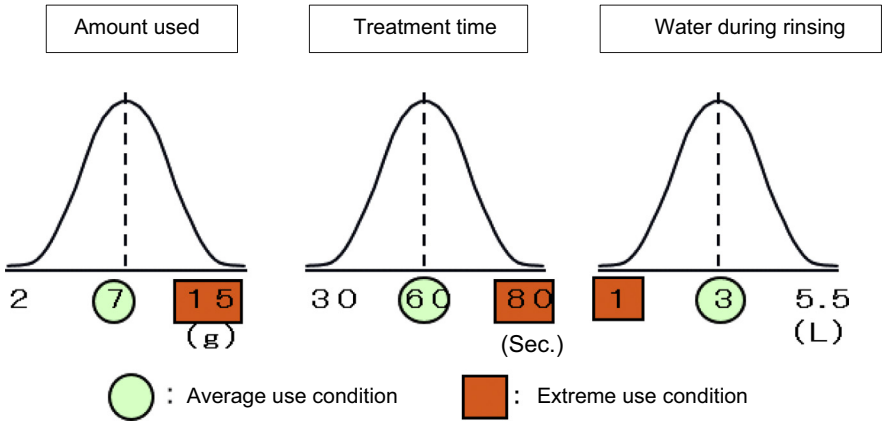



**FIGURE 50.6** Use conditions of shampoo. *Illustrated based on Miura K, et al. Determination of the quantity of piroctone olamine and surfactants on the skin after treatment of hair shampoo and/or hair rinse. J Jpn Cosmet Sci Soc 1983;7(2):172–7.*

safety assessment technology is continuously evolving. Scientific or technical developments may arise concerning or questioning the safety of products that have been on the market and regarded as safe. It may be necessary to reassess the safety-in-use of either existing ingredients or finished products using up-to-date science. There are many sources of safety information relevant to cosmetics. Some of information resources, such as the Scientific Committee on Consumer Safety in the European Union (http://ec.europa.eu/health/scientific_committees/consumer_safety/index) and the Cosmetic Ingredient Review in the United States (http://www.cir-safety.org) provide safety assessments specific to active ingredient use in cosmetics. A lot of toxicology data on existing chemicals has been published as the results of progress on chemical management programs in various countries, and not only for cosmetic ingredients. OECD launched "eChemPortal" (http://www.echemportal.org) in 2007 and began to provide results of safety evaluations for high-production-volume chemicals in OECD including characteristics of the chemical and hazard information; viewers can search multiple databases established by their member countries. There is also a need to continue to grasp such a reevaluation situation after the launch.

In addition, postmarketing surveillance and health complaints after the launch are the important information to reevaluate the safety of the products. The person in charge of the safety assessment should always monitor the information of health complaints. The amount of complaints is important, and, in the case of the human health issues, it is also essential to analyze the nature of them and to find out the cause that should lead to the next action, after marketing reevaluation.

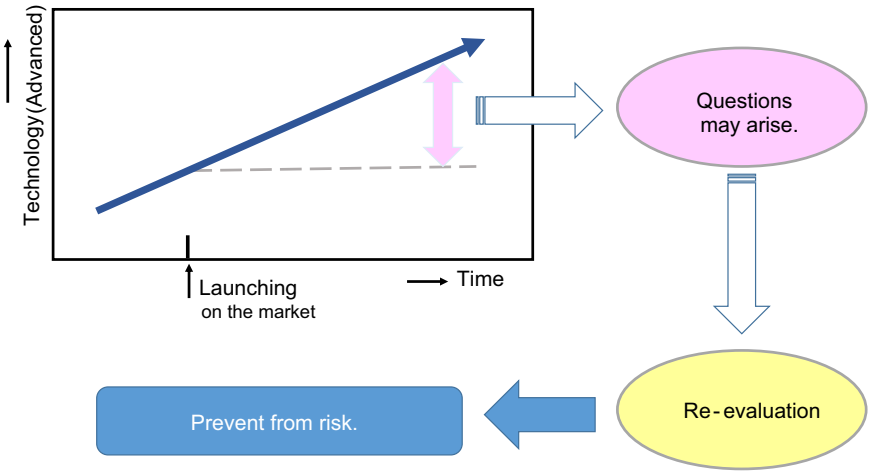



**FIGURE 50.7** Postmarketing safety reevaluation.

## 50.8 CONCLUSION

Several measures for strengthening the in-house safety assessment activities have been taken, such as double- or triple-check systems, the complaint information exchange system, and so on. However, the most important point is to implement safety evaluation with high quality. As mentioned in the previous sections, key activities on safety evaluation should be started by gathering accurate data and information at the first survey and be followed by picking up issues and data gaps with excellent sensitivity toward appropriate solutions. Therefore, we must always accumulate knowledge and experiences and implement the proper safety evaluation with depth.

For reference, guidance documents are provided for safety assessors from Japan, the European Union, and the United States: "Guidance for the Safety Evaluation of Cosmetics" (2015) by the Japan Cosmetics Industry Association,[13] SCCS's "Notes of Guidance for the Testing of Cosmetics Ingredients and Their Safety Evaluation by Scientific Committee on Consumer Safety in the European Union,"[9] and the PCPC 2014 "Safety Evaluation Guidelines" by the Personal Care Products Council in the United States.[14]

## References


1. Deichmann WB, et al. What is there that is not poison? A study of the third defense by Paracelsus. *Arch Toxicol* 1986;**58**:207–13.
2. Giovacchini RP. Adequately substantiating the safety of cosmetic products. *CTFA Cosmet J* 1976;**8**(3):7–11.
3. Van Abbe N. The interpretation of predictive data on the safety-in-use of toiletries and borderline products. *SPC* 1985;**56**:217–20.
4. Van Abbe N. Interpretation of predictive data on safety-in-use of toiletry products. *Int J Cosmet Sci* 1984;**6**:293–9.
5. PL Editors Committee, The Union of Japanese Scientists and Engineers, *Technologies and systems for ensuring the safety*, vol. 2, Product liability and product safety, The Union of Japanese Scientists and Engineers, Tokyo, 1992.
6. National Institute of Technology and Evaluation (Japan). Classification of "improper usage" and who is responsible. In: *Handbook for prevention of accidents arising from improper use or human error (for businesses)*; 2005 [Chapter 1].
7. Dupuis G, Benezra C. *Allergic contact dermatitis to simple chemicals*. New York: Marcel Dekker Inc.; 1982.
8. The Japanese Dermatological Association. Safety use of cosmetics – learned from health issues on cosmetics. In: *Lecture open to the public at 114th annual meeting of the Japanese Dermatological Association*; May 31, 2015. https://www.dermatol.or.jp/uploads/uploads/files/news/20150605shiminkoukaikouzashiryou.pdf.
9. Cosmetic Ingredient Review. *Safety assessment of hydrolyzed wheat protein and hydrolyzed wheat gluten as used in cosmetics*. June 2014.
10. Scientific Committee on Consumer Safety. The SCCS notes of guidance for the testing of cosmetic ingredients and their safety evaluation, 9th revision. In: *The SCCS adopted this guidance document at its 11th plenary meeting of 29 September 2015*; 2015.
11. American Cleaning Institute. *Consumer product, ingredient safety- exposure and risk screening methods for consumer product ingredients*. 2nd ed. 2010.
12. Miura K, et al. Determination of the quantity of piroctone olamine and surfactants on the skin after treatment of hair shampoo and/or hair rinse. *J Jpn Cosmet Sci Soc* 1983;**7**(2):172–7.
13. Japan Cosmetic Industry Association. *Guidance for the safety evaluation of cosmetics 2015*. Yakuji Nippo Limited; 2015.
14. The Personal Care Products Council. *Personal care products council technical guidelines, safety evaluation guidelines*. 2014 ed. 2014.

CHAPTER

# 51

# Safety Assessment of Cosmetic Ingredients

*H. Kojima*

**National Institute of Health Sciences (NIHS), Tokyo, Japan**

## 51.1 INTRODUCTION

Cosmetic products have seldom been associated with serious hazards to health. And although it is not possible to attain either zero risk or absolute safety in any kind of human activity, reasonable efforts have always been made to minimize the risks from cosmetic products in accordance with the state of the art at the time.[1] The goal of any safety evaluation of cosmetic products and ingredients is to ensure that the consumer will experience no adverse effects under either recommended and customary conditions of use or reasonably foreseeable conditions of misuse.[2] This does not mean, however, that cosmetics are absolutely safe, nor does it rule out possible effects of long-term use. But given the potential for these products to be used extensively over a large part of the human life span, there is a clear need to ensure safe use by controlling the content and toxicity of ingredients.[1] The manufacture of cosmetic products should therefore take into consideration the general profile of the ingredients, their chemical structures, and level of exposure.

The European Union (EU) has mandated an approach to the safety assessment of cosmetics that is also widely requested by buyers and authorities in North America, the ASEAN Cosmetics Directive, Saudi Arabia, and other countries like China, Korea, and Japan.[3] There are a number of international regulations for the safety assessment of cosmetic products. And insofar as every cosmetic product contains a combination of ingredients, manufacturers are free to include other, unregulated ingredients in their products, provided those products conform to all aspects of safety assessment as required by regulation, including requirements that cosmetic products be clearly labeled with a list of all ingredients in their formulations.[3]

Ingredients used in the formulation of cosmetics worldwide are classified under the International Nomenclature for Cosmetics Ingredients (INCI),[4] and all manufacturers are required to conform to this system. This would guarantee that ingredients are all described in a standardized form on all product labels worldwide. The INCI list is updated regularly and currently contains descriptions for more than 14,000 ingredients. The nature and preparation of some of these ingredients affect the data necessary to identify them properly. One goal of regulating cosmetic products is to ensure that they contain only safe ingredients. Technical annexes included in regulations contain information used to govern the manner in which certain substances are used in the formulation of cosmetics. Negative lists specify banned substances as well as those subject to specific restrictions. Positive lists specify substances that have been approved for use in cosmetics as coloring agents, preservatives, and UV filters.[3]

There are now concerns about cosmetic ingredients containing complex substances derived from minerals, animals, or plants using biotechnology. These concerns include aromatic ingredients, potential endocrine disruptors, and animal-derived cosmetic ingredients that could contain bovine spongiform encephalopathy and carcinogenic, mutagenic, or toxic-to-reproduction substances.[3] The use of such substances in the manufacture of cosmetics requires special consideration of safety issues.

It is generally possible to assess the safety of a formulation by analyzing the relevant toxicological endpoints of each ingredient in relation to the expected product exposure. This does require, however, that an adequate volume of information be provided to enable a proper assessment of the safety of the final product. Sufficient information, including the results of toxicological testing, about cosmetic ingredients generally obviates the need to test the finished cosmetic product, provided that the toxicological information on the ingredients includes evaluations of the most relevant toxicological endpoints.[1] There are some cases, however, in which the formulations used in the finished product were different from what was used in the toxicological studies of the ingredients. Thus, when

*Cosmetic Science and Technology: Theoretical Principles and Applications*
http://dx.doi.org/10.1016/B978-0-12-802005-0.00051-3



Copyright © 2017 Elsevier Inc. All rights reserved.

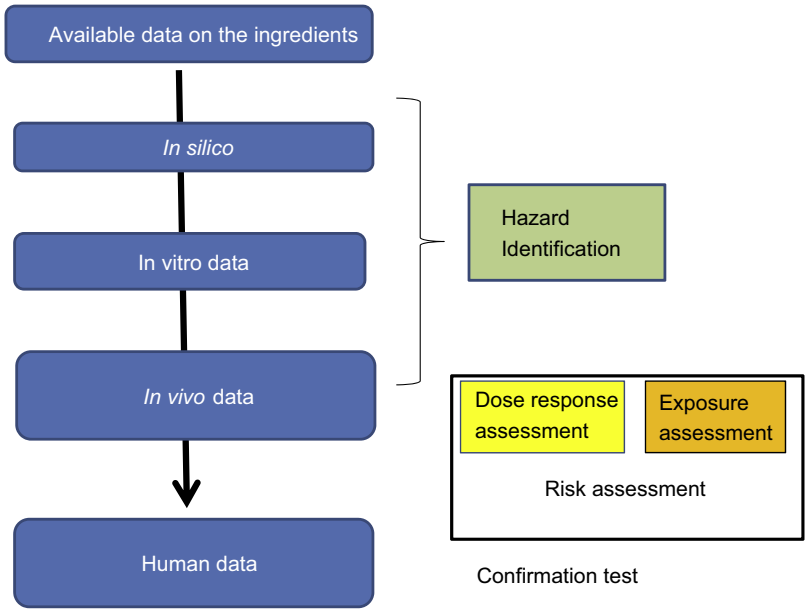



**FIGURE 51.1** Flow for the safety evaluation of cosmetic ingredients.

increases in penetration or irritancy of the ingredients are a concern, additional information on the finished products themselves is necessary to enable a more accurate assessment of safety.[1]

The safety assessment of finished products must take into account any number of different things, including the physicochemical and toxicological data as well as chemical structure of the ingredients, data from in vitro, animal, and clinical testing of finished products, and potential product exposure.[2] A first step in the safety evaluation of a finished product is a thorough review of the toxicological profile of the ingredients, based on the items shown in Fig. 51.1. Put another way, careful selection of ingredients is a primary consideration in ensuring the safety of finished products.[2] It is essential to consider industry and regulatory standards as well as legal requirements associated with certain ingredients as part of the selection process. The Cosmetic Ingredient Review[5] and Scientific Committee for Consumer Safety notes and the advisory body to the European Commission[6] are valuable sources of information specific to the safety of cosmetic ingredients, which primarily are chemicals of synthetic or natural origin as well as mixtures thereof. These databases are a valuable source of information for selecting ingredients. Nevertheless, additional safety testing is warranted when the existing information is inadequate to ensure the safety of a product or when a new safety issue arises. Additional testing is also desirable to provide confirmatory evidence of the safety of an ingredient or product[2] for which safety data exists. Computer predictions made using structure–activity relationships, also known as in silico methods, can also be used as a part of the safety evaluation. When the degree of purity and the physical, chemical and physicochemical properties of an ingredient are known, it is often possible to devise in silico methods for identification as well as qualitative and quantitative control.[1] Safety evaluations should be done with a variety of software, since it is always necessary to be on the alert for biased interpretation. Among the factors that must be taken into consideration are the degree of chemical purity and stability, possible interactions with other ingredients in the formulation, and the potentiation of skin penetration. In general, the presence of impurities is technically unavoidable. But these impurities must have no significant toxicological relevance in the finished product. As a next step, it is necessary to perform toxicological tests that are representative of those required to assess the safety of cosmetic ingredients, which is also a good indication of the great number of tests that are necessary to assure safety in humans. Recently, the United Nations (UN) Globally Harmonized System for the Classification and Labeling of Chemicals (GHS)[7] created definitions of some toxicological endpoints that follow the application of a chemical, and this information is useful for confirming the toxicological profile.

## 51.2 TOXICOLOGICAL STUDY

The toxic potential of a cosmetic ingredient is generally determined through a series of toxicological studies and forms a part of hazard identification, which is the first step in overall risk assessment.[3] At present, a majority of these toxicological tests still involve the use of animals, as is also the case for other chemical substances. Traditionally, toxicological data relevant to humans have been obtained by investigating the toxicological profiles of the

ingredients under consideration on animals, using the same topical, oral, or inhalation route in the laboratory animal as would be expected for human exposure.[3] In this way, a cosmetic ingredient is determined to be at a no-effect level or a nonobserved adverse effect level, and the likely effects after the exposure to high levels are observed.[1,3]

The cosmetic industry complies with guidelines and guidance from regulatory agencies in each country or region for assessing the safety of cosmetic products and novel cosmetic ingredients. Table 51.1 shows a high degree of similarity between regulatory guidelines and guidance in the EU, United States, and Japan.[1,2,8] In contrast, Table 51.2 shows that there is far less concordance between guidelines issued by regulatory agencies in Japan, the EU, China, and Korea, although these countries have proposed that toxicological data for novel cosmetic ingredients be maintained.[3,9,10] Additionally, Japan, China, and Korea all recognize a category of functional cosmetic products that are called quasi-drugs, special cosmetics, and functional cosmetics, respectively. Table 51.2 shows the types of analytical and toxicological data that regulatory agencies in these three countries request prior to approval of functional cosmetic products. Needless to say, a significant volume of animal testing is needed to obtain these toxicological data.

These guidelines apply primarily to new cosmetic ingredients but could also be applied to other ingredients for which there are concerns over safety-in-use, bearing in mind the relevant toxicity data already in existence. Such guidelines have been drawn up in general terms and will require amendment as scientific knowledge advances in the future.[1] This includes brief descriptions of a number of standard toxicological test procedures applicable to finished products and their ingredients. These descriptions can be an aid to the selection and design of appropriate procedures for safety testing as well as to identifying representative tests that, in the judgment of trained industry toxicologists, are suitable for substantiating the safety of ingredients and finished products.

**TABLE 51.1** Test Methods for Safety Evaluation of Cosmetic Ingredients Defined by Each Cosmetic Industry Association

|  |  |  |
|---|---|---|
| **JCIA Safety Evaluation Guidance (2015)[8]** | **PCPC Safety Evaluation Guideline (2014)[2]** | **Cosmetic Europe, COLIPA Guideline (2004)[1]** |
| Single-dose toxicity | Oral toxicity | Acute toxicity (oral or inhalation) |
| Repeat-dose toxicity | Dermal toxicity | Subchronic toxicity (oral or inhalation) |
| | Inhalation toxicity | |
| Primary skin irritation | Primary dermal irritation | Dermal irritation |
| Cumulative skin irritation | | |
| Skin sensitization | Dermal sensitization | Skin sensitization |
| Phototoxicity | Phototoxicity and photoallergy | Phototoxicity |
| Photosensitization | | |
| Ocular irritation | Eye irritation | Eye irritation |
| Genotoxicity | Genotoxicity | Mutagenicity |
| Human patch test | Controlled use studies in human | Human data |
| | | Toxicokinetics |
| | Mucous membrane irritation | Mucous membrane irritation |
| Skin absorption | Skin absorption | Dermal absorption |
| Reproductive and developmental toxicity | Reproductive and developmental toxicity | Reproductive toxicity, carcinogenecity, additional genotoxicity |

TABLE 51.2 Test Methods for Safety Evaluation of Ingredients for Regulatory Use

|  |  |  |  |
|---|---|---|---|
| **Quasi-drug Safety Evaluation Guidance (2008)[9]** | **SCCS Safety Evaluation Guidance/(2012)[3]** | **Special Cosmetic Safety Evaluation Guideline[10]** | **Functional Cosmetic Safety Evaluation Guideline[10]** |
| Acute toxicity | Acute toxicity | | Acute toxicity |
| Repeat-dose toxicity (subchronic, chronic) | Repeat-dose toxicity | | |
| Reproductive toxicity | Reproductive toxicity | | |
| Skin irritation | Corrosivity and irritation | Acute skin irritation | Primary skin irritation |
| | - | Cumulative skin irritation | - |
| Skin sensitization | Skin sensitization | Skin sensitization | Skin sensitization |
| | Photo-induced toxicity | | Phototoxicity |
| Photosensitization | | Photosensitization | Photosensitization |
| Mucous membrane irritation | | Acute eye irritation | Eye or mucous membrane irritation |
| Genotoxicity | Mutagenicity/genotoxicity | Genotoxicity | |
| | Human data | Human patch test | Human patch test |
| | | Controlled-use studies in human | Human repeat insult patch test |
| ADME | Toxicokinetics | | |
| | Dermal/percutaneous absorption | | |
| Carcinogenecity | Carcinogenecity | | |

## 51.3 CURRENT UPDATE

The European Cosmetics Directive provides a regulatory framework for the phasing out of animal testing in the development of cosmetics in accordance with the "three Rs" of the use of animals in testing.[11] The directive includes a testing ban, which prohibits the use of animals in the testing of either finished cosmetic products or cosmetic ingredients, as well as a marketing ban, which prohibits the marketing and sales in the EU of either finished cosmetic products or cosmetic ingredients that were tested using animals. These same provisions are contained in the Cosmetics Regulation, which replaced the Cosmetics Directive as of July 11, 2013. The testing ban on finished cosmetic products has been in effect since September 11, 2004, and the testing ban on ingredients or combinations of ingredients has been in effect since March 11, 2009. The marketing ban has been in effect since March 11, 2009 for all human health effects with the exception of repeated-dose toxicity, reproductive toxicity, and toxicokinetics. Since March 11, 2013, however, the marketing ban has been in effect for even these specific health effects, irrespective of the lack of availability of alternative nonanimal tests.[12] Expert opinion in this field has confirmed that it will take at least another 7–9 years to adequately replace the battery of in vivo animal tests currently used to assess the safety of cosmetic ingredients for skin sensitization. In the field of toxicokinetics, the timeframe has been given as 5–7 years to develop new models for predicting lung absorption and renal/biliary excretion and even longer to integrate these methods so as to fully replace toxicokinetic models based on animals. There is no estimate available for the full replacement of models used in the assessment of systemic toxicological endpoints of repeated-dose toxicity, carcinogenicity, or reproductive toxicity.[13] Despite these issues, a political decision was made to enact the directive and subsequent regulation. However, the cosmetic industry has defined a variety of test methods for safety evaluation of cosmetic ingredients, as shown in Table 51.1.

Data for assessing the safety of finished products have traditionally been obtained from animal tests on both the individual ingredients and the final formulation or on one of these two alone. The cosmetic industry has been at the forefront of research into the development of nonanimal alternative methods for more than 25 years and is

committed to the eventual elimination of animal testing as soon as practicable. The enactment of the EU Cosmetics Regulation, however, has been followed by the enactment of similar animal testing bans on the development of cosmetic products and ingredients worldwide.

We believe that there is an urgent need for international deliberation of the EU directive itself as well as of how to handle new cosmetic products and ingredients that were developed without animal testing.

## 51.4 INTERNATIONAL TEST GUIDELINES

The OECD assists countries in harmonising test methods for chemical safety. The following OECD test guidelines (TGs),[14] including draft TG and ICH test guidelines,[15] describe methods for testing cosmetic ingredients based on common toxicological principles. Table 51.3 shows a variety of in vitro test methods that are suitable for use as an alternative to animal testing. Although a number of in vitro methods for evaluating the toxicological potential of chemical substances have been reported in the literature, most have not yet been sufficiently validated for use in areas other than screening for genotoxicity and prescreening for severe irritancy.[1] Moreover, the in vitro methods available so far have not yet been validated thoroughly enough to be included in regulatory guidelines at this time. Nor do the results of in vitro tests lend themselves easily to quantitative risk assessment, since they are used more commonly in the assessment of nonsystemic endpoints. The use of suitable alternative methods in the context of safety assessment should be limited to methods that have undergone formal validation by a national validation body.

The following are current in vitro test methods that are suitable for use as alternatives to animal testing and for which OECD TGs[14] are available. Though any test method that either reduces or refines animal use can be considered an "alternative," in consideration of EU regulations,[12] the following list focuses on in vitro test methods.

### 51.4.1 Acute Toxicity

#### *51.4.1.1 Acute Oral Toxicity*

The fixed-dose method (TG 420), the acute toxic class method (TG 423), and the up-and-down procedure (TG 425) have been approved by the OECD as alternative test methods.

There is no fully validated in vitro test method that is suitable to replace in vivo acute oral toxicity testing for regulatory use. EURL ECVAM has, however, published a recommendation on the 3T3 Neutral Red Uptake (3T3 NRU) Cytotoxicity Assay[16] for the Identification of Substances Not Requiring Classification for Acute Oral Toxicity According to the EU Classification, Labeling and Packaging System (CLP).

#### *51.4.1.2 Acute Inhalation Toxicity*

The fixed concentration procedure (TG 433) and the acute toxic class method (TG 436) have been approved by the OECD as alternative test methods.

There is no fully validated in vitro test method that is suitable to replace in vivo acute inhalation toxicity testing for regulatory use.

#### *51.4.1.3 Acute Dermal Toxicity*

The fixed concentration procedure (TG 434) is being discussed by the OECD as an alternative test method.

There is no fully validated in vitro test method that is suitable to replace in vivo acute dermal toxicity testing for regulatory use.

### 51.4.2 Corrosivity and Irritation

#### *51.4.2.1 Corrosion*

There are three in vitro test methods that have been approved by the OECD as alternative test methods for evaluating skin corrosion. They were revised in 2015 to enable evaluation of the reductants.

- TG 430: In vitro Skin Corrosion: Transcutaneous Electrical Resistance Test Method (TER) is an alternative to TG 404: Acute Dermal Irritation/Corrosion. It was last revised in 2015.

**TABLE 51.3** OECD Test Guidelines for In Vitro Test Method (2015)[14]

| Class | Test Methods |
|---|---|
| Corrosion | In vitro Skin Corrosion: Transcutaneous Electrical Resistance Test Method (TER): TG 430 |
| | In vitro Skin Corrosion: Reconstructed Human Epidermis (RHE) Test Method: TG 431 |
| | CORROSITEX Skin Corrosivity Test: TG 435 |
| Skin irritation | In vitro Reconstructed Human Epidermis (RhE) Test Methods, EpiDerm, EPISKIN, SkinEthic, LabCyte EPI-Model: TG 439 |
| Phototoxicity | 3T3 NRU Phototoxicity Test: TG 432 |
| Eye irritation | Bovine Corneal Opacity and Permeability Test Method for Identifying (i) Chemicals Inducing Serious Eye Damage and (ii) Chemicals Not Requiring Classification for Eye Irritation or Serious Eye Damage: TG 437 |
| | Isolated Chicken Eye Test Method for Identifying (i) Chemicals Inducing Serious Eye Damage and (ii) Chemicals Not Requiring Classification for Eye Irritation or Serious Eye Damage: TG 438 |
| | Fluorescein Leakage Test Method for Identifying Ocular Corrosives and Severe Irritants: TG 460 |
| | Short Time Exposure In vitro Test Method for Identifying (i) Chemicals Inducing Serious Eye Damage and (ii) Chemicals Not Requiring Classification for Eye Irritation or Serious Eye Damage: TG 491 |
| | Reconstructed Human Cornea-like Epithelium (RhCE) Test Method for Identifying Chemicals Not Requiring Classification and Labeling for Eye Irritation or Serious Eye Damage: TG 492 |
| Skin sensitisation | In Chemico Skin Sensitisation, Direct Peptide Reactivity Assay (DPRA): TG 442C |
| | In Vitro Skin Sensitisation, ARE-Nrf2 Luciferase Test Method: TG 442D |
| Endocrine disrupter screening | Performance-based Test Guideline for Stably Transfected Transactivation In vitro Assays to Detect Estrogen Receptor Agonists and Antagonists: TG 455 |
| | H295R Steroidogenesis assay: TG 456 |
| | BG1Luc Estrogen Receptor Transactivation Test Method for Identifying Estrogen Receptor Agonists and Antagonists: TG 457 |
| | Performance-Based Test Guideline for Human Recombinant Estrogen Receptor (hrER) In vitro Assays to Detect Chemicals with ER Binding Affinity: TG 493 |
| Genotoxicity | Bacterial Reverse Mutation Test: TG 471 |
| | In vitro Mammalian Chromosome Aberration Test: TG 473 |
| | In Vitro Mammalian Cell Gene Mutation Tests Using the Hprt and xprt Genes: TG 476 |
| | In vitro Micronucleus Test: TG 487 |
| | In Vitro Mammalian Cell Gene Mutation Tests Using the Thymidine Kinase Gene: TG 490 |
| Skin absorption | Skin Absorption: In vitro Method: TG 428 |

- TG 431: In vitro Skin Corrosion: Reconstructed Human Epidermis (RhE) Test Method (EpiSkin, EpiDerm SCT, Skin Ethic RHE, epiCS) is an Alternative to TG 404: Acute Dermal Irritation/Corrosion. It was last revised in 2015.
- TG 435: In vitro Membrane Barrier Test Method for Skin Corrosion is an Alternative to TG 404: Acute Dermal Irritation/Corrosion. It was last revised in 2015.

#### 51.4.2.2 Skin Irritation

This TG describes an in vitro procedure suitable for use in hazard identification of UN GHS Category 2 irritant chemicals (substances and mixtures).

- TG 439: In vitro Skin Irritation Testing: Reconstructed Human Epidermis Test Method (Episkin, Epiderm, SkinEthics and LabCyte EPI-Model) is an alternative to TG 404: Acute Dermal Irritation/Corrosion. It was last revised in 2015.

#### 51.4.2.3 Eye Irritation

There is no fully validated in vitro test method that is suitable to replace the in vivo Draize test for eye irritation, and the use of anesthetics is recommended to reduce the pain and distress inherent in performing the revised TG 405: Acute Eye Irritation/Corrosion. The following in vitro test methods are useful in either a bottom-up or top-down approach.[17]

- TG 437: Bovine Corneal Opacity and Permeability Test Method for Identifying (i) Chemicals Inducing Serious Eye Damage and (ii) Chemicals Not Requiring Classification for Eye Irritation or Serious Eye Damage
- TG 438: Isolated Chicken Eye Test Method for Identifying (i) Chemicals Inducing Serious Eye Damage and (ii) Chemicals Not Requiring Classification for Eye Irritation or Serious Eye Damage
- TG 460: Fluorescein Leakage Test Method for Identifying Ocular Corrosives and Severe Irritants
- TG 491: Short Time Exposure In Vitro Test Method for Identifying (i) Chemicals Inducing Serious Eye Damage and (ii) Chemicals Not Requiring Classification for Eye Irritation or Serious Eye Damage
- TG 492: Reconstructed Human Cornea-like Epithelium (RhCE) Test Method for Identifying Chemicals Not Requiring Classification and Labeling for Eye Irritation or Serious Eye Damage

### 51.4.3 Skin Sensitization

The Local Lymph Node Assay (LLNA) (TG 429) was developed in 2002 as an alternative test method for evaluating the skin sensitization potential of cosmetic ingredients and revised in 2010. In chemico and in vitro TGs have since been developed to assess the human health hazard of skin sensitization, which, as defined by the UN GHS, is an allergic response following skin contact with a test chemical. These assays are recommended for use as part of an Integrated Approach to Testing and Assessment (IATA)[18] in order to discriminate between sensitizers and nonsensitizers for the purpose of hazard classification and labeling.

- TG 442C: In chemico Skin Sensitisation: Direct Peptide Reactivity Assay (DPRA) (2015)
- TG 442D: In vitro Skin Sensitisation: ARE-Nrf2 Luciferase Test Method (2015)
- TG442E: In vitro Skin Sensitisation: h-CLAT Test Method

### 51.4.4 Skin Absorption

TG 428 describes a test method that was designed to provide information on the absorption of a test substance (preferably radiolabeled) that is applied to the surface of a skin sample separating the donor chamber and the receptor chamber of a diffusion cell. Either static or flow-through diffusion cells are suitable.

- TG 428: Skin Absorption: In vitro Method Is an Alternative to TG 427: Skin Absorption: In vivo Method (2004)

It is considered an essential combination of the OECD test guideline and basic criteria on Scientific Committee for Consumer Safety for in vitro dermal/percutaneous absorption studies.[5]

### 51.4.5 Repeated-Dose Toxicity

There is no fully validated in vitro test method that is suitable to replace in vivo acute dermal toxicity testing for regulatory use. Safety Evaluation Ultimately Replacing Animal Testing (SEURAT) is a research initiative to address the long-term strategic targets.[19] The first step in this process is called SEURAT-1, a name that is intended to indicate that more steps will have to be taken before the final goal is reached. SEURAT-1 will develop knowledge and technology building blocks required for the development of solutions to replacing current in vivo repeated dose systemic toxicity testing used for the assessment of human safety.

### 51.4.6 Reproductive Toxicity

There is no fully validated in vitro test method that is suitable to replace in vivo acute dermal toxicity testing for regulatory use.

During the 1990s, three alternative methods were developed, but these were restricted to embryotoxicity: the whole embryo culture test, the micromass test, and the embryonic stem cell test (EST).[20] The applicability domain of these three tests is still under discussion, and they are not yet available for use in risk assessment. The EST is considered a screening test and will require further research.

### 51.4.7 Genotoxicity

The following options for a standard test battery are considered equally suitable.

- TG471: Bacterial Reverse Mutation Test
- TG473: In vitro Mammalian Chromosome Aberration Test
- TG476: In vitro Mammalian Cell Gene Mutation Tests Using the Hprt and xprt Genes
- TG 487: In vitro Micronucleus Test
- TG490: In vitro Mammalian Cell Gene Mutation Tests Using the Thymidine Kinase Gene

### 51.4.8 Carcinogenicity

There is no fully validated in vitro test method that is suitable to replace in vivo carcinogenicity testing for regulatory use. Although a TG for the in vitro cell transformation assay is desirable, it is still an OECD guidance document.[18]

### 51.4.9 Toxicokinetic Studies

There is no fully validated in vitro test method that is suitable to replace in vivo toxicokinetic studies for regulatory use.

### 51.4.10 Phototoxicity

TG 432 describes a method for assessing photocytotoxicity by exposing cells to a test chemical and then comparing the relative viability of the cells as measured in the absence of light and in the presence of light. In addition to light absorption and distribution to light-exposed tissue, the generation of a reactive species from drug candidates following absorption of UV−visible light is described as a key characteristic of chemicals that cause phototoxic reactions in the ICH S10 guideline.[15]

- TG 432: In vitro 3T3 NRU Phototoxicity Test (2004)
- The Reactive Oxygen Species (ROS) assay and in vitro 3T3 NRU Phototoxicity Test for Screening Substances for Photosafety Evaluation of Pharmaceuticals S10 under ICH Guideline (2013)

### 51.4.11 Human Data

Human patch test and controlled-user test data are available to confirm the absence of toxicological concerns. It is inconceivable that the testing of human volunteers could replace animal tests. Both animal testing and testing with alternative methods are known to be of limited value in predicting response in human beings. Therefore, the testing of human volunteers is invaluable, both scientifically and ethically,[3] to confirm that the absence of harmful effects when applying a cosmetic product to humans or to mucous membranes for the first time.

In vitro test methods are considered necessary for regulatory within merits and demerits that can be characterized as follows:

1. In vitro test methods are useful for hazard identification but not for risk assessment, with the exception of in vitro skin absorption assays (dose−response, exposure route, etc.). For example, the in vitro skin irritation method (TG 439)[14] provides an in vitro procedure that may be used for hazard identification of substances and mixtures

classified as UN GHS Category 2 (irritants). TG 439 can also be used to identify chemicals classified as No Category, provided that there is no need to identify the optional UN GHS Category 3 (mild irritants).

2. In vitro test methods are likely not to be sufficient as a stand-alone method to evaluate the toxic potential of chemicals based on the activation of pathways.
3. Combinations of in silico, in chemico, in vitro, and other alternative methods within IATA[18] will be needed to substitute for the animal tests currently in use for specific Adverse Outcome Pathway[18] mechanistic coverage.

## 51.5 INTERNATIONAL TRENDS IN REGULATORY USE FOR COSMETICS

### 51.5.1 International Cooperation on Cosmetic Regulation[21]

The International Cooperation on Cosmetic Regulation (ICCR) is an international group of regulatory authorities from Canada, the EU, Japan, and the United States. ICCR members work together to promote regulatory alignment, in order to maximize consumer protection while minimizing barriers to trade. The following provides more information on ICCR.

Alternatives to animal testing in the area of cosmetics has been a working item for ICCR since its first meeting in 2007, when regulatory authorities committed to increased collaboration in the area of validation of alternative methods. This lead to the creation of the International Cooperation on Alternatives to Animal Testing (ICATM)[22] in 2008 to promote consistent and enhanced voluntary international cooperation, collaboration, and communication among the partners of the ICATM, which were Canada, the EU, Japan, Korea, and the United States. Updates on the validation of alternative methods in the ICCR regions were first presented at ICCR 3 in 2009 and continue to this day. At ICCR 5 in 2011, a report, "Applicability of Animal Testing Alternatives in Regulatory Frameworks within ICCR Regions," described processes and proposed mechanisms in each jurisdiction for regulatory acceptance of the use of alternative methods in the area of cosmetics.

On the other hand, at ICCR 6 in 2012, an overview was provided on the potential application of quantitative structure–activity relationship (QSAR) prediction models for the safety assessment of cosmetic ingredients. Thereafter, it was agreed that "QSAR/in silico" computational toxicology be added to the ICCR agenda, and a new working group was formed to further explore in silico models applicable to personal care products. The working group presented its report, "In silico Approaches for Safety Assessment of Cosmetic Ingredients" at ICCR 8 in 2014, when it was agreed that QSAR/in silico should remain on the ICCR agenda. Additionally, the ICCR Steering Committee requested the working group to develop a draft Terms of Reference that will be provided to the steering committee for input. The working group will also provide an update of activities at the ICCR 10 meeting in July 2016.

### 51.5.2 Cosmetics Europe[23]

Cosmetics Europe has taken the challenge and will continue to work with its research partners to take advantage of new scientific insights and technologies to improve its toolbox for assessing substances for safe use in cosmetic products with the Long Range Science Strategy (LRSS) Research Program for 2016–20.

The research program will focus mainly on repeat-dose toxicity, bioavailability [absorption, distribution, metabolism, and excretion (ADME)], and systemic toxicity.

The major goals are:

1. Animal-free prediction of risk of human toxicity (for cosmetic ingredients and products), which will:
   a. Maintain the possibility to innovate with new substances and
   b. Allow the cosmetics industry to keep safely using the existing substances.
2. Broad scientific and regulatory acceptance

   To develop new alternatives approaches, the LRSS research program uses a framework that combines exposure and hazard information and can be flexibly applied depending on the context and degree of acceptable uncertainty.

   An international consortium of 39 partner organizations including Cosmetics Europe will be funded by the European Commission to work on the integration of new concepts for regulatory chemical safety assessment. These new concepts involve cutting-edge human-relevant in vitro *non*animal methods and in silico computational technologies to translate molecular mechanistic understanding of toxicity into safety testing strategies. The ultimate goal is to deliver reliable, animal-free hazard and risk assessment of chemicals.

**TABLE 51.4** Guidance for Alternative Test Methods for Novel Ingredients Using Quasi-drugs in Japan[24]

| No. | Guidance for Alternative Test Methods |
|---|---|
| 1 | Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, the Ministry of Health, Labor and Welfare, administrative notice entitled "guidance on the use of alternative test methods for skin-sensitization and phototoxicity in safety assessment of cosmetics and quasi-drugs (Appendix 2: Guidance on the use of the in vitro 3T3 NRU phototoxicity test as an alternative test method in safety assessments of cosmetics and quasi-drugs), dated April 26, 2012 |
| 2 | Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, the Ministry of Health, Labor and Welfare, administrative notice dated May 30, 2013, entitled "guidance on the use of alternative test methods for skin-sensitization (LLNA:DA, LLNA:BrdU-ELISA) in safety assessments of cosmetics and quasi-drugs" |
| 3 | Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labor and Welfare, notification 0204, no. 1, dated February 4, 2014, and entitled "guidance on the use of the Bovine Corneal Opacity and Permeability (BCOP) test as an alternative method for testing ocular irritation in the safety assessment of cosmetics and quasi-drugs" |
| 4 | Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labor and Welfare, administrative notice entitled " Points of consider for ocular irritation testing in the safety assessment of cosmetics and quasi-drug, dated February 27, 2015 |
| 5 | Alternative test method guidance review meeting on safety assessment of quasi-drugs and other products, November 16, 2015, "guidance on use of the Isolated Chicken eye (ICE) test as an alternative method for testing ocular irritation in the safety assessment of cosmetics and quasi-drugs" |

EU-ToxRisk program (2016–20) intends to become the European flagship for animal-free chemical safety assessment. It builds on testing strategies and knowledge developed in previous national and European projects, including the SEURAT-1 program,[19] a cluster of seven projects in the field of animal-free safety assessment: 2010–15.

3. Guidance for quasi-drugs in Japan

As described in a Ministry of Health, Labor and Welfare (MHLW) notification in 2011,[24] the Japanese Center for the Validation of Alternative Methods (JaCVAM)[25] is strengthening its support of the development of new in vitro testing methods in Japan and since 2012 has been helping coordinate guidance on the use of alternative test methods in assessing the safety of cosmetics and quasi-drugs. JaCVAM members include dermatologists, delegates of cosmetic companies, technical officers from the Pharmaceuticals and Medical Devices Agency, and specialists from the National Institute of Health Sciences, who are involved in the drafting of guidance based on OECD test guidelines as well as JaCVAM evaluation documents for each alternative test method. MHLW-approved guidance is shown in Table 51.4.

**a.** Guidance on the use of alternative test methods for skin sensitization and phototoxicity in safety assessment of cosmetics and quasi-drugs (Appendix 2: Guidance on the Use of the in vitro 3T3 NRU Phototoxicity Test as an Alternative Test Method in Safety Assessments of Cosmetics and Quasi-drugs),

**b.** Guidance on the use of alternative test methods for skin sensitization (LLNA:DA, LLNA:BrdU-ELISA) in safety assessments of cosmetics and quasi-drugs

**c.** Guidance on the use of the bovine corneal opacity and permeability test as an alternative method for testing ocular irritation in the safety assessment of cosmetics and quasi-drugs

**d.** Points of consideration for ocular irritation testing in the safety assessment of cosmetics and quasi-drug

**e.** Guidance on use of the isolated chicken eye test as an alternative method for testing ocular irritation in the safety assessment of cosmetics and quasi-drugs

## 51.6 CONCLUSION

There are a number of alternative methods and approaches available that contribute useful information in the context of a weight-of-evidence approach to safety assessment. In vitro tests, cell and tissue culture models, read-across approaches, QSAR modeling data, and results of in silico computational methods are all examples of useful alternative tests. Nevertheless, scientific evidence of the capability of an alternative test to predict particular

aspects of toxicity in a cosmetic ingredient is of fundamental importance. In cases where no validated alternative methods are available, users must confirm intralaboratory reproducibility and predictive capacity through in-house validation studies, and authorities might still require manufacturers to predict the toxicity of ingredients or chemical substances and formulations either with or without animal testing. Even if there are no in vitro test methods available, the use of animal testing should in all cases be minimized as much as possible.

## References


1. Cosmetic Europe. *Guideline for the safety assessment of a cosmetic product*. 2004.
2. *PCPC safety evaluation guideline*. Washington (DC): CTFA; 2014.
3. *The SCCS's notes of guidance for the testing of cosmetic ingredients and their safety evaluation, 9th revision*. 2012. Available at: http://ec.europa.eu/health/scientific_committees/consumer_safety/docs/sccs_o_190.pdf.
4. INCI, 2015. Available at: http://www.personalcarecouncil.org/science-safety/what-inci.
5. CIR, 2015. Available at: http://www.cir-safety.org/ingredients.
6. SCCS Opinions, 2015. Available at: http://ec.europa.eu/health/scientific_committees/all_opinions/index_en.htm.
7. Globally Harmonized System of Classification and Labelling of Chemicals (GHS), 2015. Available at: http://www.unece.org/fileadmin/DAM/trans/danger/publi/ghs/ghs_rev04/English/ST-SG-AC10-30-Rev4e.pdf#search='GHS+WHO+classification.
8. Japan Cosmetic Industry Association. *Guidance for the safety evaluation of cosmetic*. Tokyo: Yakuji Nippo Ltd.; 2015.
9. *Guide to quasi-drug and cosmetic regulations in Japan 2011–2012 (in Japanese)*. Tokyo: Yakuji Nippo Ltd.; 2011.
10. Nakamura J. *Cosmetic regulation worldwide*. Tokyo: Jiho, Inc.; 2013.
11. Russell WMS, Burch RL, 1959. Available at: http://altweb.jhsph.edu/pubs/books/humane_exp/het-toc.
12. Commission Staff Working Documents. *Time Tables for the phasing-out of animal testing in the framework of the 7th Amendment to the Cosmetics Directive (Council Directive 76/768/EEC; EN, SEC82004) 1210*. 2004.
13. Adler S, et al. Alternative (non-animal) methods for cosmetics testing: current status and future prospects-2010. *Arch Toxicol* 2011;**85**(5): 367–485.
14. OECD Test Guideline, 2016. Available at: http://www.oecd.org/document/40/0, 3746,en_2649_34377_37051368_1_1_1_1,00.html.
15. ICH, 2015. Available at: http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/GuidancesInformationSheetsandNotices/ucm219488.htm.
16. EURL ECVAM Recommendations, 2015. Available at: https://eurl-ecvam.jrc.ec.europa.eu/eurl-ecvam-recommendations.
17. Scott L, et al. *Toxicol In Vitro* 2010;**24**:1–9.
18. OECD series on testing and assessment: non-testing methods. Available at: http://www.oecd.org/chemicalsafety/testing/seriesontestingandassessmentnon-testingmethodsegqsarandgrouping.htm.
19. SEURAT-1. Available at: http://www.seurat-1.eu/.
20. Marx-Stoelting P, et al. *ATLA* 2009;**37**(3):313–28.
21. ICCR, 2015. Available at: http://www.personalcarecouncil.org/global-strategies/iccr.
22. ICATM, National Toxicology Program, 2015. Available at: http://ntp.niehs.nih.gov/pubhealth/evalatm/iccvam/international-partnerships/index.html.
23. Cosmetic Europe, 2015. Available at: https://www.cosmeticseurope.eu/.
24. PMDA, 2015. Available at: https://www.pmda.go.jp/review-services/drug-reviews/about-reviews/q-drugs/0002.html [in Japanse].
25. Japan: Japanese Center for the Validation of Alternative Methods (JaCVAM), 2016. Available at: http://www.jacvam.jp/en/.

# Index

'*Note:* Page numbers followed by "f" indicate figures, "t" indicate tables and "b" indicate boxes.'


**A**

AA/MAPTAC. *See* Acrylamide/methacrylamidopropyl trimethylammonium chloride (AA/MAPTAC)
ABCA12 function, 782
ABHD5. *See* α/β-Hydrolase domain containing protein 5 (ABHD5)
ABS. *See* Access and benefit sharing (ABS)
ABs. *See* Alkyldimethylbetaines (ABs)
Absorption, distribution, metabolism, and excretion (ADME), 801
Acceptable Exposure Level (AEL), 280
Access and benefit sharing (ABS), 306
Accords, 273
Acerola, 312
Acetohexamide, 721
Acetone, 686
N-Acetyl cysteine (NAC), 293
N-Acetyl phytosphingosine (NAPS), 261–262
*N*-Acetyl-D-glucosamine, 355
N-Acetylglucosamine, 261–262, 262f
"Acid soap", 563–564
Acidic ceramidase, 691
Acne, 681, 760
Acne cosmetics, 117
Acne vulgaris, 760
Acrylamide, 201
Acrylamide/methacrylamidopropyl trimethylammonium chloride (AA/MAPTAC), 465f
2-Acrylamido-2-methylpropanesulfonic acid. *See* N-acryloyl taurate
Acrylate, 183
  acrylates/beneneth-25-methacrylate, 185
  copolymer, 206
  polymers, 292
Acrylic acid. *See* Acrylate
Acrylic carboxylate emulsion polymers, 184
Acrylomorpholine/methacrylamidopropyl trimethylammonium chloride (AMP/MAPTAC), 465f
N-Acryloyl taurate, 183–184
Acryloyl taurate/vinyl pyrrolidone copolymer, 183–184
Acryloyldimethyltaurate polymeric rheology modifiers, 183–184
ACTH. *See* Adrenocorticotropic hormone (ACTH)
Actinic aging, 205
Activated water, 164
Active delivery, 513, 516
Active interfacial modifier (AIM), 387, 503
Acute dermal toxicity, 797
Acute eye irritation/corrosion, 799
Acute inflammation, 715
Acute inhalation toxicity, 797
Acute oral toxicity, 797
Acute toxicity, 797
Acyl amino acids, 294
Acyl glutamate salt, 564, 564f
N-Acylation, 689
ω-O-Acylceramide, 688–689
  synthesis, 689–690
1-O-Acylceramide, 689
Acylglutamate, 294
AD. *See* Atopic dermatitis (AD)
Additives, 480–482, 494, 495f
Adenosine, 771–772, 775, 775f
Adenosine monophosphate disodium salt, 733, 733f
Adenosine triphosphate (ATP), 774
Adhesion process, 373
Adipocyte triacylglyceride lipase (ATGL), 689–690
ADME. *See* Absorption, distribution, metabolism, and excretion (ADME)
Adrenocorticotropic hormone (ACTH), 97
Adsorption, 39–41, 463–464, 464f
  isotherm, 239–240, 242
ADSPs. *See* Asian dust storm particles (ADSPs)
Advanced glycation end products (AGEs), 712
AE. *See* Alcohol ethoxylate (AE)
AEC. *See* Alkyl ether carboxylate salt (AEC)
AEL. *See* Acceptable Exposure Level (AEL)
AES. *See* Alkyl ether sulfate (AES); Alkyl ethoxylate sulfate (AES)
2AFC test. *See* Two-alternative forced-choice test (2AFC test)
Affective tests. *See* Subjective test methods
AGA. *See* Androgenetic alopecia (AGA)
Age-associated decline and disintegration of homeostasis, 720–721
AGEs. *See* Advanced glycation end products (AGEs)
Aggregation process, 199
Aging *vs.* senescence, 711
AgNPs. *See* Silver nanoparticles (AgNPs)
Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS Agreement), 128b
AHA. *See* α-Hydroxy acids (AHA)
AHAs. *See* Alpha hydroxy acids (AHAs)
AhR. *See* Aryl hydrocarbon receptor (AhR)
AIM. *See* Active interfacial modifier (AIM)
Air pollutants, 761
Air pollution, 757, 759. *See also* Skin-air pollution
Air–water interface adsorption, 238–239
AKD. *See* Alkylketene dimer (AKD)
β-Alanylhistidine. *See* Carnosine
Alcohol ethoxylate (AE), 402, 410
Alcohols, 270
Aldehydes, 270–271
Alginates, 179–180, 179f
Alginic acids, 179–180
Aliphatic higher alcohol, 248
Alkali fluorosilicates, 224
Alkaline ceramidase, 691
Alkaloids, 776
Alkonium. *See* N,N-dimethyl N-alkyl benzyl
Alkyl chain, 233–234, 239
  effect of, 405–406, 405f
  length, 396–397, 410–411
  phase behavior and melting temperature dependence on, 400–402
    dioctadecyldimethyl ammonium chloride, 402f
Alkyl ether carboxylate salt (AEC), 564–565, 565f, 568–569
Alkyl ether sulfate (AES), 562–563
Alkyl ethoxylate sulfate (AES), 395
n-Alkyl HASE polymers, 185
Alkyl isocyanates, 184
Alkyl monoglycerides, 423
Alkyl sulfate (AS), 397, 397t, 562, 562f
Alkyl-β-*D*-glycoside ($C_m$Glyco$_1$), 410, 410f
Alkylamidopropyldimethyl betaines (APBs), 566, 566f
Alkyldimethyl amine oxides, 566, 566f
Alkyldimethylbetaines (ABs), 566, 566f
Alkylketene dimer (AKD), 380–381, 380f–381f
All-trans retinoic acid (atRA), 344
Allergic contact dermatitis, 315
Allergic march, 90
Alpha hydroxy acids (AHAs), 342, 722–723

Alpha phase, 660, 661f
Alpha-gels (α-gels), 248, 248f–249f, 418–419, 423, 519, 552
  bilayer, 443
  characterization of liquid crystal and, 521–523, 522f
  in cosmetic emulsions, 523–524
  equilibration of, 443
  formation of molecular assemblies, 519–521
  stabilization of, 531–532
  transforms to β-crystal, 441–442
Alpha-type crystals. *See* Alpha-gels (α-gels)
Alpha-type hydrate crystals, 552f, 556–557
Alumina, 224
Aluminum oxide. *See* Alumina
American Chemical Society, 157–158
American Society for Testing and Materials (ASTM), 623
Amino acids, 93, 285–286, 286f, 287t, 288f, 326, 776
  amino acid-based anionic surfactants, 605t
  as biochemical compounds, 286–291
  as building blocks of living body, 286
  chemistry, 285–286
  in cosmetics, 291–296
    antioxidant activity, 292
    cysteine, 292–293
    hair care, amino acids for, 293, 293f
    humectants, 291
    neutralizer/pH adjuster, 292
    production of amino acids, 291
  derivatives, 293–296, 293f
    amino acid surfactants, 294
    oil gelatinization agents, 295–296
    powdery material, 294
  homopolymers, 299
Amino proteins, 164
Amino sugars, 181
Aminofunctional silicones, 203
5-Aminolevulinic acid, 776
Aminoplasts, 184
Amla, 311–312
AMP/MAPTAC. *See* Acrylomorpholine/methacrylamidopropyl trimethylammonium chloride (AMP/MAPTAC)
Amphibians, 673–674
Amphipathic arborols, 208–209
Amphipathic block copolymers, 188
Amphipathic polymers. *See* Side-chain crystalline polymers
Amphipathic self-associating peptides, 203–204, 204f
Amphiphilic molecules, 519, 521t
Amphiphilic polymer self-assembly, 452–453
  association between surfactant and hydrophobically modified water-soluble polymer, 453f
  hydrophobically modified water-soluble polymer associates, 453f
  micelle growth, 454f
  viscosity of solutions of hydrophobically modified cellulose derivative, 454f
Amphiphilic polymers, 490–491
Amphiphilic structure, 231
Amphiphilic substances, 150, 163
"Ampho", 156–157
Amphoteric/fatty acid mixed surfactant systems, 240
β-Amyrin, 316
*Anacystis nidulans* (*A. nidulans*), 353
Analysis of variance (ANOVA), 629–630
*Anastatica hierochuntica* (*A. hierochuntica*), 314
Androgenetic alopecia (AGA), 773
Androgenic alopecia, 117
Angola, 771–772
Anhydroglucose unit, 174–175
Animal testing, 724, 800
Anionic polyelectrolyte, 177
Anionic Polyester-5, 197
Anionic polymerization, 196
Anionic polymers, 604
Anionic surfactants, 395–398, 396f. *See also* Cationic surfactants; Nonionic surfactants; Sugar-based surfactants
  alkyl chain length and melting temperature, 396–397
  molecular structure of hydrophilic groups and phase behavior, 395–396, 396t
  surfactant mixtures and melting temperature, 397–398
Anionic/amphoteric mixed surfactant systems, 240–241
Anodically oxidized aluminum, super oil-repellent fractal surfaces made of, 381–382
ANOVA. *See* Analysis of variance (ANOVA)
Antiagings, 333, 342–347, 711
  agents, 116–117
  antioxidants, 342–343
  botanicals, 343–344
  ceramides, 345–346
  depigmenting agents, 346–347, 346t
  exfoliants, 347
  focusing on wrinkling, 259–262
    collagen and bioactive ingredients, 260–262
    elastin fibers and bioactive ingredients, 262
    fibroblasts in construction of dermal matrix, 259–260
  hyaluronic acid, 345
  hydroxy acids, 342
  retinoids, 344–345
  studies from dermal perspectives, 28
  topical peptides, 347
Antibacterial effects, 227
  of essential oils, 277–278
Antidandruff, 601
Antifrizz, 326
Antimicrobial agents, 209
Antioxidants, 261, 342–343
  activity, 292
  network, 760–761
Antiperspirants, 117
Antipollution/reconstruction, 332
Antisenescence, 711
  antisenescence cosmetics, research and development for, 721–723
  efficacy, 723–724
Antiwrinkle
  agents, 116–117
  antiwrinkle treatment, hyaluronic acid for, 205
Antiwrinkle treatment, hyaluronic acid for, 205
APBs. *See* Alkylamidopropyldimethyl betaines (APBs)
Apocrine glands, 168, 340, 681
Appearance, determination of, 675
Appendages, 675, 681
  sebaceous gland, 681
  sweat glands, 681
Aquaporin (AQP), 165–166
Aquaporin-3 transport channel, 781–782
Aquasomes, 353
Aquatic life, skin in, 673
Aqueous formulations, 198
Aqueous poloxamer solutions, 181–182
Aqueous solution, 231–232
Aqueous systems, 450
Aqueous-based formulations, 195
Arabinogalactan. *See* Galactoarabinan
Arachidonic acid, 732
*Arboro*, 208
Arborols, 208
Arbutin, 258, 258f, 355, 731
ARCI. *See* Autosomal recessive congenital ichthyosis (ARCI)
ARE-Nrf2 Luciferase test method, 799
Arginine, 292
L-Arginine hexadecyl phosphate, 531, 531f–532f
Aroma chemicals, 270–272
  physical chemistry of, 276–277
Aromatherapy, 282
Artemisia, 314
Artemisia indica *Var.* maximowiczii. *See* Artemisia
Arthropods, 673
Artificial makeup film, 581t
*Artocarpus incisus* (*A. incisus*), 346–347
Aryl hydrocarbon receptor (AhR), 759, 761
AS. *See* Alkyl sulfate (AS)
Ascorbic acid, 181, 722–723, 729–730, 760–761
ASEAN. *See* Association of Southeast Asian Nations (ASEAN)
Ashwagandha, 312
Asian dust storm particles (ADSPs), 758
Asiaticoside, 260–261, 260f
Asn-Pro-Ala (NPA), 166
Asparagine, 166
Association of Southeast Asian Nations (ASEAN), 137

Associative phase separation, 454–455, 458
Associative thickeners, 184–186
Astalift Jelly Aquarysta, 346
Astaxanthin, 261f
Astilbin, 775
ASTM. *See* American Society for Testing and Materials (ASTM)
ATGL. *See* Adipocyte triacylglyceride lipase (ATGL)
Atopic dermatitis (AD), 256–257, 757–758, 760, 782
  exacerbation, 757–758
ATP. *See* Adenosine triphosphate (ATP)
atRA. *See* All-trans retinoic acid (atRA)
Attributes, 628–629
Autocorrelation function, 639–640
Autologous cell-based therapy, hair follicle regeneration by, 777–778
Autosomal recessive congenital ichthyosis (ARCI), 688
Avalanche
  behavior, 181
  fluids, 62
  fluids, 181–182
Ayurveda, 311–312

**B**

Baden Aniline and Soda Factory (BASF), 77
  Technology Scouting Network Workshops, 77
"Bancroft rule", 29
BAPDMA. *See* Behenyl amidopropyl dimethylamine (BAPDMA)
Bar soaps, 561, 568
Bare skin–appearing effects, 580
Bare-skin look, 574–576
Barium sulfate ($BaSO_4$), 224
Barrier ceramide
  formation, 691f
  synthesis, 690–692
Barrier disruption by excessive moisturization, 683
Barrier function, 92–93, 92f, 674–675, 781, 783
  skin, 682–683, 782
  stratum corneum, 782
Basal layer, 676
Base excision repair system (BER system), 712
Basement membrane (BM), 94
BASF. *See* Baden Aniline and Soda Factory (BASF)
BAT. *See* Brown adipose tissue (BAT)
*beautés d'ailleurs*, 102
Beauty in Japan, 9
Beauty massage, 104–105
Behentrimonium chloride (BTAC), 418, 422
Behentrimonium methosulfate (BTAMS), 417f, 418, 428–429, 430f, 432f
Behenyl amidopropyl dimethylamine (BAPDMA), 423, 424f
Behenyl trimethyl ammonium chloride, 423
Bending vibration band, 160
Benserazide, 721
Benzaldehyde, 270
Benzalmalonate, 590
Benzo[a]pyrene, 759
Benzophenone derivatives, 588
Benzophenone-4, 332
6-Benzylaminopurine. *See* Cytopurine
Benzyliden-camphor derivatives, 589
BER system. *See* Base excision repair system (BER system)
Berry number, 60
BET. *See* Brunaue–Emmett–Teller isotherm (BET)
Beta-catenin, 772
1,3BG. *See* 1,3 Butylene glycol (1,3BG)
BHA. *See* β-Hydroxy acids (BHA)
Bicontinuous cubic liquid crystalline phase, 352
Bicontinuous microemulsion, 553
Bilayers phases, 477
Binary system, 389–391, 390f
Bioactive ingredients
  antiaging focusing on wrinkling, 259–262
  corneocytes and, 256
  for dry skin and rough skin, 255–256
  intercellular lipids in SC and bioactive ingredients, 256
  NMF and, 257
  pigmented spots, 257–259
  on regulation of epidermal terminal differentiation, 257
  sensitive skin and, 257
  tight junctions in barrier function and bioactive ingredients, 256–257
Biochemical compounds
  amino acids in skin
    NMF, 289, 290f
    urocanic acid, 289
  peptides in body, 291
  proteins in skin and hair, 286–289
    collagen, 288–289
    elastin, 289
    filaggrin, 288
    keratin, 287–288
Biomembrane-composing phospholipids, 540
Biomimicry, 197
Biomolecules, senescence of, 712–713
Biopolymer latex, 197
Biotin-encapsulated liposome, 546–547
Birefringence of liquid crystals, 644
Bis-ethoxydiglycol cyclohexane 1, 4 dicarboxylate, 249–250, 249f
Bis-ethylhexyloylphenol methoxyphenyl triazone, 590
Bisoctrizole. *See* Methylene bis-benzotriazolyl tetramethylbutylphenol
Black iron oxide, 225
Bleomycin hydrolase, 92–93
Block copolymers, 57, 188–189, 193–194, 197
Block polymer surfactants, 407–408, 409f
Blood vessels, 96
Blooming beauty, safety requisites for, 360
BM. *See* Basement membrane (BM)
BMDBM. *See* Butyl methoxy dibenzoylmethane (BMDBM)
BMDBM-OCR combination, 592, 592f
BMDBM-OCR-OMC combination, 592, 592f
BMP. *See* Bone morphogenic protein (BMP)
BN. *See* Boron nitride (BN)
Body care cosmetics. *See also* Skin care cosmetics
  body cleansers, 561
    primary surfactants, 562–563
  cultural orientation, 565
  foaming technology
    foam boosters, 566
    foam boosting, 565–566
    foaming properties, 566–567
    superfatting for foam boosting, 567–568
  mildness to skin and sensory feeling
    history, 561–562
    skin mildness, 562–565
Body care market, 561
Body cleansers, 561
  primary surfactants, 562–563
    sodium alkyl sulfate, 562–563
    sodium cocoyl isethionate, 563
    sodium polyoxyethylene AES, 563
Body oil absorption, 584
Body temperature
  adjustment, 162
  control of, 675
Body washes, 39
Boiling point of hydrogen, 161
Boltzmann constant, 640
Boltzmann kinetic considerations, 171
Bond angle, 159
Bone morphogenic protein (BMP), 772
Boron nitride (BN), 224
Botanical aroma compounds, effectiveness of, 315
Botanical ingredients, 305
  botanical substances, 305–306
  effectiveness of botanical substances, 309–315
  future and challenges in botanical substance development, 315–316
  organic cosmetics, 307–308
  regulations regarding botanical substances, 306–307
Botanical materials, effectiveness of, 309–315
  *A. hierochuntica*, 314
  Acerola, 312
  Amla, 311–312
  Artemisia, 314
  Ashwagandha, 312
  *C. unshiu*, 314
  *D. grandiflora*, 312

Botanical materials, effectiveness of (*Continued*)
Ginkgo, 314
Glycyrrhiza, 309–311
Green Perilla, 314
*V. album Subsp*. oxypetalum, 314
*X. granatum*, 315
Botanical names, 157
Botanical substances, 305–306
development
by fermentation of botanical substance, 316
safety of botanical substances, 315–316
diversity of, 305–306
effectiveness
of botanical aroma compounds, 315
of botanical materials, 309–315
as ingredients, 306
regulations regarding, 306–307
actual industrial use and issues of genetic resources, 307
CBD, 306–307
Botanical/herbal ingredients, 331–332
Botanicals, 343–344
Bottom–up emulsification, 502f, 503
Bound cer formation, 692
Bovine corneal opacity and permeability test method, 799
Bragg's law, 699–701
β-Branched L-arginine hexyldecyl phosphate ($R_6R_{10}$MP-Arg), 526
Brown adipose tissue (BAT), 686
Brownian motion, 65, 181–182
Brunaue–Emmett–Teller isotherm (BET), 239–240
BTAC. *See* Behentrimonium chloride (BTAC)
BTAMS. *See* Behentrimonium methosulfate (BTAMS)
Buffering function, 675
Bulge, 768–769
Bulk water, expelling interlamellar water to, 441–442
Bulk water phase (BW phase), 435–438, 437f–438f, 442
*Bushi*, 7
*Busho*, 7
Butter, 622
Butyl methoxy dibenzoylmethane (BMDBM), 588–589, 591–593, 591f–592f
4-Butyl resorcinol, 258, 258f
1,3 Butylene glycol (1,3BG), 236
4-n-Butylresorcinol. *See* Rucinol
*Butyrospermum parkii* (*B parkii*), 157
BW phase. *See* Bulk water phase (BW phase)

## C

c-UCA. *See Cis*-urocanic acid (c-UCA)
$C_{10}$MEGA. *See N*-Methyldecanoylglucamide ($C_{10}$MEGA)
C12–C32 alkyl substitution, 200–201
$C_{16}$TAB. *See* Hexadecyltrimethyl ammonium bromide ($C_{16}$TAB)
CAC. *See* Critical aggregation concentration (CAC)
Calcitonin gene–related peptide (CGRP), 737–738
Calcium, 177
Calcium alginate gels, 173
Calcium carbonate ($CaCO_3$), 227
Calcium guluronate, 180
Calming function of Langerhans cells, 98f
Calorie restriction (CR), 717
Calorimetry, 649
Canadian government, 211
Canceling, 104
*Candida albicans* (*C. albicans*), 209–210, 354
*Candida glabrata* (*C. glabrata*), 354
*Candida tropicalis* (*C. tropicalis*), 209–210
Cannabinoid receptor (CB receptor), 693–694
Cannabinoids, 693–694
Capillary phenomena, 374–375, 374f
Capillary pressure, 173, 374–375
CAPs. *See* Concentrated air particles (CAPs)
Capsaicin, 739
Carbomer, 182–183, 604, 611
Carbon black, 225–226
Carbon chain, 686
Carbon dioxide, 163–164
Carbon footprint, productivity by reducing
applications of "Less Is More" principle and LEE, 670
cosmetics industry, 657–658
HLB method to find optimal surfactant combinations for emulsification, 666–667
importance of finding Z-point, 660–661, 661f
LEE, 659–660, 660f
low-surfactant emulsification, 665–666, 666f
problem making clear hair conditioner in production, 663–664
solving batch failure problem in making large batch of O/W emulsion, 663
stability problem in production of spray-type sunscreen emulsion, 664–665, 665f
to preventing batch failure, improving product quality, and save energy, 663–666
"Less Is More" LEE processing, 662
principle of Less Is More, 659
solubilization method in low-surfactant emulsification, 668–669, 668f
understanding nature and effects of variables, 658–659
ways to carry out LEE, 660
Carbon gas, 163–164
α carbon, 164–165
Carbon-based nanoparticles
fullerene, 357
nanodiamond, 358
Carboxyl groups, 225–226
Carboxymethyl cellulose, 174–175
N(ε)-(Carboxymethyl) lysine (CML), 712
Carcinogenic, mutagenic, reproductive toxicity (CMR), 141–142
Carcinogenicity, 800
Carnosine, 291
Carob gum. *See* Locust bean gum
β Carotene, 228
Carpronium chloride, 774, 775f
Carrageenans, 177–179
CAS numbers, 157–158
Cassie–Baxter theory, 378, 378f
wetting on pillar-structured surface, 379f
CATA. *See* Check-All-That-Apply method (CATA)
Cationic
cellulose ethers, 197
conditioning polymers, 198
galactomannan, 200
guar, 200–201
hydrophobically modified galactomannan ethers, 200–201
hydroxyethylcellulose, 200
hyperbranched copolymers, 209
monomers, 208
nanoemulsions, 349
polymers, 188–189, 198, 200, 202, 205, 326
polysaccharides, 197
Cationic surfactants, 398–402, 398t, 607–608. *See also* Anionic surfactants; Nonionic surfactants; Sugar-based surfactants
hair "repairing" with, 608f
phase behavior and melting temperature dependence on alkyl chain, 400–402
structure of hydrophilic group and phase behavior, 398–400
CB receptor. *See* Cannabinoid receptor (CB receptor)
CBD. *See* Convention on Biological Diversity (CBD)
CDs. *See* Cyclodextrins (CDs)
CE. *See* Cell envelope (CE); Cornified envelope (CE)
Cell culture media injection, 777
Cell envelope (CE), 256
Cell membranes
aquaporin, 166
proteins and water, 164–165
and substance distribution, 165–166
and water, 165
water channels, 166
Cell senescence, 713, 715–716
relationship between SIRT1, p53, and, 719f
in vitro studies on, 714–715
Cells, 90, 165–166
Cellulose, 173–174, 174f
cellulosic rheology modifiers, 174–176
degree of substitution, 174, 174f–175f

hydroxypropyl methylcellulose, 176
hydroxypropylcellulose, 176
molar substitution, 174–176
CEN. *See* European Standardization Organization (CEN)
Central location test, 625
Centralized organizational scouting models, 79
Cepharanthine, 775f, 776
Ceramide synthesis, 689–690, 689t
Ceramide transfer protein (CERT), 690
Ceramides, 17, 248–249, 256, 338, 345–346, 513, 532, 690, 738
CERT. *See* Ceramide transfer protein (CERT)
Cetostearyl alcohol, 415, 417, 419–420
differential scanning colorimetry, 422f
hexagonal, monoclinic, and orthorhombic crystal forms of fatty alcohols, 420f
hydrocarbon chain packing viewed from alkyl chain axis, 421f
influence of 1-octadecanol on melting point, 420f
polarized microscopy photographs of cetrimide/cetostearyl alcohol gel network, 421f
Cetyl trimethyl ammonium chloride, 423
Cetyltrimethylammonium tosylate (CTAT), 433
Cetyltrimonium bromide (CTAB), 431f
Cetyltrimonium chloride (CTAC), 418, 430, 431f, 445f
CGRP. *See* Calcitonin gene–related peptide (CGRP)
Chain structure, 412
Chalcone, 314
Chamomilla extract, 732
Champagne foam, 48–49
Channel-dominated flow, 49–50
Chassis, 267
Check-All-That-Apply method (CATA), 625–626
Chemical Abstracts Service, 157–158
Chemical agents, 701–702
Chemical exfoliants, 347
Chemical gels, 458–462
Chemical structure of surfactant, 393
Chitin, 202
Chitin nanofibrilhyaluronan (CN-HA), 346–347, 346t
Chitosan, 196, 202, 355
Chlorine dioxide, 278
Cholesterols, 338
effect on glucose leakage, 542–544, 543f
*Chondrus crispus* (*C crispus*), 178–179
Chromametric method, 750
Chromium hydroxide, 225
Chronic inflammation, 715
cell senescence, 716f, 721f
inflammaging-senescence, 715–717, 716f
and senescence, 715–717
Chronological aging, 348
*Chrysanthemum*, 342
Cinnamates, 589
CIR. *See* Cosmetic Ingredient Reviews (CIR)
*Cis*-urocanic acid (c-UCA), 289, 597
*Citrus unshiu* (*C. unshiu*), 314
Classic sensory tests, 627–628
Classification, Labeling and Packaging System (CLP), 797
Clay, 223
CLE. *See* Corneocyte lipid envelope (CLE)
Cleansing
adsorption, 39–41
conditioners, 322, 568
dispersions, basics of, 62–68
emulsions, basics of, 68–72
physical principles for use of polymers in cosmetics, 52–62
surfactants, 39–41
and cleansing, 45–47
and foam, 47–50
micelles, 41–45, 41f–43f
phase diagrams and pseudophase diagrams, 50–52
Clear gels, 186–187
Clinical trials on hair loss treatment, 778
Clog P, 275
Cloud point, 186, 235–236, 235f–237f, 240–241, 406, 406t, 410t, 491–492
Cloud temperature, 408f
Clouding phenomenon, 390–391
CLP. *See* Classification, Labeling and Packaging System (CLP)
CLSM. *See* Confocal laser scanning microscopy (CLSM)
Cluster of $sp^2$ carbon atoms, 357
CMC. *See* Critical micelle concentration (CMC)
CML. *See* N(ε)-(Carboxymethyl) lysine (CML)
CMR. *See* Carcinogenic, mutagenic, reproductive toxicity (CMR)
CN-HA. *See* Chitin nanofibrilhyaluronan (CN-HA)
Co-washing conditioners, 322
Coacervate(s), 200, 603, 604f
deposition, 200–201
in foam, 201–202
formation, 199–200
liquid phase, 198
precipitation, 199–200
Coacervation, 604
Coagulation, 497–498
changes in attractive potential, 496f
Coalescence, 66–68, 498, 544–545, 555
coalescence-accelerating polymer emulsion, 35
lamellar film formation and interfacial state, 497f
Cocamide MEA, 602
Coelenterates, 673
Coenzyme $Q_{10}$ ($CoQ_{10}$), 261, 261f
*Coffea arabica* (*C. arabica*), 344
Coherent anti-Stokes Raman methods, 90
Coherent scattering effect, 641
Cohesive energy density, 53–54
Cold cream, 245
Cold pressing, 267
COLIPA guidelines. *See* European Cosmetic, Toiletry and Perfumery Association guidelines (COLIPA guidelines)
Collagen, 288–289, 712, 721–722
and bioactive ingredients, 260–262
antioxidants, 261
isoflavone and triterpenoids, 260–261
natural products, 261–262
vitamins, 261
turnover, 712, 723
Collagenases, 722–723
Collagens, 680
Colloidal/colloids
characterization, 636
cosmetic products, 635
dispersion systems, 635
particles, 65f
solute, 58
solutions, 642–643
systems, 507, 635
Color cosmetics, transfer-resistant, 190–195, 193f–195f
Color Index name, 158
"Color maintenance" products, 333
Color pigments, 31–32
Color refresher products, 333
Colored pigments, 225–226
carbon black, 225–226
chromium hydroxide, 225
iron oxide, 225, 225f
manganese violet, 225
pearlescent pigments, 227, 227f
ultramarine, 225
white pigments, 226–227
Coloring, 143–145, 144t
"Combination bars", 562
Commercialization, 210
Community Trade Mark (CTM), 131
Comparative approach, 790
Compatible gels, 197
Complex coacervates, 207
Complex silicones, 190–191
Compliance, 618
Composition variables (CVs), 658
Compounded mixtures, 156
Concealers, 117
Concentrated air particles (CAPs), 758
Concrete, 268
Condensation, 544–545
Conditioners, 321, 326
chassis, 321
co-washing conditioners, 322
hair conditioners, 606–608, 606t, 663–664
rinse-off, 606
Conditioning
oils, 604
polymers, 327–329
shampoo formula, 602t
shampoos, 200, 603
washing, 322
Conference of Parties (COP), 306

Confidentiality agreement, 135
Confocal laser scanning microscopy (CLSM), 504f, 650
Confocal microscopy, 747
Conjugates of drug molecules, 208
Connective tissue sheath cells. *See* Dermal sheath cells (DS cells)
Constancy scaling, 107
Consumer(s), 329
  exciter, 631–632
  goods, 151
  needs and drivers, 334t, 335
  products, 137
Contact angle, 373–375
Continuous cubic phases, 43–44
Continuous soothing, 105
Contrast ratio
  of dry powder films, 582t
  of wet powder films, 582t
Controlled delivery, 207–208
Controlled release, 277
Controlled-user test data, 800
Convention on Biological Diversity (CBD), 306–307
Conventional conditioning agents, 205
COP. *See* Conference of Parties (COP)
Copolymers, 56–57, 183, 188, 197
  acrylate, 206
  acryloyl taurate/vinyl pyrrolidone, 183–184
  amphipathic block, 188
  block, 57, 188–189, 193–194, 197
  conventional random, 195
  ethylene acrylic acid, 205
  foam enhancement by amphipathic block, 188–189, 189f
  hyperbranched, 209
  non-cross-linked linear acrylic, 206
  side-chain crystalline, 188
  silicone, 194
  synthetic, 201, 203
  triblock, 192
Copyrights
  and development of cosmetics, 133
  time of accrual and duration of, 133–134
  work, 133
$CoQ_{10}$. *See* Coenzyme $Q_{10}$ ($CoQ_{10}$)
Coagel, 233–234
Core shelletype solubilization, 235
Coriander, 776
Corneocyte lipid envelope (CLE), 692
Corneocytes, 743
  and bioactive ingredients, 256
  differentiation into, 677
Corneodesmosomes, 348, 680
Cornification, 91–92, 676
Cornified envelope (CE), 167–168, 677, 679, 686
Corporate
  corporate management, R&D and marketing as, 12
  responsibilities for accountability in science and technology, 10–11
Corporations, consumers, and society binding with maternal communication, 11, 11f
"Correlation length" in dilute solution, 172
Corrosion, 797–798
Cortex, 202
Corticosteroids, 749
Corticotropin releasing hormone (CRH), 97
CosIng, 158
Cosmetic Ingredient Review and Scientific Committee for Consumer Safety, 794
Cosmetic Ingredient Reviews (CIR), 140
  Expert Panel, 787
Cosmetic materials, 149–151
  adding functions and effects, 150–151
    materials adding or improving emotional value, 151
    materials adding or improving functional value, 150–151
    materials for quality control, 151
  challenges in development, 152–154
    exploring new raw materials, 153
    redesigning production methods, 153–154
  formulation structuring materials, 149–150
  precautions on choosing and using cosmetic ingredients, 151–152
  wetting of on human hair and skin, 386
Cosmetic science, 39, 87–90, 285
  cultural/social aspects with biological aspects in, 3–4
  functions of skin, 91–98
  and society, 3–4
  technologies supporting, 90–91
  technology, and marketing
    4Ps and best timing of science, technology, and marketing, 12–13
    R&D and marketing, 12
  technology, and social demands
    binding corporations, consumers, and society with maternal communication, 11, 11f
    corporate responsibilities for accountability in science and technology, 10–11
    soft science to reading changes of trends, 11–12
  wetting phenomena in cosmetic science and technology, 386–387
    surface tensions of human hair and skin, 382–383, 383t
    water-repellent treatments of cosmetic components, 386
    wetting behaviors of human hair with water, 383–385, 385f
    wetting behaviors of human skin, 385–386
    wetting in formulation technologies of cosmetics, 386–387
    wetting of cosmetic materials on human hair and skin, 386
Cosmetic Toiletry and Fragrance Association (CTFA), 13, 155
  CTFA Adopted Names, 155
  CTFA Cosmetic Ingredient Dictionary, 155
Cosmetic(s), 3, 87–88, 210–211, 389, 539, 541–542, 622, 720, 741, 785
  applications of microemulsions and nano-emulsions, 512–513
  artists, 207
  cosmetic emulsions, liquid crystal and α-gel in, 523–524
  culture and establishment philosophy, 7–9
  Directive, 796
  establishment of humans and society, 5–6
  Europe, 801–802
  formulations, 241–242, 471, 635
  future treatment in, 777–778
  history of, 102–103
  industry, 210–211
  ingredients, 155, 226, 590–591
  NPs in, 350–359
  prehistory of, 101–102
  products, 793
  proteins, 332
  regulation, 796
  scientific technology and history of cosmetics industry in Japan, 9–10
  sensory application for, 621–622
  society and foundation of cosmetic culture, 7
  surgeries, 777
  therapy, 101, 111
  wetting technologies in, 387–388
    dreamy technologies of cosmetics utilizing wetting phenomena, 387–388
    emulsion technologies utilizing wetting phenomena, 387
Cosmos, 6
COSMOS-standard, 307–308
Cosurfactants, 480, 606
Counterion
  counterion–bending of bilayer, 428–429
  entropy effect, 449
Cox–Mertz rule, 473, 474f
CPP. *See* Critical packing parameter (CPP)
β-CPX. *See* β-Cryptoxanthin (β-CPX)
CR. *See* Calorie restriction (CR)
Creaming, 68, 497, 554–555
  of liposomes, 544–545
  prevention of, 71–72
Creams and lotions, 348
Creating youthful-looking skin, 579–580
CRH. *See* Corticotropin releasing hormone (CRH)
Critical aggregation concentration (CAC), 200, 451–452
Critical association concentration. *See* Critical aggregation concentration (CAC)

Critical micelle concentration (CMC), 185, 206, 233, 239–240, 390, 426f, 450, 473–474, 491–492, 540–541, 564, 636
  CMS-500, 574–576
  temperature curve, 236
Critical packing parameter (CPP), 233, 389, 390f, 394–395, 422–423, 494, 521, 541
Critical surface tension, 375–376
Critical wavelength (λc), 588, 596
Cross-linked DNA, 461–462, 461f
Cross-linked siloxanes, 191
Crude fatty alcohols, 415
Cryo-scanning electron microscopy (Cryo-SEM), 25
Cryo-SEM. *See* Cryo-scanning electron microscopy (Cryo-SEM)
cryo-TEM method. *See* Cryofixation TEM method (cryo-TEM method)
Cryofixation TEM method (cryo-TEM method), 638–639
β-Cryptoxanthin (β-CPX), 314
β-Crystal, α-gel transforms to, 441–442
CTAB. *See* Cetyltrimonium bromide (CTAB)
CTAC. *See* Cetyltrimonium chloride (CTAC)
CTAT. *See* Cetyltrimethylammonium tosylate (CTAT)
CTFA. *See* Cosmetic Toiletry and Fragrance Association (CTFA)
CTM. *See* Community Trade Mark (CTM)
Cuachalalate extract, 776
Cubic liquid crystals, 645, 647
  dye staining method and identification, 648f
Cubic phases, 43–44, 474
Cubosomes, 43–44, 352
Cultural/social aspects with biological aspects in cosmetic science, 3–4
Culture and establishment philosophy of cosmetic
  evolution of Japanese cosmetic culture, 7–8
  philosophy of grooming through *Miyako-Fuzoku Kewai-Den*, 8–9
  sanitary care and philosophy through *Yojo-Kun*, 8
Culture supernatant therapy, 777
Cultured cells, in vitro studies on cell senescence using, 714–715
Cutaneous adipose tissue, lipids in, 686
Cuticle, 202
CVs. *See* Composition variables (CVs)
Cyclodextrins (CDs), 278, 279f, 358
  cyclodextrin-containing polymers, 208
1-Cyclohexylethyl butyrate. *See* Veilex 1
Cycloparaffin, 247
CYP4. *See* Cytochrome P450 gene 4 family (CYP4)
CYP4F2 homolog, 782
CYP72A154 enzyme, 316
Cysteine, 292–293
Cysteine-rich angiogenic inducer 61 or CCN family member 1 (CYR61/CCN1), 260
Cystine bonds, 205
Cytochrome P450 gene 4 family (CYP4), 688
Cytopurine, 775–776, 775f
Cytoskeletal proteins, 203
Cytotoxicity Assay, 797

## D

D-phase emulsification method, 499
DAC. *See* Dodecyl ammonium chloride (DAC)
Daidzein, 260–261, 260f
Damage-associated molecular pattern (DAMP), 95, 715
DAMP. *See* Damage-associated molecular pattern (DAMP)
Dandruff, 603
Danger signals, 95, 95f
Davies' equation, 492, 493t
DCS. *See* Dorfman–Chanarin syndrome (DCS)
DDAC. *See* Dodecyldimethyl ammonium chloride (DDAC)
DDC′. *See* 2′,3′-Dihydroxy-4′,6′-dimethoxychalcone (DDC)
DDSs. *See* Drug-delivery systems (DDSs)
De Novo ceramide synthesis pathway, 689–690
DEA. *See* Diethanolamide (DEA)
Deborah number, 172
Debra number, 42–43
Debye interactions, 64–65
Debye–Scherrer rings, 701
Decompose organic compounds, 226
Decorin, 260
DEEDMAC. *See* Di(2-stearoyloxyethyl) dimethylammonium chloride (DEEDMAC)
Defoaming, 50
Delayed tanning (DT), 587
Delboeuf size illusion, 106
Delta CMC, 206
Dendrimers, 59, 208, 359
Dendritic macromolecules, 359
Dendritic polymers, 208
Denucleated layers of epidermal lipids, 686
Deodorants, 33, 117
Depigmenting agents, 346–347
Depletion stabilization, 66
DEPs. *See* Diesel exhaust particles (DEPs)
Derjaguin, Landau, Verwey, and Overbeek theory (DLVO theory), 65–66, 497, 545–546
Dermal matrix construction, fibroblasts in, 259–260
Dermal papilla cells (DP cells), 767–769, 778
Dermal perspectives, antiaging studies from, 28
Dermal sheath cells (DS cells), 767–770
Dermatology. *See also* Hair cosmetics; Regulations on cosmetics
  dermatological benefits of cosmetics
    acne cosmetics, 117
    antiperspirants and deodorants, 117
    antiwrinkle and antiaging agents, 116–117
    hair growth agent, 117
    makeup products, 117–118
    skin care products, 115–116
  ichthyoses, 782
  irritant contact dermatitis, 782
  maturation of keratinocytes, 781
  noninvasive techniques and methods, 783
  psoriasis, 781–782
  stratum corneum barrier, 781
  therapeutic approach, 782
Dermatopharmacokinetic (DPK), 749
Dermis, 96, 338–339, 680–681, 781–782. *See also* Epidermis
Desaturase-1 (DES-1), 689
Desaturase-2 (DES-2), 689
Descriptive profile test
  attributes, 628–629
  notation method, 629
  reference samples, 629
  standardization enables reproducibility, 628
  statistical data analysis, 629–630
  test requirements of, 627–630
Design Patent Law. *See also* Trademark Law; Unfair Competition Prevention Law
  duration of design patent rights, 131
  intellectual property rights protection under, 130
  requirements for design patent registrations, 130
  scope of rights of registered design patent, 130–131
  search for registered designs in commercialization stage, 131
Design patent rights duration, 131
Desmosomes, 676–677
Desquamation, 93–94, 94f, 678, 722–723
Destabilizing factors of emulsions and handling methods, 495–499
  coagulation, 497–498
  coalescence, 498
  creaming, 497
  Ostwald ripening, 498–499
Detergents, 116, 562
DGAT. *See* Diacylglyceride acyltransferase (DGAT)
DHICA. *See* Dihydroxyindole carboxylic acid (DHICA)
DHT. *See* Dihydrotestosterone (DHT)
Di(2-stearoyloxyethyl) dimethylammonium chloride (DEEDMAC), 424, 441–442
Diacylglyceride, 688
Diacylglyceride acyltransferase (DGAT), 688

Dialkyl quats, 607–608
Diallylamine, 198
Dialon face lift, 358
Diamines, 187
Dibenzoylmethane derivatives, 588–589
Dibutyl lauroyl glutamide (LGDB), 295, 296f
Didodecylammonium bromide, 514
Dielectric spectroscopy, 169
Diesel exhaust particles (DEPs), 758
Diethanolamide (DEA), 566, 566f
Differential scanning calorimetry (DSC), 236, 419–420, 435, 520–521, 649–650, 692, 705
Differentiation into corneocytes, 677
Differentiation into spinous cells and granular cells, 676–677
Dihydrotestosterone (DHT), 774
2′,3′-Dihydroxy-4′,6′-dimethoxychalcone (DDC), 314, 314f
L-3,4-Dihydroxy-L-phenylalanine (DOPA), 197, 258, 730
Dihydroxyindole carboxylic acid (DHICA), 258
*o*-Dihydroxypheny, 197
L-3,4-Dihydroxyphenylalanine. *See* L-3,4-Dihydroxy-L-phenylalanine (DOPA)
Dilatant fluids, 61
Dilution method, 648
Dimethicones, 172
  layer, 198
Dimethyl ether, 55
N,N-Dimethyl N-alkyl benzyl, 156–157
Dimethylsulfoxide, 739
Dioctadecyl dimethylammonium (X = $Cl^-$and $Br^-$) (DODAX), 428–429
Dioctadecyl dimethylammonium chloride (DODAC), 425f, 428–429, 434–435, 435f
Dioctadecyl dimethylammoniumbromide (DODAB), 428–429
Dioctadecyldimethyl ammonium chloride (DSDMAC), 401–402, 402f, 424
Dioctyl-4-methoxy-benzylidene-malonate (DOMBM), 591f–592f, 593
Dipalmitoyl phosphatidylcholine (DPPC), 427f, 433–434
  gel-to-liquid crystal transition of, 652f
Diphenyl-acrylate derivatives, 590
1,6-Diphenylhexatriene (DPH), 651
Dipole-induced dipole interactions, 64–65
Dipole–dipole interactions, 64–65
5,5′-Dipropyl-biphenyl-2,2′-diol. *See* Magnolignan
Dipropylene glycol (DPG), 270
Direct beam, 699
Direct Peptide Reactivity Assay (DPRA), 799
Direct transmittance (DT), 574
Disaccharides, 179
Discontinuous cubic phases, 43–44
Discrimination tests, 624–625
Disfigurement, 106
Disjoining pressure (Π), 49
Disk-like micelles, 477
Dispersed-phase particles, 635
Dispersions, 62–68. *See also* Emulsions
  coalescence, 66–68
  electrical charges with surfaces and barriers to aggregation, 64–66
    stabilization of dispersions by electrical double layer, 65–66
    steric stabilization of dispersions by adsorbed polymer, 66
  methods, 29
  penetration of liquid, 63f
  spreading wetting of capillary interstices, 62f
Dissolution processes, 59
Dissolvable porous solid shampoos, 189–190
Distearoyl phosphatidylcholine (DSPC), 427, 445f
Distearoyl phosphatidylglycerol (DSPB), 427
Distearyldimonium chloride. *See* Dioctadecyldimethylammonium chloride (DSDMAC)
Distributed/Isolated organizational scouting models, 79
Disturbed skin barrier, 757
Disulfide bonds, 612–613
DL-LGA. *See* Racemic LGA (DL-LGA)
DLS. *See* Dynamic light scattering (DLS)
DLVO theory. *See* Derjaguin, Landau, Verwey, and Overbeek theory (DLVO theory)
DMAC. *See* Dodecylmethyl ammonium chloride (DMAC)
DNA, 457, 460f
  repair system, 721
    age-associated decline and disintegration of homeostasis, 720–721
DODAB. *See* Dioctadecyl dimethylammoniumbromide (DODAB)
DODAC. *See* Dioctadecyl dimethylammonium chloride (DODAC)
Dodecyl ammonium chloride (DAC), 398–399
Dodecyl polyglycoside ($C_{12}Glyco_\alpha$), 411
Dodecylalcohol ethoxylates ($C_{12}EO_m$), 402–403, 403f
Dodecyldimethyl ammonium chloride (DDAC), 398–399
Dodecylmethyl ammonium chloride (DMAC), 398–399
Dodecyltrimethyl ammonium chloride (DTAC), 398–399, 399f
DOMBM. *See* Dioctyl-4-methoxy-benzylidene-malonate (DOMBM)
DOPA. *See* L-3,4-Dihydroxy-L-phenylalanine (DOPA)
Doppler shift, 649
Doppler shift theory of scattered light, 650–651
Dorfman–Chanarin syndrome (DCS), 689–690
Double-stranded DNA (dsDNA), 457, 458f, 460, 461f
Double-tail surfactants, 424, 424f
DP cells. *See* Dermal papilla cells (DP cells)
DPG. *See* Dipropylene glycol (DPG)
DPH. *See* 1,6-Diphenylhexatriene (DPH)
DPK. *See* Dermatopharmacokinetic (DPK)
DPPC. *See* Dipalmitoyl phosphatidylcholine (DPPC)
DPRA. *See* Direct Peptide Reactivity Assay (DPRA)
DPRSA method, 87–88
Dreamy technologies of cosmetics utilizing wetting phenomena, 387–388
Drometrizole trisiloxane, 590
Droplet size of dispersed phase, 648–650
  DSC, 649–650
  dynamic light scattering, 649
  laser diffraction, 649
  laser Doppler, 649
  microscopes, 650
  optical microscope, 649
Drug-delivery systems (DDSs), 539
Dry skin, bioactive ingredients for, 255–256
DS cells. *See* Dermal sheath cells (DS cells)
DS cup cells (DSC cells), 770, 770f
DSC. *See* Differential scanning calorimetry (DSC)
DSC cells. *See* DS cup cells (DSC cells)
DSDMAC. *See* Dioctadecyldimethyl ammonium chloride (DSDMAC)
dsDNA. *See* Double-stranded DNA (dsDNA)
DSPB. *See* Distearoyl phosphatidylglycerol (DSPB)
DSPC. *See* Distearoyl phosphatidylcholine (DSPC)
DT. *See* Delayed tanning (DT); Direct transmittance (DT)
DTAC. *See* Dodecyltrimethyl ammonium chloride (DTAC)
*Duabanga grandiflora* (*D. grandiflora*), 312
Dubin model, 199
Dubin's hypothesis, 200
Dutasteride, 774
Dynamic light scattering (DLS), 639–640, 649
Dysfunction of telomeres, 716–717

## E

e-nose. *See* Electronic nose (e-nose)
EC. *See* European Commission (EC)
Eccrine glands, 168
"eChemPortal", 790–791
ECM. *See* Extra cellular matrix (ECM)
6ED. *See* Polyoxyethylene (6) dodecyl ethers (6ED)
Edar, 773

EDNRA. *See* Endothelin A receptors (EDNRA)
EDX. *See* Energy dispersive X-ray analysis (EDX)
Effective interference effect, 638
EGF. *See* Epidermal growth factor (EGF)
Einstein viscosity theory, 58
Einstein's equation, 643
Einstein–Stokes equation, 640
Elastin, 289, 680
  fibers and bioactive ingredients, 262
Elastomeric blocks, 188
Elastosis, 680–681
Electric conductivity method, 648
Electrical charges with surfaces and barriers to aggregation, 64–66
  stabilization of dispersions by electrical double layer, 65–66
  steric stabilization of dispersions by adsorbed polymer, 66
Electrical colloidal stability, 65
Electrical double layer, stabilization of dispersions by, 65–66
Electrolytes, 163
Electrolyzed water, 164
Electron micrograph of "hybrid powder", 33f
Electron microscopy, 650
Electron paramagnetic resonance (EPR). *See* Electron spin resonance (ESR)
Electron spin resonance (ESR), 529–530, 530f, 650–653
Electronic application process, 158
Electronic nose (e-nose), 275
Electrospinning technique, 356
Electrostatic interactions, 163, 199–200, 449
Electrostatic repulsions, 183
Ellagic acid, 258, 258f, 731, 731f
Elongation of very long chain FAs protein (ELOVL protein), 687–688
Emblica officinalis. *See* Amla
Embryonic stem cell test (EST), 800
EMI. *See* Epithelial–mesenchymal interaction (EMI)
Emollients, 115–116, 245. *See also* Cosmetic(s)
  aliphatic higher alcohol and fatty acids, 248
  ceramides, 248–249
  creams, 245
  effect, 245
  emollient-based mild psoriasis treatment, 781–782
  evaluation, 250–252
  fatty acid esters, 247–248
  future, 252
  in human history, 245
  hydrocarbons, 246–247, 247t
  lanolin, lanolin derivatives, and sterol esters, 248
  natural oils, 247
  water-soluble oils, 249–250
Emotion control device, cosmetic behavior as, 110–112, 110f–111f
Emotional factors, 109
Emotional value, materials adding or improving, 151
Emulsification, 46, 489, 510–511, 555
  of detergency, 46f
  from dynamic behavior of liquid crystal membrane, 528–531
  emulsifier suitable to applications, 490–493
  HLB
    method to find optimal surfactant combinations, 666–667
    number of oil, 493–495, 494t
  interlayer spacing of alpha gel, 557f
  liquid crystal formation in, 524–526, 525f–526f
  methods, 499–505
    bottom–up emulsification, 502f, 503
    control of interfacial phase, 503–505
    HIPRE, 500f, 501
    multiple emulsion, 501–502
    oil-in-water emulsion, 499
    sf-emulsion, 501f, 502
    water-in-oil emulsion, 501
  O/W emulsification, 555–559
  properties of surfactant on emulsification, 490
  self-diffusion coefficient for water molecules, 558f
  sodium stearoyl methyltaurine/behenyl alcohol/water system, 556f
  technologies, 29–31, 30f
  volume fraction of alpha gel and separated water, 558f
Emulsification preparation by hybrid-type polymer, 504–505
Emulsifiers, 197, 241–242
  suitable to applications, 490–493
Emulsifying wax, 438
Emulsions, 68–72, 210, 471, 483, 484f, 489, 525f, 554–555, 622, 635, 647–654. *See also* Dispersions; Nano-emulsions
  classification, 489
    comparison of size among variety of colloidal objects, 490f
    optical microscope images of emulsions, 490f
  concentrate, 660, 661f
  destabilizing factors of emulsions and handling methods, 495–499
  disruption, 496–497
  droplet size of dispersed phase, 648–650
  α-gel in cosmetic emulsions, 523–524
  HLB
    for emulsification, 70f
    number of oil, 493–495, 494t
  interfacial layer, 650–654
  liquid crystal
    in cosmetic emulsions, 523–524
    formation in emulsification, 524–526, 525f–526f
  Ostwald ripening, 71
  performance of emulsifiers, 69f
  polymerization, 183
  prevention of creaming and sedimentation, 71–72
  products, 552
  stability, 71
  technologies utilizing wetting phenomena, 387
  type, 648
Encapsulated chemical magnesium ascorbyl phosphate (VC-PMG), 542–544
Encapsulation, 205, 207, 277
End-to-end distance, 57
Endo180, 259–260
Endogenous amino acids/proteins, functions of, 285
Endoplasmic reticulum (ER), 690, 729
Endorsement of "GOODWILL", 121
Endothelin A receptors (EDNRA), 314
Endothelin B receptors (EDNRB), 314
Endothelin-1 (ET-1), 259
Endothermic reaction, 163
Energy dispersive X-ray analysis (EDX), 650
Energy transfer system, 592–593
Enfleurage, 267
Enthalpic contributions, 508–509
Entropic contributions, 508–509
Entropy, 233
Environmental exposure, 760
Environmental factors, 719–720
Enzymes, 165–166
EO. *See* Ethylene oxide (EO)
EPC. *See* European Patent Convention (EPC)
Ephrin, 772
Epidemiological studies, 737
Epidermal
  barrier function, 28
  cells, 94, 95f
  differentiation, 686
  epidermal keratinocytes, homeostatic proliferation and differentiation of, 676–677
  epidermal terminal differentiation, bioactive ingredients on regulation of, 257
  turnover, 676, 713, 722–723
Epidermal growth factor (EGF), 772
Epidermal lipid synthesis
  barrier ceramide synthesis, 690–692
  bound cer formation, 692
  ceramide synthesis, 689–690
  cholesterol synthesis, 687
  FA elongation, 688t
  fatty acid synthesis, 687–688
  glucosylceramide synthesis, 690
  lamellar membrane structure, 692
  lipid-mediated epidermal permeability barrier, 693
  skin diseases with lipid abnormality, 693t
  sphingomyelin synthesis, 690
  triacylglyceride synthesis, 688

Epidermal lipid synthesis (*Continued*)
wax ester synthesis, 689
Epidermis, 167, 337–338, 339f, 743, 781–782. *See also* Dermis
homeostatic proliferation and differentiation of epidermal keratinocytes, 676–677
inflammation, 95
lipids in
epidermal lipids, 686
epidermal structures, 686
structure and function of SC, 677–680
Epimorphin, 776
Epithelial–mesenchymal interaction (EMI), 767–768
EPO. *See* European Patent Office (EPO)
ER. *See* Endoplasmic reticulum (ER)
L-Ergothioneine, 261, 261f
Erodible shells, 206
ESR. *See* Electron spin resonance (ESR)
EST. *See* Embryonic stem cell test (EST)
Esters, 270
oils, 608
quats, 607–608
ET-1. *See* Endothelin-1 (ET-1)
Ethanol, 701–702
Ether-bonded oxygen atoms, 235
Ethnicity, gender, and anatomical site, 743
Ethosomes, 351, 745
Ethoxylated alcohols, 156–157
Ethoxylation, 174–175
Ethyl-hexyl triazone, 590
Ethylene acrylic acid copolymers, 205
Ethylene oxide (EO), 235, 494–495
chain, 406, 406t
group, 236
units, 395
2-Ethylhexyl 2-cyano-3,3-diphenyl-2-propenoate (OCR), 591f–592f, 592
Ethylhexyl methoxycinnamate, 332
Ethylhexyl triazone. *See* Bis-ethylhexyloylphenol methoxyphenyl triazone
EU. *See* European Union (EU)
*Eucheuma cottonii* (*E. cottonii*), 178–179
*Eucheuma spinosum* (*E. spinosum*), 178–179
Europe, 255
European Commission (EC), 158
European Cosmetic, Toiletry and Perfumery Association guidelines (COLIPA guidelines), 596, 624
European Cosmetics Directive, 796
European Patent Convention (EPC), 130b
European Patent Office (EPO), 128
European Standardization Organization (CEN), 594
European Union (EU), 131, 137, 144, 145t, 308, 793
cosmetics regulations, 360–361
Ex vivo studies, 746–747
Exemplary hydrophobic deposits, 206
Exfoliants, 347
"Exogen phase", 768
Exopolysaccharide, 177
Expelling interlamellar water to bulk water, 441–442
Exposure, 787–789
consumer exposure for cosmetics, 788t
Extender pigments
inorganic pigments
barium sulfate, 224
BN, 224
clay minerals, 224
silica, 224
organic pigments, 227–228
colored pigments, 228
polymer resin, 227
surfactants and metal salt, 227–228
Extensional rheology modifiers, 210
External Scouting resources, 79
Extra cellular matrix (ECM), 716
Extrinsic aging, 205
Eye
irritation, 799
shadows, 228

## F

FA. *See* Fatty acids (FA)
FA 2-hydroxylase (FA2H), 688
FA2H. *See* FA 2-hydroxylase (FA2H)
Face, 681–682
Facial Features Map, 108–109, 108f
Fair Packaging and Labeling Act, 155
FAS. *See* Fatty acid synthase (FAS)
Fashion, 3, 11–12
"Fast water", 558–559
Fat tissue. *See* Cutaneous adipose tissue
Fatty acid synthase (FAS), 687–688
Fatty acids (FA), 248, 338, 567–568, 685
esters, 247–248
hydroxylation, 688
isethionate salt, 563f
soaps, 562, 571–572
Fatty alcohols, 415, 418, 418f, 419t, 523, 567–568
hydrated crystal, 438–440
crystal structure of hydrated fatty alcohol, 441f
example WAXS chart of lamellar gel network, 440f
FD&C Act. *See* US Federal Food, Drug, and Cosmetic Act (FD&C Act)
FDA. *See* US Food and Drug Administration (FDA)
Female AGA, 773
Female pattern hair loss (FPHL), 773
Fermentation, 153–154
Fermentation of botanical substance, development by, 316
FF-TEM. *See* Freeze fracture transmission electron microscopy (FF-TEM)
FGF. *See* Fibroblast growth factor (FGF)
Fibrils, 203–204
Fibroblast growth factor (FGF), 771–772
FGF-18, 771–772
FGF-5 factor, 771–772
FGF-7, 771–772, 775
Fibroblast-derived elastase, 262
Fibroblasts in construction of dermal matrix, 259–260
Fick equation, 749
Fick's law, 750
Fight–flight stress response, 104
Filaggrin, 257, 288
"Film-former plus plasticizer" combination, 191
Film-forming polymers in cosmetics and personal care products, 195–197
hair fixatives, 195–196
hair grooming with whipping, 197
macromolecular compatibility and controlled segregation to confer multifunctionality, 196–197
polymers for delivery of long-lasting, quick-change styles, 197
temporary style with easy restylability, 197
Films, 207–208
drainage, 50
Finasteride, 774
Fine three-phase emulsions by liquid crystal emulsification, formation of, 528
First country application, 128
Fixative polymers, 609
Flash Profile, 624–625
Flat surfaces, wetting on, 373–377. *See also* Rough surfaces, wetting on
capillary phenomena, 374–375
estimation of surface tension of solid, 375–377
Young's equation, 373–374
Flavor Profile method (FPM), 627
FLIM. *See* Fluorescent lifetime imaging (FLIM)
Flocculation, 555
Flory–Fox equation, 59
Flory–Huggins theory, 55
Flow behavior, 471
Fluid systems, 471
Fluocinolone acetonide, 346
Fluorescein leakage test method, 799
Fluorescence polarization technique, 651
Fluorescent anisotropy, 651
Fluorescent lifetime imaging (FLIM), 747
Foam(s), 47–50, 48f, 188–189, 485
coacervate in, 201–202, 201f–202f
defoaming, 50
drainage, 49–50
enhancement by amphipathic block copolymers, 188–189, 189f
formation, 47–48
lamellae, 188–189
rupture and collapse, 50
stability, 48–49, 567
Foamability, 566–567
Foaming technology
foam boosters, 566
foam boosting, 565–566
superfatting for, 567–568
foaming properties, 566–567
Folding process, 267

Follicular transplant units (FTUs), 777
"Foolproof", 786
Forkhead box, subgroup O (FOXO), 717
Formaldehyde, 757–758
Formulation structuring materials, 149–150
  amphiphilic substances, 150
  oleaginous/hydrophobic base materials, 150
  water/hydrophilic base materials, 149
Formulators, 44–45, 210
  phase diagram use by, 52
Foundations, 571–573
  O/W foundation, 571–572
  oil-type foundation, 573
  powder foundations, 572–573, 572t
  spray-type foundation, 573
  W/O foundation, 572
  water-based gel-type foundation, 573
Fourier transform infrared spectroscopy (FT-IR), 692
FOXO. *See* Forkhead box, subgroup O (FOXO)
FPHL. *See* Female pattern hair loss (FPHL)
FPM. *See* Flavor Profile method (FPM)
Fractal surfaces, wettability theory on, 378–379, 379f
Fragrance, 110, 267
  antibacterial effects of essential oils, 277–278
  applications, 276
  aroma chemicals, 270–272
  creation and duplication, 272–275
  diluents, 271f
  encapsulation and controlled release, 277
  fragrance materials criteria algorithm, research institute for, 280f
  malodor, 278
  marketers, 282
  and mind, 282
  natural, green, organic, and sustainable fragrances, 281–282
  natural products, 267–269
  physical chemistry of aroma chemicals, 276–277
  polarity, 275–276
  psychology, 109–110
  regulation of, 281
  safety and regulatory concerns, 279–281
Franz diffusion cell, 746, 747f
Free Choice Profiling, 624–626
Free Descriptive Panels, 628
Free radical, 188
  polymerization, 196
Free-from alternatives, 330–331
"Free" amino acids, 286
Freeze fracture transmission electron microscopy (FF-TEM), 478f–479f, 638–639
Freeze-thaw stability, 198
Friedmann's test, 629
Front-end homework/creation of "needs" brief, 81, 82f
FT-IR. *See* Fourier transform infrared spectroscopy (FT-IR)
FTUs. *See* Follicular transplant units (FTUs)
Full ingredient labeling, 139–140
Fullerene, 357
Functional cosmetics, molecular assemblies to
  multilamellar emulsions of pseudo-stratum corneum lipids, 532–535, 534t
  stabilization of β-gel and new-type cosmetic base, 531–532
Functional formulations, innovative, 33–35
  deodorant, 33
  long-lasting glossy lipstick, 34–35
  nail enamels, 35
  sunscreen, 34
Functional materials for hair
  alternatives for sulfates, 325, 325t
  antiaging, 333
  botanical/herbal ingredients, 331–332
  co-washing/conditioning washing/cleansing conditioners, 322
  color statements/protection/renewal, 333
  conditioners, 326
  conditioning polymers, 327–329
  consumer needs and drivers, 334t, 335
  free-from alternatives, 330–331
  hair damage and causes, 327
  for hair shampoos, 321–322, 323t–324t
  interactions with hair, 326–327, 328t
  leading global hair care market trends, 330, 331t
  mild shampoos, 322
  new age of connectivity, 330
  pre-damage/pre-shampoos, 325
  scalp protecting, 333
  sensorial experience, 333
  silicone-free alternatives, 329, 330t
  skin care–inspired solutions, 332
  sun care–inspired solutions, 332
  sustainable solutions, 333–334
Functional powders, 31–33
Functional value, materials adding or improving, 150–151
Functional water, 164
*Funshoku Kessai*, 9
*Furcellaria fastigiata* (*F. fastigiata*), 179

## G

GAG. *See* Glycosaminoglycan (GAG)
Galactoarabinan, 180
Galactomannans, 176–177, 176f, 176t
Galactose, 200
Gardenia, 228
Garnier, 321
Garnier Color Styler Intense Wash Out Color, 333
Gas chromatograph (GC), 274, 274f
Gaussian curvature, 394, 394t
GC. *See* Gas chromatograph (GC)
Gelation mechanism, 187
Gellan Gum, 178
Gellant, 197
Gelling agents, 622
Gels, 178, 458–462, 484
  calcium alginate, 173
  chemical, 458–462
  clear, 186–187
  compatible, 197
  cross-linked dna gels shrink by cationic surfactant, 461f
  ionization of microgel particles leads to swelling, 462f
  phases, 43, 519
  polymer, 173
Generalized indirect Fourier transformation (GIFT), 641
Generally regarded as safe elements (GRAS elements), 350
Genetic factors, 719–720
Genetic resources, actual industrial use and issues of, 307
Genistein, 260–261, 260f
Genome editing, 90, 91f
Genotoxicity, 800
Gestures, 630
GHS. *See* Globally Harmonized System (GHS)
GHS for Classification and Labeling of Chemicals, 794
Gibbs triangle, 391, 392f
Gibbs–Helmholtz equation, 239
Gibbs–Marangoni effect, 50
Gibbs–Marangoni elasticity, 50
GIFT. *See* Generalized indirect Fourier transformation (GIFT)
*Gigartina acicularis* (*G. acicularis*), 178–179
*Gigartina pistillata* (*G. pistillata*), 178–179
Ginkgo, 314
Ginkgo biloba. *See* Ginkgo
Ginseng extract, 776
Glabridin structure, 311f
Glass transition, 192
  transition temperatures, 197
Glassy blocks, 188
Glassy methacrylate polymers, 192
Global cosmetic R&D trends
  award-winning papers, 17, 18t–25t
  formulation technologies and new materials, 29–35
    functional powders, 31–33
    innovative functional formulations, 33–35
    studies on emulsification technologies, 29–31, 30f
  hair and scalp, 35–37, 36f
  history of articles presenting at IFSCC congresses/conferences, 16, 16f
  IFSCC, 15–16
  skin biology, 17–28, 26t, 27f
  trends interpreted from award-winning papers, 17–37
Globally Harmonized System (GHS), 794
Globular micelles, 473–474
GLP. *See* Good laboratory practice (GLP)
β-Glucogallin structure, 312f

β-D-Glucopyranoside derivative of hydroquinone, 731
Glucosylceramide, 691
  synthesis, 690
Glupal-19S, 316
Glutamine, 679–680
Glutathione, 291
Glycerin, component of, 247
Glycerol, 781–782
Glycerol monooleate (GMO), 423
Glycerol monostearate (GMS), 423
Glycols, 270
Glycosaminoglycan (GAG), 345
Glycyrrhetic acid, 310
Glycyrrhetinic acid, 205, 776
Glycyrrhiza, 309–311
*Glycyrrhiza glabra* (*G. glabra*), 309–310, 309f
*Glycyrrhiza inflata* (*G. inflata*), 309–310
*Glycyrrhiza uralensis* (*G. uralensis*), 309–310
Glycyrrhizic acid, 260–261, 260f, 309, 316
Glycyrrhizin, 310f
  pathway for biosynthesis of, 317f
GM-CSF. *See* Granulocyte macrophage colony-stimulating factor (GM-CSF)
GMO. *See* Glycerol monooleate (GMO)
GMS. *See* Glycerol monostearate (GMS)
Goddard's hypothesis, 200
Gold nanoparticles (GNPs), 354
Golgi apparatus, 729
Good laboratory practice (GLP), 623
Government restrictions, 137
Granular cells, 167
  differentiation into, 676–677
Granular layer, 676
Granulocyte macrophage colony-stimulating factor (GM-CSF), 259
Grapefruit oil, 315
GRAS elements. *See* Generally regarded as safe elements (GRAS elements)
Grassroots organizational scouting models, 79
Green chemistry, 307–308
Green fragrances, 281–282
Green Perilla, 314
Griffin's equation, 492
Grooming philosophy through *Miyako-Fuzoku Kewai-Den*, 8–9
Growth factor cocktail, 777
Guar gum, 177, 200
Guar hydroxypropyltrimonium chloride, 199
Guidelines for Management of Androgenetic Alopecia, 773–774
Guinier region, 640–641

## H

HA. *See* Hydroxy acids (HA)
Haarmann and Reimer's classification table, 109
Hair, 35–37, 36f, 203, 339
  bulb, 767–768
  cell culture media injection, 777
  conditioner in production, 663–664
  cycle, 767–768
  damage and causes, 327
  fixatives, 195–196
  future treatment in cosmetics, 777–778
  grooming with whipping, 197
  growth
    agent, 117
    factor cocktail, 777
    induction factor, 772
  growth–promoting compounds
    approved drugs, 774
    chemical compounds, 776
    Guidelines for Management of Androgenetic Alopecia, 773–774
    hair growth–promoting reagents, 773
    natural plant extracts, 776–777
    quasi-drugs, 774–776
  hair-styling formulations, 195
  light-emitting diodes, lasers, and other cosmetic surgeries, 777
  loss
    autologous cell-based therapy for, 777–778
    diseases and causes, 773
  matrix cells, 768
  platelet-rich plasma, 777
  proteins in, 286–289
  shaft, 675
  shampoos, functional materials for, 321–322, 323t–324t
  shedding, 768
  shine, 608
  styling products, 609–611
  transplantation, 777
  trophic factors affecting hair growth, 770–773
Hair care, 331–332, 349
  amino acids for, 293, 293f
  cosmetics, 601, 601t
  hair coloring products, 611–612, 611t
  hair conditioners, 606–608, 606t
  hair styling products, 609–611
  key ingredients in hair conditioning cosmetics, 607t
  permanent hair waving products, 612–613
  shampoos, 602–606
    cleansing effect, 603f
    conditioning shampoo formula, 602t
Hair conditioning, 602
  polymers, 198–205, 198f–199f, 201f
    coacervate in foam, 201–202
    enhancing mildness, 202
    polymers for improvements in hair coloring, 205
    polymers mitigate hair damage, 202–204, 204f
    polymers to strengthening permed hair, 205
Hair follicle, 349, 767
  capillary plexus around, 771f
  growth cycle, 769f
  regeneration of, 777–778
  stem cells, 768–769
  structure, 767–768, 768f
  target cells and tissues in, 768–770
Hansen solubility parameter (HSP), 187, 275
Hansen solubility parameter in practice (HSPiP), 275
Haptic–sensory fundamentals
  finger as natural sensor, 620f
  hierarchy of senses, 619–620
  mouthfeel *vs.* skinfeel, 619
  resolution of touch, 620
  sensitivity of single skin receptors, 621t
  skin sensitivity, 620–621
Hard keratin, 673–674
HARG therapy, 777
HASE. *See* Hydrophobically modified alkali-swellable emulsion (HASE)
Hazards, 785
hCLAT method, 87–88, 88f, 799
HD. *See* 1-Hexadecanol (HD)
HDM. *See* House dust mite (HDM)
HEA/MAPTAC. *See* Hydroxyethyl acrylate/methacrylamidopropyl trimethylammonium chloride (HEA/MAPTAC)
Health, 6, 9
  care products, 337, 358
    in Japan, 9
Heat, 162
HEAT. *See* Hydrophobically modified aminoplast technology (HEAT)
Heavy water, 159
HEC. *See* Hydroxycellulose (HEC)
α-Helix, 164–165
Henry's law, 277
Heterocyclics, 271, 272f
Heterogeneous ceramide species, 690
HEUR. *See* Hydrophobically modified ethoxylated urethanes (HEUR)
1-Hexadecanol (HD), 427, 444
Hexadecylpyridinium bromide ($C_{16}$PyB), 400–401
Hexadecyltrimethyl ammonium bromide ($C_{16}$TAB), 400–401, 401f, 514
Hexagonal
  hexagonally packed crystal, 415
  hydrocarbon-chain packing structures, 699–700, 700f
  orthorhombic structures, 692
  phase, 51
HHL. *See* Histidinohydroxylysinonorleucine (HHL)
High internal phase emulsion (HIPE), 482
High internal phase microemulsion (HIPME), 482, 482f
High internal phase ratio emulsions (HIPRE), 500f, 501
Histidine, 679–680
Histidinohydroxylysinonorleucine (HHL), 712
HLB. *See* Hydrophilic-lipophilic balance (HLB)
HM. *See* Hydrophobically modified (HM)
HMG-CoA. *See* 3-Hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA)
HMHEC. *See* Hydrophobically modified hydroxyethyl cellulose (HMHEC)

*Hofmeister series*, 494
"Home use test", 625
Homeostasis, 489
  age-associated decline and disintegration of, 720–721
  homeostatic proliferation and differentiation of epidermal keratinocytes, 676–677
*Homo ludens* (*H. o ludens*), 6
*Homo sapiens* (*H. sapiens*), 5–6
*Homo technicus* (*H. technicus*), 6
Homopolymer–ionic surfactant systems, 450–451. *See also* Polyelectrolyte–surfactant systems
  pearl-necklace model, 450f
  plot of concentration dependence of surface tension, 451f
Homopolymers, 56–57
Honda–Fujishima effect, 226
Horny cell, 167–169
  layer, 168f, 686
House dust mite (HDM), 757–758
Hoy's approach, 54
HPA axis. *See* Hypothalamo–pituitary–adrenocortical axis (HPA axis)
HPA/DMAM. *See* Hydroxypropyl acrylate/dimethylaminoethyl methacrylate (HPA/DMAM)
HQ. *See* Hydroquinone (HQ)
HSP. *See* Hansen solubility parameter (HSP)
HSPiP. *See* Hansen solubility parameter in practice (HSPiP)
Human data, 800–801
Human hair
  surface tensions of, 382–383
  with water, wetting behaviors of, 383–385, 385f
  wetting of cosmetic materials on, 386
Human patch test, 800
Human skin
  surface tensions of, 382–383
  wetting
    behaviors of, 385–386
    of cosmetic materials on, 386
Human volunteer studies, 747
HUMC. *See* Hydrogel-based ultramoisturizing compound (HUMC)
Humectants, 291
Humidity-dependent swallowing, 692
Hyaluronate, 542–544
Hyaluronic acid, 345
Hyaluronic acid for antiwrinkle treatment, 205
Hybrid organizational scouting models, 79
Hybrid-type polymer, emulsification preparation by, 504–505
Hydrated solids, 233–234
Hydration, 159, 163, 429–431
Hydroalcoholics, 276
Hydrocarbon(s), 163, 246–247, 247t, 480
  hydrocarbon-chain packing structures, 699–700, 700f
  polymers, 172
Hydroclustering, 61
Hydrodynamic radius, 57–58
Hydrogel-based ultramoisturizing compound (HUMC), 348
Hydrogel(s), 171, 188, 355, 484–485
  cationically modified cellulose in water, 485f
Hydrogen
  atoms, 159
  water, 164
Hydrogen bond(s), 159, 161, 236
  formation, 161
  structure of water and, 160–161
Hydrogen bonds, 160–161
α/β-Hydrolase domain containing protein 5 (ABHD5), 689–690
Hydrolysis, 270, 291
Hydrolyzed
  proteins, 299
  yeast extract, 776
Hydrophile-lipophile balance. *See* Hydrophilic-lipophilic balance (HLB)
Hydrophilic, 512–513
  amphiphile, 519–520
  area, 165
  base materials, 149
  cationic polyethylenimine, 192
  interfaces, 165
  molecules penetration route of, 702–703
  polyether polyol adduct, 184
  polymer, 173
  shell, 490
  substances, 163
  surfactants, 232
Hydrophilic group(s), 167–168, 231, 233, 236, 389, 394t
  effect of conformation of, 411–412, 412f
  molecular structure of, 395–396
  structure of, 398–400
Hydrophilic-lipophilic balance (HLB), 29, 232, 391–392, 402, 508–509, 510f, 666–667
  number, 395, 490–493, 492t
  system, 69, 69f–70f
Hydrophilic-lipophilic balance temperature ($T_{HLB}$), 508–509
Hydrophilic–lipophilic character, 482
Hydrophobes, 163, 184, 200–201
Hydrophobic
  actives, 206
  alkyl chain, 418
  association, 184
  base materials, 150
  blocks, 188
  coating, 173
  film-forming polymer, 190
  group, 167–168, 231
    associations, 185–186
  interaction, 40, 163, 233, 449, 452, 490
  liquid, 173
  modification, 200
  molecules, penetration route of, 704–705
  monomer, 186
  nanoparticles, 196
  penetration enhancer, 701–702
  substances, 163
  surface, 198
Hydrophobic aminopropyl terminated polydimethylsiloxane, 192
Hydrophobically modified (HM), 483
  hydrophobically-modified hydrophilic polymers, 485
  microgel thickeners, 72
  polymers, 480–481, 481f
Hydrophobically modified alkali-swellable emulsion (HASE), 184, 198
  polymers, 186
  thickeners, 185
Hydrophobically modified aminoplast technology (HEAT), 184
Hydrophobically modified ethoxylated urethanes (HEUR), 184
Hydrophobically modified hydroxyethyl cellulose (HMHEC), 184
Hydrophobicity, 185–186, 608
Hydrophobins, 190
Hydroquinone (HQ), 346
Hydroscopic powders, 182–183
Hydrotropes, 45
Hydroxy acids (HA), 342
α-Hydroxy acids (AHA), 342
β-Hydroxy acids (BHA), 342
5-Hydroxy-2-hydroxymethyl-4-pyranone. *See* Kojic acid
3-Hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA), 687
Hydroxycellulose (HEC), 480–481
Hydroxyethyl acrylate/methacrylamidopropyl trimethylammonium chloride (HEA/MAPTAC), 465f
N-Hydroxyethyl ethylenediamine, 156–157
Hydroxyethylcellulose, 174–176
Hydroxyl-terminated precursor, 194
Hydroxylation of fatty acids, 688
2(α)-Hydroxylation, 688
ω-hydroxylation. *See* Omega-hydroxylation (ω-hydroxylation)
4-(4-Hydroxyphenyl)-2-butanol. *See* Rhododendrol
Hydroxypropyl acrylate/dimethylaminoethyl methacrylate (HPA/DMAM), 465f
Hydroxypropyl guar, 177
Hydroxypropyl methylcellulose, 176
Hydroxypropylcellulose, 176
Hyperbranched
  functional polymer, 194
  polymers, 208
Hyperdermis, 339
*Hypericum perforatum* (*H. perforatum*), 775
Hypermoisturization, 683
Hyperreactors, 739
Hypothalamo–pituitary–adrenocortical axis (HPA axis), 97f, 104

## I

I&I. *See* Industrial and Institutional (I&I)
IATA. *See* Integrated Approach to Testing and Assessment (IATA)
ICATM. *See* International Cooperation on Alternatives to Animal Testing (ICATM)
ICCR. *See* International Cooperation on Cosmetic Regulation (ICCR)
Ichthyoses, 782
Ichthyosis
  autosomal recessive congenital, 689
  subtypes, 782
ICID. *See* International Cosmetic Ingredient Dictionary and Handbook (ICID)
Ideal solution, 277
IEP. *See* Isoelectric point (IEP)
IF. *See* Intermediate filament (IF)
IFRA. *See* International Fragrance Association (IFRA)
IFSCC. *See* International Federation of Societies of Cosmetic Chemists (IFSCC)
IGF. *See* Insulin-like growth factor (IGF)
IL-1α. *See* Interleukin-1α (IL-1α)
Immediate pigment darkening (IPD), 587
Immediate tanning. *See* Immediate pigment darkening (IPD)
Immune system, 716
Immunological
  barrier, 682–683
    system, 682–683
  function, 675
Impaired barrier function, 737–738, 782
In silico, 280
  models, 750–751, 794
  "QSAR/in silico" computational toxicology, 801
In vitro
  membrane barrier test method for skin corrosion, 798
  skin corrosion, 797–798
  studies, 746–747
    on cell senescence, 714–715
In vivo
  microdialysis, 750
  skin blanching/vasoconstrictor assay, 749–750
  tape stripping, 749
In-vitro in-vivo correlation (IVIVC), 746
INC. *See* International Nomenclature Committee (INC)
INCI. *See* International Nomenclature Cosmetic Ingredients (INCI)
Indigo naturalis, 256–257
Individual senescence, 712–713, 715
Individual Ultraviolet A protection factor (UVAPFi), 595
Indoor air pollution, 757–758
Industrial and Institutional (I&I), 77
Industrial Research Institute (IRI), 77
Infinite periodic minimal surface (IPMS), 522
Inflammaging-senescence induced by chronic inflammation, 715–717, 716f
Inflammation, 715, 758
Inflammatory diseases
  Acne, 760
  AD, 760
  psoriasis, 760
Information Technology (IT), 86
Ingredient labeling, 155–156
Inner root sheath cells (IRS cells), 767–768
Inorganic
  coatings, 226
  electrolytes, 163
  nanoparticles, 351
  pigments, 224–227
  salts, 159, 163
  substances, 160
Inorganic materials, 223
Inorganic nanoparticles, 354. *See also* Organic nanoparticles; Polymeric NPs
  Nanogold, 354
  nanosilver, 354
  silica nanoparticles, 354
  ZnO and $TiO_2$, 354
Inorganic organic balance (IOB), 251
Inorganic value (IV), 493
Instrumental data modeling, 631–632
Insulin-like growth factor (IGF), 772
Integrated Approach to Testing and Assessment (IATA), 799
Integrated surfactant property (ISP), 494–495
Intellectual Property (IP), 81
Intellectual property rights, 121–122. *See also* Regulations on cosmetics
  cooperative research and development agreement, 135–136
    confidentiality agreement, 135
    joint research and development agreement, 135–136
  copyrights, 133–134
  Design Patent Law, 130–131
  need for, 121–122
  Patent Law, 122–130
  Trademark Law, 131–133
  Unfair Competition Prevention Law, 134–135
Interbilayer forces, 429–431
Intercellular lipids, 28, 167–168, 679, 781
  in SC and bioactive ingredients, 256
Interdigitated bilayer, 434, 434f
Interfacial
  curvature, 394, 394f
  energy, 490
  layer, 650–654
  phase control, 503–505
  rheology, 653–654
  tension, 238–239, 373–374, 554–555
Interlamellar space, 233–234, 431
Interlayer spacing, 556–557, 557f
Interleukin-1α (IL-1α), 737–738, 758
Intermediate filament (IF), 286–288, 288f
Intermolecular hydrogen bonds, 161, 295–296
International Cooperation on Alternatives to Animal Testing (ICATM), 801
International Cooperation on Cosmetic Regulation (ICCR), 801
International Cosmetic Ingredient Dictionary and Handbook (ICID), 140, 155
International Federation of Societies of Cosmetic Chemists (IFSCC), 15–16, 629
  awards by societies, 26f
  awards by theme, 26f
International Fragrance Association (IFRA), 279, 281
International Nomenclature Committee (INC), 155
International Nomenclature Cosmetic Ingredients (INCI), 139, 140t, 155, 793
  names, 186–187
    applications for, 158
    and CAS, 157–158
    and CosIng, 158
  nomenclature system, 156–157
International Organization for Standardization (ISO), 623
  ISO 24442, 595
  ISO 24443:2012, 595–596
  ISO 24444, 594
International phase, 128–129
International Preliminary Examination Report, 128
International Search Report, 128
International test guidelines, 797–801
  acute toxicity, 797
  carcinogenicity, 800
  corrosivity, 797–799
  genotoxicity, 800
  human data, 800–801
  irritation, 797–799
  phototoxicity, 800
  repeated-dose toxicity, 799
  reproductive toxicity, 800
  skin
    absorption, 799
    sensitization, 799
  toxicokinetic studies, 800
International trend of organic cosmetics and natural cosmetics, 308
Intracellular water, 166
Intrinsic
  aging, 205, 348
  viscosity, 58–59
Inversion emulsification method, 499, 500f
IOB. *See* Inorganic organic balance (IOB)
Ion hydration, 163
Ionic
  attraction, 193–194
  ionic-bonded ion pairs, 240–241
  surfactants, 231–232
Iontophoresis, 208
IP. *See* Intellectual Property (IP)

IPD. *See* Immediate pigment darkening (IPD)
IPMS. *See* Infinite periodic minimal surface (IPMS)
IRI. *See* Industrial Research Institute (IRI)
Iron oxide, 225, 225f
Irritant contact dermatitis, 744
Irritation
  eye, 799
  skin, 799
IRS cells. *See* Inner root sheath cells (IRS cells)
Isethionates, 202
ISO. *See* International Organization for Standardization (ISO)
Isoelectric point (IEP), 44–45, 164
Isoflavone, 260–261
Isolated chicken eye test method, 799
Isolates, 268
Isoliquiritin, 310
Isoparaffin, 247
Isoprene, 268, 268f
Isopropanol, 573
ISP. *See* Integrated surfactant property (ISP)
IT. *See* Information Technology (IT)
IV. *See* Inorganic value (IV)
IVIVC. *See* In-vitro in-vivo correlation (IVIVC)

## J

JaCVAM. *See* Japanese Center for Validation of Alternative Methods (JaCVAM)
Japan
  case study
    evolution of Japanese cosmetic culture, 7–8
    philosophy of grooming through *Miyako-Fuzoku Kewai-Den*, 8–9
    sanitary care and philosophy through *Yojo-Kun*, 8
  quasi-drugs in, 802, 802t
  scientific technology and history of cosmetics industry in, 9–10
Japan Patent Office (JPO), 128
Japanese Center for Validation of Alternative Methods (JaCVAM), 802
Japanese Cosmetic Industry Association (JCIA), 595
JCIA. *See* Japanese Cosmetic Industry Association (JCIA)
Joint research and development agreement, 135–136
JPO. *See* Japan Patent Office (JPO)
JR-400 system, 465

## K

K15. *See* Keratin15 (K15)
*Kagaku Kougei Houkan*, 9–10
*Kaibustu-Sousetsu*, 9–10
*Kaki-Mayu-Kesho*, 7
Kawakami's equation, 493
Keratin(s), 203, 287–288, 677–678
  powder, 239–240, 242
Keratin15 (K15), 768–769
Keratinization, 676
Keratinocyte growth factor (KGF). *See* FGF-7
Keratinocyte(s), 256, 287–288, 337–338, 687, 712, 781–782
  and bioactive ingredients, melanosome transfer into, 259
  cornification, 88
  keratinocyte-targeted QDs, 729
  maturation of, 781
*Kesho-hin Seizou-hou*, 9–10
*Kesho-hin/Hifu Setsuyo-hin/Mohatsu Setsuyo-hin*, 9–10
Ketoconazole, 775f, 776
Ketones, 270
3-Ketosphinganine, 689
Kinesthesia, 620f
Kinetic
  emulsion stability, 495f, 496
  stability, 510–511
*Klotho* gene, 714
Kojic acid, 203, 258, 258f, 730–731
*kommôtikê technê*, 102
*Koryo Oyobi Kosho-hin*, 9–10
KOSMET database, 16, 17f
*kosmêtikê technê*, 102
Kovats index system, 208
Krafft point, 41, 236–238, 238f, 240–241, 390, 397t, 401t, 425
  of alkyl ammonium salts, 399t
  $L_\beta$ phase with solid amphiphiles above solubility limit and below, 426
  of typical cationic surfactants, 401t
Krafft temperature, 390, 418
Krieger–Dougherty equation, 474
Kuhn length, 171

## L

L-LGA. *See* N-Lauroyl-L-glutamic acid (L-LGA)
$L_3$-phase, 479–480, 479f
Labeling, 139–140
  full ingredient labeling, 139–140
  usable product lifespan, 139
Lactic acid, 739
Lactones, 272, 272f
Laid-open publication, 124
LAM correlations, 580, 583f
Lamellar bodies, 167–168, 691
Lamellar gel network, 415
  α-gel, 418–419
    crystal structure of amphiphile, 416f
  advantages, 415–417
  BW phase, 435–438, 437f–438f
  cetostearyl alcohol, 419–420
  fatty alcohol hydrated crystal, 438–440
  formulation spaces of, 443–446
  multiphase network structure, 425
  oil phase, 438
  representation of all trans-alkyl chain conformations by *n*-butane, 416f
  stability of, 440–443
  structure of water containing hydrophilic ointment, 416f
  surfactants for lamellar gel networks, 420–424
Lamellar gel phase (LGP), 443, 444f
  counterion–bending of bilayer, 428–429
  domain size and shape of, 427–428
    optical microscope images, 428f
    SEM picture, 429f
    temperature–shear-rate phase diagram, 429f
    three-dimensional synthesis of confocal microscope images, 428f
  identification, 435
  interdigitated bilayer, 434, 434f
  $L_\beta$ phase, 425–435
  and phase transition thermodynamics, 433–434, 434f
  with solid amphiphiles above solubility limit and below Krafft point, 426
  spontaneous curvature, 431–433
  swelling, hydration, and interbilayer forces, 429–431
  thermal history and formation of, 434–435
Lamellar liquid crystal, 415
  oil-in-liquid crystal gel emulsion using, 526–528
Lamellar membrane structure, 692
Lamellar network, 431–433
Lamellar phase, 43, 417, 606–607
Langerhans cells (LCs), 338, 675
  calming effect, 97–98, 98f
Langmuir type, 239–240
Lanolin, 248
  derivatives, 248
Lapis lazuli, 225
Larch galactoarabinan, 180–181
*Larix occidentals* (*L. occidentals*), 180
LAS. *See* Sodium laurylbenzene sulfonate (LAS)
Laser Doppler, 649
Laser(s), 777
  diffraction, 649
Laurionite (PbOHCl), 223
N-Lauroyl-L-glutamic acid (L-LGA), 295
N-Lauroyl-N-methyl-β-alanine sodium (NaLMA), 239–241, 243
LCs. *See* Langerhans cells (LCs)
LCST. *See* Lower critical solution temperature (LCST)
LDL. *See* Low-density lipoproteins (LDL)
LDP. *See* Lower-degradation point (LDP)
LEDs. *See* Light-emitting diodes (LEDs)
LEE. *See* Low-energy emulsification (LEE)
Less Is More principle, 659, 663
  applications, 670
  "Less Is More" LEE processing, 662
LGDB. *See* Dibutyl lauroyl glutamide (LGDB)
LGP. *See* Lamellar gel phase (LGP)
Licochalcone A structure, 311f
Licorice, 309, 310t, 312t
Light microscopy, 638
Light-emitting diodes (LEDs), 777

*D*-Limonene, 704
Linear poly (chloroethylvinylether-co-vinylbenzoylchloride), 209–210
Linear polysaccharides, 179
β-(1–4)-Linked D-glucosamine, 355
Linnaean binomial system, 157
Linoleic acid, 259, 689–690, 732, 732f
Lip care, 350
Lipid nanoparticles (LNPs), 351
Lipid(s), 149, 167–168, 326, 409, 685, 743, 781
  barrier care, 694
  bilayer structures, 652f
  in cosmetics, 694
  in cutaneous adipose tissue, 686
  emulsion, 533, 534f
    reconstruction of lamellar structure by treatment of, 536f
    scanning electron microscopic image of, 534f
  epidermal lipid synthesis, 687–693
  in epidermis
    epidermal lipids, 686
    epidermal structures, 686
  lipid-mediated epidermal permeability barrier, 693
  mediators, 693–694
  metabolism, 781–782
  modulator, 687t
  in sebaceous gland, 685
  in skin, 685–686
  skin surface lipid, 693
Lipidated galactoarabinan, 181
Lipofullerene, 357
Lipofuscin, 713
Lipophilic
  group, 231, 235–236, 389
  ingredients, 512–513
  molecules, 165
Lipophilic *Malassezia* fungi, 116
Liposomes, 351, 745
  biotin-encapsulated, 546–547
  in cosmetics, 540
  creaming, 545
  formation conditions, 540–541
  formulations
    average particle diameter change, 544f
    cutaneous absorption, 548
    effectiveness, 546–548
    stratum corneum storability with biotin, 547f
    TEM image of sheared liposome, 548f
    TEM image of water-evaporated liposome, 547f
  lipids effect on geleliquid crystal phase transition temperatures, 545f
  morphology, 541–542, 542t
  pH change of liposome solutions, 540f
  stability
    with electrostatic repulsive force, 545–546
    influencing factors, 542–544
    stabilizing dispersion, 544–545
    TEM image of multilamellar liposome, 544f
12R Lipoxygenase (12R-LOX), 692, 782
Lipoxygenase-3, 782
Lipstick, 223, 228
Liquid
  body washes, 561, 564
  crystalline phase, 519
  lip makeup, 191
  membrane system, 353
  oils, 551
    phase, equilibration of, 443
  paraffin, 246, 523
  shampoos, 189–190
  water, 162
    molecules, 161
Liquid crystals, 233, 355, 390, 486, 520, 644–647
  characterization ofc, 521–523
  in cosmetic emulsions, 523–524
  cubic liquid crystals, 647
  emulsification, 499, 527f–529f
    from dynamic behavior of liquid crystal membrane, 528–531, 530f
    formation in, 524–526, 525f–526f
    formation of fine three-phase emulsions by, 528
    preparation of oil-in-liquid crystal gel emulsion using lamellar liquid crystal, 526–528
  NMR, 646, 647f
  polarized optical microscope, 644, 644f
  SAXS, 644–646, 645f, 646t
Liquiritigenin, 311f
Liquiritin, 310, 311f
*Litchi chinensis* (*L. chinensis*), 332
LLLT. *See* Low-level laser therapy (LLLT)
LLNA. *See* Local Lymph Node Assay (LLNA)
LMO correlations, 580, 583f
LMOGs. *See* Low molecular-mass oil gelators (LMOGs)
LNPs. *See* Lipid nanoparticles (LNPs)
Local Lymph Node Assay (LLNA), 799
Locust bean gum, 177
London force interactions, 64–65
Long lamellar
  spacing, 705–706
  structure, 699, 700f, 701–704
Long Range Science Strategy Research Program (LRSS Research Program), 801
Long-lasting
  fragrance, 333
  glossy lipstick, 34–35
Longevity, 711, 714
Loss modulus, 643
"Lotion", 635
"Lotus effect", 190
Low molecular-mass oil gelators (LMOGs), 296
Low-density lipoproteins (LDL), 687
Low-energy emulsification (LEE), 659–660, 660f
  applications of, 670
  "Less Is More" LEE processing, 662
  to preventing batch failure, improving product quality, and save energy, 663–666
  low-surfactant emulsification, 665–666, 666f
  problem making clear hair conditioner in production, 663–664
  solving batch failure problem in making large batch of O/W emulsion, 663
  stability problem in production of spray-type sunscreen emulsion, 664–665, 665f
Low-level laser therapy (LLLT), 777
Low-surfactant emulsification, 665–666, 666f
  solubilization method in, 668–669, 668f
Lower critical solution temperature (LCST), 176, 181–182
Lower-degradation point (LDP), 669, 669f
LPA. *See* Lysophosphatidic acid (LPA)
LPS. *See* Lysophosphatidylserine (LPS)
LRSS Research Program. *See* Long Range Science Strategy Research Program (LRSS Research Program)
"Luteolin", 157
Lymph, 341
Lyophobic colloids, 636
Lyotropic liquid crystals, 389–390, 519
  characterization of liquid crystal and α-gel, 521–523
  formation of molecular assemblies, 519–521
Lysophosphatidic acid (LPA), 257, 261–262
Lysophosphatidylserine (LPS), 261–262
Lβ phase. *See* Lamellar phase

## M

Macromonomer, 185–186
Magnesium ascorbyl phosphate storage property, 542–544, 543f
Magnesium hydroxide, 224
Magnetic resonance imaging (MRI), 25
*Magnolia obovata* (*M. obovata*), 733
Magnolignan, 258–259, 258f, 733–734, 733f
Maker Suggested Retail Price (MSRP), 139
Makeup, 4–6, 31–33, 87–88, 110, 223, 255. *See also* Emollients
  cosmetics, 571
  durability, 584
    body oil absorption, 584
    improving wettability, 584
  finishes, 573–584
    artificial makeup film, 581t
    contrast ratio of dry powder films, 582t
    contrast ratio of wet powder films, 582t
    creating youthful-looking skin, 579–580
    effects on face shapes and expressions, 580–583

natural-looking makeup, 574–576
photochromic effect, 583–584
reflection patterns of acrylic-coated talc and talc only, 574f
soft-focus effect, 574
supercovering makeups, 577–579
foundations, 571–573
products, 117–118
psychology, 106–109
skin protection, 585
UV blocking, 584–585
Malachite $Cu_2(CO_3)(OH)_2$, 223
*Malassezia* species, 603, 685
Male-pattern baldness, 117
Malodor, 278
Malondialdehyde (MDA), 758
Malpighia emarginata. *See* Acerola
Malpighian layer, 338
Mammalian sirtuins, 717
Manganese violet, 225
Mann–Whitney-Use test. *See* Wilcoxon test
Marangoni flow, 50
Marine brown algae, 179–180
Market, nanocosmeceuticals in, 361
Marketing
science, technology and cosmetics
4Ps and best timing of science, technology, and marketing, 12–13
R&D and marketing, 12
Mark–Houwink–Sakurada equation, 59
Mass spectrometer (MS), 274
Massage, 104
beauty, 104–105
Material Transfer agreements (MTA), 79
Materiality of prior patent search
commercialization stage, 126–127
measures to cope with patent rights of other persons, 127
research and development stage, 126
Materials
adding or improving
emotional value, 151
functional value, 150–151
for quality control, 151
Maternal communication, corporations, consumers, and society binding with, 11, 11f
*Matricaria recutita* (*M. recutita*), 343
Matrix metalloproteinases (MMPs), 680–681, 720–721, 758–759
MMP-1, 259–260, 722–723
Matter patent composition, 123
Max RAO, 576
MBC. *See* 4-Methyl benzylidene camphor (MBC)
MDA. *See* Malondialdehyde (MDA)
MEA. *See* Monoethanolamide (MEA)
18-MEA. *See* 18-Methyleicosanoic acid (18-MEA)
Mean curvature, 394
Meander structure, 235
MED. *See* Minimum erythema dose (MED)
Medulla, 202
MEE. *See* Methyl ester ethoxylate (MEE)
Mehrabian's rule, 5
*Melaleuca alternifolia* (*M. alternifolia*), 315
Melanin, 203, 257–258, 729
synthesis, 729–730
and bioactive ingredients, 258–259
inducing instability of tyrosinase, 259
inhibitors of tyrosinase activity, 258
Melanocyte(s), 96, 720
stimulation factors and bioactive ingredients, 259
Melanogenesis, 587
melanin synthesis, 729
skin-lightening QDs in Japan, 729–735
Melanoma, 760
Melanosome(s), 257–258
transfer into keratinocytes and bioactive ingredients, 259
Melatonin, 760–761
Melting
point, 188, 237–238
of hydrogen, 161
temperature, 396–397, 398f
dependence on alkyl chain, 400–402
Membranes, 747
in skin permeability studies, 748t
Menthyl carbamate, 203
Mesenchymal cells, 767–768
Mesomorphic structures, 188
Mesoscopic scale, 638
Methoxy pectins, 180
4-Methoxy Potassium Salicylate (4MSK), 733, 733f
4-Methyl benzylidene camphor (MBC), 589
Methyl caps and ester groups, effect of, 403–405
$C_{12}EO_{12.\ 9}$ sharp EO distribution, 405f
lauroyl methylester ethoxylate, 404f
Methyl ester ethoxylate (MEE), 403–405
Methyl methacrylate crosspolymers, 227
*N*-Methyl-ethanolamine, 721–722
*N*-Methyldecanoylglucamide ($C_{10}$MEGA), 412, 413f
18-Methyleicosanoic acid (18-MEA), 607
Methylene bis-benzotriazolyl tetramethylbutylphenol, 590
*N*-Methylethanolamide (NMEA), 566, 566f
4-(Methylnitrosoamino)-1-(3-pyridyl)-1-butanone, 759
Mexico City subjects, 758
MFAP-4. *See* Microfibrillar-associated protein 4 (MFAP-4)
MHLW. *See* Ministry of Health, Labor and Welfare (MHLW)
Mica, 224
Micellar structures
bilayers, disk-like micelles and phases, 477
globular micelles, 473–474
$L_3$-phase, 479–480
vesicle phases, 477–479
viscoelastic solutions from worm-like micelles, 474–477
Micelles, 41–42, 163, 231, 389–390, 486, 519–520, 540–541, 553, 636–643, 637f
micellization of surfactants, 233–235
properties of, 233–234
solubilization, 235
microscopy, 638–639, 638f
PGSE-NMR, 641–642, 642f
Rheology, 642–643, 642f–643f
scattering methods, 639–641, 639t, 640f
light scattering, 639–640
X-ray and Neutron Scattering, 639t, 640–641, 641f
Micellization, hypotheses of, 240
Microbeads FreeWaters Act, 210
Microcapsules, 207
Microdialysis, 750
Microemulsions, 352, 482–483, 483f, 507–510, 508f, 553, 553f, 641–642. *See also* Emulsions
components, 513–514
cosmetic applications of, 512–513
percutaneous absorption of actives from, 515–516
Microencapsulation, 277, 277f
Microfibrillar-associated protein 4 (MFAP-4), 262
Microfibrils, 262
Microgel particles, 458–462
Microneedles, 746
Microrelief, 675
Microscopes, 650
Microspheres, 197
Microvasculature, 675, 680, 770
Mild anionic surfactants, 564–565, 568–569
Mildness to skin, 561–565
Miller indices, 644–645
Minimal persistent pigment darkening dose (MPPDD), 595
Minimal persistent pigment darkening dose on product-protected skin (MPPDDp), 595
Minimal persistent pigment darkening dose on unprotected skin (MPPDDu), 595
Minimum erythema dose (MED), 593–594
Ministry of Health, Labor and Welfare (MHLW), 729, 802
Minoxidil, 774
Misnomer, 507
Mitigation of skin irritation and inflammation, 205–206
Mitochondrial impairments, 713
Mixed surfactant system, 564
adsorption behavior of, 241–243, 242f–243f
interaction of surfactants, 240
solubility of, 240–241, 241f
Mixing fatty acids, 568
*Miyako-Fuzoku Kewai-Den*, grooming philosophy through, 8–9
MLV. *See* Multilamellar vesicles (MLV)
MMPs. *See* Matrix metalloproteinases (MMPs)

Modern Carbomers, 182
Modern light scattering methods, 639
Modern makeup, 223
Moisture
  balance, 551
  evaporation, 251
  reservoir, 332
  retaining, 92–93, 92f, 167–168, 167f–168f
  in stratum corneum, 17–25
Moisturization, barrier disruption by excessive, 683
Moisturizers, 115–116, 245, 348
Moisturizing function, 679, 683
Molar substitution, 174–176
Molecular aggregation number, 236
Molecular assembly, 523–526
  formation, 519–521
    appearances of surfactant/water system, 520f
    dissolution behavior of surfactant/water system, 520f
  to functional cosmetics, 531–535
Molecular colloids, 635
Molecular persistence length, 172
Molecular structure of hydrophilic groups and phase behavior, 395–396, 396t
Mono-alkyl phosphate salt, 564, 564f
Monodisperse, 59
Monoethanolamide (MEA), 566, 566f
Monoi Conditioning Dry Shampoo, 333
Monomolecular surfactants, 233
Moroccan Oil Dry Shampoo, 333
Mouthfeel, 619
MPPDD. *See* Minimal persistent pigment darkening dose (MPPDD)
MPPDDp. *See* Minimal persistent pigment darkening dose on product-protected skin (MPPDDp)
MPPDDu. *See* Minimal persistent pigment darkening dose on unprotected skin (MPPDDu)
MPT. *See* Multiphoton laser scanning tomography (MPT)
MQ resins, 191, 203
MRI. *See* Magnetic resonance imaging (MRI)
MS. *See* Mass spectrometer (MS)
4MSK. *See* 4-Methoxy Potassium Salicylate (4MSK)
MSRP. *See* Maker Suggested Retail Price (MSRP)
MT 1-MMP, 722–723
MT resins, 191
MTA. *See* Material Transfer agreements (MTA)
Mucopolysaccharides, 680
Mulberry root bark extract, 776
Multilamellar emulsions of pseudo-stratum corneum lipids, 532–535, 534t
Multilamellar vesicles (MLV), 431–433, 477, 478f
Multiphase network structure, 425
Multiphoton laser scanning tomography (MPT), 747
Multiple emulsions, 353, 501–502
Multisensory approaches, 631
Multispectral FLIM (SLIM), 747
Musks, 273f
Myristyl Theobroma Grandiflorum Seedate, 156
*Mytilus edulis*(*M edulis*), 197

## N

NA. *See* Nicotinamide (NA)
NAC. *See* N-Acetyl cysteine (NAC)
$NAD^+$. *See* Nicotinamide adenine dinucleotide ($NAD^+$)
Nagoya protocol, 307
Nails, 340
  care, 350
  enamels, 35
  polish, 223
NaLMA. *See* N-Lauroyl-N-methyl-β-alanine sodium (NaLMA)
Nano-emulsions, 352, 489, 507, 508f, 510–512. *See also* Emulsions
  components, 513–514
  cosmetic applications of, 512–513
  percutaneous absorption of actives from, 515–516
Nanobiotechnology, 337
Nanocapsules, 277, 355
Nanocosmeceuticals
  applications, 341–350
    antiagings, 342–347
    hair care, 349
    lip care, 350
    moisturizers, 348
    nail care, 350
    skin cleanser, 349
    sunscreens, 348–349
  future trends in, 364
  in market, 361
    nanotechnology-based cosmeceutical products in market, 361t–363t
Nanocrystals, 356
Nanodiamond, 358
Nanofibers, 356–357
Nanogold, 354
Nanomaterials, 360–361
  nanomaterial-based delivery of actives, 745
Nanoparticles (NPs), 337, 350
  in cosmetics, 350–359
    carbon-based nanoparticles, 357–358
    CDs, 358
    dendrimers, 359
    inorganic nanoparticles, 354
    nanoparticulate systems, 356–357
    organic nanoparticles, 351–353
    polymeric NPs, 354–355
  toxicity of, 359
Nanoparticulate systems, 356–357
  nanocrystals, 356
  nanofibers, 356–357
  nanoparticulate forms of cubic phase, 43–44
  nanopigments, 357
  nanospheres, 356
  nanotopes, 356
Nanopigments, 357
Nanoscale roughening, 190
Nanosilver, 354
Nanosomes, 351
Nanospheres, 356
Nanostructured lipid vehicles (NLCs), 350–351
Nanostructuring, 196
Nanotechnology in cosmetics. *See also* Cosmetic(s)
  mechanism of skin penetration, 340–341
  nanocosmeceuticals
    applications, 341–350
    future trends in, 364
    in market, 361
  nanomaterials and EU cosmetics regulations, 360–361
  NPs
    in cosmetics, 350–359
    toxicity of, 359
  safety requisites for blooming beauty, 360
  skin function, 340
  skin structure, 337–340, 338f
Nanotechnology-based nail beauty products, 350
Nanotopes, 356
Napping, 624–625
NAPS. *See* N-Acetyl phytosphingosine (NAPS)
Nasolabial fold, 738
National Formulary (NF), 182
National phase, 129
Natural cosmetics trend, 307–308
Natural fragrances, 281–282
Natural ingredients, 196
Natural moisturizing factors (NMF), 28, 93f, 167, 245, 255–256, 288–289, 289t, 290f, 551, 679–680
  and bioactive ingredients, 257
Natural oils, 247, 608, 622
Natural phospholipids, 539
Natural plant extracts, 776–777
Natural polymers, 190
Natural products, 261–262, 267–269
Natural rheology modifiers, 171
Natural-looking makeup, 574–576
Natural/renewable ingredients, 333–334
  botanicals/herbal extracts; natural oils/butters, 334t
NDA. *See* Nondisclosure agreements (NDA)
Near-infrared (NIR), 25
"Needs" brief, 77
  front-end homework/creation of, 81, 82f
Negatively staining method, 638
NER system. *See* Nucleotide excision repair system (NER system)
Nerve growth factor (NGF), 257

NESIL. *See* No expected sensitization induction level (NESIL)
Network, 177–178, 181, 183, 185–186, 188, 193, 417
Neural factors, 97
Neuro-immuno-cutaneous endocrinology, 97
Neuro-immuno-cutaneous-endocrionology theory (NICE theory), 88–90
Neurogenic inflammation, 737–738
Neuropeptides, 737–738
Neutralizer, 292, 610
Neutron
  diffraction, 638
  neutron-ray scattering methods, 639
  scattering, 640–641
New Product Development (NPD), 79
New-type cosmetic base, 531–532
Newtonian black films, 50
Newtonian fluids, 61, 642–643
NF. *See* National Formulary (NF)
NGF. *See* Nerve growth factor (NGF)
Niacinamide, 258, 258f, 355, 734, 734f
NICE theory. *See* Neuro-immuno-cutaneous-endocrionology theory (NICE theory)
Nicotinamide (NA), 717, 719, 776
Nicotinamide adenine dinucleotide ($NAD^+$), 717
NIH. *See* Not Invented Here (NIH)
Niosomes, 351, 745
NIR. *See* Near-infrared (NIR)
Nitriles, 272
NLCs. *See* Nanostructured lipid vehicles (NLCs)
NMEA. *See* *N*-Methylethanolamide (NMEA)
NMF. *See* Natural moisturizing factors (NMF)
NMR. *See* Nuclear magnetic resonance (NMR)
No expected sensitization induction level (NESIL), 280
$NO_2$, 757–759
Noggin, 772
Nomenclature of ingredients
  applying for INCI name, 158
  botanical names, 157
  history, 155
  INCI, 155
    basics, 156–157
    names and CAS, 157–158
    names and CosIng, 158
Nominal data, 629
Non-cross-linked linear acrylic copolymers, 206
Non-guar galactomannans, 200
Non-Newtonian behavior, 642–643
Non-Newtonian system, 628–629
Nondisclosure agreements (NDA), 79
Nonelectrolytes, 163
Nonequilibrium state, 489
"Nonessential" products, 786
Noninvasive methodologies, 723–724
Noninvasive techniques and methods, 783
Nonionic surfactants, 231–232, 235, 272, 402–409, 402t, 523, 524f, 744–745. *See also* Anionic surfactants; Cationic surfactants; Sugar-based surfactants
  block polymer surfactants, 407–408
  micelles, 233
  PEO surfactants, 402–406
  polyglycerin surfactants, 407–408
  solutions, 235
Nonionic thickeners, 184
Nonmelanoma, 760
Nonsteroidal antiinflammatory drugs (NSAIDs), 716–717, 722
Nonverbal communication, 5
Nonvolatile oil, 193
Not Invented Here (NIH), 81
Notation method, 629
Note, 273
NPA. *See* Asn-Pro-Ala (NPA)
NPD. *See* New Product Development (NPD)
NPs. *See* Nanoparticles (NPs)
NSAIDs. *See* Nonsteroidal antiinflammatory drugs (NSAIDs)
Nuclear magnetic resonance (NMR), 450, 556, 646, 647f
Nucleated layers of epidermal lipids, 686
Nucleotide excision repair system (NER system), 712
*Nuka-bukuro*, 103
"Null" hypothesis, 630
Nutrition, 6

## O

O/LC emulsion. *See* Oil-in-liquid crystal emulsion (O/LC emulsion)
O/W. *See* Oil-in-water (O/W)
Objective test methods, 626–627
Occlusion, 551
  effect, 251, 251f
  occlusive dressing technique, 683
Occupational skin diseases (OSD), 744
OCR. *See* 2-Ethylhexyl 2-cyano-3,3-diphenyl-2-propenoate (OCR); Octocrylene (OCR)
OCT. *See* Optical coherence tomography (OCT)
Octadecyl trimethyl ammonium chloride (OTAC), 556
Octocrylene (OCR), 590
Octyl-4-methoxycinnamate (OMC), 355, 589, 591–592, 591f–592f
OECD
  "eChemPortal", 791
  TGs, 797, 798t
Office for Harmonization in Internal Market (OHIM), 131
*Ohaguro*, 7
OHIM. *See* Office for Harmonization in Internal Market (OHIM)
OI. *See* Open innovation (OI)
Oil
  droplets, 523
  friction and stickiness evaluation, 250–251
  gelatinization agents, 295–296
  HLB number of, 493–495, 494t
  phase, 438
    polarized microscopy photographs of cetrimide, 439f
    representation of liquid oil emulsified by lamellar gel network, 439f
    SAXS pattern of cetrimide/cetostearyl alcohol gel network, 440f
Oil-in-liquid crystal emulsion (O/LC emulsion), 527–528, 529f
  gel emulsion using lamellar liquid crystal, 526–528
Oil-in-water (O/W), 29, 31f, 352, 489, 508–509, 509f, 659
  emulsification, 555–559
  emulsions, 68–69, 443, 483, 499, 555, 648
    solving batch failure problem in making large batch, 663
  foundation, 571–572
  lotion, 590–591
  mixtures, 622
  nanoemulsions, 352
  products, 552
  solution, 491–492
Oil-type foundation, 573
Oleaginous materials, 150
Oleth-15. *See* Polyoxyethylene (15) oleyl ether (Oleth-15)
Olfactory communication, 101
Olsen vasoconstriction scale, 750
OMC. *See* Octyl-4-methoxycinnamate (OMC)
Omega-hydroxylation (ω-hydroxylation), 688
Omega-O-acylceramide, 688
One-chained surfactants, 233
Open innovation (OI), 78
Optical coherence tomography (OCT), 35–37, 90, 723–724
Optical microscope observation
Optical microscopy, 638, 649
Optical tomographic microscopy (OTM), 650
Optically isotropic liquid crystals, 644
Optimal microscopic structure, 635
Optimal surfactant combinations for emulsification, HLB method to find, 666–667
*Opuntia ficus-indica* (*L.*), 513
Order parameter, 652–653
Ordinal data. *See* Nominal data
Organ formation factor, 776
Organic
  agriculture, 307
  chemistry, 270
  compounds, 776
  conceptual diagram, 493, 493t
  cosmetics
    green chemistry, 307–308

Organic (*Continued*)
international trend of natural cosmetics and, 308
"natural cosmetics" trend, 307
organic agriculture, 307
fragrances, 281–282
modified clay minerals, 553
emulsification, 555
substances, 160
Organic nanoparticles, 351–353. *See also* Inorganic nanoparticles; Polymeric NPs
aquasomes, 353
cubosomes, 352
ethosomes, 351
liposomes, 351
LNPs, 351
microemulsions, 352
multiple emulsions, 353
nanoemulsions, 352
nanosomes, 351
niosomes, 351
photosomes, 353
transferosomes, 352
ultrasomes, 353
Organic pigments, 227–228
extender pigments, 227–228
colored pigments, 228
polymer resin, 227
surfactants and metal salt, 227–228
Organic value (OV), 493
Organizational scouting models, 79
Organogels, 484–485
cationically modified cellulose in water, 485f
Organopolysilsesquioxanes, 191
Original transfer-resistant
color cosmetics, 191
lipsticks, 191
ORS cells. *See* Outer root sheath cells (ORS cells)
Orthorhombic hydrocarbon-chain packing structures, 699–700, 700f
Oscillatory measurement, 643
OSD. *See* Occupational skin diseases (OSD)
Osmophores, 270
Osmoprotective complexes, 181
Osmosis, 165
"Osmotic gradient", 352
Osmotic pressure, 166
Ostwald ripening, 71, 496–499, 502, 510–511, 555
of emulsion destabilization, 653
Ota nevus, 577–578
OTAC. *See* Octadecyl trimethyl ammonium chloride (OTAC)
OTC. *See* Over-the-counter (OTC)
OTM. *See* Optical tomographic microscopy (OTM)
Ouidad Sun Shield Leave-In Spray product, 332
Outer root sheath cells (ORS cells), 767–768
"Ouzo effect", 511
OV. *See* Organic value (OV)
Over-the-counter (OTC), 137–138
Overgeneralization effect, 109
Overhead illumination hypothesis, 107
Oxidation
dye precursors and couplers, 614t
oxidative stress, 758
oxidizing agents, 205
process, 760–761
8-Oxo-guanine (8oGua), 342–343
Oxygen atoms, 159, 166
Oxygen free radicals, 342–343
Ozone, 759–761
water, 164

## P

P&G. *See* Pantene Pro-V (P&G)
Packing factor, 42–45, 42f
PAD. *See* Peptidyl arginine deimidase (PAD)
PAHs. *See* Polycyclic aromatic hydrocarbons (PAHs)
Palisade-type solubilization, 235
Palmitoyl KTTKS, 347
PAM. *See* Polyacrylamide (PAM)
PAMPs. *See* Pathogen-associated molecular patterns (PAMPs)
Panels, validation of, 623
Pantene Pro-V (P&G), 321
Pantothenyl ethyl ether, 776
Paraffin, 247
Parametric tests, 629
Paris Convention, 127–128, 128b
Particles, 490–491
Particulate matter (PM), 757, 759
Patent Cooperation Treaty (PCT), 128
filing of patent applications in other countries using, 128–130
amendment in international phase, 128–129
characteristics of PCT applications, 130
first country application, 128
International Preliminary Examination Report, 128
International Search Report, 128
national phase, 129
PCT applications, 128
Patent Law. *See also* Trademark Law; Unfair Competition Prevention Law
Design Patent Law
duration of design patent rights, 131
intellectual property rights protection under, 130
requirements for design patent registrations, 130
scope of rights of registered design patent, 130–131
search for registered designs in commercialization stage, 131
duration of patent right, 126
flow from filing of patent application, 127–130
in accordance with Paris Convention, 127–128
using PCT, 128–130
flow from filing of patent application to registration
examination, 124
filing of patent application, 124
laid-open publication, 124
notice of allowance, 125
notice of reasons for rejection, 124–125
patent gazette, 125
response to notice of reasons for rejection, 125
intellectual property right to protection under, 122–123
composition of matter patent, 123
patent for method for use, 123
patent for method of manufacturing, 123
substance patent, 122–123
materiality of prior patent search
commercialization stage, 126–127
measures to cope with patent rights of other persons, 127
research and development stage, 126
effect of patent right, 125–126
patent rights in foreign countries, 127
requirements for obtaining patent, 123–124
prior applicant, 123–124
description requirement, 124
inventive step, 123
novelty, 123
Patent right
effect of, 125–126
duration of, 126
Pathogen-associated molecular patterns (PAMPs), 715
Patterned hair loss, 773
PC. *See* Phosphatidylcholine (PC)
PCA. *See* Principal Component Analysis (PCA); Pyrrolidone carboxylic acid (PCA)
PCP. *See* Personal care product (PCP)
PCPC, 158
PCPC. *See* Personal Care Products Council (PCPC)
PCT. *See* Patent Cooperation Treaty (PCT)
PDADMAC. *See* Poly(diallyldimethylammonium chloride) (PDADMAC)
PE. *See* Phosphatidyl ethanolamine (PE)
Pearlescent pigments, 227, 227f
PEC. *See* Predicted environmental concentration (PEC)
Pectin, 180
PEG. *See* Polyethylene glycol (PEG)
PEG/PPG. *See* Polyoxyethylene/Polyoxypropylene (PEG/PPG)
PEG/PPG random copolymer dimethylether, 249–250, 249f
Penetration mechanism, 46–47, 46f
Penetration route
of hydrophilic molecules, 702–703
of hydrophobic molecules, 704–705
Pentadecan, 775f, 776

Pentaglyceryl laurate ($C_{12}Gly_5$), 407–408, 408f
PEO. *See* Polyethyleneoxide (PEO)
Peptides, 285, 342
  in body, 291
    carnosine, 291
    glutathione, 291
  bonds, 164
  chemistry of, 285–286
  in cosmetics, 296–299, 297t–298t
    production of peptides, 299
  topical peptides, 347
Peptidyl arginine deimidase (PAD), 257
Percutaneous absorbents, 539
Percutaneous absorption, 746
  of actives from microemulsions and nano-emulsions, 515–516
Percutaneous penetration, 539
  control of, 683
Perfumes, 208, 274
Perilla frutescens *Var.* crispa *f.* viridis. *See* Green Perilla
Permanent coloring, 611f–612f, 612
Permanent dipole moment, 159
Permanent hair waving products, 612–613
  chemical bonds between hair protein chains, 613f
  mechanism of permanent waving, 613f
  oxidation dye precursors and couplers, 614t
Permanent waving, 205
Perming, 602, 607, 612–613
Peroxisome proliferator-activated receptor γ (PPARγ), 717
Persistent pigment darkening (PPD), 595
Personal care industry, 186
Personal care product (PCP), 171, 210–211, 360
Personal Care Products Council (PCPC), 139, 155, 210–211
Perspiration, mechanism of, 168
Petrolatum, 202
Petrolatum emulsion, 533
PG. *See* Propylene glycol (PG)
γ-PGA. *See* γ-Polyglutamic acid (γ-PGA)
PGC-1α. *See* PPARγ coactivator 1α (PGC-1α)
$PGE_2$. *See* Prostaglandin $E_2$ ($PGE_2$)
PGSE-NMR. *See* Pulsed-gradient spin-echo nuclear magnetic resonance (PGSE-NMR)
pH, 44–45, 286
  adjuster, 292
  dependence of foamability of sodium acyl glycinates and sodium fatty acids, 294f
PHA. *See* Polyhydroxy acids (PHA)
Phantom networks, 42–43
Pharmaceutical Affairs Law (2009), 155
Pharmaceutical products, 245
Phase behavior
    molecular structure of, 395–396
    in PEO surfactant system, 402–403
    polyoxyethylene dodecylether, 404f
    structure of, 398–400
    on alkyl chain, 400–402
    of dodecyltributyl ammonium bromide, 400f
    of guanidine cationic surfactants, 400f
Phase diagram, 393f, 471
  notations in, 389
  in surfactant system, 389–392
    binary system, 389–391
    ternary system, 391–392, 391f–392f
  use, 52f
    by formulator, 52
    process/scale-up engineer, 52
Phase inversion composition (PIC), 503, 511, 512f
Phase inversion temperature (PIT), 392, 494–495, 498f, 508–509, 512f, 664
  emulsification, 499, 555
Phase separation for polymeresurfactant mixtures, 454–458, 455f
  mixed solutions of oppositely charged hydrophobically modified polyelectrolytes, 458f
  polyelectrolyte–ionic surfactant systems, 457f
Phase transition thermodynamics, 433–434, 434f
Phenol coefficient, 277–278, 278f
Phenolic structures, 271f
Phenols, 270
Phenylbenzimidasol, 590
Phenylbenzotriazol, 590
Phlogopites, 224
Phosgenite ($Pb_2Cl_2CO_3$), 223
Phosphatidyl ethanolamine (PE), 545–546
Phosphatidylcholine (PC), 539
  high PC purity, 542–544
Phosphatidylcholine, 343
Phosphatidylserine (PS), 261–262, 545–546
Phospholipase D inhibition, 721–722
Phospholipids, 165, 261–262, 539, 541
  biomembrane-composing, 540
  property, 539–540
  zeta potential of phospholipid components, 546f
Photoaging, 680–681, 711, 719–720
Photocatalysis, 226
Photochromic effect, 583–584
Photochromic titanium dioxide, 32
Photosomes, 353
Photostability, 591, 800
*Phyllanthus emblica* (*P. emblica*), 346–347
Physical principles for use of polymers in cosmetics, 52–62
  copolymers, 56–57
  polymer
    conformation, 57–58
    molecular mass distribution, 59
    semidilute solutions, 60–61
    solubility and compatibility, 53–55
    solution viscosity and its relation, 58–59
  polymer/disperion rheology basics, 61–62, 62f
Physicochemical properties, 161
Phytosphingosine (PS), 262f, 516
PIC. *See* Phase inversion composition (PIC)
Pickering emulsion, 505
  wettability of particles and emulsion type, 503f
Pigmentation, 257–258
Pigmented spots, 257–259
  melanin synthesis and bioactive ingredients, 258–259
  melanocyte stimulation factors and bioactive ingredients, 259
  melanosome transfer into keratinocytes and bioactive ingredients, 259
Pigments, 164
Pinning effect of wetting, 380, 380f
PIT. *See* Phase inversion temperature (PIT)
Placental extract, 730
Plain vinyl polymers, 171
Planar barium sulfate, 224
Plant
  classification, 157
  extracts, 157
  names, 157
Plasmin, 732
Plastic microbeads, 211
Plasticizer, 610
Plateau border, 188–189
Plateau–Rayleigh instability, 210
Platelet-rich plasma, 777
  therapy, 777
PM. *See* Particulate matter (PM)
Pmel-17, 258
PNEC. *See* Predicted no effect concentration (PNEC)
POE. *See* Polyoxyethylene (POE)
Polar organic solvents, 183
Polar substances, 163, 165
Polarity, 275–276
Polarization-sensitive spectra domain optical coherence tomography (PS-SD-OCT), 724
Polarized microscope, 644
Poly (1,4-butadiene), 57
Poly (chloroethylvinylether-co-vinylbenzoylchloride), 209–210
Poly (methylmethacrylate-co-vinylbenzoylchloride), 209–210
Poly (N-isopropylacrylamide) solutions, 173
Poly (N-vinyl-2-pyrrolidone) (PVP), 56–57, 195, 326, 357, 480–481
Poly (vinyl acetate) (PVA), 56–57
Poly(diallyldimethylammonium chloride) (PDADMAC), 464f
Poly(ethylene glycol), 450
Poly(pglyceryl-6-dioleate), 514
Poly(vinyl pyrrolidone), 450
Polyacrylamide (PAM), 480–481
Polyacrylate-2 Crosspolymer, 195–196
Polyamides, 187
Polyampholytes, 198
Polycaprolactone oligomers, 207
Polycyclic aromatic hydrocarbons (PAHs), 757, 760
Polydisperse, 59

Polyelectrolyte, 200, 449, 455f–456f, 459f, 480–481
Polyelectrolyte microgel thickeners, 71–72
Polyelectrolyte–surfactant adsorption, 463–464
Polyelectrolyte–surfactant systems, 451–452. *See also* Homopolymer–ionic surfactant systems
Polyethylene glycol (PEG), 430–431
Polyethylene oxide-block-poly(-caprolactone), 516
Polyethylenenimine polymers, 209
Polyethyleneoxide (PEO), 390–391, 402, 480–481
  surfactants
    effect of alkyl chain, 405–406
    EO chain and cloud point, 406, 406t, 410t
    effect of methyl caps and ester groups, 403–405
    phase behavior in PEO surfactant system, 402–403
Polyethylenimine layer, 198
Polyfluorocarbons, 192
γ-Polyglutamic acid (γ-PGA), 299
Polyglycerin surfactants, 407–408
  effect of temperature on phase behavior, 408f
Polyglycerol partial esters, 204
Polyhydroxy acids (PHA), 342, 722–723
Polyisobutene, 247
ε-Polylysine, 299
Polymeric
  antimicrobials, 209–210
  backbone, 185
  emulsifiers, 183
  particle, 208
  quaternary ammonium chloride, 198
  thickeners, 183, 606
Polymeric NPs, 354–355
  chitosan, 355
  hydrogels, 355
  liquid crystals, 355
  nanocapsules, 355
Polymerization, 182, 194, 204
  degree, 299
    effect of sugar, 411, 411f
  solvent, 194
Polymers, 42–43, 277, 326, 480–482, 546–547
  backbone, 177
  blends, 196
  chains, 171
  conceptual exercise on polymer dimensions, 58
  conformation, 57–58
    conceptual exercise on polymer dimensions, 58
    end-to-end distance, 57
    hydrodynamic radius, 57–58
    radius of gyration, 57
  as controlled release matrices, 207–208
    enhanced delivery, 208
  in cosmetic products, 171
    foam enhancement by amphipathic block copolymers, 188–189, 189f
    molecular tailoring for simultaneous enablement of contrasting qualities, 188–190
    polymers modifying surfaces, 190
    rheology modifiers, 171–187
    side-chain crystalline copolymers, 188
    solid foams, 189–190
    transfer-resistant color cosmetics, 190–195, 193f–195f
  dendritic polymers, 208–209
  film-forming polymers in cosmetics and personal care products, 195–197
  formulation, 197
  hair-conditioning polymers, 198–205, 198f–199f, 201f
  modifying surfaces, 190
  molecular mass distribution, 59
  molecules, 454
  polymer/disperion rheology basics, 61–62, 62f
  polymeric antimicrobials and bacteriostats, 209–210
  resin, 227
  semidilute solutions, 60–61
  in skin products for ecological sustainability, 210–211
  solubility and compatibility, 53–55
  solutions, 635
    viscosity and relation to polymer molecular dimensions, 58–59
  stabilization, 189–190
  thermal behavior of polymer gels, 173
  for treatment of skin
    hyaluronic acid for antiwrinkle treatment, 205
    mitigation of skin irritation and inflammation, 205–206, 206f
    multicomponent complexes for cleansing and treatment of skin, 206
    removing wrinkles by external tensioning and "playing tricks with light", 207
Polymer–surfactant complex phase, 200
Polymer–surfactant interactions, 449. *See also* Surfactants
  amphiphilic polymer self-assembly, 452–453
  gels, 458–462
  homopolymer–ionic surfactant systems, 450–451
  phase separation for polymer–surfactant mixtures, 454–458, 455f
  polyelectrolyte–surfactant systems, 451–452
  surfactant–polyelectrolyte mixtures at interfaces, 462–467, 463f
Polymethylsilsesquioxane, 207
Polyolefin oils, 608
Polyols, 542–544
Polyoxyethylene (POE), 492
  alkyl ether sulfate salt, 563f
  hydrophilic surfactants, 555
  nonionic surfactants, 235
Polyoxyethylene (POE), 562
Polyoxyethylene (15) oleyl ether (Oleth-15), 418
Polyoxyethylene (6) dodecyl ethers (6ED), 236
Polyoxyethylene/Polyoxypropylene (PEG/PPG), 246
Polypeptides, 164–165, 286
Polyperfluoromethylisopropyl ether, 192
Polyphenol *trans*-resveratrol, 314
Polypropylene chain (PPO chain), 409
Polypropylenesilsesquioxane waxes, 192
Polyquaternium-7, 199–200
Polyquaternium-10, 198–200, 199f
Polyquaternium-11, 198, 198f
Polyquaternium-24, 200
Polyquaternium-55, 198
Polyquaternium-76, 201, 201f
Polysaccharide(s), 176, 180–181, 197
  emulsifiers, 197
  polysaccharide-zein complexes, 207–208
Polysilicone-15, 590
Polystyrene, 57
Polyvinylalcohol (PVA), 480–481
Pomade, 267
POMC. *See* Proopiomelanocortin (POMC)
Porod rule, 641
Porous solids, 189–190
Postmarketing
  safety reevaluation, 791f
  surveillance, 791
Powder(s)
  in cosmetics, 223
    inorganic pigments, 224–227
    organic pigments, 227–228
  foundations, 572–573, 572t
  powder-based makeup cosmetics, 31–32
Powdery material, 294
PPARγ. *See* Peroxisome proliferator-activated receptor γ (PPARγ)
PPARγ coactivator 1α (PGC-1α), 717
PPD. *See* Persistent pigment darkening (PPD); Prolonged pigment darkening (PPD)
PPO chain. *See* Polypropylene chain (PPO chain)
Pre-shampoos, 325
Precipitated polymer, 205
Preconcentrated microemulsions, 514
Predicted environmental concentration (PEC), 280
Predicted no effect concentration (PNEC), 280
Preference Mapping, 621
Premature aging, 714
Preservatives, 143–145
Primary metabolites, 305–306
Primary skin irritation. *See also* Skin penetration
  comparative assessment on, 790f
  practical assessment of, 789f
Principal Component Analysis (PCA), 626

Principles of Humane Experimental Technique, 741
Process variables (PVs), 658
Product
  evaluation, 617
  forms, 333–334
  lifespan, 139
Profilaggrin, 257, 288
Progeria syndrome, 714
Prolonged pigment darkening (PPD), 587
Proopiomelanocortin (POMC), 97, 737–738
Propellant, 610
*Propionibacterium acnes* (*P. acnes*), 39–40, 315, 681
Propylene glycol (PG), 236
Prostaglandin $E_2$ ($PGE_2$), 259
Protease-activated receptor-2, 259
Protein(s), 149, 285, 322, 480–481, 490–491
  as biochemical compounds, 286–291
  chemistry of, 285–286
  in cosmetics, 299
  hydrolysates, 203
  hydrolysis, 299
  primary structures of, 164
  secondary structure of, 164–165
  tertiary structures of, 165
  water molecules and, 165
Proteogenic amino acids, 286
Proteoglycan, 338–339
Proteolysis, 169
PRP therapy. *See* Platelet-rich plasma therapy (PRP therapy)
PS. *See* Phosphatidylserine (PS); Phytosphingosine (PS)
PS-SD-OCT. *See* Polarization-sensitive spectra domain optical coherence tomography (PS-SD-OCT)
Pseudo-plastic system, 643
Pseudo-stratum corneum lipids, multilamellar emulsions of, 532–535
Pseudophase
  diagrams, 50–52
  separation model, 240
Pseudoplastic fluids, 61
Psoriasis, 758, 760, 781–782
Psoriatic skin, 781–782
Psychology
  cosmetic behavior
    emotion control device, cosmetic behavior as, 110–112, 110f–111f
    features of cosmetic customs in western world and Japan, 103t
    fragrance psychology, 109–110
    history of cosmetics, 102–103
    makeup psychology, 106–109
    prehistory of cosmetics, 101–102
    skin care psychology, 104–106, 104f
  psychological sweating, 681
Pullulan polymer, 178
Pulsed-gradient spin-echo nuclear magnetic resonance (PGSE-NMR), 641–642, 647
Pure rubbers, 172
Purified water, 164
Putrefaction, 151
PVA. *See* Poly (vinyl acetate) (PVA); Polyvinylalcohol (PVA)
PVP. *See* Poly (N-vinyl-2-pyrrolidone) (PVP)
PVs. *See* Process variables (PVs)
Pyrimidine-pyrimidone 6–4 photoproducts, 712
Pyrrolidone carboxylic acid (PCA), 289, 679–680

**Q**

Q silane functional groups. *See* Quatrifunctional silane functional groups (Q silane functional groups)
QDA. *See* Quantitative Descriptive Analysis (QDA)
QDs. *See* Quantum dots (QDs); Quasi-drugs (QDs)
QOL. *See* Quality of life (QOL)
QRA. *See* Quantitative risk assessment (QRA)
QSAR. *See* Quantitative structure–activity relationship (QSAR)
"QSAR/in silico" computational toxicology, 801
QSPRs. *See* Quantitative structure–permeation relationships (QSPRs)
Qualitative evaluation, 789
Quality control, materials for, 151
Quality of life (QOL), 9, 118, 711
Quantitative Descriptive Analysis (QDA), 627
Quantitative evaluation, 789
Quantitative risk assessment (QRA), 280
Quantitative structure–activity relationship (QSAR), 801
Quantitative structure–permeation relationships (QSPRs), 750
Quantum dots (QDs), 350
Quasi-drugs (QDs), 137–138, 729, 773–776
  adenosine, 775, 775f
  carpronium chloride, 774, 775f
  cepharanthine, 775f, 776
  cytopurine, 775–776, 775f
  in Japan, 802, 802t
  ketoconazole, 775f, 776
  mechanistic classification of, 730t
  pentadecan, 775f, 776
  skin-lightening QDs in Japan, 729–735
  t-Flavanone, 775, 775f
Quaternary ammonium salts, 423
Quaternary structure, 165
Quatrifunctional silane functional groups (Q silane functional groups), 191
Quenching method, 499
Quercitrin. structure, 313f
Quick-dispersing emollients, 631
Quinone-type oxygen atoms, 225–226

**R**

R&D. *See* Research and development (R&D)
12R-LOX. *See* 12R Lipoxygenase (12R-LOX)
RA. *See* Retinoic acid (RA)
Racemic LGA (DL-LGA), 295
Radius of gyration, 57
RAGE. *See* Receptor for AGEs (RAGE)
Raman method, 90
Raman scattering methods, 90
RAO. *See* Ratio of acute incident angle/acute reflection angle to obtuse incident angle/obtuse reflection angle (RAO)
Raoult's law, 277
Ratio of acute incident angle/acute reflection angle to obtuse incident angle/obtuse reflection angle (RAO), 576
Raw material formulation on sensor, 622–623
Reactive oxygen species (ROS), 260, 291, 596–597, 712, 758, 800
Receptor for AGEs (RAGE), 722–723
Reconstructed Human Cornea-like Epithelium Test Method (RhCE Test Method), 799
Reconstructed Human Epidermis Test Method (RhE Test Method), 798–799
Rectification process, 268
Red iron oxide, 225
Reductase Ψ5α-Ψ, 774
Reference samples, 629
Refinement, reduction, and replacement principle (3Rs principle), 741, 796
Reflector board effect powder, 32–33
Refractive index method (RI method), 648
Regional variation of skin, 682
Regulation(s)
  of epidermal terminal differentiation, bioactive ingredients on, 257
  of fragrance, 281
  regarding botanical substances, 306–307
    actual industrial use and issues of genetic resources, 307
    CBD, 306–307
Regulations on cosmetics. *See also* Dermatology; Intellectual property rights
  cosmetics ingredient restrictions, 140–145
    coloring, 143–145, 144t
    preservatives, 143–145
    prohibited materials, 140–142, 141t–142t
    restricted materials, 142–143, 143t
    UV-absorbing materials, 143–145, 145t
  labeling, 139–140
  per region, 137–138
  regional regulations, 138t
Relative humidity (RH), 333
Repeated-dose toxicity, 799
Reproductive toxicity, 800
Research and development (R&D), 12, 15, 78
Research Institute for Fragrance Materials (RIFM), 279

Restylability, temporary style with, 197
Resveratrol, 717–719
Retention of basal cells, 676
Reticular dermis, 338–339
Retinoic acid (RA), 261, 722–723
Retinoids, 344–345
Revolutionary analysis technique, 223
REXPAN. *See* RIFM Expert Panel (REXPAN)
RH. *See* Relative humidity (RH)
RhCE Test Method. *See* Reconstructed Human Cornea-like Epithelium Test Method (RhCE Test Method)
RhE Test Method. *See* Reconstructed Human Epidermis Test Method (RhE Test Method)
Rheology, 471, 642–643, 642f–643f, 653. *See also* Dermatology
  additives, 480–482
  emulsions, 483, 484f
  foams, 485
  hydrogels, 484–485
  liquid crystals, 486
  micellar structures, 473–480
  microemulsions, 482–483, 483f
  organogels, 484–485
  property, 233–234
    emulsions, 523, 524f
  rheological parameters and measurements, 472–473, 473f
  rheological properties, 473–480
  surfactant solutions, 473–482
Rheology modifiers, 171–187
  acryloyldimethyltaurate polymeric rheology modifiers, 183–184
  alginates, 179–180, 179f
  associative thickeners, 184–186
  carrageenans, 178–179
  cellulose and starches, 173–176
  with film-forming capability, 186
  galactomannans, 176–177, 176f, 176t
  gellan gum, 178
  guar gum, 177
  larch galactoarabinan, 180–181
  locust bean gum, 177
  particulate thickeners, 181–183, 182f
    carbomer, 182–183
  pectin, 180
  practical considerations, 173
  pullulan, 178
  stimuli-responsive, 186
  thermal behavior of polymer gels, 173
  thickening oil, 186–187, 187f
  xanthan gum, 177–178, 178f
Rhododendrol, 258, 258f, 734, 734f
RI method. *See* Refractive index method (RI method)
Ribonucleotide (RNA), 775
RIFM. *See* Research Institute for Fragrance Materials (RIFM)
RIFM Expert Panel (REXPAN), 279
Rinse-off conditioners, 606
Risk-benefit balance, 786, 786f
RNA. *See* Ribonucleotide (RNA)
Rodlike micelles. *See* Worm-like micelles
Rollup
  mechanism of detergency, 46f
  of oil droplets, 45–46
ROS. *See* Reactive oxygen species (ROS)
Rough skin, bioactive ingredients for, 255–256
Rough surfaces, wetting on, 377–380. *See also* Flat surfaces, wetting on
  Cassie–Baxter theory, 378, 378f
  pinning effect of wetting, 380, 380f
  theory of wettability on fractal surfaces, 378–379
  Wenzel theory, 377–378, 378f
Rouse–Zimm modes, 172
Rouse–Zimm theories, 171
3Rs principle. *See* Refinement, reduction, and replacement principle (3Rs principle)
Rucinol, 731–732
Rule of thumb, 70
Rupture and collapse, foam, 50

## S

Saarbrücken Penetration Model (SB-M), 742
SAF. *See* Sensitization assessment factors (SAF)
Safety, 785
  assuring safety of cosmetics, 786–787
  of botanical substances, 315–316
  consumer exposure for cosmetics, 788t
  of cosmetics and ingredients, 785–786
  evaluation, 785, 789t
    practical evaluation process, 788f
    process of, 787–788
  implementation of tests, 789–790
  postmarketing safety reevaluation, 791f
  primary skin irritation, 789f
  reevaluation after launch, 790–791
  and regulatory concerns, 279–281
  risk-benefit balance between cosmetics and drugs, 786f
  use conditions
    of products, 787f
    of shampoo, 791f
Safety assessment
  of cosmetic ingredients, 794f
  cosmetic products, 793
  current update, 796–797
  international test guidelines, 797–801
    acute toxicity, 797
    carcinogenicity, 800
    corrosivity, 797–799
    genotoxicity, 800
    human data, 800–801
    irritation, 797–799
    phototoxicity, 800
    repeated-dose toxicity, 799
    reproductive toxicity, 800
    skin absorption, 799
    skin sensitization, 799
    toxicokinetic studies, 800
  international trends in regulatory use
    Cosmetics Europe, 801–802
    guidance for alternative test methods, 802t
    ICCR, 801
  test methods for, 795t–796t
  toxicological study, 794–795
Safety Evaluation Ultimately Replacing Animal Testing (SEURAT), 799
Safflower, 228
Salicylates, 588
SALT. *See* Skin-associated lymphoid tissue (SALT)
Salvage synthesis pathway, 690
SAM models. *See* Senescence accelerated mice models (SAM models)
SAM P series (SAMP), 714
*Samurai. See Bushi*
Sanitary care and philosophy through *Yojo-Kun*, 8
SANS. *See* Small-angle neutron scattering (SANS)
SAPDMA. *See* Stearamidopropyl dimethylamine (SAPDMA)
SASP. *See* Senescence-associated secretary phenotype (SASP)
SASPase. *See* Skin-specific retroviral-like aspartic protease (SASPase)
Saturated solution, 163
SAW sensors. *See* Surface acoustic wave sensors (SAW sensors)
SAXD. *See* Small-angle X-ray diffraction (SAXD)
SAXS. *See* Small-angle X-ray scattering (SAXS)
SB. *See* Stratum basale (SB)
SB-M. *See* Saarbrücken Penetration Model (SB-M)
SC. *See* Stratum corneum (SC)
Scalp, 35–37, 36f
  care cosmetics, 601
  and hair thinning care, 602
  protecting, 333
Scanning electron microscope (SEM), 25, 380, 381f, 638
Scattering
  angle, 700–701
  light scattering, 639–640
  methods, 639–641
  X-ray and Neutron Scattering, 639t, 640–641, 641f
Schiff base, 271, 271f
SCI. *See* Sodium cocoyl isethionate (SCI)
Science, technology, cosmetics and marketing
  4Ps and best timing of science, technology, and marketing, 12–13
  R&D and marketing, 12
  and social demands, 10–12
    binding corporations, consumers, and society with maternal communication, 11, 11f
    corporate responsibilities for accountability in science and technology, 10–11
    soft science to reading changes of trends, 11–12

Science-based sensory analysis, 618
Science-technology-society (STS), 4, 4f
  balance and generalist perceptions for corporate operation, 4
Scientific approach, 724
Scouting, 77
  benefits, 85–86
  challenges, 81
  front-end homework/creation of "needs" brief, 81, 82f
  function, 79
  organization, 78
  organizational scouting models, 79
  process, 80, 80f
  resources, 83–85
  technology scout, 78
  value of technology scouting, 77–78
SDBS. *See* Sodium dodecylbenzene sulfonate (SDBS)
SDS. *See* Sodium dodecyl sulfate (SDS)
Sebaceous gland(s), 340, 681
  lipids in, 685
Sebocytes, 675, 681
Sebum, 39–40, 167
  film, 245
  production, 681
  secretions, 322
Secondary hair germs, 768
Secondary metabolites, 305–306
SECosomes, 745
Sedimentation, 68
  prevention of, 71–72
Self-assembly, 44–45, 181–182
  amphiphilic polymer, 452–453
  chiral, 295–296
  molecular, 296
  surfactant, 450
Self-diffusion coefficients, 641, 642f
"Self-emulsification" method, 511
Self-microemulsifying drug delivery systems (SMEDDS). *See* Preconcentrated microemulsions
Self-organized structure, 393–395
  comparison between molecular dispersion and self-organized solution, 393t
  CPP, 394–395
  HLB number, 395
  interfacial curvature, 394
SEM. *See* Scanning electron microscope (SEM)
Semaphorin 3A (sema3A), 257
Semicrystalline polymer, 173
Semipermanent coloring, 611, 611f
Semisolid oils, 551
Senescence
  aging *vs.*, 711
  chronic inflammation and, 715–717
  methods to quantifying, 723–724
  from molecular level to systemic level, 712–713, 712f
    biomolecules, 712–713
    cells and tissues, 713
    systemic senescence of individual, 713
  progress and issues in, 713–715
    individual senescence, 715
    premature aging and longevity, 714
    in vitro studies on cell senescence, 714–715
    using wild-type mice and SAM models, 714
  skin, 719–720
Senescence accelerated mice models (SAM models), 714
Senescence-associated secretary phenotype (SASP), 715–716, 721–722
Senescence-associated β-galactosidase assay, 723
Senescent cells, 715–716, 722
Senile xerosis, 115
Sense of touch, 619–620
Senses, hierarchy of, 619–620
Sensing function, 675
Sensitive skin, 737, 759–760
  assessment, 738–739
  and bioactive ingredients, 257
  physiological parameters, 737
  stratum corneum, 738
Sensitivity
  of single skin receptors, 621t
  skin, 620–621
Sensitization assessment factors (SAF), 280
Sensometrics, 629
Sensory
  analysis, 617–619
  application for cosmetics, 621–622
  assessment, 630
  evaluation, 617
  factors, 109
  feeling, 561–565
  and measured instrumental data correlation, 631–632
  perception, 171
  science, 618
Sensory measurement
  haptic–sensory fundamentals, 619–621
  instrumental data modeling, 631–632
  methods, 624–627
  multisensory approaches, 631
  raw material formulation influence on sensor, 622–623
  test requirements of descriptive profile test, 627–630
Sensory-test methods, 618, 625t
  application site and quantity, 624
  environmental factors, 623–624
  interactions with skin, 624
  quality of sensory testing, 623
  validation of panels, 623
Serine palmitoyltransferase (SPT), 256–257
Serine palmitoyltransferase 1 (SPTL1), 689
Serine palmitoyltransferase 2 (SPTL2), 689
SEURAT. *See* Safety Evaluation Ultimately Replacing Animal Testing (SEURAT)
sf-emulsions. *See* Surfactant-free emulsions (sf-emulsions)
SG. *See* Stratum granulosum (SG)
Shampoo(s), 39, 116, 321, 601–606, 643
  cleansing effect, 603f
  conditioning shampoo formula, 602t
  mild shampoos, 322
  shampoo-dispersible synthetic polymers, 195
Shear rate, 472
Shear thickening, 477
Shear-induced structures (SIS), 477
Shear-thinning systems, 472, 643
β-Sheet, 164–165
Shellac, 195
Shh. *See* Sonic Hedgehog (Shh)
Shikonin, 228
Shiny lipsticks, 192
Short chain fatty acids, 33
Short lamellar structure, 699, 700f, 701–703, 705–706
Short time exposure in vitro test method, 799
Shrinkage, 461–462
Side-chain crystalline copolymers, 188
Side-chain crystalline polymers, 188
Silanols, 209
Silica, 224
  nanoparticles, 354
Silicate, 224
Silicic acid anhydride. *See* Silicon dioxide ($SiO_2$)
Silicon dioxide ($SiO_2$), 224, 337
Silicone(s), 172, 604–605, 608
  copolymer, 194
  droplets, 200
  oils and derivatives, 327–329, 329t
  resins, 191
  silicone-free alternatives, 329, 330t
  silicone-free shampoos, 605–606
  silicone-treated and untreated hair surfaces, 605f
Siloxane, 224
Silsesquioxane wax alkyl substitution, 192
Silver locus protein, 258
Silver nanoparticles (AgNPs), 354
Silver sulfadiazine, 354
Simvastatin, 722
Single gene mutation, 714
Single nucleotide polymorphism (SNP), 88
Single-stranded DNA (ssDNA), 457
*Sir*2. *See* Silent Information Regulator two (*Sirtuin* 2)
Sirtuin, 717–718
  enzymatic activity of SIRT1, 718f
  relationship between SIRT1, p53, and cell senescence, 719f
  roles of SIRT1, 718f
  *Sirtuin* 2, 717
SIS. *See* Shear-induced structures (SIS)
Site-specific interactions, 200
Skin, 167–169, 673, 685, 742f, 758. *See also* Melanogenesis
  absorption, 799
  amino acids
    NMF, 289, 290f
    urocanic acid, 289
  appendages, 681

Skin (*Continued*)
cancer, 760
cleanser, 349
cleansing, 206
colors, 225
corrosion, 797–798
cosmetics, 741
creams, 552
derivative structure, 339–340
hair, 339
nails, 340
sebaceous glands, 340
sweat glands, 340
dermis, 680–681
and development, 673–674, 674f
disorders, 744
epidermis, 676–680
flexibility test, 251–252, 252t
functions, 91–98, 92t, 340
barrier functions and moisture retaining, 92–93, 92f
blood vessels, 96
dermis, 96
epidermal cells, 94, 95f
epidermis inflammation, 95
melanocytes, 96
stratum corneum formation, 93–94
total body system, 97–98
humans, 741–742
hygiene, 206
interactions with, 624
irritation, 799
lipids in, 685–686
liposomes affinity, 546–547
makeup properties, 188
mechanism of moisture retaining, 167–168, 167f–168f
mechanism of perspiration, 168
models, 90
moisture measurement, 168–169
phospholipids effect, 539
polymers for treatment
hyaluronic acid for antiwrinkle treatment, 205
mitigation of skin irritation and inflammation, 205–206
multicomponent complexes for cleansing and treatment of skin, 206
removing wrinkles by external tensioning and "playing tricks with light", 207
principal functions, 674–675
products, 359
protection, 585
proteins in, 286–289
reactions, direct measurement of, 596–597
regional variation of, 682
senescence, 719–720
sensitivity, 620–621
sensitization, 799
skin moisture measurement, 168–169
structure, 337–340, 338f, 675, 676f
dermis, 338–339
epidermis, 337–338, 339f
hyperdermis, 339
structure/properties, 742–743
surface lipid, 693
toners, 552
type by Fitzpatrick, 594t
Skin aging, 259, 758–759
evaluating anti-senescence efficacy, 723–724
evaluation of effective ingredients for cosmetic, 724
methods to quantifying senescence, 723–724
QOL, 711
resveratrol, 717–719
senescence
aging *vs.*, 711
chronic inflammation and, 715–717
from molecular level to systemic level, 712–713
progress and issues in, 713–715
sirtuin, 717–718
strategies in research on, 719–723
age-associated decline and disintegration of homeostasis, 720–721
cell senescence and chronic inflammation, 721f
genetic and environmental factors, 719–720
research and development for antisenescence cosmetics, 721–723
Skin barrier, 737–738, 742
assessing, 744
disturbed, 757
factors affecting, 743–744
functions, 682–683, 782
overcoming, 744–745
Skin biology, 17–28, 26t, 27f
antiaging studies from dermal perspectives, 28
epidermal barrier function, 28
moisture in SC, 17–25
Skin blanching
test, 749
and vasoconstrictor assay, 749–750
Skin care, 87–88, 760–761. *See also* Emollients
products, 88, 110, 115–116
program, 722–723
psychology, 104–106, 104f
skin care–inspired solutions, 332
Skin care cosmetics, 551. *See also* Body care cosmetics
alpha-type hydrated crystal, 552f
emulsification, 555
emulsions, 554–555
functions, 551–552
polyoxyethylene-type surfactant aqueous solution, 554f
solubilization, 553
structuring components and technology, 552–553
ultrafine emulsification, 553–554
Skin mildness, 562–565
mild anionic surfactants, 564–565
mixed surfactant system, 564
superfatting, 563–564
Skin penetration, 514–516, 745–746
evaluation
in silico models, 750–751
in vitro/ex vivo studies, 746–747
in vivo imaging, 747
in vivo microdialysis, 750
in vivo skin blanching/vasoconstrictor assay, 749–750
in vivo studies, 747
in vivo tape stripping, 749
mechanism, 340–341
transappendageal route, 341
transepidermal route, 341
translocation, 341
membranes in skin permeability studies, 748t
skin structure and pathways, 745f
Skin-air pollution
inflammatory diseases, 760
materials and methods, 757
ozone, 759
results
atopic dermatitis exacerbation, 757–758
development of psoriasis, 758
disturbed skin barrier, 757
inflammation, 758
oxidative stress, 758
skin aging, 758–759
sensitive skin, 759–760
skin cancer, 760
skin care, 760–761
Skin-associated lymphoid tissue (SALT), 682–683
Skin-lightening QDs in Japan, 729–735
adenosine monophosphate disodium salt, 733, 733f
arbutin, 731, 731f
ascorbic acid and derivatives, 730
chamomilla extract, 732
ellagic acid, 731, 731f
Kojic acid, 730–731
linoleic acid, 732, 732f
magnolignan, 733–734, 733f
4MSK, 733, 733f
niacinamide, 734, 734f
placental extract, 730
rhododendrol, 734, 734f
rucinol, 731–732
tranexamic acid, 732, 732f
tranexamic acid cetyl ester hydrochloride, 734–735, 734f
Skin-specific retroviral-like aspartic protease (SASPase), 257
Skinfeel, 619
SLES. *See* Sodium lauryl ether sulfate (SLES)
SLIM. *See* Multispectral FLIM (SLIM)
SLNs. *See* Solid lipid NPs (SLNs)
"Slow water", 558–559
SLS. *See* Sodium lauryl sulfate (SLS); Static light scattering (SLS)

Small unilamellar vesicles (SUV), 477
Small-angle neutron scattering (SANS), 486, 640
Small-angle X-ray diffraction (SAXD), 701–703
Small-angle X-ray scattering (SAXS), 406, 433, 436f–437f, 486, 640, 644–647, 645f, 646t
SMT. *See* Stearoyl methyltaurine (SMT)
SNP. *See* Single nucleotide polymorphism (SNP)
Soap molecule, 231–232
Social demands, cosmetics
  binding corporations, consumers, and society, 11, 11f
  corporate responsibilities for accountability, 10–11
  soft science, 11–12
Social diversity, 585
Society
  establishment of humans and
    aspects of human beings, 5f
    cosmetics, 5
    makeup, 5–6
  and foundation of cosmetic culture, 7
  science-technology-society balance and generalist perceptions, 4
Sodium alkyl sulfate, 562–563
Sodium ascorbyl phosphate, 514
Sodium chloride (NaCl), 430, 432f, 442f
Sodium cocoyl isethionate (SCI), 562–563
Sodium dodecyl sulfate (SDS), 233, 395, 418, 453–454, 465–466, 562, 686
Sodium dodecyl tetraoxyethylene sulfate ($C_{12}E_4S$), 395
Sodium dodecylbenzene sulfonate (SDBS), 433
Sodium laurate ($C_{12}$Soap), 395
Sodium lauryl ether sulfate (SLES), 52, 325
Sodium lauryl sulfate (SLS), 325, 562
Sodium laurylbenzene sulfonate (LAS), 395
Sodium POE, 562
  AES, 563
Sodium polyacrylate and cationic surfactant, mixtures of, 451–452, 451f
Soft colloidal systems, 637t
Soft science, 11–12
Soft-focus effect, 574, 580
Solid, surface tension of, 375–377
Solid amphiphiles, 426
Solid foams, 189–190
Solid lipid NPs (SLNs), 344, 351
Solid phase
  microextraction, 274
  reaction synthesis, 224
Solid solution, 397–398
Solid surface, 373
Solid–liquid interfacial tension, 374
Solids, isoelectric point of, 164
Solubility, 163
  of water
    Ion hydration inside body, 163
    water-soluble substances, 163
Solubility parameter (SP), 53–54, 275
Solubilization, 47, 235, 508, 553, 668–669, 668f
Solvent, 610
Sonic Hedgehog (Shh), 772
*Sophora* extract, 776
Soy phospholipids, 539
SP. *See* Solubility parameter (SP); Substance P (SP)
Space groups, 645
Specific viscosity, 58
Spectrum Descriptive Analysis Method, 627–628
SPF. *See* Sun protection factor (SPF)
Spherical micelles, 453
Spherical polymers, 227
Sphingoid bases, 691
Sphingomyelin synthesis, 690
Sphingosine recycling pathway. *See* Salvage synthesis pathway
Spinous cells, differentiation into, 676–677
Spinous layer, 676
Spontaneous curvature, 431–433, 433f
Spray-type
  foundation, 573
  sunscreen emulsion, stability problem in production of, 664–665, 665f
Spreading
  of liquid on solid surface, 63
  value, 250, 250f
SPT. *See* Serine palmitoyltransferase (SPT)
SPTL1. *See* Serine palmitoyltransferase 1 (SPTL1)
Spunbonded fibers, 210
Squalane, 246
SS. *See* Stratum spinosum (SS)
ssDNA. *See* Single-stranded DNA (ssDNA)
Stability/stabilization
  of dispersions by electrical double layer, 65–66
  emulsions, 71
  foam, 48–49
  of lamellar gel network, 440–443
    diffusion of polymer, 443
    equilibration of liquid oil phase and α-gel, 443
    α-gel transforms to β-crystal, expelling interlamellar water to bulk water, 441–442
    relaxation of entangled lamellar gel network structure, 442
    surfactant exchange between α-gel bilayer and oilewater emulsion, 443
    water movement, 442
STAC. *See* Stearyl trimethyl ammonium chloride (STAC)
Staining
  agent, 638
  method, 641–642, 647
Standardization enables reproducibility, 628
*Staphylococcus aureus* (*S. aureus*), 39–40
Starches, 173–176
Static light scattering (SLS), 639
Statins, 687
Statistical data analysis, 629–630
Steam distillation, 268, 268f
Stearamidopropyl dimethylamine (SAPDMA), 418, 443, 444f
Stearoyl methyltaurine (SMT), 556
Stearyl trimethyl ammonium chloride (STAC), 239–240, 243
Stemoxydine, 776
*Stephania cepharantha hayata*, 776
Steric stabilization of dispersions, 66
Steroid sulfatase, 782
Sterol esters, 248
Stiff polymer molecules, 172
Stimuli-responsive
  rheology modifiers, 186
  system, 198
Stinging test, 738–739
Stokes–Einstein equation, 474
Stratum basale (SB), 337–338
Stratum corneum (SC), 255–256, 285, 337–338, 533–535, 535f, 673–674, 699, 713, 722–723, 738, 742, 744, 749, 757
  absorption, 743–744
  barrier, 781
  behavior of water in, 705
  biosynthetic process of constituents of, 678f
  composite structure of, 677–678
  constituents of, 678–680
  formation, 93–94
  function of, 677–680
  gradients in, 680
  highly sensitive detection of minute structural change, 701–702
  hydrocarbon-chain packing structures, 700f
  intercellular lipids, 248–249, 256
  moisture in, 17–25
  penetration route
    of hydrophilic molecules in, 702–703
    of hydrophobic molecules in, 704–705
  structural studies, 700
  structure of, 677–680, 677f
  water regulation mechanism in, 705–708
  X-ray diffraction study on, 700–701, 701f
Stratum granulosum (SG), 337–338
stratum lucidum, 338
Stratum spinosum (SS), 337–338
*Streptococcus pyogenes* (*S. pyogenes*), 39–40
Stress, 715–716, 737–738
  fight–flight stress response, 104
  hormone, 97
  oxidative, 758
Strong-holding hairstyles, 196
Structural analysis of formulations
  characterization of colloids, 636, 637t
  colloidal dispersion system, 635, 636f
  cosmetic formulations, 635
  emulsions, 647–654
    droplet size of dispersed phase, 648–650
    interfacial layer, 650–654

Structural analysis of formulations (*Continued*)
type, 648
liquid crystals, 644–647
cubic liquid crystals, 647
NMR, 646, 647f
polarized optical microscope, 644, 644f
SAXS, 644–646, 645f, 646t
micelles, 636–643, 637f
microscopy, 638–639, 638f
PGSE-NMR, 641–642, 642f
Rheology, 642–643, 642f–643f
scattering methods, 639–641, 639t, 640f
Structure factor, 641
Structure-building peptides, 203–204
Structuring polymer, 210
STS. *See* Science-technology-society (STS)
Student's t-test, 630
Styling
gel, 609
mousse, 609
polymer, 609, 610f
spray, 609
water, 609
"Subcell structure", 699
Subcutis, 339, 675
Subjective test methods, 625–626
Substance identification, 157–158
Substance P (SP), 737–738
Substance patent, 122–123
Substantivity, 326
Substrates, 717
Sugar-based surfactants, 409–412, 410t. *See also* Anionic surfactants; Cationic surfactants; Nonionic surfactants
effect of alkyl chain length, 410–411
effect of conformation of hydrophilic group, 411–412
effect of polymerization degree of sugar, 411, 411f
effect of shape, ring, 412
Sulfate(s)
alternatives for, 325, 325t
sulfate-based anionic surfactants, 605
sulfate-containing surfactant systems, 325
sulfate-free shampoos, 605–606
Sulfonated wool keratin, 203
Sulfonylurea receptor (SUR), 774
Sun care
products effectiveness, 593–594
sun care–inspired solutions, 332
Sun care cosmetics
evaluation and declaration of sunscreen capacity
determination method of SPF, 594–595
direct measurement of skin reactions, 596–597
effectiveness of sun care products, 593–594
skin type by Fitzpatrick, 594t
sunscreen product, 596
UV-A protection, 595–596
importance, 587
required functionality
characteristic UV-absorption spectrum and photostability, 591
development of novel UV-B absorber, 592–593
properties as cosmetic ingredients, 590–591
sunscreen agents, 587–590
benzalmalonate, 590
benzyliden-camphor derivatives, 589
cinnamates, 589
diphenyl-acrylate derivatives, 590
phenylbenzimidasol, 590
phenylbenzotriazol, 590
sunscreen powders, 588
triazine derivatives, 590
UV absorbers, 588–590, 589t
Sun exposure, 678, 682
Sun protection factor (SPF), 354, 587, 594–595
Sunscreen(s), 34, 116, 348–349
powders, 588
product, 596
Sunsilk, 321
Super oil-repellent fractal surfaces, 381–382, 382f
Super water-repellent fractal surfaces, 380–381
Supercovering makeups, 577–579
Superfatting, 563–564
for foam boosting, 567–568
Superhydrophobicity, 190
Supersonic treated water, 164
Supramolecular
polymer, 194
structures, 193–194
SUR. *See* Sulfonylurea receptor (SUR)
Surface
deposition, 464–465
energy, 40
roughness, 380, 388
smoothness, 608
treatment agents, 227–228, 241–242
Surface acoustic wave sensors (SAW sensors), 275
Surface tension
effect, 40
gradient, 47–48, 47f
of human hair and skin, 382–383, 383t
method, 636
of solid, 374–377
Surfactant-free emulsions (sf-emulsions), 183, 501f, 502
Surfactant(s), 39–41, 47–50, 231, 326, 386, 389, 471, 494, 540–541, 568, 602, 610, 636, 641, 744–745. *See also* Polymer–surfactant interactions
adsorption, 238–240, 238t
amino acid, 294
amino acid-based anionic, 605t
anionic surfactants, 395–398
cationic, 607–608
surfactants, 398–402
characteristics and classification of, 231–232, 232f
and cleansing, 45–47
defoaming, 50
on emulsification, properties of, 490
exchange between $\alpha$-gel bilayer and oil–water emulsion, 443
foam drainage, 49–50
foam formation, 47–48
foam rupture and collapse, 50
foam stability, 48–49
for lamellar gel networks, 420–424
alkyl amidoamines, 423
alkyl monoglycerides, 423
double-tail surfactants, 424, 424f
quaternary ammonium salts, 423
and metal salt, 227–228
micelles, 41–45, 41f–43f, 636–638
micellization of, 233–235
properties of, 233–234, 234f
solubilization, 235
mixed surfactant systems
adsorption behavior of, 241–243, 242f–243f
interaction of surfactants, 240
solubility of, 240–241, 241f
mixtures and melting temperature, 397–398
molecules, 40–41
nonionic surfactants, 402–409
phase diagram
notations in, 389
in surfactant system, 389–392
phase diagrams, 50–52
self-organized structure, 393–395
solubility, 235–238
solutions, 473–480, 644
and cosurfactants, 480
and hydrocarbons, 480
and polymers, 480–482
sugar-based surfactants, 409–412, 410t
surfactant–polyelectrolyte mixtures, 462–467, 463f
dilution of solutions of anionic surfactant, 466f
effect of polymer charge density on adsorption, 466f
effect of rinsing on adsorbed layers of cationic hydroxyethyl cellulose, 467f
system, 200
phase diagram in, 389–392
Sustainable fragrances, 281–282
Sustainable solutions, 333–334
SUV. *See* Small unilamellar vesicles (SUV)
Sweat glands, 168, 340, 681
Swelling, $L_\beta$ phase, 429–431, 431t
Synthetic
anionic surfactants, 566
conditioning polymers, 198
copolymers, 201, 203
polymer, 196
surfactants, 562
Systemic factors, 724

## T

T lymphocytes, 682–683
T silane functional groups. *See* Trifunctional silane functional groups (T silane functional groups)
t-Flavanone, 775, 775f
"T-zone", 681
T-β1R. *See* TGF-β1 receptor (T-β1R)
3T3 Neutral Red Uptake (3T3 NRU), 797
Tabletop Profiling, 624–625
Talc, 224
TAPE. *See* Tetraallyl pentaerythritol (TAPE)
Tape stripping, 749
TAPS. *See* Tetra-acetyl phytosphingosine (TAPS)
Tc. *See* Transition temperature (Tc)
TCC. *See* Toxicological concern (TCC)
TEAS diagram, 57
  for polycaprolactone, 54f
  solubility
    parameter diagram, 54f
    range of polycaprolactone, 56f
    range of polyvinylpyrrolidone, 56f
  superimposed solubility, 55f
Technical Scouting/Technology Scouting, 77–78, 81
  advantage of, 79
  organizational model, 79
  process, 80
  tool box
    e-scouting resources, 84f
    external and internal scouting resources, 83f
    external service providers, 84f
    scouting brokers, 85f
    universities, 84f
  value of, 77–78
Technical Scouts, 78, 81
Technology Scouting External Resources, 85t
Telomeres, 713
Telomeric oxidative damage, 713
TEM. *See* Transmission electron microscopy (TEM)
Temperature-controlled gelation, 459, 459f
Temporary
  coloring, 611, 611f
  hair styling, 197
  style, 197
TER Test Method. *See* Transcutaneous Electrical Resistance Test Method (TER Test Method)
Terminators, 187
Ternary phase diagram for water-oil-surfactant system, 51f
Ternary system, 391–392, 391f–392f
Terpene(s), 268–269, 269f, 704
Terrestrial life, skin in, 673–674
Test guidelines (TGs), 797
  TG 430, 797
  TG 431, 798
  TG 435, 798
  TG 439, 799
Tetra-acetyl phytosphingosine (TAPS), 261–262
Tetraallyl pentaerythritol (TAPE), 182
Tetraglycerol lauryl ether ($C_{12}Gly_4$), 407, 407f
Tetrasaccharide, 178
TEWL. *See* Transepidermal water loss (TEWL)
Texture profile test, 626
Tgel, 233–234
TGF-β. *See* Transforming growth factor-β (TGF-β)
TGF-β/SMAD pathway, 719
TGF-β1 receptor (T-β1R), 260
TGF-β2 receptor (T-β2R), 260
TGs. *See* Test guidelines (TGs)
Thermal behavior of polymer gels, 173
Thermal energy, 161
Thermal gelation, 458–462
Thermodynamic stability, 508–509, 512–513
Thermoplastic elastomers, 188, 193, 197
Thermotropic liquid crystals, 643
"Theta" (θ) condition, 57
Thickener, 611
Thickening
  approaches, 606
  oil, 186–187, 187f
Thin-layer chromatography (TLC), 494–495
Thixotropic fluids, 62
Thixotropic yield stress materials, 181
$T_{HLB}$. *See* Hydrophilic-lipophilic balance temperature ($T_{HLB}$)
Threadlike micelles Worm-like micelles
Three-phase emulsion, 503f, 505
Threshold temperature (Tt), 236
Tight junctions (TJs), 682, 757
  in barrier function and bioactive ingredients inducing, 256–257
Tightly-packed orthorhombic structures, 692
TINODERM nanotopes, 356
Tissue(s)
  organ cultures, 90
  repair system, 721–722
    age-associated decline and disintegration of homeostasis, 720–721
  senescence of, 713
Titanium oxide ($TiO_2$), 223, 226, 226f, 337, 354, 588
TJs. *See* Tight junctions (TJs)
TLC. *See* Thin-layer chromatography (TLC)
TLR2. *See* Toll-like receptor 2 (TLR2)
Tobacco, 758–760
Tocopherol, 760–761
Toll-like receptor 2 (TLR2), 256–257
Tomographic microscopy, 650
Tooth paste, 643
Topical glucocorticoids, 749
Topical retinoid therapy, 117
Total body system, 97–98
Total light transmittance (TT), 574
Total volatile organic compounds (TVOCs), 757–758
Touch
  points, 620
  resolution of, 620
Toxic Substances Act, 211
Toxicity of NPs, 359
Toxicokinetic studies, 800
Toxicological concern (TCC), 280
Toxicological hazards, 785
Trademark Law, 122–130. *See also* Patent Law
  functions of trademarks, 132
  intellectual property rights protection under, 131
  scope of rights of registered trademarks, 132
  selection of trademark, 133
Trademark rights
  duration, 132
  requirement for effectuation of, 131–132
Tragon Corporation, 627
Tranexamic acid, 258, 258f, 732, 732f
Tranexamic acid cetyl ester hydrochloride, 734–735, 734f
Trans-aminomethylcyclohexanecarboxylic acid. *See* Tranexamic acid
Trans-Golgi network, 691
*Trans*-resveratrol, 314f
*trans*-UCA. *See Trans*-urocanic acid (*trans*-UCA)
*Trans*-urocanic acid (*trans*-UCA), 289, 597
Trans-zigzag structure, 233–234
Transappendageal route, 341
Transcutaneous Electrical Resistance Test Method (TER Test Method), 797
Transdermal
  drug delivery, 683
  permeation, 515–516, 515f
Transepidermal route, 341
Transepidermal water loss (TEWL), 168–169, 255–256, 738, 743, 757, 781–782
Transfer-resistant color cosmetics, 190–195, 193f–195f
Transferosome(s), 350, 352, 745
Transforming growth factor-β (TGF-β), 775
Transglutaminase 1, 692
Transient receptor potential vanilloid family 1 (TRPV1), 738
Transition temperature (Tc), 519
Translocation, 341
Translucent emulsions, 489
Transmission electron microscopy (TEM), 532, 533f, 542–544, 638, 691
Transplantation, hair, 777
Traube's rule, 40–41
Tretinoin, 346
Triacylglyceride, 686
  synthesis, 688
Triacylglycerol, 686
Triazine derivatives, 590
Triblock copolymers, 192
Triethyl citrate, 249–250, 249f

Trifunctional silane functional groups (T silane functional groups), 191
3-Trimethylammonium-2-hydroxypropyl-N-chitosan, 209
Trimethylated silica, 190–191
TRIPS Agreement. *See* Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS Agreement)
Triterpene, 316
Triterpenoids, 260–261
Trophic factors, affecting hair growth, 770–773
  BMP, 772
  Edar, 773
  EGF, 772
  FGF, 771–772
  IGF, 772
  modulators, 771t
  Shh, 772
  Wnt, 772
Tropoelastin, 262
TRPs. *See* Tyrosinase-related proteins (TRPs)
TRPV1. *See* Transient receptor potential vanilloid family 1 (TRPV1)
Tryptophan, 203
Tt. *See* Threshold temperature (Tt)
TT. *See* Total light transmittance (TT)
TVOCs. *See* Total volatile organic compounds (TVOCs)
12 Principles of Green Chemistry, 307–308
Two-alternative forced-choice test (2AFC test), 626
2-in-1 shampoos, 603
Type II 5α-Reductase, 774
Tyrosinase, 733
  activity, inhibitors of, 258
  inducing instability of, 259
Tyrosinase-related proteins (TRPs), 732
  receptors, 315
  TRP-2, 258
Tyrosine, 203

## U

Ubiquinone. *See* Coenzyme $Q_{10}$ ($CoQ_{10}$)
UDP. *See* Upper-degradation point (UDP)
UFPs. *See* Ultrafine particles (UFPs)
Ultra long chain FA (ULCFA), 687–688
Ultrafine
  emulsification, 552–554
  emulsion, 489, 554
Ultrafine particles (UFPs), 757
Ultramarine, 225
Ultrarefined arabinogalactan, 180
Ultrasomes, 353
Ultraviolet (UV), 150, 181, 223, 337, 587, 685, 712, 729
  absorbers, 247, 276, 588–590, 589t
    benzophenone derivatives, 588
    dibenzoylmethane derivatives, 588–589
    salicylates, 588
  absorption, 309
  blocking, 226, 584–585
  exposure of skin, 259
  filters, 588–590
  irradiation, 202
  light, 289
  protection, 332, 572
  radiation, 203, 595, 618
  rays, 10, 28, 95, 226, 257, 292, 675
  UV-A, 587, 593f, 712, 730
    protection, 595–596
    protection efficacy, 592–593
    radiation, 203
  UV-absorbing agents, 145
  UV-absorbing materials, 143–145, 145t
  UV-absorption spectrum, 591
  UV-B, 587, 593f, 712, 730
    absorber development, 592–593
    radiation, 203
  UV-C, 587
  UV-filters, 587–588
  UV-scattering agents, 34
Ultraviolet care cosmetics. *See* Sun care cosmetics
UN. *See* United Nations (UN)
UNCED. *See* United Nations Conference on Environment and Development (UNCED)
Undifferentiation, 676
Unfair Competition Prevention Law, 134–135. *See also* Patent Law; Trademark Law
Unilamellar vesicle, 431–433
United Nations (UN), 794
United Nations Conference on Environment and Development (UNCED), 306
United Nations Environmental Program, 211
United States trade association, 155
Unmet needs, 77, 80
Upper-degradation point (UDP), 669, 669f
Urocanic acid, 289
"Urokinase", 33
US Federal Food, Drug, and Cosmetic Act (FD&C Act), 39
US Food and Drug Administration (FDA), 39, 140, 155, 280–281, 345, 360, 590, 694, 746, 773
Use conditions
  of products, 786–787, 787f
  of shampoo, 791f
UV. *See* Ultraviolet (UV)
UV-A Protection Factor (UVAPF), 595
UVAPFi. *See* Individual Ultraviolet A protection factor (UVAPFi)

## V

van der Waals forces, 53–54, 163, 239–240
  interactions, 64–65
Vascular endothelial cells, 770, 774
Vaseline, 247, 551
Vasoactive intestinal peptide, 737–738
Vasoconstrictor assay, 749
VC-PMG. *See* Encapsulated chemical magnesium ascorbyl phosphate (VC-PMG)
VEGF, 774
Veilex 1, 278
Venustron, 252
*Veratrum album* (*V. album*), 314
Verbalized emotions, 628–629
Vesicle(s), 540–542
  FF-TEM, 478f
  moduli and complex viscosity against frequency, 478f
  phases, 477–479
  Weissenberg effect, 478f
Vinyllactam monomers, 198
Visceral WAT, 686
Viscoelastic
  fluid, 472
  liquid, 643
  solutions from worm-like micelles, 474–477
  thickeners, 186–187
Viscosity, 474, 476f, 483
  of surfactant system, 276
Visible difference, 106
Visible light, 638, 648
Vitamin A, 344
Vitamin $B_3$, 734
Vitamin C. *See* Ascorbic acid
Vitamin D, 97
Vitamin D deficiency, 10
Vitamin E, 353, 758–761, 776
Vitamin(s), 261, 334, 723
*Vitellaria paradoxa* (*V paradoxa*). *See Butyrospermum parkii* (*B parkii*)
VOCs. *See* Volatile organic compounds (VOCs)
Volatile oils, 190–191
Volatile organic compounds (VOCs), 77, 757–759
Volatile silicones, 190–191
Volatile solvents, 193

## W

W/O. *See* Water-in-oil (W/O)
W/O/W emulsion. *See* Water-in-oil-in-water emulsion (W/O/W emulsion)
(W/O)/W-type double emulsion, 666, 667f
*Wa* makeup, 7
  evolution of Japanese cosmetic culture through, 7–8
Wants, Finds, Gets, and Manages (WFGM), 79
Warm-blooded animals, 161–162
WAT. *See* White adipose tissue (WAT)
Water, 149, 159, 173–174
  adsorbion to powder surfaces, 164
  in biological environments, 163–164
  cell membranes and, 165
    aquaporin, 166
    and substance distribution, 165–166
    water channels, 166
  in cosmetics, 164
    functional water, 164
  movement, 442
  phase, 389

of matter, 159
physical properties and biological roles of
phase diagram of water, 160, 160f
structure and hydrogen bonds, 160–161, 161f
structure of water molecules, 159, 160f
pool, 683
proteins and, 164–165
regulation mechanism in SC, 705–708
in SC, 705, 708f
skin and water, 167–169
small-angle diffraction profiles, 707f
solubility of water, 163
surface tension and wettability, 162, 162t
thermal properties of, 161–162
water-based gel-type foundation, 573
water-repellent treatments of cosmetic components, 386, 387f
water-rich O/W emulsions, 622
water/oil resistance, 584
wetting behaviors of human hair with, 383–385, 385f
Water-in-oil (W/O), 29, 245, 352, 373, 489, 508–509, 509f, 641–642, 659
emulsion, 70, 483, 501, 648
foundation, 572
lotion, 590–591
products, 552
w/o-type emollients, 245
Water-in-oil-in-water emulsion (W/O/W emulsion), 490f
Water-soluble
oils, 249–250
polymers, 208, 452, 457
substances, 163
Wax(es), 186–187
ester synthesis, 689
super water-repellent fractal surfaces made of, 380–381
WAXD. *See* Wide-angle X-ray diffraction (WAXD)
WAXS. *See* Wide-angle X-ray scattering (WAXS)
Wenzel theory, 377–378, 378f
Western Cultures, evolution of Japanese cosmetic culture through, 7–8
Wettability, 162, 584
Wetting, 373
in cosmetic science and technology, 382–387
on flat surfaces, 373–377
on rough surfaces, 377–380
super oil-repellent fractal surfaces, 381–382
super water-repellent fractal surfaces, 380–381
technologies in cosmetics, 387–388
WFGM. *See* Wants, Finds, Gets, and Manages (WFGM)
Whipped emulsions, 197
White adipose tissue (WAT), 686
White pigments, 226–227
calcium carbonate, 227
titanium oxide, 226, 226f
zinc oxide, 226–227
Wide-angle X-ray diffraction (WAXD), 701–703
Wide-angle X-ray scattering (WAXS), 426, 435, 436f, 640, 650, 653
Wilcoxon test, 629
Wild-type mice models, 714
Withaferin A structure, 313f
Withania somnifera. *See* Ashwagandha
Wnt, 772
World Health Organization, 9, 88–90
"World patent", 127
World Trade Organization (WTO), 128b
Worm-like micelles
to bilayer phases, 480, 481f
viscoelastic solutions from, 474–477
Wormlike polymer molecules, 172
WPRP method, 777
Wrinkling, antiaging focusing on, 259–262
collagen and bioactive ingredients, 260–262
elastin fibers and bioactive ingredients, 262
fibroblasts in construction of dermal matrix, 259–260
*WRN* gene, 714
WTO. *See* World Trade Organization (WTO)

## X

X-ray diffraction, 522–523, 523f
measurement, 233–234
patterns, 532, 533f
on SC, 700–701, 701f
technique, 699
X-ray scattering, 640–641
Xanthan gum, 177–178, 178f, 180–181, 197
*Xanthomonas campestri* (*X. campestri*), 177
*Xylocarpus granatum* (*X. granatum*), 315

## Y

Yellow iron oxide, 225
Yield stress, 484, 484f
fluids, 61–62, 181
Yield value, 183
*Yojo-Kun*, sanitary care and philosophy through, 8
Young's equation, 373–374, 374f
Young–Laplace equation, 49

## Z

Z-point, 659–661, 661f
Zein, 207–208
Zero-shear viscosity, 471, 476
Zeta potential, 650–651
Zimm branching factor, 59
Zinc, 185, 278
Zinc oxide (ZnO), 226–227, 337, 354, 588
Zinc ricinoleate, 279f
Zisman plot, 375, 376f
Zonulae occludens-1 (ZO-1), 256–257
Zurich University of Applied Sciences (ZHAW), 624