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This edition first published 2017
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John Wiley & Sons, Inc., 111 River Street, Hoboken, NJ 07030, USA
John Wiley & Sons Ltd, The Atrium, Southern Gate, Chichester, West Sussex, PO19 8SQ, UK

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Library of Congress Cataloging-in-Publication Data

Names: Kleinebudde, Peter, 1958- editor. | Khinast, Johannes, 1964- editor. | Rantanen, Jukka, editor.
Title: Continuous manufacturing of pharmaceuticals / edited by Peter Kleinebudde, Dsseldorf, Johannes Khinast, Graz, Jukka Rantanen, Copenhagen.
Description: First edition. | Hoboken, NJ : Wiley, 2017. | Series: Advances in pharmaceutical technology ; 7703 | Includes bibliographical references and index. |
Identifiers: LCCN 2017010476 (print) | LCCN 2017014317 (ebook) | ISBN 9781119001331 (pdf) | ISBN 9781119001355 (epub) | ISBN 9781119001324 (hardback)
Subjects: LCSH: Pharmaceutical technology. | Pharmaceutical industry. | BISAC: SCIENCE / Chemistry / Industrial & Technical.
Classification: LCC RS192 (ebook) | LCC RS192 .C67 2017 (print) | DDC 615.1/9–dc23
LC record available at https://lccn.loc.gov/2017010476

Cover design by Wiley
Cover images: (Background image and bottom right) Image courtesy of the editors; (Bottom left) Image courtesy of Angewandte Chemie Int Ed (see chapter 4 for details); (Bottom centre) Image provided courtesy of GEA

Set in 10/12pt, TimesLTStd by SPi Global, Chennai, India

10 9 8 7 6 5 4 3 2 1

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Johannes Khinast

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Jukka Rantanen

Jukka Rantanen is Professor of Pharmaceutical Technology and Engineering at the Department of Pharmacy, University of Copenhagen. He received his PhD from the University of Helsinki in 2001, completed a post-doctoral visit at the Department of Industrial and Physical Pharmacy, Purdue University (Lafayette, USA) in 2003, and joined the faculty at the University of Copenhagen in 2006 as a full professor. Jukka has 200+ publications in scientific peer-reviewed journals and is an editorial board member of four leading scientific journals within the pharmaceutical sciences. He was the recipient of the AAPS "Outstanding Graduate Research Award in Pharmaceutical Technologies" in 2001and the APV "Research Award for Outstanding Achievements in the Pharmaceutical Sciences" in 2016.

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Series Preface

The series *Advances in Pharmaceutical Technology* covers the principles, methods and technologies that the pharmaceutical industry uses to turn a candidate molecule or new chemical entity into a final drug form and hence a new medicine. The series will explore means of optimizing the therapeutic performance of a drug molecule by designing and manufacturing the best and most innovative of new formulations. The processes associated with the testing of new drugs, the key steps involved in the clinical trials process and the most recent approaches utilized in the manufacture of new medicinal products will all be reported. The focus of the series will very much be on new and emerging technologies and the latest methods used in the drug development process.

The topics covered by the series include the following:

***Formulation*:** The manufacture of tablets in all forms (caplets, dispersible, fast-melting) will be described, as will capsules, suppositories, solutions, suspensions and emulsions, aerosols and sprays, injections, powders, ointments and creams, sustained release and the latest transdermal products. The developments in engineering associated with fluid, powder and solids handling, solubility enhancement, colloidal systems including the stability of emulsions and suspensions will also be reported within the series. The influence of formulation design on the bioavailability of a drug will be discussed and the importance of formulation with respect to the development of an optimal final new medicinal product will be clearly illustrated.

***Drug Delivery*:** The use of various excipients and their role in drug delivery will be reviewed. Amongst the topics to be reported and discussed will be a critical appraisal of the current range of modified-release dosage forms currently in use and also those under development.

The design and mechanism(s) of controlled release systems including macromolecular drug delivery, microparticulate controlled drug delivery, the delivery of biopharmaceuticals, delivery vehicles created for gastrointestinal tract targeted delivery, transdermal delivery

and systems designed specifically for drug delivery to the lung will all be reviewed and critically appraised. Further site-specific systems used for the delivery of drugs across the blood–brain barrier including dendrimers, hydrogels and new innovative biomaterials will be reported.

***Manufacturing*:** The key elements of the manufacturing steps involved in the production of new medicines will be explored in this series. The importance of crystallisation; batch and continuous processing, seeding; and mixing including a description of the key engineering principles relevant to the manufacture of new medicines will all be reviewed and reported. The fundamental processes of quality control including good laboratory practice, good manufacturing practice, Quality by Design, the Deming Cycle, Regulatory requirements and the design of appropriate robust statistical sampling procedures for the control of raw materials will all be an integral part of this book series.

An evaluation of the current analytical methods used to determine drug stability, the quantitative identification of impurities, contaminants and adulterants in pharmaceutical materials will be described as will the production of therapeutic bio-macromolecules, bacteria, viruses, yeasts, moulds, prions and toxins through chemical synthesis and emerging synthetic/molecular biology techniques. The importance of packaging including the compatibility of materials in contact with drug products and their barrier properties will also be explored.

Advances in Pharmaceutical Technology is intended as a comprehensive one-stop shop for those interested in the development and manufacture of new medicines. The series will appeal to those working in the pharmaceutical and related industries, both large and small, and will also be valuable to those who are studying and learning about the drug development process and the translation of those drugs into new life saving and life enriching medicines.

Dennis Douroumis
Alfred Fahr
Jürgen Siepmann
Martin Snowden
Vladimir Torchilin

Preface

Pharmaceutical drug products have traditionally been manufactured in a batch mode, which remains the dominant method of production and involves the following steps: a predefined amount of material is processed for a certain time and then released as a batch. This batch production cycle typically involves several consecutive unit operations; the intermediate products can be analysed *off-line* and released for the next production step. Final products are typically released based on the analysis of the end-product and inspection of a subset of the final product batch. However, in recent years continuous manufacturing of pharmaceuticals has rapidly been gaining importance. During continuous manufacturing, the material flows at a predefined rate through all involved unit operations. Only a relatively small amount of material is processed at a given time. During the manufacturing process, raw materials are continuously introduced and the finished drug product is continuously released, based on the true utilization of high-end *on-line* and *in-line* process analytics and control solutions.

Continuous manufacturing provides several advantages over the current batch-based approach, including safer and more cost-effective production of highly-customized drug delivery systems, faster time to market, smaller and greener production facilities, and minimum requirements for scale-up and maintenance. Another major benefit is a higher quality of drug products due to the integrated real-time quality control, which is a prerequisite for continuous production. Finally, continuously operating lines are more flexible platforms that can be effective with regard to implementing customized and patient-oriented solutions for medications. In summary, continuous manufacturing eliminates current bottlenecks and makes possible the production of many innovative and life-saving medicines.

The implementation of continuous manufacturing of pharmaceuticals was hindered by several hurdles, both real and perceived. A major perceived obstacle was the lack of a regulatory framework for the new production paradigm. However, due to the initiatives of the

United States Food and Drug Administration (FDA) during the last decade, many uncertainties have been eliminated, providing a strong support for exploring the possibilities of continuous manufacturing. In addition, equipment suppliers have made major steps towards developing innovative continuous manufacturing concepts. Moreover, PAT tools for process monitoring and integrated process control platforms are now offered by several suppliers. Recently, new suppliers of equipment and quality control solutions have entered the market, creating more competition and – as a consequence – better solutions for the industry.

In terms of implementation, large pharmaceutical companies are paving the way to demonstrating the feasibility of this new manufacturing paradigm. However, small and medium-sized enterprises have also begun to evaluate the possibilities and benefits of continuous manufacturing. In the meantime, the first new product developed for continuous manufacturing has received regulatory approval (i.e., Orkambi by Vertex Pharmaceuticals). Recently, for the first time the FDA approved a manufacturer's change in production method from batch to continuous (Janssen products in Puerto Rico).

In this context, a book addressing the main aspects of continuous manufacturing of pharmaceuticals has been missing. This gap is now closed. Leading authors from industry and academia offer their contributions on relevant topics. The first part of the book provides a snapshot of key chemical engineering principles and a background on the regulatory and quality considerations associated with continuous manufacturing. Chapter 3 is a reprint of a commentary published in the *Journal of Pharmaceutical Sciences*. Important issues regarding regulatory and quality considerations for continuous manufacturing are addressed. The following two parts cover existing technologies for manufacturing both small- and large-molecule products (i.e., biopharmaceuticals). In the last two sections, the integration of several individual parts of processing into a fully operating continuous process environment is discussed and the state of the art of innovative manufacturing principles is summarized. On the whole, this book provides a comprehensive review of existing technologies for continuous manufacturing of pharmaceuticals, as well as an overview of promising future approaches that may enable the production of highly-innovative pharmaceutical products.

The editors would like to thank all the authors for their valuable contributions and the reviewers for their constructive critique and comments. We also thank the publisher for continuing support and help in transforming a large number of scientific contributions into a high-quality book.

Peter Kleinebudde, Düsseldorf
Johannes Khinast, Graz
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June 2016

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Continuous Manufacturing: Definitions and Engineering Principles

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1.1 Introduction

1.1.1 Definition of Continuous Manufacturing

In chemical engineering, manufacturing processes can be categorized in different ways, one being the mode of operation with respect to the strategy of feeding and removing materials from a process unit. Specifically, one distinguishes between:

- *Batch manufacturing:* All materials are charged before processing and are discharged at the end of processing (example: batch crystallization).
- *Semi-batch manufacturing:* Some materials may be continuously added during processing and discharged at the end (example: air feed during batch fermentation).
- *Continuous manufacturing*: Material is simultaneously charged and discharged from the process (example: flow-through reactor cell).
- *Quasi-continuous manufacturing*: Material is treated in batches, yet removed in defined intervals (example: fluid-batch drying of intermediate batches).
- *Semi-continuous manufacturing*: Like continuous manufacturing, but for a defined time period (example: continuous manufacturing on a campaign basis).

Continuous Manufacturing of Pharmaceuticals, First Edition.
Edited by Peter Kleinebudde, Johannes Khinast, and Jukka Rantanen.
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Thus, continuous manufacturing (CM) is a method of manufacturing products and processing materials without interruption and with constant material feed and removal. Also tableting, which actually is a batch operation on the scale of a single die, can be viewed as a continuous process. In contrast to batch manufacturing, in a continuous process materials remain constantly in motion, undergo chemical transformations, or are subject to mechanical or heat treatment. Continuous processing on a large scale generally means operating 24 h/day, 7 days/week (often called 24/7) with infrequent (weekly, monthly, semi-annual, or annual) planned maintenance shutdowns. However, continuous manufacturing can also be carried out on a campaign basis, that is, semi-continuous manufacturing of an intermediate chemical compound for a few weeks in a continuous plant.

The concept of continuous processing is not new. It has widely been used across the industry, including oil refining and the production of chemicals, fertilizers, paper, and foods. One of the earliest continuous processes relates to the paper industry (Fourdrinier paper machine, patented in 1799). Automotive manufacturing (at least the assembly part) can also be viewed as a continuous process. Here, the first assembly lines were installed at the beginning of the twentieth century by Olds (Oldsmobile) and, with more publicity, several years later by Ford (Ford model T).

1.1.2 Continuous Manufacturing in the Pharmaceutical Industry

Although not used on a broad basis, continuous manufacturing is not new to the pharmaceurical sector. Some pharmaceutical manufacturing processes (e.g., separations) have operated continuously for decades [1]. Furthermore, many pharmaceutical unit operations, such as plug-flow reactors, roller compaction, tablet compression, extrusion, and capsule filling, are inherently continuous process steps. Yet, since continuous quality assurance was not integrated in these processes in the past, they remain continuous processes operated in a batch way and will only become truly continuous when real-time quality assurance is fully implemented in the process control.The first publication by ICI, clearly outlining the advantages of continuous manufacturing (as they are cited today), dates back to 1984 [2].

On the academic side, continuous manufacturing of pharmaceuticals has been studied for more than two decades. In the early 1990s, Muzzio at Rutgers University launched the first research program for the continuous manufacturing of pharmaceuticals. In addition, Leuenberger (University of Basel) early on pointed out the advantages of continuous manufacturing in the pharmaceutical industry [3]. Since then, significant efforts have been made in this field, and several focused research programs are currently underway. For example, the Novartis-MIT center for continuous manufacturing (USA) focuses on primary active pharmaceutical ingredient (API) manufacturing and integrating drug synthesis into a continuous production line [4]. Continuous manufacturing and crystallisation (CMAC) at Strathclyde University (UK) investigates related topics that range from synthesis to crystallization. A series of white papers from the International Symposium on Continuous Manufacturing of Pharmaceuticals [5], organized jointly by MIT and CMAC, highlights the current view on CM. In the field of secondary manufacturing (drug product), together with its partners at Purdue University, NJIT, and University of Puerto Rico, Rutgers University developed a continuous manufacturing plant based on blending and direct compaction

within their NSF-funded research center C-SOPS [6]. The Research Center for Pharmaceutical Engineering (RCPE) currently leads the European Consortium for Continuous Manufacturing, fearuring three continuous lines. Its partners are the groups of Ketolainen at University of Eastern Finland (roller-compaction based granulation), Remon and De Beer at Ghent University (wet granulation lines), Kleinebudde at Heinrich-Heine University (roller compaction), and Graz University of Technology (hot-melt extrusion and downstreaming).

Several system suppliers have developed GMP-certified continuous manufacturing lines. One approach to integrating multiple continuous unit operations into a continuous downstream line is the Consigma system by GEA. It is an integrated tableting line with continuous wet granulation via co-rotating twin-screw extrusion, semi-continuous drying in a segmented fluid bed and tableting with state of the art online monitoring systems [7]. Recently, GLATT introduced the "MODCOS" system, which is a continuous rotary chamber insert for converting Glatt's GPCG drying batch system into a continuous fluidized bed drying system. In combination with various associated continuous process equipment from other companies [e.g., feeders, process analytical technology (PAT), and continuous granulation systems] it makes an integrated continuous wet granulation line possible. Moreover, other advanced industrial systems are under development, such as the continuous manufacturing line(s) by Bohle for blending, dry and wet granulation, tableting, and coating. Bosch is another equipment company developing downstream continuous manufacturing systems in cooperation with RCPE. Continuus Pharmaceuticals, a spin-off from MIT is offering equipment for continuous synthesis and dosage-form manufacturing. Similarly, suppliers of continuous flow chemistry systems are increasingly active on the market (Thalesnano, Syrris, Ehrfeld, AM Technology, Uniqsis, Chemtrix, Future Chemistry, Vapourtec and others).

In addition, several pharmaceutical companies have started significant programs on continuous manufacturing, such as Novartis, Pfizer (recently in a joint effort with GEA), AstraZeneca, GSK, Bayer, UCB and many others. In fact, in 2015 the FDA approved a continuous manufacturing plant by Vertex in the USA (for Orkambi, a drug treating cystic fibrosis) and in 2016 a continuous line by Jannsen (for Darunavir, a drug for treating HIV infections) in Puerto Rico. At time of the writing of this book, also other approvals are in the pipeline, not only in the United States, but also in Europe and other regulatory regions.

1.1.3 Our View of Continuous Manufacturing

Traditional batch manufacturing follows a sequential approach. Before processing, the materials are introduced into a specific unit operation, then transformed into a processed intermediate product and finally discharged at the end of processing. After each production step the intermediate products are collected and analyzed, if required, and physically transported in various containers (IBCs) to the next process step. Typically, the intermediate and final products are extensively tested off-line in a quality assurance laboratory. Frequently, intermediates are shipped across the globe from one production site to the next one that has suitable equipment using cold-chain systems or freeze containers, which may lead to segregation or instability. Depending on the number and nature of the unit

operations (typically 10–30), a batch manufacturing process on a commercial scale may last from several weeks to a year (or longer).

In contrast, it only takes a few hours or days to make the final product via a CM process that consists of the same unit operations as the batch process. Simultaneously introduced into and discharged from the process, the material is automatically transferred and monitored and controlled in-line along the manufacturing path. Based on the implemented control strategy, the process can be adjusted by means of in-process measurements. The quality is assured (QA) in real-time, and – in theory – real-time release is possible.

Pharmaceutical manufacturing is typically divided into primary and secondary. Primary manufacturing is the production of an API and excipient materials. Secondary manufacturing is the production of a final dosage form. In oral dosage form production, crystallization, filtration, washing, and drying steps are considered primary steps, and dry API is made at primary manufacturing plants. Lyophilization of proteins, that is, manufacturing final dry protein materials, is considered secondary manufacturing. In batch manufacturing primary and secondary production typically occur at different sites and often on different continents. This physical distance between primary and secondary manufacturing can cause major physico-chemical problems, in addition to communication challenges. In contrast, CM can be more integrated.

Figure 1.1 provides a general overview of an end to end continuous manufacturing process. Here, primary manufacturing is divided into the synthesis part and the finish part, that is, the crystallization and drying of an API. The first box in Figure 1.1 describes the synthesis of APIs (and excipients). A wide variety of methods exists, including chemical synthesis, biochemical processes (such as cell cultures), extraction processes from plants or tissues, and countless combinations thereof.

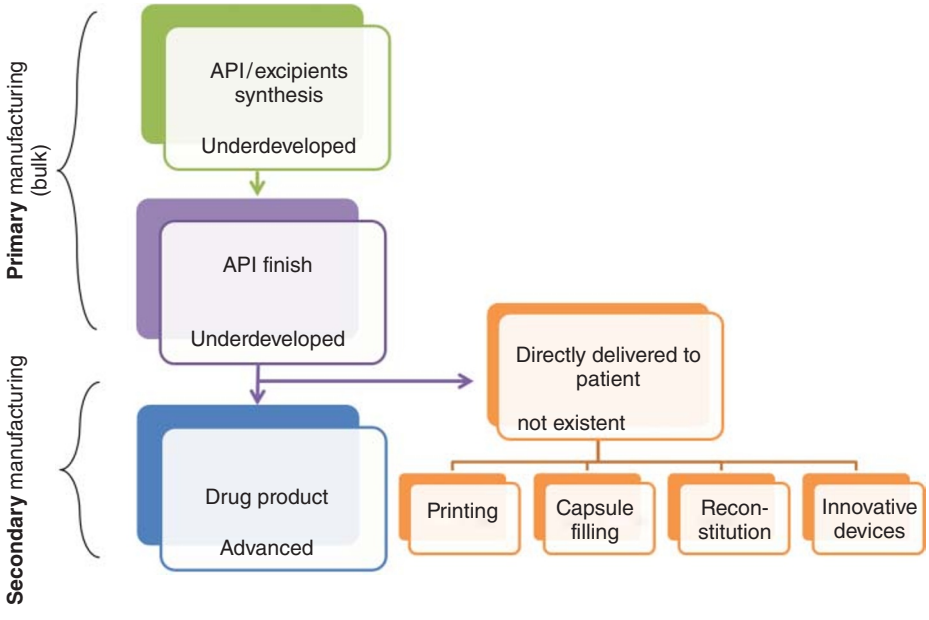

Figure 1.1 *General overview of a CM process chain.*

The advantages of continuous primary manufacturing are not as apparent as those of secondary manufacturing. A typical synthesis requires numerous (often chiral) steps involving different catalysts and different solvents. Since multiple purification and solvent change steps have to be carried out continuously, directly translating batch synthesis chemistry into continuous flow chemistry is impractical. To make the most of CM, special chemistries have to be developed that could benefit from the characteristics of a flow-through system. For example, fast, highly exothermic reactions that can only be carried out in a small volume in a flow-through reactor (which would not be possible in batch) and require much more active and selective catalysts. The same is true for biochemical synthesis, which can greatly profit from CM, for example, via perfusion reactors.

The second box in Figure 1.1 stands for the API finish. For small molecules, this includes particle formation and particle engineering, such as crystallization, filtration, washing, and drying or spray drying. For biopharmaceuticals, purification, polishing, and possibly, lyophilization or protein crystallization are required. The third box relates to secondary manufacturing. The processes include tableting and filling of capsules for oral or inhalative applications. Primary packaging is part of secondary manufacturing as well. In the biopharmaceutical field, the filling of ampules, injections, or infusion bags is part of secondary manufacturing.

Figure 1.1 also shows a "visionary side-stream" of APIs provided to patients via innovative routes, for example, via printing, direct filling into capsules, injecting protein solutions with micro-needles, or other innovative technologies. Practically non-existent today, these methods may become a major way of delivering "freshly made" drugs to a specific target patient population once individualized medicine and the associated individualized (and continuous) manufacturing processes gain importance. Although significant efforts are still required to bring these concepts to the market and patients, they may turn into major medical and business drivers of tomorrow.

The boxes in Figure 1.1 contain qualifiers. Continuous API (and excipient) synthesis and the associated continuous API finish are still not widely used as of today. (This, however, does not mean that significant progess in research has been made, which will have impact on the industry in the years to come.) In contrast, continuous secondary manufacturing and the associated process equipment are increasingly implemented in industry on a broader basis. Important technological developments have brought forth advanced secondary CM technology, although many aspects still require improvements and entirely new approaches (e.g., continuous coating).

Note that typically, it is neither necessary nor helpful to implement a continuous end-to-end manufacturing process, from chemical reactants to the final packaged product. Depending on the critical parts and bottlenecks in the supply chain, it often makes economic sense to apply CM only to certain parts of the manufacturing process. For example, it may be feasible to continuously mix, granulate, and tablet, but to use a traditional batch coater (one reason may be that compressed tablets need to rest for a certain amount of time to permit elastic expansion before coating).

Figure 1.2 shows the major processes and steps in primary manufacturing. In that regard, there is a distinction between small molecules and biophamaceucals: while small molecules are manufactured via synthesis and biosynthetic processes, biopharmaceuticals (such as MABs or growth factors) are exclusively produced via biosynthetic processes (e.g., bacterial/fungal fermentions, cell cultures, or extraction from natural sources). The

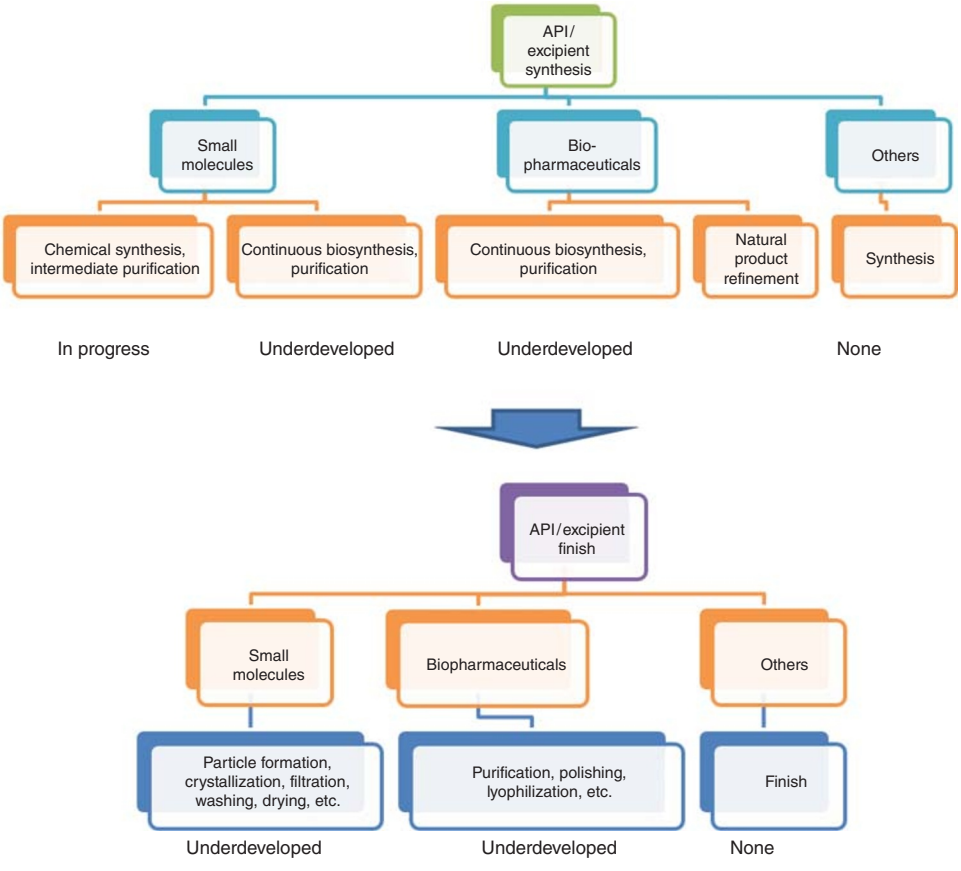

Figure 1.2 *Overview of continuous primary pharmaceutical manufacturing.*

box "others" accounts for drugs that do not fit in particular categories, such as vaccines, gene-therapeutics, or companion diagnostics. It is clear that continuous processes for pharmaceutical API manufacturing, both for synthesis and finish, are still in development, although the first successful implementations of end to end syntheses have been reported [4, 8]. Moreover, an ample body of literature exists in the continuous manufacturing and downstreaming of biopharmaceuticals [9].

Continuous API and excipient finish involves particle formation steps, purification polishing and lyophilization. While significant research efforts have been made in continuous crystallization [10–15], other processing steps in continuous pharmaceutical manufacturing are still to be developed and no GMP-certified equipment has been developed yet.

Figure 1.3 provides an overview of continuous secondary manufacturing. In this case, there is a distinction between large-scale manufacturing, which represents the current methods of drug production, and individualized (stratified) manufacturing for patient-specific needs, in line with the increasing trend towards personalized and/or individualized medicine. As in large-scale manufacturing, technical solutions do exist, although there is room for improvement, including in the context of advanced (i.e., easy to use and accurate) sensor technology. In the field of individualized manufacturing, no solutions are currently available on the market.

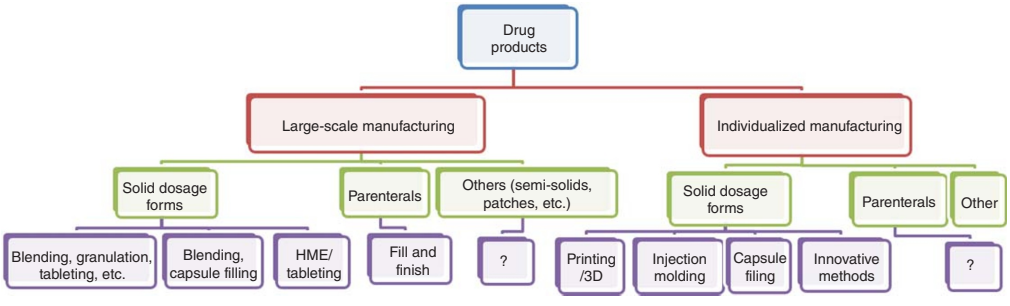

Figure 1.3 *Overview of continuous secondary pharmaceutical manufacturing.*

1.1.4 Regulatory Environment

In general, regulators in the United States and the European Union advocate CM as the means for improving the quality, reducing the risk of failure and minimizing response time to the changing demands. With various guidelines and programs, the FDA has been paving the way for CM in the pharmaceutical industry. The first initative "*Pharmaceutical CGMPs for the 21st century – a risk based approach*" [16] dates back to 2003 and was followed by others, such as *PAT Guidance 2004* [17]. The ICH has supported CM indirectly, for example, via ICH Q8 and Q9 in 2006, ICH Q8 R1 in 2009, and ICH Q11 in 2013. The FDA-EMA pilot program on quality by design (QbD) also supports this shift from empirical towards mechanistic process understanding, which will offer companies more freedom and enable CM [18].

However, a key factor for the successful implementation of continuous manufacturing is an effective plant-wide control strategy. With that regard, the main objective is to deliver excellent and steady product quality and reduce high quality costs associated with offline end-product testing. If a fully automated and controlled process concept is implemented, real time release testing (RTRT) can be performed.

1.2 Advantages of Continuous Manufacturing

Continuous pharmaceutical manufacturing provides significant benefits to society, patients, manufacturers, and pharmaceutical companies [19].

1.2.1 Flexibility

Flexibility is a major advantage of CM: new processes can be developed rapidly using the existing continuous manufacturing lines. In contrast to other industries (e.g., petrochemical), in the pharmaceutical industry CM does not require processes that run for 365 days/year. On the contrary, continuous processes may last from one to several weeks, followed by another process. For some products, a dedicated line that operates yearlong may be suitable. Using the same systems to develop and implement a manufacturing process offers additional flexibility. Moreover, by reducing the manufacturing time and adding to the industry's response capacity in case of emergencies, the amount of material produced can be increased or decreased using CM, depending on current needs.

Introducing a selected number of steps into a continuous process may bring additional flexibility in the manufacturing environment. For example, blending, granulating and compacting could be performed continuously and coating may still be accomplished in the batch mode.

1.2.2 Effect on the Supply Chain

One of CM's most important advantages is speeding up the supply chain. Existing supply chains may stretch over a few months or a year or longer. For example, contract manufacturing company A performs several synthesis steps and ships the intermediates to contract manufacturing companies B and C, which carry out further synthesis steps. Finally, the API is shipped back to the original company A, where the drug product is manufactured.

Using this approach, companies may take a long time to react to changing market demands and fail to act in the case of immediate needs (e.g., pandemics). Furthermore, long supply chains complicate the clinical development stage. For example, the transition from phase II to phase III requires a significantly increased amount of API material. To avoid significant delays, the decision to invest in phase III has to be made way before phase II results are available. Wrong choices in that regard may lead to substantial losses caused by investing in the equipment and site that may not be required or by entering the market too late and losing revenues due to a shorter patented life cycle phase. End to end CM plants can dramatically improve this situation and reduce storage and intermediary shipping costs.

1.2.3 Agility and Reduced Scale-up Efforts

Although there are products that require a market volume of many tons per year, they are the exceptions. Typically, a yearly supply of a few up to a few hundred kilograms of API is sufficient. As such, continuous manufacturing lines can be designed in a range of 0.1–5.0 kg/h production rate for APIs and about fivefold throughput for secondary manufacturing. In some cases, scale-up can be reduced or eliminated altogether (more often scale-down is necessary to process the required low throughput continuously). For example, a typical 18 mm HME extruder can produce a few kilograms of the product per hour. Running it for a month will yield a few thousand kilograms of material, which might be enough to satisfy the annual worldwide demand. Thus, the same extruder can be used in the development phase, which makes the complex and tricky scale-up redundant and eliminates one of the main sources of delays and out of specification (OoS) batches. The same applies to all systems that are difficult to scale-up, such as bio-reactors, bio-separation processes, and powder blenders or fluid bed systems.

By eliminating the scale-up that could become a significant bottleneck on the product's path to market, CM enables more agile manufacturing processes that can quickly be adapted to changes in the demand and increase the production volume without scale-up related problems. Moreover, it can dramatically facilitate clinical development required for targeted therapies and, particularly, breakthrough drugs.

1.2.4 Real-Time Quality Assurance and Better Engineered Systems

CM in general depends on: (1) well-designed engineered processes and (2) process control, that is, measuring the system parameters (e.g., RH, temperature, concentration) and material products and adapting/controlling the process parameters (e.g., feed rate or stirring speed). In this way, the quality attributes (QAs) of the materials remain within a specific limit – the design space. Process analyzers that measure these properties are critical for every continuous process. Together with appropriate process design and process control methods, they secure the correct QAs and, especially, the critical quality attributes (CQAs). Adapting the processes to variations in the environmental and material properties can vastly improve the quality. If process analyzers can ensure the appropriate CQAs, in conjunction with the demonstration of process understanding, real time release (RTR) can be achieved.

1.2.5 Decentralized Manufacturing

Although portable end to end CM plants are far from reality today, manufacturing can be decentralized and local. Since CM plants have a small footprint, they can be set up in flexible and portable environments, such as containers. A small desktop setup with a few flexible cartridge-based feeders, a tabletop hot-melt extruder, a die-face cutter, and a small-scale capsule filling machine only take a few square meters of floor space. Such flexible manufacturing plants can be shipped to a specific location (e.g., in developing countries) and have a wide range of applications (e.g., local epidemics, military use, space travel).

1.2.6 Individualized Manufacturing

Individualized manufacturing offers significant benefits to patients and healthcare providers. For example, in the geriatric, medicine swallowing can pose a major problem. It could be solved by manufacturing a flexible (not "fixed") dose combination, for example, by dosing various pellets into one capsule or into a liquid. Although many ideas are circulating with that regard (printing, 3DP, direct filling, etc.) and despite the benefits that they could bring, to date few systems have been developed that could be deployed in geriatrics centers, care centers, hospitals, and pharmacies. Even ATM-like systems or home-based dosage system can be envisioned. To that end, significant research and development are required to ensure ease of use, robustness, reliability, and a viable business model.

1.2.7 Reduced Floor Space and Investment Costs

CM plants require less floor space since multi-step equipment and quality control are combined in a single unit housed in one room with one air/water system and one common access port. Moreover, intermediate storage and stockpiling can drastically be reduced. The reduction in floor space is estimated to be up to 80%. In that context, investment costs can be reduced up to 76% [20], although higher costs in the field of online analytics and process control can be expected. Lastly, operating costs can be decreased: CM plants can significantly increase the current equipment use of 2–20%.

1.2.8 More Efficient Chemistries

In the area of primary manufacturing of small molecules, stoichiometric–reagent chemistries or catalytic systems that ideally have moderate reaction rates and moderate exothermicity are typically used since thermal runaway and explosions must be avoided at any costs at large reaction volumes. However, if reaction volumes are in the order of milliliters, flow-chemistries can be used, and safety concerns do not prohibit the deployment of better and more effective synthesis routes. More selective catalytic routes and much faster, more exothermic, and more elegant chemistries can be applied, involving unstable intermediates or products, high pressures, or temperature extremes (e.g., organo-metallic reactions, nitrations, halogenations, and diazo reactions).

1.2.9 Societal Benefits

With its low environmental impact and as a source of high-tech jobs, CM positively affects society. Moreover, it helps to reduce the cost of drugs and their development, benefiting the healthcare system and potentially enabling more investment in new products. Using CM, a much wider range of novel dosage forms can be developed for the patients and a wider range of doses can be manufactured without extensive alterations to the process. Finally, CM improves the quality of medicines or at least reduces the costs associated with today's QA systems.

1.3 Engineering Principles of Continuous Manufacturing

This chapter briefly reviews the fundamental principles of process design as the basis of CM.

1.3.1 Pharmaceutical Unit Operations

CM plants can be systematized, described, modelled, and controlled based on the well-established principles of chemical engineering science. For example, the concept of a unit operation can be used to describe (continuous) chemical plants and can thus be applied to pharmaceutical manufacturing as well. In general, a unit operation is a clearly defined processing step, during which a specific transformation is carried out. Unit operations can be categorized according to their:

1. Underlying physico-chemical effects,
2. Phases involved,
3. Contacting method,
4. Flow mode,
5. Mode of operation.

A short overview is provided below.

1.3.1.1 Categorization According to the Underlying Physico-chemical Principles

The underlying physico-chemical principles are either physical, chemical, or bio-chemical modifications of a material (or substrate). There are three types of unit operations (Table 1.1).

1.3.1.2 Categorization According to the Phases Involved

A phase is defined as a distinctive form of matter (i.e., solid, liquid, gas or plasma). Super-critical phases may sometimes form where there is no distinction between the gas and liquid phases. Pharmaceutical manufacturing processes include all phases (except for plasma), often with more than one phase involved. For example, many chemical reactions occur in gassed liquid phase reactor involving catalysts (i.e., a three-phase gas–liquid–solid system). In powder granulation, gas, liquid (binder solution), and solids are used (i.e., also a three-phase system or in case of different solids even a multi-phase

Table 1.1 *Unit operations relevant to continuous pharmaceutical manufacturing*

Type	Form	Operations
Physical unit operations	Mechanical	Emulsification, spraying, cell rupture, filtration, sieving, sedimentation, flotation, milling, mixing, blending, granulation, agglomeration, tableting, extrusion, packaging
	Mass and heat transfer	Absorption, distillation, extraction, adsorption, drying, evaporation, crystallization, coating, lyophilization, chromatography
	Electrical and magnetic	Electrophoresis, mainly separations
Chemical unit operations	Single phase	Stoichiometric liquid-phase reactions, homogeneously catalyzed liquid-phase reactions (e.g., chiral transformations)
	Multi-phase	Gas–liquid reactions (e.g., oxidations), liquid–solid reactions, heterogeneously catalyzed reactions (e.g., hydrogenations, couplings), gas–liquid–liquid reactions
Biological unit operations		Fermentation and cell cultures, refolding, enzymatic processes, sterilization

system). Although several solid (different crystals, amorphous vs. crystalline materials) and liquid (oil, water) phases exist, there is only one gaseous phase. A single-phase system (e.g., a homogeneously catalyzed liquid phase reaction) only has a single phase.

However, in many cases multiphase systems can be viewed as single phases. For example, granular flows of reasonably large particles, which always involve gas (air) and solid particles, can effectively be described without the air impact.

Different phases can occur in different dispersion forms. Typically, we distinguish between:

- A continuous phase (phase is connected);
- A dispersed phase (drops, particles or bubbles, not connected to each other).

In a fluid bed coating process, the air flow is continuous, while the granules (or pellets) and liquid droplets are dispersed. In the production of solid foams, the solid is continuous and the air is dispersed. In a gassed stirred tank, the liquid is continuous and the catalyst particles and the gas bubbles are dispersed. Which phase is dispersed typically depends on the underlying mass transfer and the phase equilibria. For example, with regard to gas absorption into a liquid it is well-known that easily soluble gases are typically processed via sprays (the liquid is dispersed), while poorly soluble gases are processed via bubble regimes (the gas is dispersed).

1.3.1.3 Categorization According to the Contacting Method

A continuous phase contact exists when phases are continously in contact with each other throughout the entire unit operation (Figure 1.4).

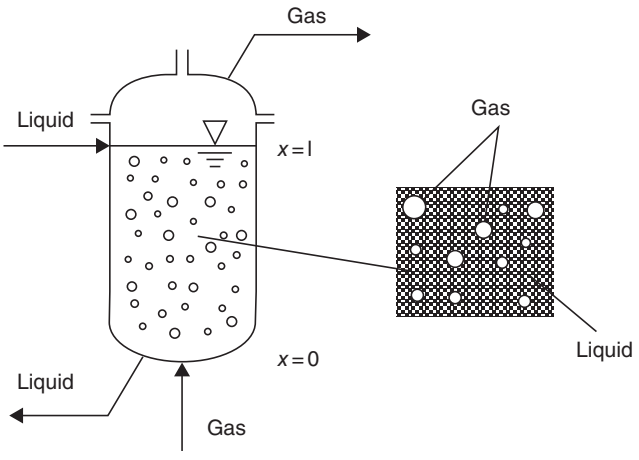

Figure 1.4 *Schematic of a system with continuous phase contact.*

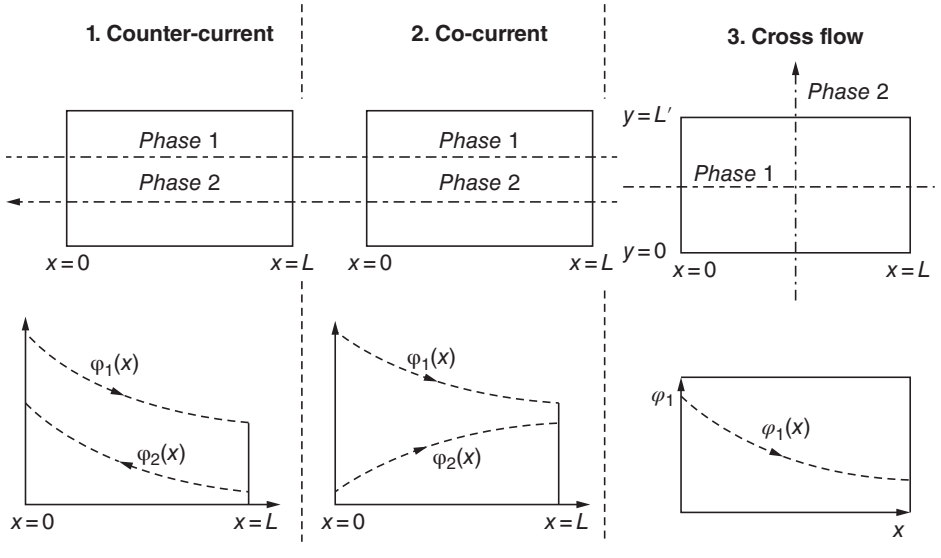

Figure 1.5 *The three principal flow modes.*

In the discontinuous mode of phase contact, phases are mixed and separated again. Depending on the contact time, an equilibrium between the phases can be established, which is important with regard to separations and mass/heat transfer operations. Based on this principle, in combination with the countercurrent flow of the phases, high seperation efficiencies can be achieved. A typical example is a tray-based distillation column with the counter-current phase flow. Categorization is according to the flow mode.

A single-phase system does not have various flow modes. In multiphase systems there are three types of flow modes, as shown in Figure 1.5.

In general, the counter-current mode is preferable if a process depends on a driving force between the phases, such as a difference in temperature or concentration. For example, for heat exchangers a counter-current operation (i.e., the cold and hot feed enter at opposite sides) is more efficient, as it is in absorbers. In a mass-transfer process run in the co-current mode, a single theoretical separation stage can be realized, that is, both phases are in an equilibrium at the exit of the unit operation. In contrast, counter-current flows can achieve many theoretical separation stages and have a higher separation efficiency (the principle of continuous distillation units or counter-current chromatography). Morover, higher relative velocities of phases in a counter-current mode yield higher mass transfer coefficients.

However, the co-current mode also has advantages. For example, since flooding occurs at higher flow rates, higher overall flow rates and higher overall productivity can be achieved in co-current mode than with a counter-current or cross-flows.

1.3.1.4 Categorization According to the Mode of Operation

There are three main operation modes:

1. Batch or discontinuous,
2. Continuous,
3. Semi-continuous.

In batch mode, the feed is introduced into the system and the process is carried out under varying conditions during the process. Subsequently, the product is discharged and the system is cleaned and readied for the next cycle. Most importantly, the system variables (temperature, concentration, particle size, titer, etc.) change over time, that is, they are time-variant, as shown in Figure 1.6.

In the continuous mode, both the feed and the product are introduced into and removed from the system continuously. Except during startup and shutdown or during control actions, the process is carried out under time-invariant conditions. In order not to accumulate or deplete the system, exactly equal amounts have to be fed into and removed from the system.

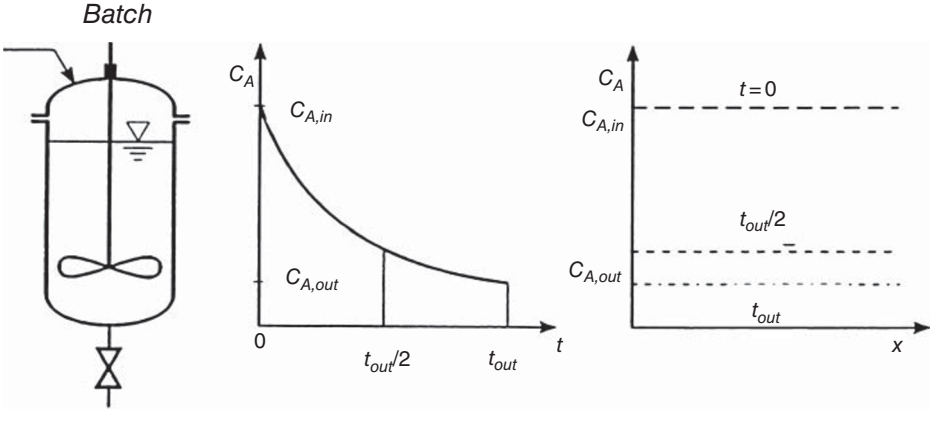

Figure 1.6 *Batch reactor and the associated temporal and spatial gradients.*

Continuous systems are typically spatially inhomogenous, that is, in between ideally mixed and plug-flow (see detailed discussion in Section 1.3.4).

1.3.2 Fundamentals of Process Modeling

Over the last century chemical engineering evolved from an art to a science, primarily due to progress in process modeling, that is, describing processes via mathematical models that are based on physical and mechanistic insights. Many examples attest to the success of this approach. Although no computers were available in the early days to make simulations possible, a wealth of understanding and knowledge was gained from process models. In pharmaceutical processing, much less attention has been devoted to process modeling, which – however – is crucial for CM.

Process models of unit operations are typically based on balance equations for the conservation of mass, species, energy, and momentum. Every balance equation has the following structure:

$$\text{Accumulation} = \text{Transport}_{\text{IN}} - \text{Transport}_{\text{OUT}} + \text{Source (sink)}.$$

The balance equation has to be written for a well-defined volume, that is, the control volume. Essentially, this equation signifies that the difference between the transport into and out of system is equal to the accumulation in the system, unless the system has a source of new material. Consider a container with 5 kg/h fed into the system and 4 kg/h being removed. In this case, the accumulation of 1 kg/h remains in the system, unless there is a source or sink that creates or removes more material.

1.3.2.1 Integral Versus Differential Balances

Balances can be written for a real system (i.e., a tank). This can be a balance for a single unit operation (e.g., heat balance of a chemical reactor), for parts of it, or even for multiple unit operations. In this case we speak of *integral balances*. A balance that is defined for a differential (infinitely small) volume is called a *differential balance.* If process variables (such as concentration and temperature) within the system under consideration do not significantly change, integral balances should be used. Typically, these are ordinary (easy to solve) differential equations. If process variable changes significantly within a system, differential balances are required, which are generally partial differential equations that are harder to solve. A typical example is a chromatographic system where the concentration of the components varies significantly along the path through the column. The next section provides balances for mass, species, energy and momentum. Balances typically involve closures for some of the terms (models of a physical or chemical effect).

1.3.2.2 Closures

Closures are important laws that are not necessarily based on first principles (such as mass, energy, and momentum conservation), but are critical for the development of the balance equations. For example, these include the transport laws for mass, heat and momentum conduction, typically using Fick's, Fourier's, and Newton's laws, respectively. Other closures

include models of reaction rates and radiation sources or constitutive behavior of solids and fluids.

1.3.2.3 Single- and Multi-phase Balances

Single-phase systems are found in a variety of processes, such as stirred tanks. However, in pharmaceutical manufacturing, most systems are multi-phase systems. They require multi-phase balances that are similar to the general single-phase balances, except that for each phase a separate balance has to be defined based on the occupied volume and transfer terms between the phases have to be included. Often some balances can be combined: for example, in reactor modeling separate mass balances for all phases can be written and a combined heat balance may be used if the temperature difference is minor.

In the momentum balances for dispersed multiphase systems (e.g., bubbles in a liquid), either the Euler–Euler or the Euler–Lagrange method can be used. The Euler–Euler methods describe both phases as interpenetrating continua, while according to Euler–Lagrange methods the dispersed phase is a large number of point sources, with an exchange between the continuous phase and the point sources. Each method has merits. Alternatively, both phases can be modeled based on the exact momentum balance with interface resolution. This provides the highest level of detail (termed direct numerical simulation or DNS) but is too expensive in most cases.

1.3.3 Balance Equations for Mass, Species, Energy and Momentum

1.3.3.1 Mass Balances

Mass balances are written for the total mass and specific components, termed species [21]. Mass balances can be based on molar or mass units. If reactions occur, molar balances are preferred.

The total integral mass balance for a certain control volume is:

$$\frac{\partial M}{\partial t} = \dot{M}_{\text{in}} - \dot{M}_{\text{out}}, \tag{1.1}$$

where M is the mass in the system and $\dot{M}$ is the transport term in kg/s. As mass can be neither created nor destroyed, no source terms occurs.

The integral component balance in a mass-based system is:

$$\frac{\partial M_i}{\partial t} = \dot{M}_{i,\text{in}} - \dot{M}_{i,\text{out}} + R_i \tag{1.2}$$

where the index i is the mass of a specific component. Since mass of one component can be transferred to another via chemical reactions, a source term for the component exists in kg/s.

The integral component balance in a mole-based system is written as:

$$\frac{\partial N_i}{\partial t} = \dot{N}_{i,\text{in}} - \dot{N}_{i,\text{out}} + \tilde{R}_i \tag{1.3}$$

where N is the number of moles and $\dot{N}$ is the molar transport rate in mole/s. The source term is also mole-based.

The differential equivalents are for the total mass:

$$\frac{\partial \rho}{\partial t} + \mathrm{d}iv(\rho \vec{v}) = 0 \tag{1.4}$$

where ρ is the density in kg/m^3 and $\vec{v}$ is the three-dimensional velocity vector in m/s. For incompressible fluids we obtain:

$$\mathrm{d}iv(\vec{v}) \equiv \frac{\partial \mathrm{v}_x}{\partial x} + \frac{\partial \mathrm{v}_y}{\partial y} + \frac{\partial \mathrm{v}_z}{\partial z} = 0 \tag{1.5}$$

The differential species balance (here only shown in molar units) is given as:

$$\frac{\partial c_i}{\partial t} + \mathrm{d}iv\, \vec{n}_i - r_i = 0 \tag{1.6}$$

where c_i is the concentration in mol/m^3, $\vec{n}$ is the vector of the molar transport density in number of moles passing through a cross-section of 1 m^2 per second, and r_i is the source term in mol/m^3 per second.

For a single-phase system the above-mentioned closure can be used. Then one would use the following expression for the molar flux:

$$\vec{n}_i = c_i \vec{v} - D_i \nabla c_i \tag{1.7}$$

The molar flux is divided into convective (flow) contribution and diffusion described by Fick's law, with D_i being the diffusion coefficient of component i in the mixture. Inserting this into the differential species balance yields:

$$\frac{\partial c_i}{\partial t} + \vec{v} \cdot \mathrm{d}iv\ c_i - D_i \nabla^2 c_i = r_i \tag{1.8}$$

In this equation, the first term is the accumulation (unsteady) term, the second is the convection, the third one is the diffusion, and the term on the right hand side is the source term due to reactions.

For the sake of completeness, a multiphase component balance is shown below, where both phases (e.g., gas and liquid) are assumed to be continuous. For each phase a balance equation is written:

$$\varepsilon_g \frac{\partial c_{i,g}}{\partial t} + \varepsilon_g \vec{\mathrm{v}}_g \cdot \mathrm{d}iv\ c_{i,g} - \varepsilon_g D_{i,g} \nabla^2 c_{i,g} = r_{i,g} + n_{t,i} \tag{1.9}$$

$$\varepsilon_l \frac{\partial c_{i,l}}{\partial t} + \varepsilon_l \vec{\mathrm{v}}_l \cdot \mathrm{d}iv\ c_{i,l} - \varepsilon_l D_{i,l} \nabla^2 c_{i,l} = r_{i,l} - n_{t,i} \tag{1.10}$$

In these equations, g and l refer to the gas and liquid phases, respectively. ε_g and ε_l are the specific volume fractions of the gas and liquid phases. The sum of all volume fractions is 1. Note an additional term $n_{t,i}$, which is the volumetric transfer rate of component i from liquid to gas.

Population balance equations (PBEs) are a special form of mass balances, in which the mass fraction is associated with another property of the material, typically the size. Population balances are mainly applied to particles of different sizes and used to describe a process

during which the particle size distribution changes during the operation, for example, crystallization, agglomeration, milling, or emulsification. The general form of a population balance is given by:

$$\frac{\partial n(r,t,\vec{x})}{\partial t} + \frac{\partial}{\partial x_i}(\mathrm{v}_{p,i} \cdot n) + \frac{\partial}{\partial r}(R \cdot n) = B - D \tag{1.11}$$

where n is the number density of size-r particles (internal coordinate) at time t and location $\vec{x}$ (external coordinate), $\partial n/\partial t$ is the accumulation of particles of a specific size at a specific location and $\partial(\mathrm{v}_{p,i} \cdot n)/\partial x_i$ are the convective flow terms of the particles (i.e., in a real flow). Note that such a term exists for each coordinate direction. Here, $\mathrm{v}_{p,i}$ is the particle velocity in the three coordinate directions that must be known *a priori*. If the particles are small, the fluid flow velocity can be used. If the particles are large, these velocities have to be computed by solving a force balance of the particles. $\partial(R \cdot n)/\partial r$ is internal convection, that is, a change in the particle size due to growth. $B - D$ are the "birth" and "death" rates of the particles, for example, via agglomeration or breakage, respectively. While the form of population balances is well-known, R, B, and D are difficult to establish. In many cases, only empirical models are available that must be tuned to match the experimental results.

1.3.3.2 Energy Balances

Energy balances are written for the chosen control volume, being either integral or differential [21].

An integral balance is given by:

$$\frac{\mathrm{d}E}{\mathrm{d}t} = \dot{Q} + \dot{E}_{\mathrm{in}} - \dot{E}_{\mathrm{out}} - W \tag{1.12}$$

where E is the energy of the system in Joules, in which all types of energy can be considered, including thermal, potential, kinetic, chemical, elastic, and other forms. In the processing industry, we usually can assume that $E = Mv^2/2 + Mgh + U$, that is, the sum of kinetic, potential, and inner energy. $\dot{Q}$ is the heat flow rate via conduction into the system in watts, $Mv^2/2 + Mgh + U$ is the energy transported via mass flow into the system, and $\dot{W}$ is the mechanical energy (via shaft work as this was initially developed for steam engines) added to the system in watts. Note that the mechanical work energy added to a system is negative by definition.

The energy transported by mass flow is:

$$\dot{E} = \dot{M}(v^2/2 + gh + u), \tag{1.13}$$

where u is the specific inner energy (J/kg). Inner energy can be calculated as a function of temperature via $u = c_{\mathrm{v}}T$, where c_{v} is the heat capacity at constant volume. Since the flow of mass increases the volume, it also adds work (volumetric increase) to the system (mechanical work). Thus, one often uses:

$$\dot{E} = \dot{M}(v^2/2 + gh + u) + p\dot{V} \tag{1.14}$$

where p is the pressure and $\dot{V}$ is the volumetric flow rate. The latter term indicates that a mass flowing into a system performs work on the system by expanding or contracting it.

In the general energy balances, only mechanical work is accounted for, the so-called shaft work $\dot{W}_{\text{shaft}}$. Since in many processes kinetic and potential energy can be neglected, the energy balance can be written as:

$$\frac{\mathrm{d}U}{\mathrm{d}t} = \dot{Q} + (\dot{M}u)_{\text{in}} - (\dot{M}u)_{\text{out}} + p(\dot{V}_{\text{in}} - \dot{V}_{\text{out}}) - \dot{W}_{\text{shaft}} \tag{1.15}$$

The differential energy balance for a fluid with constant density can be written as follows [21]:

$$\rho \cdot \frac{\partial h}{\partial t} + \rho \cdot (\vec{v} \cdot \nabla)h = \frac{\lambda}{c_p} \cdot \nabla^2(h) - (\tau : \nabla\vec{v}) + \dot{q}_h \tag{1.16}$$

This is a scalar equation with dimension [W/m^3], where h is a specific enthalpy ($h = u + pV/M$), $\tau : \nabla\vec{u}$ is a heat source (due to viscous dissipation), and $\dot{q}_h$ is a specific heat source (e.g., due to chemical reactions).

1.3.3.3 Momentum Balances

Momentum in a closed system is conserved and can change only due to external forces. As such, it can be used to describe the acceleration of mass, for example, acceleration of particles and fluids due to forces [21].

In process modeling, integral momentum balances are used if entire solid bodies accelerate (or decelerate). For a single point source with finite mass i after time derivation, this momentum balance is Newton's second law, that is:

$$m_i \frac{\mathrm{d}\vec{v}_i}{\mathrm{d}t} = \sum \vec{F}_i \tag{1.17}$$

This vector equation describes the acceleration of particle i as a function of the sum of all forces. According to the discrete element method (DEM), these include the contact forces (e.g., friction and normal forces), cohesive forces, body forces (e.g., gravity and buoyancy), and other forces (e.g., electrical and mechanical forces).

The rotational momentum is conserved, that is:

$$\frac{\mathrm{d}\vec{G}}{\mathrm{d}t} = \vec{T} \tag{1.18}$$

where $\vec{G}$ is the angular momentum (rotational) and $\vec{T}$ is the torque.

The differential momentum balance for fluids is the Navier–Stokes equation, which describes the flow of Newtonian fluids and gases. For incompressible flows (i.e., most flows not too close to supersonic speed), this vector equation becomes:

$$\rho\left(\frac{\partial\vec{\mathrm{v}}}{\partial t} + (\vec{v} \cdot \nabla)\vec{v}\right) = -\nabla P + \mu\Delta\vec{v} + \vec{f} \tag{1.19}$$

where μ is the viscosity and $\vec{f}$ are the body forces (mainly gravity). Note that incompressibility does not necessarily mean constant density but rather implies that, locally, the flow is divergence-free, that is, $\nabla\vec{v} = 0$. This equation, together with the continuity equation above, is the basis for all computational fluid dynamics (CFD) models with ample applications and refined simulation codes.

For non-Newtonian liquids, this equation has to be modified.

1.3.4 Residence Time Distribution

Residence time distribution (RTD) is critical for CM since it directly affects the definition of a batch. If the RTD is very broad (i.e., a part of the fed material is quickly processed and a part stays in the system for a long time) in a continuous process, tracing out of specification material becomes problematic and it is impossible to obtain a well-defined batch. Thus, narrow RTDs are preferable, with all material elements remaining in the process for approximately the same amount of time. Note, however, that a very narrow RTD implies that no mixing occurs in the system, eliminating the possibility of smoothening out potential fluctuations (e.g., of a feeder). $E(t)\mathrm{d}t$ is the fraction of molecules exiting the system that have spent a time between (t) and ($t + \mathrm{d}t$) in the system. The theory of RTD is based on the assumptions that the system is at steady-state, the transport at the inlet and the outlet takes place only by advection and the flow is incompressible. RTD is based on the concentration $C(t)$ of a tracer (inert) measured at the outlet of the processing unit. For a certain amount of tracer fed into the system instantaneously, the residence time function $E(t)$ is defined as:

$$E(t) = \frac{C(t)}{\int_0^\infty C(t)\mathrm{d}t} \tag{1.20}$$

A schematic of RTD is shown in Figure 1.7.

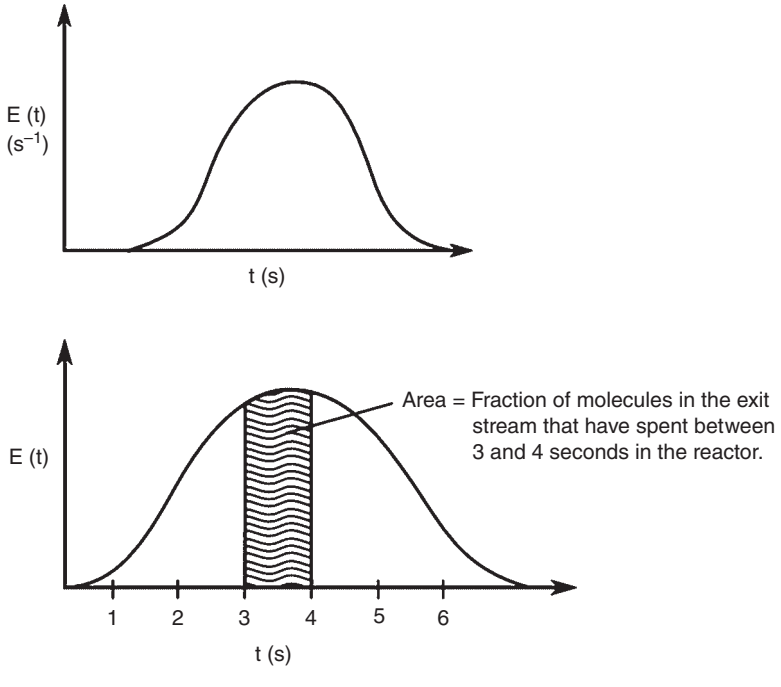

Figure 1.7 *Schematic of residence time distribution.*

The cumulative distribution function $F(t)$ is defined as:

$$F(\tau) = \int_0^{\tau} E(t)\mathrm{d}t \tag{1.21}$$

$F(\tau)$ is the fraction of molecules that have spent a time τ or less in the reactor.
The mean residence time is defined as:

$$t_m = \int_0^{\infty} tE(t)\mathrm{d}t \tag{1.22}$$

Variance is defined as:

$$\sigma^2 = \int_0^{\infty} (t - t_m)^2 E(t)\mathrm{d}t \tag{1.23}$$

Internal age distribution:

$$I(t) = \frac{1}{t_m}[1 - F(t)] \tag{1.24}$$

$I(t)\mathrm{d}t$ is the fraction of molecules inside the reactor that have been inside the reactor between t and $t + \mathrm{d}t$.

RTDs are measured by introducing a non-reactive tracer into the system at the inlet. The concentration of the tracer is changed according to a known function and the response is measured at the outlet. The selected tracer should not modify the physical characteristics of the fluid (e.g., equal density, equal viscosity) and introducing the tracer should not modify the hydrodynamic conditions. In general, the change in the tracer concentration will be either a pulse or a step. Other functions are possible, but they require more calculations to de-convolute the RTD curve.

1.3.5 Classical Reactor Types as a Basis for Process Understanding

1.3.5.1 Ideal Plug-flow System

In an ideal plug-flow reactor, there is no axial dispersion or mixing and the fluid elements exit in the same order as they entered. Although there is a change in the state variables along the reactor axis, the system is time-invariant. A schematic of an ideal plug-flow system is shown in Figure 1.8. All fluid elements have the same residence time (i.e., the volume divided by the volumetric flow rate).

Therefore,

$$E(t) = \delta(t - t_m) \tag{1.25}$$

where δ is the Dirac delta function. Clearly, the variance in an ideal plug-flow reactor is zero.

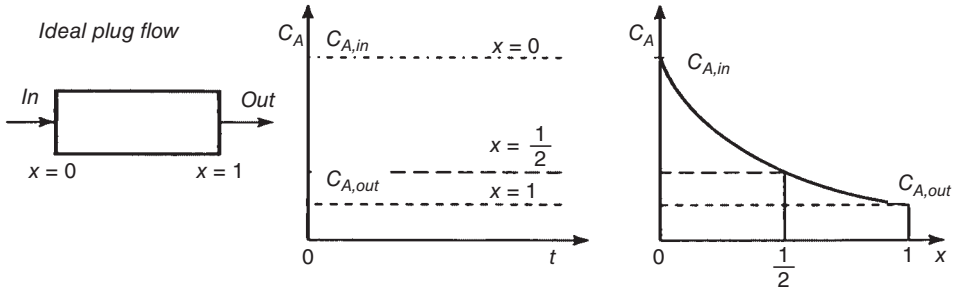

Figure 1.8 *Schematic of a plug-flow reactor and temporal and spatial profile.*

1.3.5.2 Ideally Mixed System

An ideally mixed system (also termed continuously stirred-tank reactor or CSTR in the field of reaction engineering) is based on the assumption that the inlet feed is instantly mixed into the bulk of the system. Moreover, the whole reactor (and also the outlet fluid) has identical, homogeneous compositions at all times (see Figure 1.9).

An ideal CSTR has an exponentially decaying RTD:

$$E(t) = \frac{1}{t_m} \exp(-t/t_m) \tag{1.26}$$

Thus, $E(0)$ is already $1/t_m$ and will subsequently decrease. Although in practice this is not observed since it takes a finite time for the tracer to be transported from the inlet to the outlet, for small-scale systems it can be a good approximation.

1.3.5.3 Cascade (Series) of Ideally Mixed Systems

A cascade of ideally mixed systems (Figure 1.10) is an intermediate case between an ideally stirred tank and a plug-flow system. It is important, since most real-life systems can be modeled by a series of ideally mixed systems, where the number of tanks in the cascade determines the degree of back-mixing (the more tanks, the less back-mixing, see Figure 1.10).

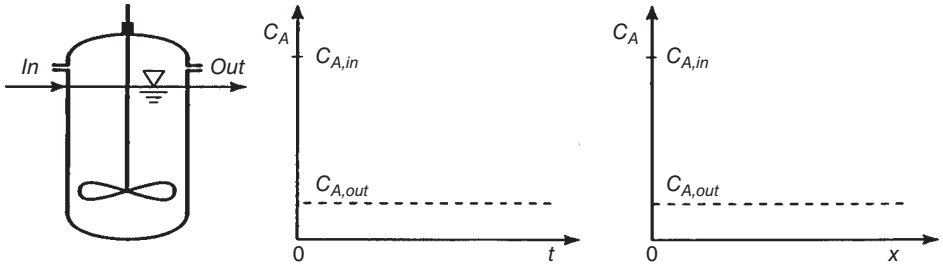

Figure 1.9 *Schematic of a ideally mixed reactor (left). Corresponding temporal and spatial profiles (right).*

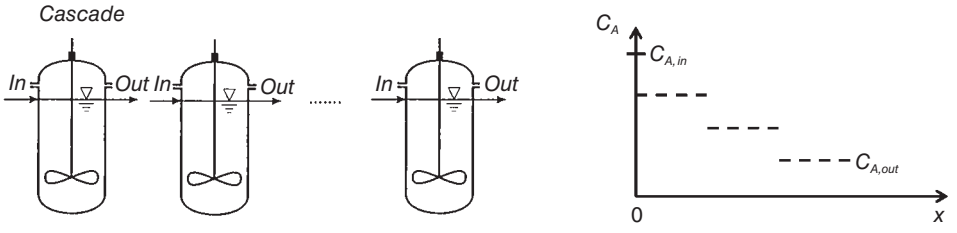

Figure 1.10 *Schematic of a cascade of CSTRs and spatial profile.*

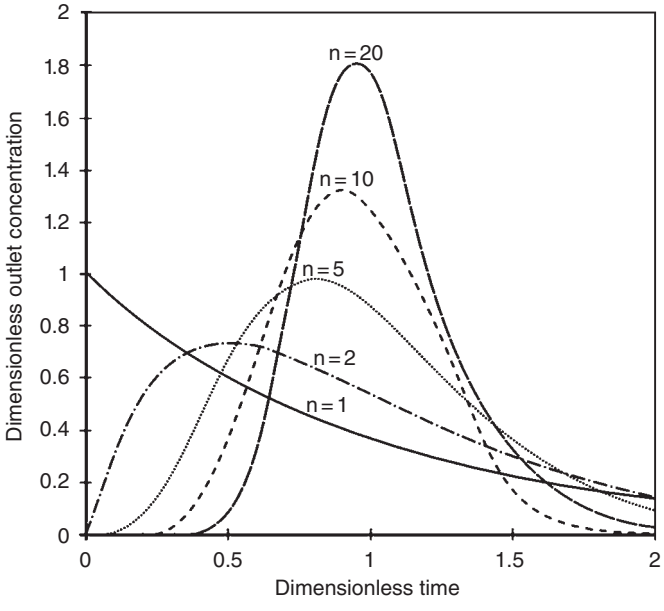

Figure 1.11 *RTD for various numbers of CSTRs.*

The RTD of a cascade is shown in Figure 1.11. For one CSTR the RSD is (obviously) that of a single CSTR with a steady decay (see above). Interestingly, for more CSTRs the width of the RTD narrows and approaches that of a plug flow reactor.

The RTD in a real system always deviates from that in an ideal reactor, depending on mixing in the vessel. For example, deviating from ideal plug-flow behavior, continuous powder mixers always have a non-zero variance, otherwise no mixing could occur in the axial direction and fluctuations of the powder feeds could not be smoothed.

If the mean of the $E(t)$ curve arrives earlier than the expected time, there have to be stagnant regions and short cuts within the vessel. If the RTD curve shows more than one main peak, it may indicate channeling, parallel paths to the exit or strong internal circulation. Short-circuiting fluid or particles within an ideally mixed reactor would appear in an RTD curve as a small pulse of concentrated tracer that reaches the outlet shortly after being injected.

1.3.6 Process Control, Modeling and PAT

Process control is an essential element of CM and no CM process can be implemented without it. Generally, it relies on two main components:

- Appropriate sensors,
- Appropriate control algorithms and their implementation.

Both aspects are far from trivial, and significant research is required to develop new and more suitable approaches with that regard. Process control is included in virtually every chemical engineering curriculum and has been implemented in the chemical industry for many decades, resulting in an ample body of literature. However, significant research efforts are still underway, especially concerning highly reactive systems, highly non-linear systems and systems with long time delays.

Although for pharmaceutical process control the same principles apply as for chemical plants, pharmaceutical manufacturing has its intricacies, for example, a significant lag time (residence time) between the start of a manufacturing cascade and the final process step. For example, in a continuous process for solid dosage forms, dry powder may be fed, wet-granulated, dried, blended, and tabletted, with a mean residence time in the order of hours, making unsuitable feedback controllers that measure the final properties (content uniformity and dissolution rate of the tablets) and control parameters at the process start (e.g., feed rate of excipient A). Faster control action is required, for example, via feed-forward controllers or model-based control algorithms that can predict the process dynamics. Advanced process control is especially important in pharmaceutical manufacturing, and model predictive control (MPC) has received considerable attention [6, 22]. Modeling is another critical element of this step [23]. A chapter in this book is devoted exclusively to process control in the pharmaceutical industry.

Another field of critical importance is PAT, focusing on the development and implementation of online sensors (process analyzers), multivariate analysis tools, process control and continuous improvement/knowledge/management systems [24]. All of these elements are key drivers for CM in the pharmaceutical industry. A wide range of sensors is available, which can be divided into several groups according to their integration into the process (in-, on-, and at-line) and the number of output variables (uni- and multi-variate). For process control, it is vital to know what information can be obtained via a sensor. An overview based on the properties of interest and associated techniques provided in Figure 1.12 is by no means exhaustive but it covers many essential aspects relating to the pharmaceutical manufacturing, for example, classical sensors, chemical composition (spectroscopic techniques such as infrared, near infrared (NIR), Raman, UV-Vis, ultrasound, laser induced fluorescence and time of flight), particle size and shape (laser diffraction, image analysis, focused beam reflectance measurement, spatial filter velocimetry), crystallinity and polymorphism (NIR, Raman, small- and wide-angle x-ray scattering), and physical properties (Terahertz, optical coherence tomography, focus variation, ultrasound). Other sensors, for example, in the field of bioprocessing, include an online measurement of dissolved oxygen (DO) or an off-gas analysis via GC. Nevertheless, important sensors, that is, for powder flow rate, do not exist as of yet. Several chapters in this book describes PAT applications in detail.

However, there are significant gaps in the array of sensors. To date there is no sensor that measures accurately the flow rate of a solid powder stream. Moreover, APIs often have a

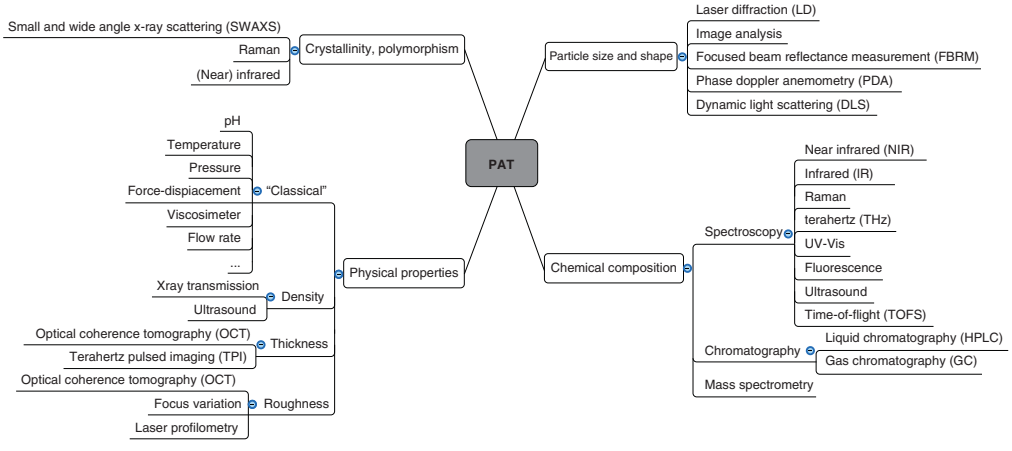

Figure 1.12 *Schematic overview of typical sequence, from multivariate raw data (e.g., spectra, images) to product quality parameters (e.g., API concentration, coating thickness of pellets or tablets).*

very low concentration, even down to the microgram range, for which no on-line sensor technology exists, since most sensors involve spectroscopic techniques with a typical sensitivity of below 1% content. Lastly, major improvements in robustness, reliability, model development, calibration, ease-of-use, fouling, and costs have to be made, creating great business and research opportunities for companies and academia.

1.3.7 Scale-Up

Scale-up is less problematic in CM than in batch manufacturing, since more product can be obtained over longer processing times and the equipment size used for process development can often be used for manufacturing. Moreover, the scale-out principle can be used, that is, installing the same unit in parallel if needed. Although the development and manufacturing scales might be more similar, scale-up is important, also for CM. Scale-down may also important since many continuous processing systems exist on a scale of 50+ kg/h that exceeds the needs of pharmaceutical production.

In general, scale-up and scale-down are processes of increasing or decreasing the scale of a unit operation in order to increase or decrease the throughput and productivity. In pharmaceutical manufacturing, all processes are based on chemical and biochemical transformations and physical manipulations of the system (e.g., milling, purification). All these processes are governed by the effects of momentum, mass and energy transfer and can be – at least in theory – described by the corresponding balances and closures (see discussion above). All these phenomena occur on different time and length scales. Even a single process (e.g., fluid mixing) is governed by different scales, such as the macro-mixing scale and the micro-scale of the smallest turbulent eddies. Often, different phenomena control the rate of a process at different scales. For example, chemical reactions are often limited by kinetics on the small scale and by mass transport on larger scales. Thus, except for the simplest cases, scale-up is a compromise and must focus on attaining a similarity of the most important and critical step.

Blenders are notoriously difficult to scale-up. In (continuous) tumble blenders (or also in any rotating drums) [25], typically only a top layer of material is flowing where the thickness is determined by the particle properties. Since the thickness does not change during scaling-up, for larger systems the ratio of flowing to stagnant material decreases. In agitated mixers [26] the spatial distribution of shear in small- and large-scale systems is very different (as it is in fluid stirred tanks). Additionally, the Froude number scaling ($\mathrm{Fr} = n^2 \cdot d/g$) leads to different shear levels since the maximum velocity at the agitator tip is scaled with $\sqrt{d}$ and the shear rate with $\frac{1}{\sqrt{d}}$. Thus, large blenders with the same Froude number impart less shear than small ones. In summary, scaling-up powder blenders is far from trivial (and to a large extent empirical), and most large-scale systems must be thoroughly tested before deployment. Recent progress in the simulation of blenders via DEM has provided design engineers with a tool for understanding the effect of scale on the blending performance.

Roller compaction is another important process. Since it is inherently continuous, scale-up is not considered to be critical. Science-based scale-up of wet granulation is more challenging, with regard to both high shear and FB granulation. One of the earliest approaches to scaling-up high shear granulation is to establish a dimensionless relationship between the power consumption and the wet mass consistency, making the relationship

general for geometrically similar high shear mixers. The power consumption of the granulation end-point is the value that corresponds to the optimal wet mass consistency. For scale-up, the dimensionless relationship can be applied again to determine the target power consumption on the new scale. Another method is to develop nucleation regime maps based on the dimensionless spray flux and drop penetration time for a given formulation. Scale-up can then be performed by defining the optimal design space as a function of dimensionless numbers and keeping these numbers constant. Similar concepts can be applied to the scale-up of extrusion-based continuous shear granulators (GEA system) as described first by Remon's group [7, 27]. Scale-up of fluid bed granulators is mostly based on the mass and heat balances, the bed's moisture content and the droplet size measurements. Recent progress in the simulation of wet granulation via CFD-DEM has provided a powerful tool for understanding the effect of scale on the granulation process.

As most processes in the pharmaceutical industry, tablet coating is performed on different scales. A process is typically designed on the lab scale (in the order of a few kilograms or 10 000 tablets) and scaled up, first, to the pilot /technical scale (in the order of 50 kg or 250 000 tablets) and then to the industrial/full scale (in the order of 300 kg or more, or 10^6 tablets). Most manufacturers operate their coating systems on all scales, using geometrically similar drums and baffle setups for reliable scale-up. As a first guideline, the relative fill level is generally kept constant across scales, and the rotation speed n (in rpm) is calculated by keeping either the dimensionless Froude number or the peripheral velocity constant. The Froude number Fr is given as:

$$\mathrm{Fr} = \frac{r\omega^2}{g} = \frac{r \cdot n^2 \cdot (2\pi)^2}{g} = \text{const.} \tag{1.27}$$

where r is the radius of the drum, g is the gravitational acceleration, and ω and n are the rotation speed in units of rad/s and rotations/s, respectively. This may lead to too high tablet velocities in the bigger drums. Alternatively, the peripheral velocity v_u can be kept constant:

$$v_u = r\omega = 2\pi rn = \text{const.} \tag{1.28}$$

In this case, there are ways to predict the velocity on the top of the tablet bed. Keeping the peripheral velocity constant leads to a lower tablet velocity and less tablet damage during the scale-up process.

Similar approaches exist for other systems and processes.

1.3.8 Dimensioning

Dimensioning of a continuous process is based on the necessary throughput, the required processing time, and the volumetric holdup of a specific unit operation process. Assuming that the necessary throughput is $\dot{M}$, the required processing (or manufacturing time) is t_m, the true density of the material (liquid, suspension, particles, fermentation broth) is ρ and the volumetric holdup of the processed phase is ε_p, $1-\varepsilon_p$ includes all head space, free space between particles and other free volume. As such, the volume of the processing unit is given by:

$$V = C\frac{\dot{M}}{\rho}\frac{1}{\varepsilon_p}t_m \tag{1.29}$$

where $C = 1$ is the equipment size is chosen to exactly match the requirements. In practice, $C > 1$ to accommodate times when more material has to be processed. In most systems, the residence time and the holdup ε_p are variable since the system is starved–fed, that is, the feed rate is constant yet below the maximum capacity of the system.

For example, in hot-melt extruders, which always operate under starved–fed conditions, the holdup corresponds to the profile of the filling ratio along the screws that depends on the actual screw geometry assembled of individual elements (e.g., conveying, kneading, and mixing elements). Each screw element type has characteristic properties in terms of conveying and pressure generation [28]. The resulting profiles for pressure and filling ratio along the screws emerge from the complex interaction between the flow and the screw elements in their actual arrangement (Figure 1.13).

Since the final screw arrangement is a complex issue and is typically unknown at the stage of dimensioning, simplified criteria are required. With regard to machine sizes, the length L of extruders is a multiple of the screw diameter D and the values of L/D are generally in the range of 30–40. As such, the free volume of the extruder is proportional to the cube of the screw diameter $V \sim D^3$. The (average) residence time t_m can be considered inversely proportional to the screw speed $t_m \sim 1/n$. Substituting this in the above equation yields:

$$\frac{\dot{M}}{\rho n D^3} \sim \frac{\varepsilon_p}{C} \tag{1.30}$$

where the left-hand side is the so-called dimensionless throughput, which can be interpreted as volumetric throughput per screw revolution in relation to the free volume of the machine. The right-hand side includes the remaining parameters, mainly the holdup that is unknown at the dimensioning stage. However, since geometries of the screw elements used in co-rotating twin-screw extruders are similar regardless of the manufacturer, the industrial experience can provide guidance values for the dimensionless throughput $\dot{M}/\rho n D^3$ for co-rotating twin-screw extruders. A typical range is 0.05–0.15, and for specific applications even 0.02–0.2, for example, values up to 0.2 can be reached for processes optimized for high throughputs (e.g., in the polymer industry) and values down to 0.02 can be reserved for processes with high degassing requirements. Dimensionless throughputs below 0.02 normally yield mechanical energy input that is too specific and above 0.2 result in filling ratios that are too high and pressure generation capabilities are too low. With that, the required screw diameter D can be estimated from the given throughput and a chosen screw speed.

For other systems and processing units, similar dimensioning rules exist. Note that usually, the unt operation with the lowest space/time yield is the bottleneck and has to be the first part to be designed.

1.4 Conclusion

In summary, continuous manufacturing has important advantages over classical pharmaceutical batch manufacturing. These advantages are significant and warrant a paradigm change in the field of pharmaceutical production. In line with these new developments the regulatory environment is changing as well, and academic interest has spurred significant new developments in conjunction with the important efforts of several pioneering pharmaceutical companies and equipment providers. Nevertheless, significant challenges remain with regard to process design, equipment development, scale-up, process control, on-line quality

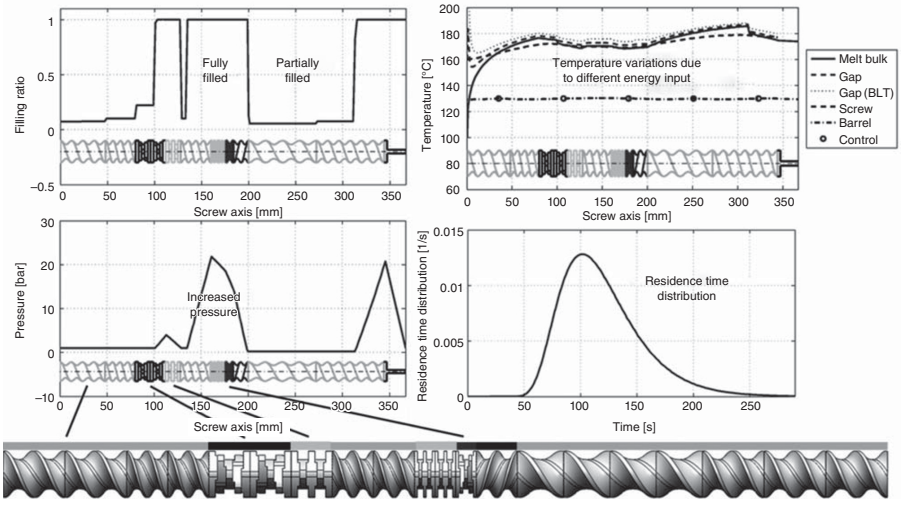

Figure 1.13 *Model simulation of an extruder with filling ratio, temperature, pressure and RTD [29].*

assurance, and the economic evaluation of these new approaches. This book is intended to provide an overview of current developments and challenges and thus is intended to define the state of the art and to clearly mark the path forward.

References

[1] Hashimoto, K., Adachi, S., Shirai, Y., Horie, M. (1988) Continuous Separation of a Cyclodextrin and Glucose Suing a Simulated Moving-Bed Adsorber. *Journal of Food Engineering* **8**(3), 187–200.

[2] Higgins, B. (1984) Pharmaceutical manufacture by continuous processing. *Process Engineering* **1984**, 35.

[3] Leuenberger, H. (2001) New trends in the production of pharmaceutical granules, Batch versus continuous processing. *European Journal of Pharmaceutics and Bio pharmaceutics* **52**, 289–296.

[4] Mascia, S., Heider, P.L., Zhang, H. *et al*. (2013) End-to-end continuous manufacturing of pharmaceuticals: integrated synthesis, purification, and final dosage formation., *Angewandte Chemie International Edition English* **52**(47), 12359–12363.

[5] ISCMP (2014), *Symposium on Continuous Manufacturing of Pharmaceuticals: Whitepapers 1–8*, Available at :https://iscmp.mit.edu/ (accessed 2 February 2016).

[6] Singh, R., Ierapetritou, M., Ramachandran, R. (2012) An engineering study on the enhanced control and operation of continuous manufacturing of pharmaceutical tablets via roller compaction. *International Journal of Pharmaceutics* **438**(1/2), 307–326.

[7] Vercruysse, J., Delaet, U., Van Assche, I. *et al*. (2013) Stability and repeatability of a continuous twin screw granulation and drying system. *European Journal of Pharmaceutics and Biopharmaceutics* **85**(3 part B), 1031–1038.

[8] Cervera-Padrell, AE., Skovby, T., Kiil, S., Gani, R., Gernaey, K.V. (2012) Active pharmaceutical ingredient (API) production involving continuous processes – A process systems engineering (PSE)-assisted design framework, *European Journal of Pharmaceutics and Biopharmaceutics* **82**, 437–456.

[9] Jungbauer A. (2013) Continuous downstream processing of biopharmaceuticals, *Trends in Biotechnology* **31**(8), 479–492.

[10] Lawton, S., Steele, G., Shering, P., Zhao, L.H., Laird, I., Ni, X.W. (2009) Continuous crystallization of pharmaceuticals using a continuous oscillatory baffled crystallizer, *Organic Process Research and Development*, **13**(6), 1357–1363.

[11] Wang, M., Rutledge, G.C., Myerson, A.S., Trout, B.L. (2012) Production and characterization of carbamazepine nanocrystals by electrospraying for continuous pharmaceutical manufacturing, *Journal of Pharmaceutical Sciences*, **101**, 1178–1188.

[12] Eder, Rafael J. P., Schrank, S.,Besenhard, M.O., Khinast, J.G. (2012) Continuous sonocrystallization of acetylsalicylic acid (ASA): control of crystal size. *Crystal Growth and Design* **12**(10), 4733–4738.

[13] Moradiya, H., Islam, M.T., Woollam, G.R., *et al*. (2014) Continuous cocrystallization for dissolution rate optimization of a poorly water-soluble drug, *Crystal Growth and Design*, **14**, 189–198.

[14] Zhang, H., Lakerveld, R., Heider, P.L. *et al*. (2014) Application of continuous crystallization in an integrated continuous pharmaceutical pilot plant. *Crystal Growth and Design*, **14**, 2148–2157.

[15] McGlone T., Briggs N., Clark C., Brown C., Sefcik J., Florence, A. J. (2015) Oscillatory flow reactors (OFRs) for continuous manufacturing and crystallization. *Organic Process Research and Development.* **19**(9), 1186–1202.

[16] U.S. Food and Drug Administration (2004a) *Pharmaceutical cGMPs for the 21st Century – A Risk Based Approach; Final Report*. FDA, Rockville.
[17] U.S. Food and Drug Administration (2004b) *Guidance for Industry. PAT – A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance*. U.S. Department of Health, FDA, Rockville, M
[18] Boukouvala F., Ramachandran, R., Vanarase, A., Fernando, J., Ierapetritou, M.G. (2011) Computer aided design and analysis of continuous pharmaceutical manufacturing processes, *Chemistry Today* **29**, 216–220.
[19] Plumb, K. (2005) Continuous processing in the pharmaceutical industry – Changing the mind set, *Chemical Engineering Research and Design* **83**(6), 83730–83738.
[20] Schaber S. D., Gerogiorgis, D.I., Ramachandran, R. *et al*. (2011) Economic analysis of integrated continuous and batch pharmaceutical manufacturing: a case study. *Industrial and Engineering Chemistry Research* **50**(17), 10083–10092.
[21] Bird, R.B., Stewart, W.E. and Lightfoot, E.N. (2007) Transport Phenomena*, revised*. John Wiley & Sons, Ltd, London.
[22] Singh R., Muzzio F. J., Ierapetritou, M., Ramachandran, R. (2015) A combined feed-forward /feed-back control system for a QbD-based continuous tablet manufacturing process. *Processes* **3**(2), 339.
[23] Mortier, S.T.F.C., Nopens, I., De Beer, T., Gernaey, K.V. (2014) Monitoring and modelling of a continuous from-powder-to-tablet process line, *Chemistry Today*, **32**, 4–8.
[24] Scott, B., Wilcock, A. (2006) Process analytical technology in the pharmaceutical industry: a toolkit for continuous improvement. *PDA Journal of Pharmaceutical Sciences and Technology* **60**, 17–53.
[25] Florian, M., Velazquez, C., Mendez, R. (2014) New continuous tumble mixer characterization, *Powder Technology*, **256**, 188–195.
[26] Portillo, P.M., Ierapetritou, M.G., Muzzio, F.J. (2008) Characterization of continuous convective powder mixing processes, *Powder Technology*, **182**, 368–378.
[27] Keleb, E.I., Vermeire, A., Vervaet, C., Remon, J.P. (2004) Twin screw granulation as a simple and efficient tool for continuous wet granulation. *International Journal of Pharmaceutics*, **273**(1/2), 183–194.
[28] Kohlgrüber K. (2008) *Co-Rotating Twin-Screw Extruders*, Carl Hanser Publishers, Munich.
[29] Eitzlmayr A., Khinast, J.G., Hörl, G. *et al*. (2013) Experimental characterization and modeling of twin-screw extruder elements for pharmaceutical hot melt extrusion, *AIChE Journal* **59**(11), 4440–4450.

2

Process Simulation and Control for Continuous Pharmaceutical Manufacturing of Solid Drug Products

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2.1 Introduction

2.1.1 Scope and Motivation

The current pharmaceutical process development and manufacturing paradigm is relatively inefficient and poorly understood when compared to other industries. Whereas most chemical industries (e.g., petrochemical, food, specialty chemicals) tend to be continuous in nature, sequential batch process scale up remains the prime process development strategy in most of the pharmaceutical industry [1, 2]. Batch manufacturing in pharmaceuticals does not necessarily correspond to the most efficient manufacturing process given the number of steps and the need to scale up in order to meet demand [3, 4]. Typical pharmaceutical processes are composed of 10 or more interacting processing steps, each one affected by several process parameters. This level of interaction makes process development a difficult and daunting task whose solutions are addressed using heuristic methods. Moreover, the constant demand of products for clinical trials, in most cases occurring in parallel with

Continuous Manufacturing of Pharmaceuticals, First Edition.
Edited by Peter Kleinebudde, Johannes Khinast, and Jukka Rantanen.
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process development, force scientist to study the manufacturing process in an expedited manner [5]. Scale up requires the purchase of larger equipment in order to increase productivity, leading to extended research efforts to maintain performance across equipment and scale. Thus, batch manufacturing processes are often poorly understood, rarely optimized, lack robustness, and are prone to unexpected failure [6–8]. Finally, risk assessment and failure mode analysis of batch processes is a substantial challenge. Delays in technological advancement have been attributed to the current regulatory framework, high profit margins that do not push for innovation, time constraints during the drug approval process, and the varying physical and chemical properties of drug molecules that affect formulation and process design [9, 10]. However, as both the pharmaceutical industry and the regulatory environment change, it is expected that some of these challenges evolve to push for manufacturing innovation. In order to overcome some of the technological challenges associated with current pharmaceutical manufacturing paradigms, the industry has been investing in continuous drug product manufacturing technologies and better understanding of process operations [3, 11–14]. This latter endeavor will be the key focus of this chapter as it applies to the development of continuous solid oral dosage manufacturing.

Continuous drug product manufacturing technologies have the potential to address the issues associated with batch processing by reducing the gap between development and manufacturing [15, 16]. Since continuous process scale up is done through increasing production time and parallelization of the same continuous train of equipment, process knowledge acquired during development can be directly applied to manufacturing processes [17]. Furthermore, continuous manufacturing practices allow for more efficient implementation of available process systems engineering (PSE) tools. PSE tools can provide insight to pharmaceutical development as means of evaluating and controlling manufacturing processes *in silico*. The use of PSE tools such as unit and process simulation, sensitivity, flexibility and feasibility analysis and optimization, as well as design of the optimal control strategy have the potential to improve process understanding and reduce product variability [18].

2.1.2 Process Simulation

Models are the collection of mathematical equations connecting multiple process inputs and outputs, known as *variables* and *responses* [19]. In manufacturing processes the behavior of equipment (i.e., unit operations), control systems, and process materials are governed by different types of phenomena, which can be described to varying degrees of accuracy and complexity using models. The selection and application of a model, depends highly on the goals set by the user. Complex phenomena often requires the application of high order, computationally expensive models, whereas simpler phenomena can be described using lower dimension, computationally cheaper models. Assumptions can be made to reduce complexity leading to mixed models that can broadly capture complex phenomena while maintaining a degree of simplicity [20, 21]. In pharmaceutical processes, modeling is divided into liquid and solid based systems based on the product and process being modeled. A combination of complex, and simplified models are used to develop process understanding, perform process simulation, and design the optimal control strategy [22]. Liquid systems, often used for the manufacturing of active pharmaceutical ingredients and

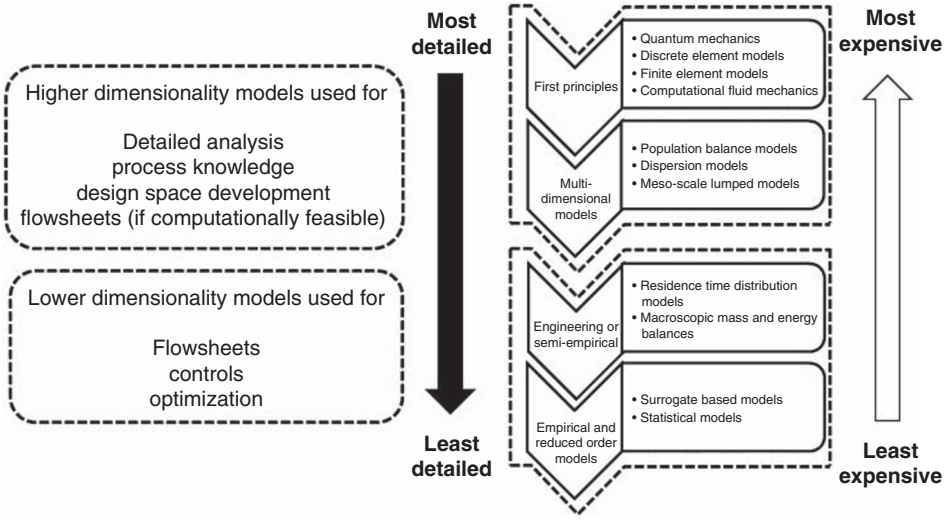


Figure 2.1 *Types of models used in the solid drug product manufacturing process.*

biological products, have been extensively modeled as part of the chemical and mechanical engineering literature [23–28]. Solids modeling, involved in the manufacturing of solid oral dosage products, has been studied to a lesser extent due to the complexity due to the discrete nature of solid materials [29]. For this reason, this chapter will focus on the solid based pharmaceutical processes.

Several model types have been applied to describe the phenomena occurring in powder systems. These model types (Figure 2.1), in order of greater to lower complexity, can be categorized as: first principle "mechanistic", multi-dimensional population balance, phenomenological (i.e., semi-empirical, engineering, or macroscopic), and surrogate based models (i.e., empirical). Details of each model are presented in the later sections of this chapter. Each model type offers advantages and disadvantages from a modeling standpoint and their application depends on the user's objectives. First principle models offer great detail of information regarding the process, but require lots of computational power to be solved in a reasonable time frame [30]. Empirical models, on the other hand, are faster to solve computationally, but are less predictive since they rely on experimental data [31–33]. It is critical to keep in mind during model development the end user goals in order to minimize computational requirements while maximizing the predictive ability and usability of the model.

One important concept to keep in mind when selecting model types is the difference between accuracy and complexity. Mechanistic models may provide a great deal of information given their number of equations and approach, but the solution may be more than or as inaccurate as an empirical model. Model accuracy does not directly relate to its complexity and level of detail. Another important consideration during modeling is the availability of data for the system being modeled. Even though data is not required for the development of some models it is critical for ensuring model validity. Experimental data is used to confirm, verify and validate models and ensure they can be utilized for various applications

Table 2.1 *Process systems engineering (PSE) tools for process development. PSE tools in order of chronological development that can be used for process development*

PSE tools	Process development objectives
Predictive models[a]	Process understanding
Flexibility and feasibility analysis[a]	Process parameter ranges
Steady state optimization[a]	Process and product design
Dynamic optimization[a]	Process improvement and efficiency
Sensitivity analysis[a]	Risk assessment
Controller design[a]	Attainment of critical quality attributes
Flowsheet modeling	Process integration and simulation

[a]PSE tools used with individual and integrated (i.e., flowsheet) models.

[34, 35]. Applying models without recognizing their limitations may lead to oversimplifications of the system and misleading results. For this reason, models must always be verified against experimental data.

Once models have been verified and validated, they can supplement expensive and time-consuming experimentation throughout product development and provide better process understanding. Models can also serve as the basis to using other mathematical tools. Design, analysis, and optimization of process operation can be performed using simulations [36], flexibility analysis [37, 38], and constrained global optimization [39]. Predictive process models can be used to develop and assess control strategies for continuous processes and set the stage for the implementation of control systems in pharmaceutical processes [40–45]. These advanced control strategies can help to ensure consistent product quality. Furthermore, predictive models, once validated, can be used to study the process dynamics in detail, to help achieve high process efficiency, and to attain the desired product quality. Overall, PSE tools and predictive models can facilitate the design of processes where consistent product quality is achieved at every step of manufacturing within the framework of QbD and process analytical technology PAT [11]. Table 2.1 summarizes the relationship between PSE tools and process development objectives.

2.1.3 Process Control

Better process understanding and controls are vital for minimizing waste due to manufacturing failures and ensure product quality with reduced end-product testing [46]. The continuous pharmaceutical manufacturing provides a suitable platform for implementation of real time monitoring and automatic control system. Therefore, a significant opportunity exists for improving product quality and optimizing the production process through the implementation of innovative solutions for online/inline monitoring, analysis and system control [42]. The United States Food and Drug Administration (US FDA) has supported the application of PAT and control systems within manufacturing industries [47]. The application of PAT systems in manufacturing paves the way for continuous process and product

improvements through process supervision based on knowledge-based data analysis, QbD concepts and through feedback and feed-forward control [48, 49]. The primary goal of PAT is to achieve better understanding of the manufacturing process, and to use that knowledge in-line/on-line to achieve better control of the process and thus consistent product quality. PAT is therefore defined as a system for designing, analyzing, and controlling manufacturing through timely measurements during processing of critical quality and performance attributes of raw and in-process materials and processes with the goal of ensuring final product quality [46]. The process flowsheet model is a valuable tool that can be used for design and evaluation of the control system before implementation to the pilot plant.

In recent years, interest has grown rapidly in continuous manufacturing processes that integrate on-line/in-line monitoring tools and advanced feed-forward/feed-back control systems [48]. Currently, major pharmaceutical companies are in process of building of continuous manufacturing plant. The development of pharmaceutical process models has been also the focal point of recent years and commercial tools (gSOLID; PSE) have been developed. Continuous manufacturing processes operate at or near steady state, allowing for closed-loop control of the entire operation, which leads to a more robust and reliable process. Moreover, since continuous processes reach the desired steady state in just a few minutes, they enable true QbD-based manufacturing. In addition to its flexibility and time and cost-saving features, continuous manufacturing is intrinsically steady, and therefore, easily amenable for model predictive design, optimization, and control methods [50]. These methods have proven to be effective approaches for improving operational efficiency and have been widely used in various process industries. Recently, the process control companies have started developing the tools needed for pharmaceutical process control. Excitingly, in the pharmaceutical industry, the application of the control system is an open area of study for researchers and technology providers [51].

Continuous processes integrated with on-line/in-line monitoring tools within automatic feedback control systems are desired by the pharmaceutical industry to satisfy regulatory constraints and flexible market demands. Over the last 30 years, process industries, such as oil refining and bulk chemical production, have made use of model predictive controller (MPC) as effective control strategies [44]. However, because of different level of complexities involved (e.g., solid handling, irregular flow) in addition to the unavailability of a suitable process model, the design and implementation of MPC in pharmaceutical manufacturing is still an open area of research. In comparison with the classical PID based control strategy, MPC requires the development of higher fidelity models and robust optimization strategies [44, 52]. Furthermore, depending on the process dynamics, an MPC scheme that involves a detailed process model and a computationally expensive optimization strategy may not be required, and a more computationally efficient proportional integral derivative (PID) control scheme can be used. A hybrid control strategy integrating the advantages of both MPC and PID is therefore highly desirable for the system-wide control of a process comprised of fast and delayed dynamics [44].

In this chapter, we will focus on the application and development of unit operation and process models of the major routes of continuous solid dose manufacturing. The emphasis will be on the current models available and their applications in process simulation and control systems. The goal of this chapter is to provide an introduction to process modeling in the pharmaceutical industry.

2.2 Pharmaceutical Solid Dosage Manufacturing Processes

2.2.1 Overview

Primarily composed of tablets and capsule formulations, solid oral dosages are the most commonly used drug product forms in the market [53, 54]. The pharmaceutical manufacturing process can be divided into two major streams: upstream and downstream product manufacturing. Upstream manufacturing involves the production of the active pharmaceutical ingredient (API) via chemical synthesis methods. This process is primarily done in liquid systems and the resulting API can be in either liquid or granular (i.e., solid) form [55–57]. Downstream manufacturing takes the API and combines it with other pharmacologically inactive solid materials, known as excipients, to create a dosage form. Multiple routes for drug product manufacturing have been established with the goal of ensuring the production of a quality product. The manufacturing method will vary between API compounds based on their inherent material properties. The major three routes for the production of solid oral dosage forms are: direct compression, dry granulation, and wet granulation [58, 59]. The latter two routes are used in cases where granular flow and dissolution properties of the API demand the use of larger particles during processing. All manufacturing routes are currently implemented in batch modes across the pharmaceutical industry, with continuous forms being developed over the last decade [17]. Given the focus of this book in continuous manufacturing forms, we will present an overview of the process for continuous manufacturing routes.

2.2.2 Continuous Manufacturing Processes

A schematic process flow diagram showing the major routes of manufacturing is shown in Figure 2.2 [60]. All continuous drug product manufacturing routes begin the same way: with constant feeding of raw solid materials into the system using feeders. These units are typically operated under loss in weight control in order to maintain a constant flow rate and set the correct API and excipient concentrations. Fed materials may pass through a high shear co-mill unit in order to eliminate large, electrostatic, soft lump of material that may impact blend uniformity. The co-milled material is then blended to achieve a uniform distribution of the API and excipients. A lubricant, which intends to reduce powder sticking during compression, is added at the blending unit operation. After this point, the different routes of manufacturing diverge into different units. In direct compression, the simplest of all manufacturing routes, the material exiting the blender is sent directly to a tablet press or capsule filling machine where the blend is compacted into tablets or placed in capsules, respectively. In the case of dry granulation, the material is sent to a roller compaction unit, were the powders are pressed into a ribbon, which is then milled into granules. Wet granulation is performed in a variety of units, which include high-shear impeller, twin screw and fluid bed granulators. The process uses a granulation liquid, also known as wetting or binding agent, to create larger particles via agglomeration. The granulation liquid is then removed at a drying step, which may reduce the granule size to a desired distribution. Optionally, a screen mill can be used to ensure a desired particle size distribution. The resulting granules obtained from either granulation step are then sent to a tablet press or capsule filling

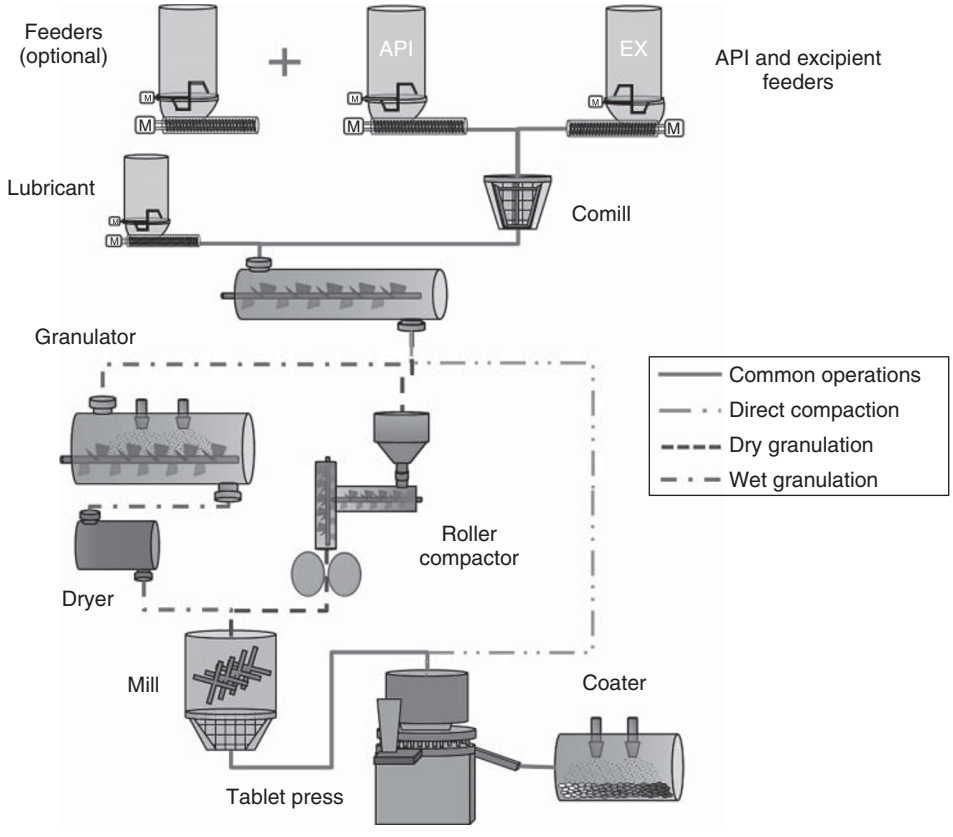


Figure 2.2 *The three major continuous solid dosage form manufacturing routes.*

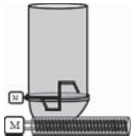
machine to produce tablets or capsules. Tablets from any of the three processes can be then sent to coater to yield a final coated product.

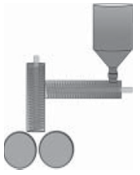
Tablet manufacturing processes are assessed based on the quality of the blends and tablets produced. Blends are characterized by their uniformity; monitored via spectroscopic and wet chemistry methods. Important tablet quality properties include tablet strength (e.g., hardness, friability), API composition, assay, tablet weight, and composition uniformity (i.e., variability measured as relative standard deviation) and dissolution time.

2.2.3 Continuous Process Equipment

As described previously continuous processes involve multiple pieces of equipment, also known as *unit operations*, to take the raw granular materials and convert them into solid dosages. Some of these units are specific to the continuous manufacturing processes, but some are also present in their batch counterparts. In order to succinctly introduce the individual units, their important process parameters, and output responses, the unit operation's name, symbol, description, design and operating parameters, and references in the pharmaceutical industry are summarized in Table 2.2.

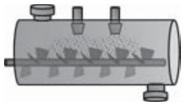
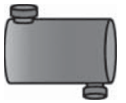
Table 2.2 *Unit operations commonly used in continuous pharmaceutical manufacturing*

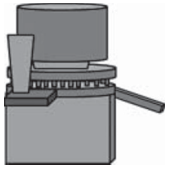
Unit	Symbol	Brief description	Design parameters	Operating variables	Unit responses	References
Feeder		Unit that accurately feeds powders into the process. Commonly operated in loss in weight control to maintain a desired flow rate. Typically consist of a hopper, a conveying, and a bridge breaking system. The conveying system is most commonly a screw given its accuracy.	• Unit tooling (e.g., screws) • Hopper size and geometry • Operating mode (gravimetric or volumetric)	• Screw rotational speed • Flow rate set point • Control constants • Refill level and frequency	• Flow Rate • Mixing of Lots	[90, 92, 221]
Co-mil		High shear milling unit composed of a single rotating blade and mesh screen. Used to break large lumps of material that may affect macromixing efforts. Has been shown to improve micromixing.	• Unit geometry • Screen size • Impeller type	• Impeller/rotor speed • Feed flow rate	• Particle size distribution • Flow rate • Micromixing	[186]
Convective mixer		Unit that convectively transport material along its geometry causing turbulence and therefore mixing. This unit has the goal of reducing the composition variability in multi-component powder blends. Most commonly this unit has a tubular geometry with blades that impart shear.	• Unit geometry • Blade type • Blade configuration • Blender and weir angle	• Feed flow rate • Impeller speed • Mixer fill level	• Flow rate • Blend uniformity • Macro/ micromixing • Variance reduction • Mean residence time	[76, 107, 110, 120]

Roller compactor		Granulation unit that compresses multi-component powder blends between two counter rotating rolls to form a ribbon. Process involves the addition of a lubricant to aid in powder compression. Material properties greatly affect unit performance.	• Roll configuration • Roll geometry • Roll roughness • Feed configuration	• Feed flow rate • Roll speed • Compaction pressure • Roll gap • Feed pressure	• Flow rate • Ribbon thickness • Ribbon density • Ribbon length	[158, 163, 222, 223]
Screw extruder		Granulation unit that adds a fluid granular materials to a screw system to agglomerate particles along with shear. The fluid, known as binding or wetting solution, is added near the inlet to allow for agglomeration followed by shear along the length of the screw barrel. Shear can be designed using different screw types and kneading elements.	• Number of screws • Screw geometry • Barrel dimensions • Binding solution • Addition of binder • Kneading elements	• Screw rotational speed • Liquid addition rate • Granulation temperature • Liquid to solid ratio • Feed flow rate • Shear rate	• Flow rate • Particle size distribution • Moisture content • Particle porosity	[67, 224, 225]

(*continued*)

Table 2.2 *(Continued)*

Unit	Symbol	Brief description	Design parameters	Operating variables	Unit responses	References
High shear continuous wet granulator		Wet granulation unit resembling a convective tubular blender with a binding solution addition port at the inlet of the blender. Shear imparted by the blades is varied by changing the blade configuration as well as the material hold up inside of the unit.	• Number of blades • Impeller type • Blade configuration • Binding solution • Addition of binder	• Impeller speed • Liquid addition rate • Liquid to solid ratio • Feed flow rate • Shear rate • Granulator fill volume	• Flow rate • Particle size distribution • Moisture content • Particle porosity	[176, 178]
Dryer		Unit that imparts some type of heat and mass transfer gradient to reduce particle moisture content and size. Many forms of heat (e.g., radiation, convective, conductive) are applied along with a mass transfer gradient (e.g., high velocity dry air) that allows for removal of binding solution from granules.	• Unit geometry • Heat source • Dissipation method • Unit inlets and outlets	• Process temperature • Liquid removal rate • Air input rate • Drying time • Feed flow rate	• Flow rate • Particle size distribution • Particle temperature • Moisture content • Particle porosity	[24, 226]

Mill		Particle size reduction unit used to reach a desired particle size distribution after a granulation process. An impeller provides shear to a bulk of granulated material, making the particles break into smaller pieces. The size target during breakage is given by the screen size through which the material must fit to exit the system.	• Mill type • Mill configuration • Unit geometry • Screen size • Air nozzle location	• Feed flow Rate • Rotor speed • Grinding pressure • Process temperature	• Flow rate • Particle size distribution • Particle temperature	[227, 228]
Tablet press/ capsule filling		Last unit during the drug product manufacturing stage; takes powders and compresses them into compacts (tablets). This unit is integrated with a feed frame that delivers the material to holes used as guides in which two vertically opposing punches compress the granular material.	• Die and punch geometry • Die filling method • Number of dies • Layering method • Feed frame impeller type • Feed frame geometry	• Feed flow rate • Pre-compression force • Compression force • Turret speed • Feed frame speed • Fill depth	• Tablet production rate • Tablet hardness • Tablet friability • Tablet weight	[62]

The parameters and responses introduced in Table 2.2 are important to consider when modeling these unit operations in order to capture the desired behaviors. Though many different types of these units are available in the market, with many more to come as the technology progresses, their goals, design, and operating parameters are similar. In the following section, we will discuss the available models to describe the phenomena occurring in these units.

2.3 Mathematical Modeling Approaches

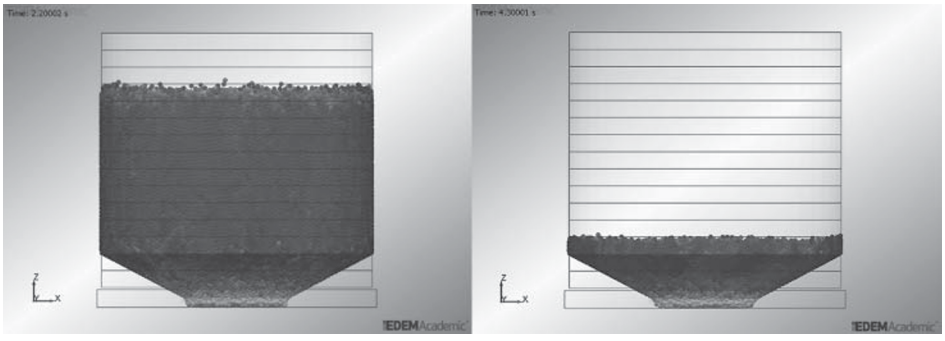
This section briefly describes the major models used in pharmaceutical process modeling. Readers interested in learning the different model types in more detail are encouraged to read the reviews by Rogers *et al.* [60] and Gernaey *et al.* [11, 12]. As mentioned previously, there are four types of models commonly used in the pharmaceutical industry: first principle "mechanistic," multi-dimensional population balances, phenomenological, and empirical or surrogate-based models.

2.3.1 First Principle "Mechanistic" Models

These models are derived from fundamental equations of motion. Using fundamental physics, these models provide a great detail of the system phenomena by describing material properties in space, such as location, momentum, and velocity. Divided into discrete and continuum models, first principles models can be used with solids, liquids, and gas system [17]. First principle models used in the pharmaceutical modeling literature include discrete element models (DEM) [61] and finite element models (FEM) [62]. DEM has been extensively used given its capability for describing the translation and rotational effects of discrete particles in space. Particles are discretized and equations of motion are written for each individual particle in the system. This degree of discretization generates a large number of equations, which limits and in some cases prohibits the use of DEM to model large number of particle systems with current computing power [30]. Nonetheless, particle and particle–fluid flow have been characterized and studied in great level of detail using DEM for a variety of industries. Confined particle flow is amongst the phenomena studied using DEM, which applies to the pharmaceutical industry through operations such as hopper emptying, continuous mixing, powder feeding, conveying, and fluidization [61]. Figure 2.3 shows a simulation of a hopper system being modeled using DEM. In addition to characterizing the motion of the particles in the system, it has been also used for modeling particle packing (i.e., compaction processes) since this model also takes into account inter and intra particle forces such as friction and collision between the discrete particles [63].

2.3.2 Multi-dimensional Population Balance Models

Population balance models (PBMs) describe the generation or development of properties in groups (i.e., populations) of entities (i.e., variables) over a set period of time. In the pharmaceutical industry, PBMs are multidimensional models used for the characterization of particle states with respect to internal (e.g., porosity, moisture content) and external (e.g.,



(a) (b)

Figure 2.3 *Side view of a discrete element model simulation of a hopper being emptied by an aperture down the bottom. The grids represent the discrete bins from which data can be collected. Each particle has its own velocity, represented using the gray gradient. (a) Hopper at time = 0. (b) Hopper at time = 2 s.*

position) coordinates [64, 65]. PBMs can be formulated depending of the dimensionality need of the problem at hand. A general form of a multidimensional balance used to describe a system with a number of dimensions of 2 + p, is given in Equation (2.1).

$$\begin{aligned}&\frac{\partial}{\partial t}F(n,z,r,u_1,\ldots,u_p,t)+\frac{\partial}{\partial z}\left[F(n,z,r,u_1\ldots u_p t)\frac{dz}{dt}\right]\\&\quad+\frac{\partial}{\partial r}\left[F(n,z,r,u_1\ldots u_p t)\frac{dr}{dt}\right]+\sum_{i=1}^{p}\frac{\partial}{\partial u_i}\left[F(n,z,r,u_1\ldots u_p t)\frac{du_i}{dt}\right]\\&=R_{\text{depletion}}(n,z,r,u_1,\ldots,u_p,t)-R_{\text{formation}}(n,z,r,u_1,\ldots,u_p,t)\end{aligned}\tag{2.1}$$

On the left hand side of this equation, p represents the number of internal coordinates being tracked, n is the number of components in the system, z and r are external spatial coordinates that describe the position of particles in the system (e.g., radial and axial) and the array of variables u are the internal coordinates that describes system properties (e.g., porosity, moisture content, gas volume). The density function $F(n,\ z,\ r,\ u_1,\ \ldots,\ u_p,\ t)$ indicates the number of type n particles of dimensions u at positions z and r at time t. On the right hand side, the rates at which this density function changes are captured. These rates are often obtained from experimental data and may depend on all or some of the internal and external coordinates in the system.

Often used in processes where particle size changes occur (e.g., granulation, milling and drying), these models have also been used in a variety of other solid-based processes, such as mixing and dissolution [66, 67]. PBMs offer a lower dimensionality model compared to mechanistic models by lumping discrete systems into groups and tracking their average state. Nonetheless, population balance models can be discretized with respect to the external coordinates in order to resemble the level of discretization achieved with DEM modeling [68]. In these cases the differential terms with respect to the external coordinates are replaced by finite differences. Discretized population balance models can be parameterized and their parameters estimated using experimental or simulated data. PBMs can

become computationally expensive if the number internal coordinates increases and the discretization grid of external coordinates is too fine [69].

2.3.3 Engineering or Phenomenological Models

Also known as engineering models because of their constant application in the field, they are derived from first principle models and applying a set of underlying assumptions reduces their complexity. Experimentally obtained parameters are introduced as a means to calibrate the model for a specific combination of material and equipment [70]. These lower dimensionality models involve macroscopic mass, force and energy balances that provide information about the system's average behavior while maintaining a relationship between model variables and process conditions. They have been used in a variety of pharmaceutical manufacturing problems in order to simplify model complexity [71–77].

Lower dimensionality population balance models also belong to this model category and have been used to characterize the probability density function of a single particle property inside of a unit. One example of low dimensional PBMs is the *residence time distribution* (RTD). Briefly described, RTD is a diagnostic tool that characterizes the time particles spend inside a unit operation using a tracer material [19, 78]. A tracer is a material that can be quantified at the outlet using visual or chemical methods. The tracer if often introduced as a pulse (i.e., instantaneous injection of material) in the system and its concentration is tracked at the outlet of the system. A probability density function (PDF) of the tracer material at the system's outlet can then be computed to determine the distribution of time a particle stays in the system [79]. The PDF used for representing the time distribution of particles, often referred to $E(t)$ function, is given in Equation (2.2).

$$E(t) = \frac{C(t)}{\int_0^\infty C(t)dt} \tag{2.2}$$

In this equation, $C(t)$ represents the instantaneous concentration of a tracer at the system's outlet as a function of time. This methodology has been extensively used in liquid systems and has served the purpose of determining the mixing behavior inside the unit. The mixing inside the unit can be viewed as a result of local mixing rates and total mixing time, which are functions of residence time. Mixing patterns can be characterized as ideal or non-ideal, based on the data collected from the RTD analysis and mixing models described in the chemical reaction engineering literatures. Ideal mixing models for example are those in which a binary mixing scenario is observed. The system can be perfectly mixed and not mixed at all. Perfect mixing is characterized by the instantaneous distribution (i.e., uniformity) of material inside of the vessel. On the other hand, plug flow in continuous units characterizes the no mixing of material over the unit's length. Combinations of these mixing models can be used to describe non-ideal mixing patterns [19]. Thus, RTD can be used to determine the appropriate throughput to ensure that the material in the unit remains in there for enough time become well mixed. Based on the RTD results, mixing models that predict the concentration of material at the outlet of a unit based on some input can be developed. RTD mixing models can be used to predict composition variance at the outlet of mixing units, evaluate the effect of disturbances along the process, track the composition of products based on raw material composition,

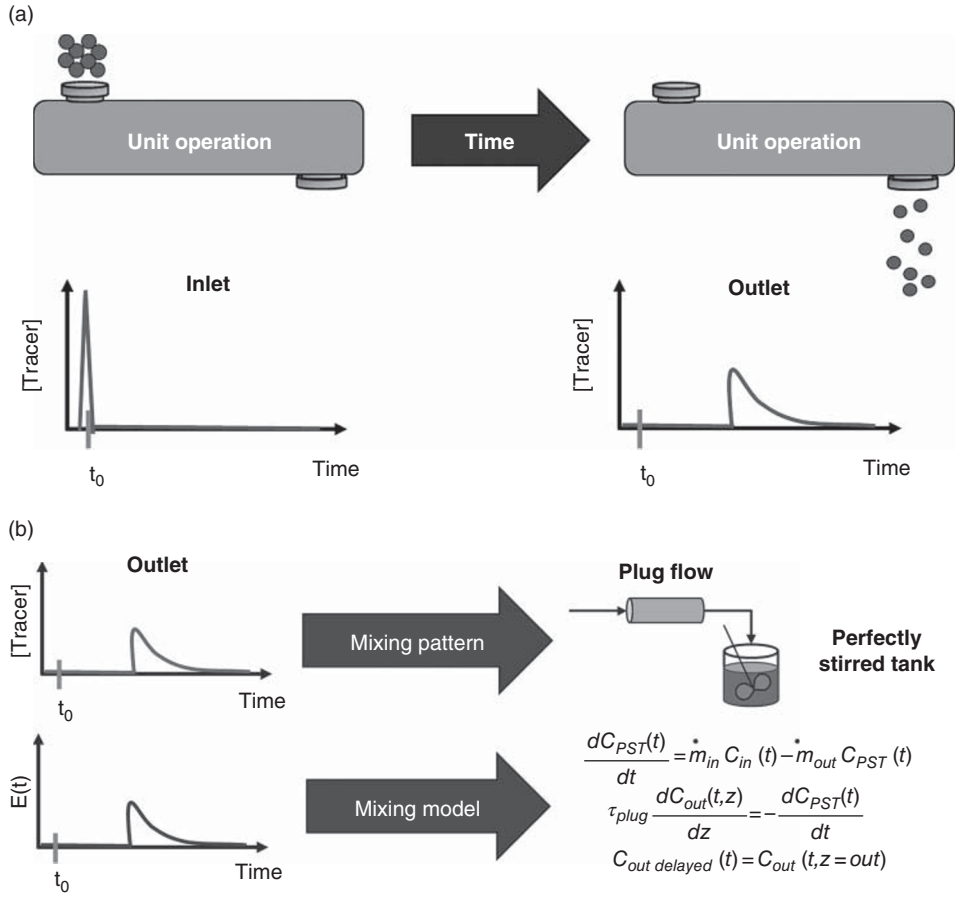


Figure 2.4 *(a) Schematic of an RTD pulse experiment for an arbitrary unit operation. (b) Development of a model based on the results obtained from the pulse experiment. This step often requires a RTD literature review to match profiles.*

and characterize powder segregation on mixing performance. The development of a RTD mixing model from a probability distribution function of a pulse is shown in Figure 2.4.

The residence time distribution of a particle in a system can be determined based on both experimentally collected data and DEM that have been properly validated [77]. Further information on RTD can be found in chemical reaction engineering literature [23] and in the introductory chapter of this book.

2.3.4 Empirical and Reduced Order Models

Empirical and reduced order models (ROM) allow for the representation of highly reliable and computationally expensive models in a lower-dimensional space using data [80]. Reduced order models are fully data driven models that allow for computationally

inexpensive modeling. These models include statistical techniques, such as black-box modeling approaches, latent variable methods, hybrid and semi-empirical models, or any combination of the previously mentioned approaches [33, 81, 82]. As opposed to any other model type previously described, empirical or reduced-order models are based on regressions of data available for the system. Experimental or higher order model simulation results (i.e., first principle or PBM) results are the main inputs for these models equations. Such dependence on data makes reduced order models ineffective for use in areas of the model where there is no information available. Nevertheless, inexpensive computational models are often preferred for control system design and development [83].

A summary of the types of models along with some examples within these categories are presented in Table 2.3.

2.4 Unit Operations Models

Unit operation models focus on characterizing the behavior of a single piece of equipment, whereas process models characterize the behavior of connected equipment. Models can be transient (i.e., dynamic) or steady state in nature. Transient models are those whose variables depend on time, meaning that they change from an initial state as a function of time either through deliberate changes or due to fluctuations in the process. In most chemical and pharmaceutical processes, the process is nearly always transient given the inherent changes occurring in the system [23]. However, when variable fluctuations over time are below some threshold, the behavior is said to be constant over time leading to a steady-state problem formulation. In steady state problems, time effects are neglected and spatial differences are modeled, often making them easier to solve. From a model-use perspective, transient models are used to simulate the behavior of unit operations over time, while steady-state formulations are used in design space, feasibility and flexibility analysis [33, 61, 84–89].

The focus of this section is the lower dimensionality models of process units used in continuous manufacturing of solid-based drug products. Those are primarily PBM, empirical, and reduced-order models. Due to the transient nature of solid systems, most of the models discussed in this section are dynamic. References to mechanistic type models are made so readers can pursue them further based on their individual interest, but are not discussed in detail. Detailed discussion of these works are not considered in the chapter because such models are not readily used in process simulation, control, and optimization on account of their computational cost.

2.4.1 Feeders

Feeders, schematically shown in Figure 2.5, are composed of a hopper, a conveying system (i.e., screws), and a flow aid mechanical unit working to deliver material. These components vary in geometry and shape based on the type of material and the feeder type [90].

Feeders can operate under two different modes: gravimetric and volumetric. Volumetric feeding maintains a constant screw speed, which leads to a constant volumetric flow rate out of the feeder. This mode of feeding is not often used due to the flow rate inaccuracy and changes over time. Gravimetric feeding involves the use of a control loop that maintains a specific flow rate by changing the speed at which the screws are rotating. Feeders are placed

Table 2.3 *Types of models used in the solid drug product manufacturing process*

Type		Model	Description	Advantages	Disadvantages	Comparative expense	References
First principles	Discrete	Quantum and statistical mechanics	Determines the mechanics and transport phenomena of fluids (liquids, gases and dense solids)	Fundamental phenomena approach; large number of commercial computer packages available for modeling.	Ignores particle-particle interactions (important in discrete systems); large number of derivate operations needing of approximation.	High	[34, 229]
		Discrete and finite element modeling	Establishes discrete particle powder behaviors using first principle physics and mechanics.	Mechanistic approach; provides particle level information; commercial computer packages readily available.	Model is computationally limited with very large number of particles; need to approximate multiple derivatives during optimization.	High – increases rapidly with particle number	[30, 61]
	Continuum	Computational fluid dynamics	Multiple gradient model that determines the mechanics and transport phenomena of continuous fluids (liquids, gases and dense solids); part of the constitutive models framework	Fundamental phenomena approach; large number of commercial computer packages available for modeling; can be implemented in both distributed and lumped formats.	Ignores particle–particle interactions (important in discrete systems); large number of derivate operations needing of approximation.	High	[88, 230, 231]

(*continued*)

Table 2.3 *(Continued)*

Type		Model	Description	Advantages	Disadvantages	Comparative expense	References
Population balance		Multidimensional "general" population balance	Describes the states of population groups over space and period of time. These states can be variables presented as internal and external coordinates.	Ability to simulate large number particle systems while reducing dimensionality by describing particle populations.	Semi-mechanistic method given the lack of process knowledge; optimum parameters from equations not easily identifiable.	Moderate to high - depends on dimensionality	[64, 182, 232, 233]
	Engineering or phenomenological	Residence time distribution models	Subset of the general population balance model focused on characterizing the time that elapses between the entering and exiting of a fluid in a vessel; these models then relate to mixing models.	Model simplicity given the one dimensionality of the model; easy to collect experimental data for development and validation.	Highly dependent on quality experimental data and model selection; multiple datasets are required in order to apply models for various conditions.	Low to moderate – depends on the model selection.	[77, 122]

	Macroscopic mass, force and energy balances	Reduced detail transport phenomena models where no spatial gradients are involved in mathematical statements; variables are lumped into averages and can be dependent on time.	Represent the lumped behavior of the system as a function of time; simplified mathematical expressions.	Loss of information concerning the performance of characteristics of the system as a function of position.	Low to moder-ate – depends on the number of equations	[1, 19, 23, 79]
Empirical and surrogate-based models	Gaussian process regression (Kriging)	Weighted inverse interpolation method fitting variogram and regression coefficients; establishes equations in a data dimensional set.	Better modeling of non-linear processes; provides the largest number of correlation models; lower prediction error.	Requires large datasets to model; requires previous simulation knowledge; requires larger number of parameters to be fitted.	Low	[93, 234, 235]
	Response surface modeling	Method of fitting data points by to a second order polynomial equation to form response surfaces on plot.	Lowest dimensional space of all the reduce order models; uses the least amount of data to build models.	Fits the equation to a polynomial equation; data requires a high degree of pretreatment.	Low	[32, 236, 237]

(*continued*)

Table 2.3 *(Continued)*

Type	Model	Description	Advantages	Disadvantages	Comparative expense	References
	High dimensional model representation	Model fits component function coefficients to a truncated analytical basis function.	Perform global sensitivity analysis; relatively small number of parameters need to be fitted.	Truncated approach may lead to model failure; relatively more difficult to use for optimization.	Low	[238, 239]
	Artificial neural network	Input–output model using data clusters to transforming inputs using weighted transformation linear or non-linear equations.	It is a widely accepted and described model; feedback and feed forward data processing; learning.	Multiple parameter fitting due to layering process; requires the use of training sets for modeling.	Low	[240]

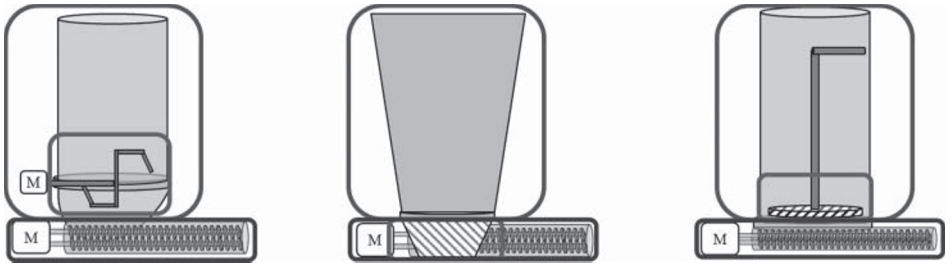


Figure 2.5 *Three different feeder types with their major components symbolized. The feeder hopper is represented inside the large top box, the flow aid system is inside the small central box, and the conveying system is shown inside the long bottom box.*

over a load cell that communicates with a control box, which monitors the rate of weight loss. Using this weight loss data the feedback control loop of the controller changes the screw speed and maintains a desired flow rate. Given the critical nature of the control loop in gravimetric feeding scenarios, a complete feeder model needs to include the system's control logic and its effects on the conveying system [90–92].

For these reasons feeder models are often empirical in nature, focusing primarily on macroscopic material balances and surrogate-based models [86, 93, 94]. Nonetheless, DEM simulations of feeder units have been developed to understand the phenomena occurring inside of the hopper and the screw conveying system [94–96]. However, the computationally expensive DEM simulations are not efficient to be applied to the process because of their prohibitive evaluation time. Efforts to improving the evaluation time of first principle and transport models for feeders would also not be effective given the number of units required in real systems. Typical continuous processes use three to eight feeders depending on the formulation, which demands the use of models that are computationally efficient to solve so they can be easily applied to process simulation [86].

2.4.1.1 Mechanistic Models

Discrete element models of the feeder have been used with the goal to understand how the hopper and conveying system geometry affect the flow rate out of the system. DEM simulations have identified the use of different screw geometries to ensure consistent flow rate and hopper emptying [97–99]. This last observation is important to consider since a consistent hopper emptying avoids an uneven depletion of the hopper, which leads to ratholing and inconsistencies in flow rate. Furthermore, the design and geometry of feeder hoppers has also been studied using DEM [96, 100]. Efficient hopper design is critical for the correct filling the conveying system.

2.4.1.2 Residence Time Distribution Models

Residence time distribution studies are critical in feeding units in order to establish the ability to trace the raw material lot in a drug product. This is a regulatory requirement in accordance to the current Good Manufacturing Practices (cGMP) set by FDA [2, 101, 102]. In batch processes, tracing the lot of raw materials is relatively simple: a specific amount

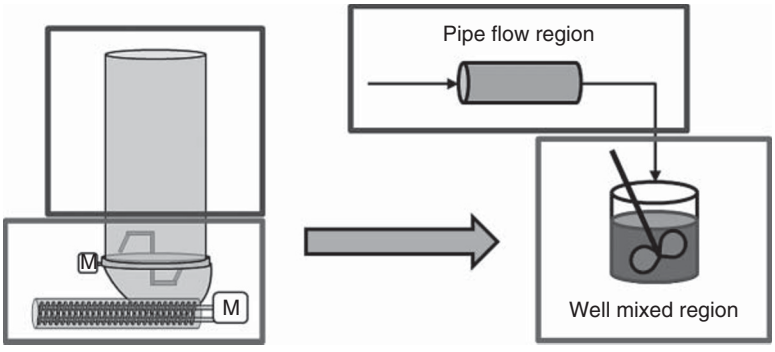


Figure 2.6 *Residence time distribution mixing model of a feeder. The model consist of an ideal no-mixing region, followed by a well-mixed region.*

of raw material from a given lot is selected to make a fixed and discrete amount of product. This means that, given a lot number of a product, the manufacturer should be able to determine the date and lots of materials from the recipe. However, in continuous processes it is more difficult to make this delineation given the nature of the process. Raw materials are constantly refilled during operation and are converted from powders to tablets without intermediates. In order to maintain the system operating it is often required to use one or more lots of each raw material during manufacturing. This practice brings into question what is the composition of materials in the final product based on the lots of raw materials used.

Residence time distribution experiments were performed in feeders to characterize the degree of mixing inside the hopper [103]. Two types of feeding units were evaluated, both showing similar mixing behavior inside of the hopper. Mixing inside of the hopper appeared to be almost perfect in nature, with some delay from the moment of tracer addition. Further inspection of the pulse propagation resembled the behavior of a plug flow region followed by a well-mixed region. The plug flow region of feeder (non-mixing) was characterized as the hopper section. The mixing region was defined as the area of back-mixing provided by the impeller in the bottom section of the units. The mixing behavior was mathematically represented using a plug flow followed by perfectly mixed tank model, similar to the one presented in Figure 2.6. The schematic representation of the feeder mixing behavior using fundamental chemical engineering units along with the mathematical representation for the probability distribution function (PDF) of the system's RTD are shown in Figure 2.6. Equation (2.3) has two parameters: the output delay time by the plug region (t_{delay}) and the mean residence time of the material in the mixed region of the feeder (τ).

$$\begin{aligned} E_{\text{Plug Flow}}(t) &= \text{Unit Step}[t - t_{\text{delay}}] \\ E_{\text{Mixed Tank}}(t) &= \frac{Exp\left[-\left(\frac{t}{\tau}\right)\right]}{\tau} \\ E_{\text{Feeder}}(t) &= \text{Unit Step}[t - t_{\text{delay}}]\,\frac{Exp\left[-\left(\frac{t-t_{\text{delay}}}{\tau}\right)\right]}{\tau} \end{aligned} \tag{2.3}$$

Mixing at the feeder hopper level may cause a great deal of overlap between lots of raw materials in the end product and therefore needs to be further understood. Future feeder studies should aim at understanding the mixing happening inside of the hopper through more RTD experiments and feeder internal modeling.

2.4.1.3 Empirical and Reduced Order Models

Empirical models for feeders are primarily focused on predicting flow rate and its variability as a function of time [93, 104]. These models intend to relate the controllable screw rotational speed and measurable feeder weight variables to the feeder's flow rate. The goal is to develop a model that can predict the flow rate of the system, while also incorporating the variability in the flow rate due to perturbations (e.g., refills) and material properties (e.g., cohesion). Current feeder units compute the relationship between screw speed and flow rate during operation by calculating the mass loss and dividing it by the number of screw revolutions during that time. The resulting variable, known as a feed factor (*ff*), is in units of mass per screw revolution. Equation (2.4) presents the relationship between mass flow rate ($\dot{m}_{\text{out}}$) and screw speed (ω) through a feed factor (*ff*).

$$\begin{aligned} \dot{m}_{\text{out}} &= \omega_{\text{Screw}}\, ff \\ ff[=] &\frac{g}{\text{rev}} \end{aligned} \tag{2.4}$$

Boukouvala *et al*. [86] presented a semi-empirical first-order equation to dynamically model the loss in weight feeder flow rate, which was coupled with the feeder's mass balance. Both the feeder mass balance and flow rate equations are shown in Equations (2.5) and (2.6), respectively. The flow rate equation takes into account controller effects on the output flow rate using a constant feed factor. The equation is a first-order non-homogeneous differential equation that models flow rate ($\dot{m}_{\text{out}}$) over time.

$$\begin{aligned} \frac{d[m_{\text{hopper}}(t)]}{dt} &= \dot{m}_{\text{in}}(t) - \dot{m}_{\text{out}}(t) \\ \dot{m}_{\text{in}}(t) \neq 0 &\rightarrow \text{ No Refills} \\ \dot{m}_{\text{in}}(t) > 0 &\rightarrow \text{ Refills} \end{aligned} \tag{2.5}$$

$$\begin{aligned} \tau_f \frac{d[\dot{m}_{\text{out}}(t)]}{dt} + \dot{m}_{\text{out}}(t) &= \dot{m}_{\text{out}}^{\text{set}} = ff\, \omega_{\text{screw}}^{\text{set}} \\ I.C: \ \dot{m}_{\text{out}}(0) &= 0 \end{aligned} \tag{2.6}$$

The first-order differential equation represents the action of a proportional controller with a set point that is part of the model input. The rate of change of the flow rate, which is dictated by the unit's control constants is summarized by a time constant variable (τ_f). The time constant is often calculated from experimental data of feeder startup or shutdown sequences. Engisch and Muzzio described an experimental approach to characterize loss in weight feeder performance of and introduce flow rate variability into a model [91, 92]. Flow rate variability is introduced by inspection and statistical analysis of experimental flow rate data for a given material. Frequency distribution of the flow rate over a period of time is performed to characterize the variance of the flow rate. Boukouvala *et al*. [105]

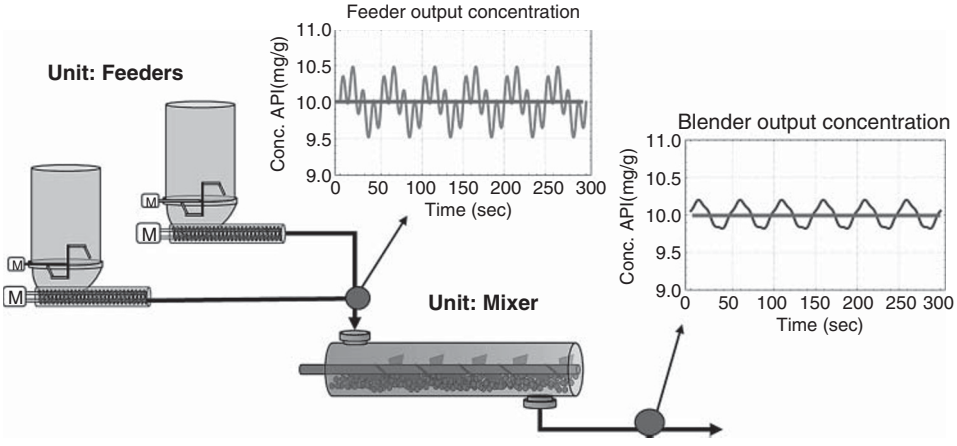


Figure 2.7 *Feeder composition variability reduction due to blender effects. High frequency variations are smoothen after the blender, emphasizing the goal of blending: filter feeding noise from the feeders.*

have demonstrated the use of response surface models, high dimensional model resolution and Kriging for calculating the flow rate variability of a feeder for a given material. These empirical models were built using experimental data and the inputs included screw rotational speed, size and configuration, and powder flow index. The response of the model was the relative standard deviation of the outlet flow rate, which could be added to the flow rate computed by Equation (2.6).

One of the limitations of the Boukouvala *et al*. model [86] is the selection of flow rate as the only modeled variable dependent on time. However, the feed factor is also time dependent. The variable that then becomes most important to model is the feed factor as a function of time. Future models should aim at relating the feed factor to the feeder weight in order to account for changes in flow rate or screw rotational speed as the feeder empties. The flow rate variability should be introduced as part of the feed factor calculation, not after the flow rate calculation. This way, the material property effects can be taken into account for the system. Models should revisit the assumption of constants bulk density and mean particle size over the course of the feeder operation [103].

2.4.2 Blenders (Mixers)

Powder mixing is a critical operation in the process of solid oral dosage manufacturing that intends to reduce composition variability in blends used for granulation or tablet production [106]. The composition variability is introduced by the flow rate variability of feeders, which feed the blending unit. Figure 2.7 depicts the concentration variability reduction by the blender after a two-feeder system.

In this section, we focus on presenting the use of metrics and modeling tools to predict the variability reduction due to the blender.

2.4.2.1 Blend Uniformity Metrics

Before presenting the models used in blending processes, the mixing metrics used to quantify the process need to be presented. Relative standard deviation (RSD), mean residence time (MRT), mean centered variance (MCV), mass hold-up (MHU), and variance reduction ratio (VRR) are the most commonly used measures to characterize mixing performance and blend homogeneity [107]. Relative standard deviation (RSD), also known as the coefficient of variance (COV), is a commonly used metric that computes the standard deviation (σ_{var}) between multiple system measurements (e.g., API concentration measurements, flow rate) and divides it by the mean concentration value ($\overline{C}$) in order to normalize the result. The equation for RSD is shown in Equation (2.7).

$$RSD = \sigma_{var} \Big/ \overline{C}$$
$$\overline{C} = \sum_{i=1}^{n} \frac{C_i}{n} \qquad \sigma_{var} = \sqrt{\frac{\sum_i^N (C_i - \overline{C})^2}{N-1}} \tag{2.7}$$

For blend processes RSD is often computed for the concentration of API in the blend. Blend RSD has been used in both batch and continuous systems given that it is a measure applicable to blend uniformity in both time and space. RSD calculated over space can be easily done for batch systems, but it becomes more difficult to perform in continuous ones. For that reason RSD is computed over time in continuous systems. Methods of how to calculate the RSD in continuous systems have been described in the literature [106, 108]. One major consideration that must be taking into account when calculating the RSD as a function of time is the selection of the time window in which results for the mean concentration are averaged. Large time windows decrease the variability of the system, while smaller windows may statistically not represent the system accurately. The MRT and MCV are measures derived from the RTD literature. MRT and MCV are used to characterize the average time a particle spends in the blending system and the spread of the RTD, respectively. Both the MRT and MCV can be determined after performing pulse RTD experiments. The MRT (τ) and MCV (σ^2) are obtained by applying Equation (2.8) on the outlet concentration data [$C(t)$] from the RTD experiment.

$$\tau = \int_0^\infty t\, E(t) dt$$
$$\sigma^2 = \frac{\int_0^\infty (t-\tau)^2\, E(t) dt}{\tau^2} \tag{2.8}$$

Typically high values of MRT (i.e., longer residence times) imply more mixing and shear imparted to the system, while smaller values (i.e., short residence times) point to less mixing. Values for the MCV range between one (1) and zero (0). MCV values close to one point to a high degree of spread, which indicates extensive mixing while values of MCV approaching zero indicate poor mixing [109, 110].

The VRR is a measure used to determine the overall performance of continuous blending system based on the variance of the input and the output. Defined as the ratio between the input and output variances, this variable can be used to calculate the variance in the outlet of a blender system if the inlet flow rate variability is known. The equation for the VRR is shown in Equation (2.9).

$$\begin{aligned} \text{VRR} &= {\sigma_{\text{in}}}^2 \Big/ {\sigma_{\text{out}}}^2 \\ \sigma^2_{\text{stream}} &= \frac{\sum_i^N (C_i - \overline{C})^2}{N-1} \end{aligned} \tag{2.9}$$

As shown in Equation (2.9), the VRR is often computed *a posteriori*, based on results from continuous blending experiments. Data collected from the flow rate out of the feeders is used to compute the inlet variance to the blender, while samples are periodically collected at the blender outlet to calculate the blend composition variance. The VRR can also be computed using the MCV values from the RTD experiments and the flow rate variance calculation.

Given the importance of blending in the process, modeling has been done at all levels of complexity. Model results are primarily focused on calculating the blend concentration at the outlet, from which the blend uniformity measures are then calculated.

2.4.2.2 Mechanistic Blender Models

Blending systems have been extensively modeled using first principles methods given the degree of insight these models provide. DEM simulations were used to represent convective mixing in a tubular blender for a wide range of design variables, material properties, and operating conditions. These simulations provide a great level of detail into powder transport and mechanics in a given geometry [61, 111, 112]. DEM simulations using periodic section approximations were shown to be more computationally efficient when compared to a full blender simulation by Gao *et al.* [113]. Periodic section modeling accurately characterized continuous mixing process with respect to variance decay and relative standard deviation at steady state. The methodology was subsequently applied to optimize a continuous mixing process [114]. A periodic section blender model was applied to cases with varying particle properties (e.g., diameter, density, cohesion) and operating parameters (e.g., fill level, blade speed) to improve mixer design and operating parameters. First principle models have also been developed to provide lower dimensional models, such as population balance models, with the internal coordinate information needed [81, 83, 115, 116]. Some of these internal coordinate data include collision frequencies and particle velocities at specific external system coordinates. Nonetheless, the direct application of DEM in an integrated process simulation is computationally intractable, so other modeling approaches such as continuum and constitutive models, data-based models or hybrid modeling are preferred.

2.4.2.3 Population Balance Models

In blending models, since there is no addition of extra phases (e.g., liquid) and no deliberate changes in particle size, PBMs are described using two-dimensional (2-D) equations

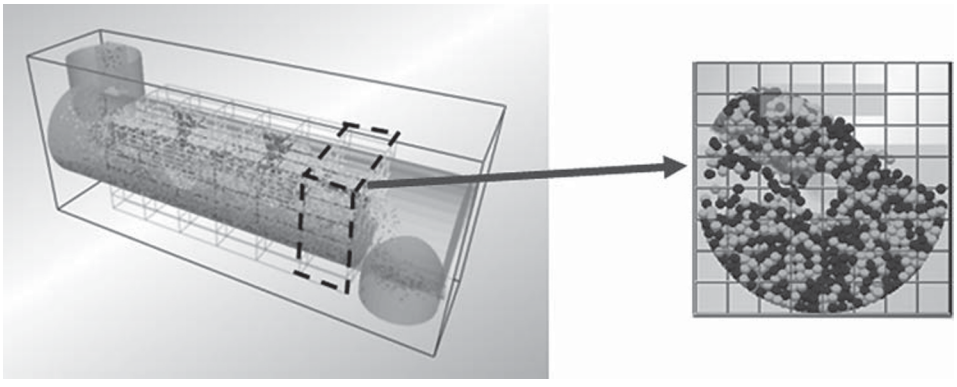


Figure 2.8 *Discretization of a DEM simulation. The information collected in each of the bins can then be allocated to the population bins in a PBM.*

[68, 117]. A sample 2-D PBM used for blending operations is shown in Equation (2.10).

$$\frac{\partial}{\partial t}F(n,z,r,t)+\frac{\partial}{\partial z}\left[F(n,z,r,t)\frac{dz}{dt}\right]+\frac{\partial}{\partial r}\left[F(n,z,r,t)\frac{dr}{dt}\right]=\text{Flow}_{\text{in}}-\text{Flow}_{\text{out}} \tag{2.10}$$

In Equation (2.8), the particle velocities in the z and r directions are given by $\frac{dz}{dt}$ and $\frac{dr}{dt}$. Since these velocities are difficult to measure in experimental systems, they must be obtained from mechanistic models such as DEM [68]. DEM models need to be discretized in a way that allows for transfer of the velocity information into the PBM model. The discretization of both the mechanistic DEM simulation and PBM is often done in a finite number of bins (Figure 2.8), were the particle velocities in either direction are tracked as a function of time and finite difference methods can be applied to solve the PBM [68].

In order to reduce the computational expense, the particle velocities from the DEM can be mapped using a reduced order models at both steady [81] and dynamic states [118, 119]. The goal is to develop a hybrid model that contains the results from DEM and uses a reduced order model to predict those results. The discrete element reduced order model hybrid (DE-ROM) can then be used to predict DEM results within the mixer and provide the needed discrete information to the PBM. The results for DEM and DE-ROM for axial particle velocities for a Gericke 250M blender have been previously reported [119].

The mixture concentration at the blender outlet is calculated using the particle populations information at the unit's end. The mean concentration at the outlet is computed by dividing the sum of the particle counts for a single component at the end of the blender over the sum of all particle counts. Since the outlet of the blender is discretized in the radial direction the RSD of the mixture can be computed by taking the concentration in each bin and dividing it over the outlet concentration. Equations (2.11) and (2.12) show how to calculate the mean concentration for component i $[\overline{C_i}(t)]$ and RSD in the radial direction using

the results from Equation (2.10), respectively.

$$\overline{C_i}(t) = \frac{\sum_{r=r_{\min}}^{r_{\max}} F(i, z_{\max}, r, t)}{\sum_{r=r_{\min}}^{r_{\max}} \sum_{n=1}^{n_{\max}} F(n, z_{\max}, r, t)} \tag{2.11}$$

$$RSD_i^{\text{Radial}} = \frac{\sqrt{\frac{\sum_{r=r_{\min}}^{r_{\max}} [F(i,z_{\max},r,t),-\overline{C_i}(t)]^2}{r_{\max}-1}}}{\overline{C_i}(t)} \tag{2.12}$$

The RSD can also be computed over time using the metrics described previously. Similarly, the VRR can be computed in both time and space given the results from the discretized PBM.

2.4.2.4 Residence Time Distribution Models

Multiple groups have evaluated the experimental RTD of continuous blenders in order to determine the effects process parameters and material properties have on mixing [76, 109, 110, 120, 121]. The results from both pulse and step change experiments point to non-ideal mixing patterns inside the blender. This non-ideality in the mixing, leads to the development or selection of mixing models to determine the concentration at the outlet of the blender. Results from the RTD can be used to predict the outlet concentration and RSD of a blender system from any given input using the convolution integral and the mixing model derived from the RTD analysis [77]. Equations (2.13) and (2.14) describe the use of the convolution integral to determine the outlet concentration [$C_{\text{out}}(t)$] of the blender from an input concentration [$C_{\text{in}}(t)$] and the probability distribution function (PDF) of the RTD [$E(t)$].

$$C_{\text{out}}(t) = C_{\text{in}}(t) \otimes E(t) = \int_0^{\infty} C_{\text{in}}(t)\, E(t-\tau) d\tau \tag{2.13}$$

$$RSD_{\text{out}}(t) = RSD_{\text{in}}(t) \otimes E(t) = \int_0^{\infty} RSD_{\text{in}}(t)\, E(t-\tau) d\tau \tag{2.14}$$

The most commonly used non-ideal mixing models based on the experimental RTD results [i.e., $E(t)$ functions] are the axial dispersion and continuous-stirred tank reactor (CSTR) in-series models [19]. The axial dispersion model is derived from the transport equation for convective flow of material inside a pipe, which also includes a dispersion term. The axial dispersion model can be written in 1-D (e.g., axial) or in 2-D (i.e., axial and radial) and with dimensions or in a dimensionless form. Equations (2.15) to (2.19) show the axial dispersion equation in 1-D axial, 2-D axial and radial, and in 1-D axial in dimensionless form, respectively:

$$\frac{\partial C_{\text{out}}}{\partial t} + v_z \frac{\partial C_{\text{out}}}{\partial z} = D_z \frac{\partial^2 C_{\text{out}}}{\partial z^2} \tag{2.15}$$

$$\frac{\partial C_{\text{out}}}{\partial t} + v_z \frac{\partial C_{\text{out}}}{\partial z} = D_z \frac{\partial^2 C_{\text{out}}}{\partial z^2} + \frac{D_r}{r} \frac{\partial}{\partial r} \left(r \frac{\partial C_{\text{out}}}{\partial r} \right) \tag{2.16}$$

$$\theta = \frac{t}{\overline{\tau}} \quad \overline{\tau} = \frac{L}{v_z} \quad \xi = \frac{z}{L} \quad Pe = \frac{v_z L}{D_z} \tag{2.17}$$

$$\overline{\tau} \frac{\partial C}{\partial \theta} + \frac{\partial C}{\partial \xi} = \frac{1}{Pe} \frac{\partial^2 C}{\partial \xi^2} \tag{2.18}$$

where C_{out} is the outlet concentration of the system, v_z is the mean axial velocity of the system, D_z is the dispersion coefficient of the material in the system in the axial direction, D_r is the dispersion coefficient in the radial direction, L is the length of the blender. Using the variables defined in Equation (2.17), Equation (2.16) can be de-dimensionalized. The 1-D axial dispersion model in dimensionless form [Equation (2.17)] is also known as the Fokker–Planck model and can be solved using Danckwert boundary conditions (open–open conditions) [122]. Even though the boundary conditions are not satisfied in powder systems, the error for the model has been characterized as small. The solution of this model, shown in Equation (2.19), leads to the axial dispersion PDF, also known as the Taylor dispersion solution:

$$\begin{gathered} E(t) = \sqrt{\frac{Pe}{4\pi\theta}}\, Exp\left[-\frac{Pe\,(1-\theta)^2}{4\theta} \right] \\ \theta = \frac{t}{\overline{\tau}} \quad \overline{\tau} = \frac{L}{v_z} \quad \xi = \frac{z}{L} \quad Pe = \frac{v_z L}{D_z} \end{gathered} \tag{2.19}$$

where $\overline{\tau}$ is the mean residence time, L is the unit's length, z is its position inside of the unit v_z is the particle's mean velocity in the axial direction, and D_z is the dispersion coefficient. The Peclet number, Pe, is a dimensionless value whose physical meaning interprets the ratio between convective and dispersive transport. All of these parameters can be regressed from experimental data.

The CSTR in-series model, as the name implies, is derived from the application of the ideal mixing perfect stirred tank model in series. Multiple perfect stirred tanks are simulated in series by placing the outlet of previous units as the inlet of subsequent ones. Each unit intends to simulate the different mixing zones along the length of the unit. Given this models empirical basis, the behavior of systems whose internal phenomena are not well described. The PDF for the CSTR in-series model is shown in Equation (2.20):

$$E(t) = \frac{(t)^{n-1} \text{Exp}\left[-t/\tau \right]}{(n-1)!\ \tau^n} \tag{2.20}$$

where n is the number of perfectly mixed tanks in series, τ_{Tank} is the mean residence time of particles inside of one single tank, and $\overline{\tau}$ is the mean residence time in the system. Both the axial dispersion and CSTR in-series models may incorporate a delay time constant that represents the time material takes to convectively travel the length of the blender while being radially mixed by the shearing blades. Equations (2.21) and (2.22) show the PDF of

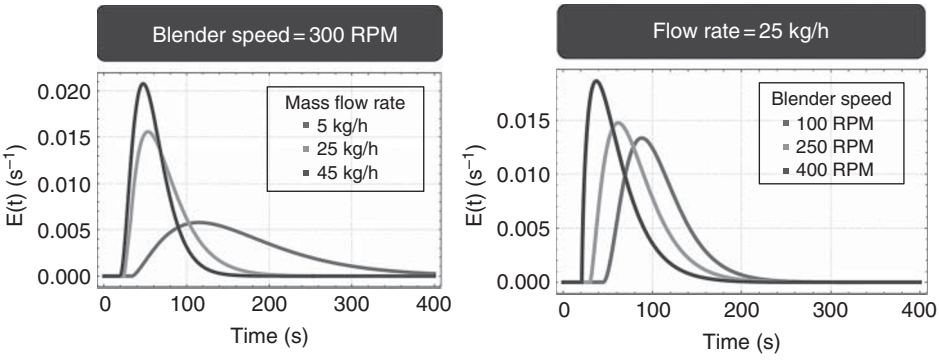


Figure 2.9 *Effects of blender process parameters on the residence time distribution. In the left, flow rate is varied, keeping blender blade speed constant. In the right, the flow rate is kept constant, while varying the blade speed. An increase in the breath of the distribution indicates the system has better mixing. Conversely, narrow distributions point to less mixing.*

the axial dispersion and CSTR in-series models with the delay, respectively.

$$E(t) = \text{Unit Step}[t - t_{\text{delay}}] \sqrt{\frac{Pe}{4\pi\left(\frac{t-t_{\text{delay}}}{\tau}\right)}} \text{Exp}\left[-\frac{Pe\left[1-\left(\frac{t-t_{\text{delay}}}{\tau}\right)\right]^2}{4\left(\frac{t-t_{\text{delay}}}{\tau}\right)}\right] \tag{2.21}$$

$$E(t) = \text{Unit Step}[t - t_{\text{delay}}] \frac{(t - t_{\text{delay}})^{n-1} \text{Exp}\left[-\left(\frac{t-t_{\text{delay}}}{\tau}\right)\right]}{(n-1)!\,\tau^n} \tag{2.22}$$

The constants in each equation (e.g., MRT, delay time, Peclet number, number of tanks) are found from the regression of the model using experimental or simulation data. Experimental designs that include varying operating conditions (e.g., blade speed, flow rate, blade configuration) for the RTD experiments can be used to correlate the values of the regressed constants and develop surrogate models [103, 120, 123]. This allows for the calculation of RTD probability density function for a wide range of operating parameters. The results of the method lead to the development of models that can simulate the PDF of the blender for various operating conditions (Figure 2.9).

A similar approach can be done with blend properties (e.g., composition, particle size distribution) and other critical process parameters. Once the PDF for the blending have been characterized and modeled, they can be used to predict the concentration at the outlet of the blender using Equation (2.13). Other methods of using the PDF from the residence time distribution have been developed, but will not be covered in this section.

2.4.2.5 Empirical and Reduced-order Models

Markov chain models and compartment models have been used for simulating the blending process as a function of time [124–129]. Reduced-order modeling approaches including Kriging [130], high dimensional model representation (HDMR) [60], and response surface modeling [131] were used to model continuous blending processes. Boukouvala *et al.*

[105] develop both a Kriging and a HDMR to model blend RSD as a function of powder flow rate, impeller speed, and blade configuration. Using these reduced-order models the blending design space was evaluated. A downside of these ROMs was the inability to predict properties of the blend outside the range of input information. Since these models mapped the output data collected to the operating conditions, important information such as powder fluxes, concentration, and RSD could not be determined as a function of position within the mixer.

2.4.3 Tablet Press

The tablet press unit is composed of two subunits: the feed frame and the turret. The feed frame transfers powders from a hopper or pipe – preceded by a blender or granulation unit – to the turret, where the compaction step is performed. For this reason, the tablet press model involves modeling powder flow into the dies and a compaction process for powder blends. In this section, we divide the two models based on literature findings for the individual subunits.

2.4.3.1 Feed Frame Models

Relatively little work has been done to independently model the feed frame in a tablet press given that in most cases this unit is not easily separated from the turret. Nonetheless, experimental efforts have been extensive for this unit, especially those surrounding shearing and mixing of powders in the unit. The mixing inside of the feed frames is critical to understand in order to determine the tablet's final concentration from a given blend. The mixing was experimentally investigated using pulse RTD experiments of the feed frame system by itself and attached to the turret [132–134]. The results pointed to a high degree of mixing in the feed frame, but were not conclusive due to variability in the data.

Mateo-Ortiz *et al.* [135] described the behavior of granular materials in feed frames using DEM simulations. The effects of turret speed and flow rate on the turret feeding efficiency were investigated. Residence time distribution experiments were performed in DEM and correlated with experimental results previously observed in the unit [136]. The results of these DEM RTD experiments were used to develop a mixing model for the feed frame that had a fundamental basis from the DEM simulation results. The RTD mixing for the feed frame resembled a perfectly mixed tank with no delay. These results agree with experimental results found in the literature. The equation of the feed frame mixing model is presented in Equation (2.23).

$$E(t) = \frac{\mathrm{Exp}\left[-t/\tau^{ff}\right]}{\tau^{ff}} \tag{2.23}$$

In order to provide the values for the mean residence time (τ^{ff}) Boukouvala *et al.* [137] developed a response surface model from experimental data collected by Mendez et al. [132]; and it is shown in Equation (2.24). The mean residence time in the feed frame is calculated as a function of feed frame rotation rate and disk rotation rate, making the model capable of handling variations of these process parameters.

$$\tau^{ff} = b_1 + b_2\omega^{ff} + b_3\omega^{\text{turret}} + b_4\omega^{ff}\omega^{\text{turret}}, \tag{2.24}$$

where the b coefficients are the response surface coefficients regressed from data, ω^{ff} is the feed frame speed, and ω^{turret} is the turret angular speed. In direct compression systems, since the tablet concentration is dependent on the blender and feed frame mixing, the concentration of the tablets can be calculated. Using Equations (2.11), (2.14), (2.15), and (2.16) the tablet concentration can be computed as a function of time [103].

2.4.3.2 Compaction Models

Powder compaction has been extensively modeled due to its relationship to the food, catalyst, ceramics, and metallurgy. One of the major challenges in pharmaceutical powder compaction is the development of models that can be used to characterize compaction profiles that take into account material properties. Since pharmaceutical formulation properties (e.g., cohesion, flow, bulk density) can greatly change based on their composition, data and models developed for these systems are high level approximations [138]. Furthermore, the varying nature of drug product dimensions, marks, and geometry (e.g., double convex, oval, scored, labeled) make models developed for powder compaction difficult to implement in many systems [139]. Nonetheless, these models can be used to predict major tablet properties with a fair degree of accuracy.

2.4.3.3 Mechanistic

Many models detailing the compaction of particle systems in confined spaces are mechanistic in nature, given the need and interest of characterizing its *mechanics*. Understanding the effects of compression on particle elastic and plastic deformation has been a subject of study in powder mechanics in many industries, including pharmaceuticals. DEM [30, 140] and FEM [141] have been primarily used to describe the compaction phenomena in tablet compaction systems. Detailed information about the effects of die filling [135, 142], particle segregation [143], tooling geometry [144] and compression rates have been obtained using these discrete models. Furthermore, models for characterizing the testing done to tablets can also be evaluated with these models.

Advantages of these models over lower dimensional ones include their ability to model in detail the effects of the tooling and changes in particle size on the compaction process. These models also provide information about the particle–particle and particle–tooling forces, which can be used in formulation development and equipment selection. One of the major disadvantages of these models is providing coefficients needed to calculate the stress and shear forces occurring in the system. Some of the data required (e.g., friction of the die wall during compression) are often difficult to obtain. Mechanistic models often depend on lower dimensional models to fill the gaps in information for the process [62].

2.4.3.4 Population Balance Models

Even though there are major changes in the internal coordinates in the system (e.g., number of particles, particle size distribution), PBMs are not commonly used for this unit operation. Engineering and discrete models are preferentially used for this unit operation.

2.4.3.5 Engineering or Phenomenological Models

Phenomenological models describing the process have been developed in order to minimize the computational time and also correlate observed variables based using regression principles. A review of these phenomenological models is presented by Patel *et al*. [145]. For the tablet compression process, it is important to model the relationship between the powder and tablet properties (e.g., tablet hardness, weight, and dimensions) with the equipment (e.g., die, rolls, turret) process variables. The tablet weight and dimensions (i.e., volume) are correlated to each other through density, making this property a key variable to model in the process [146]. Since powder density changes with the applied force from the system, the goal is to correlate the property with the compression force provided by the tablet press. Two of the most popular approaches for modeling powder densification are the Heckel [147, 148] and Kawakita [149, 150] models. In the Heckel equation [Equation (2.25)], a first-order relationship between compression pressure and powder density is established [148].

$$\begin{gathered} D = \frac{\rho}{\rho_T} \\ \frac{1}{k}\frac{dD}{dP} + D = 1 \\ \therefore\ D = 1 - \exp[-kP + A] \end{gathered} \tag{2.25}$$

In this equation, D is the relative density, k a material-specific compressibility constant, P the applied pressure, and A the constant densification term related to the die filling, slippage, and rearrangement of particles. Both A and k can be regressed from experimental data and correlated to material properties of the system. Equation (2.26) shows this relation for the A parameter.

$$\begin{gathered} A = \ln\left(\frac{1}{1 - D_0}\right) + B \\ D_0 = \frac{\rho_0}{\rho_T} \end{gathered} \tag{2.26}$$

In Equation (2.26), the logarithm term is correlated to the initial die filling process and B corresponds to densification from slippage and rearrangement of particles. Once again, these variables can be solved for once the A value has been found via regression of experimental data.

The Kawakita model [Equation (2.27)] assumes a constant relationship between applied pressure and powder volume provided by the assumption that particle volumes are at equilibrium throughout the compression process [149].

$$\begin{gathered} \frac{P}{C} = \frac{P}{a} + \frac{1}{ab} \\ C = \frac{V_0 - V}{V_0} = 1 - \frac{\rho_{\text{ini}}}{\rho_{\text{apparent}}} \end{gathered} \tag{2.27}$$

where a is the initial porosity of the material and $1/b$ is the pressure due to compression of powder by one half of the total possible volume. Similarly to the Heckel parameters,

the Kawakita parameters can be found experimentally from force-displacement data for a specific formulation. In most pharmaceutical cases, the compaction of materials involves a mixture of several powders. Kawakita parameters for binary powders mixtures were considered by Frenning *et al*. [151]. The authors suggested the use of effective Kawakita parameters for mixtures by calculating a weighted average of individual material Kawakita parameters. The weighted average is performed based on composition and the assumption that component volumes were additive. Mazel *et al*. [150] proposed a method that also assumes that the volumes are additive and apply the Kawakita equation to each component in the blend separately and then perform a weighted average. The implementation of these mixture models is particularly useful for blends in which the various components have different physical properties.

As mentioned previously, the effectiveness of the tablet press compression is measured by assessing the tablet properties. Tablet hardness, an important tablet property related to its dissolution, is correlated with the tablet press compression force and dwell time. Kuentz and Leuenberger proposed an empirical model for tablet hardness prediction using a first order relationship between tablet hardness and density [152, 153]. This model predicts hardness based on the changes in relative density based due to the effects of applied pressure. The Kuentz and Leuenberger model, shown in Equation (2.28), incorporates a critical density parameter, defined as the density beyond which pressure effects cannot be defined due to a lack of rigid structure [52, 153].

$$\begin{aligned} \rho_r &= \frac{V_{\text{solid}}}{V_{\text{tablet}}} \\ \lambda_{\text{hard}} &= \log\left(\frac{1-\rho_r}{1-\rho_{rc}}\right) \\ H_{\text{tablet}} &= H_{\max}\left[1 - e^{(\rho_r - \rho_{rc} + \lambda_{\text{hard}})}\right] \end{aligned} \tag{2.28}$$

In this equation, ρ_r is the relative density of the material in the compression process, defined as the ratio of the tablet volume under zero porosity and actual tablet volume. ρ_{rc} is the critical density of the material (i.e., density at which the material is not densified to a compact due to compression forces). $H_{\max}$ is the experimentally found maximum hardness, evaluated from increasing the compression of the tablet press until no further changes are observed in hardness.

Another tablet quality commonly evaluated is tensile strength. This quality is a critical tablet property associated with its dissolution profile. Tensile strength (T) is related to tablet porosity (ε) via the empirical Ryshkewitch–Duckworth equation, shown in Equation (2.29) [154, 155].

$$T = \overline{T}\,\text{Exp}[-k_b\varepsilon] \tag{2.29}$$

where $\overline{T}$ is the tensile strength at zero porosity and k_b is is the bonding capacity of the material. These constants can be found by regressing tensilte strength data for tablets. The Ryshkewitch–Duckworth equation has also been modified to account for the effects granulation units have (i.e., loss) on the compactibility of material.

Finally, a material balance around the tablet press is written based on the rate of tablet production. The rate of tablet production (R_{tablet}) is given by multiplying the turret speed (ω_{turret}) by the number of die stations (N_{stations}). Using the mean tablet weight ($\overline{W}_{\text{tablet}}$), a

"flow rate" of tablets can be computed in mass per hour. The equation for the flow rate of tablet as a function of their production rate is shown in Equation (2.30).

$$\begin{aligned} R_{\text{tablet}} &= \omega_{\text{turret}} N_{\text{stations}} \\ \dot{m}_{\text{tablet}} &= R_{\text{tablet}} \overline{W}_{\text{tablet}} \end{aligned} \tag{2.30}$$

Overall, Singh *et al*. [52, 156] described a detailed model, which includes a total of 23 equations that can be used for process modeling and control of a tablet press. This model is based on the Kawakita and the Kuentz and Leuenberger equations and was put in place in flowsheet models developed by Boukouvala *et al.* [86].

2.4.4 Roller Compactor

A roller compactor is a unit operation often composed of feeding, compaction, and milling equipment. The objective of a roller compactor unit is to compress loose powder between two rolls to create a compact ribbon of material, which is then milled to obtain a desired particle size. Since loose powder with smaller particle size is amassed into a larger size, this unit operation is part of the granulation processes. Models developed for this unit operation have the objective of relating the operating conditions of the unit and the physical properties of the feed material with the outlet ribbon properties. Given the compression nature of this system, the models primarily focus on the use of force and energy balances around the two compression rolls [157]. In this section, we focus on the models developed to characterize the compaction step of this unit.

2.4.4.1 Mechanistic Models

Similarly to the tablet press, mechanistic models for roller compaction use FEM and DEM to describe the forces occurring during compaction. Multiple studies focus on calculating the fundamental forces and energy being imparted by the system. In the literature, FEM models appear to be used more frequently given the availability of software and ease for simulating the compression section. Some of the unit variables studied using FEM are transient in nature and include the deformation energy, shear and normal stress, pressure distribution of the rolls, roll speed, and tooling pattern (e.g., smooth or knurled rolls) effects on pressure [158, 159]. Most FEM models are 2-D in space: for the height and length of the ribbon [160]. Three-dimensional (3-D) models help to determine the effects of roll compression along the width of the ribbon, yet are not often performed since these effects are assumed to be negligible over the width of the ribbon. However, 3-D FEM simulation results have shown that feeding has an important effect on the pressure across the roll's width [160, 161]. Regardless of the dimensionality of the models, FEM simulations were shown to accurately predict the relative density changes and material flow at the outlet of the rolls for a single component. These results were also shown to agree with previously developed and widely used phenomenological models [162]. Furthermore, FEM models were used to characterize the compression of powder mixtures. The goal was to understand the effects of varying powder friction angle coefficients by changing the formulation (i.e., varying the content of lubricant). The studies showed that the nip angle is strongly affected by the powder and roll surface wall friction, yet it was independent of other process parameters.

Effects of adhesive forces and roll speed on the compressive flow property of particles were simulated using DEM [163, 164]. Disadvantages with these models, as well as other mechanistic models, is parameter estimation for physical values, such as material friction coefficients. Understanding in detail how the material properties affect the process is critical in order to improve predictive capabilities. Nonetheless, mechanistic models have the great potential to improve this units design and scaling by providing reliable information about the physics occurring in the system.

2.4.4.2 Population Balance Models

Even though roller compactors are granulation units, population balances have not been reported as a model for this unit's compaction operation since the system's internal coordinates (i.e., granulation variables) are not treated as distribution. The inlet properties for this system may or may not be a distribution, but the outlet ribbon is not treated as an intermediate material with a distribution. Nonetheless, the dimensions of the outlet ribbon, which is later milled, are often defined as a distribution to be used as input for the milling process.

2.4.4.3 Engineering or Phenomenological Models

Several phenomenological models have been developed for roller compaction. Two of the most prominently used and discussed models in the literature are Johanson's model and the slab method [165]. These models primarily focus on developing a correlation between the compression forces and the ribbon properties, while aiming at reducing dimensionality. Johanson proposed a 1-D rolling theory for granular solids. This model was the first to predict the compression region's extent. It also predicted with accuracy the pressure distribution after the powder was gripped by the rolls [166, 167]. The slab method, developed shortly after, produced an analytical model using the slab method adapted from metal working. In this model, it was assumed that the roll are fed a "slab" of material in order to avoid the simplifications of powder behavior at the nip region done by Johanson. The predicted parameters are the pressure distribution and separating forces of the roll [168].

Johanson's model makes several assumptions in order to reduce the dimensionality of the problem. Some of the most important assumptions include: the material is isotropic, frictional and cohesive; the rolls are rigid and flat (no deformation); material undergoes continuous shear; the contact area is much smaller than the rolls (flat surface in contact with the powder); Coulomb's frictional law applies for material–roll surfaces; the material is fed gravimetrically; and the material fed into the rolls leaves at a width equal to the minimum roll gap. This last assumption, even though not possible due to the effect of decompression after the roll, appears to retain the models accuracy while reducing complexity. Given these assumptions, the model is divides the compression zone into two regions: a slip region where material is slipping along the roll's surface edge and a nip region where a no slip boundary condition applies [169]. Both these regions are shown in Figure 2.10a. A third region, known as the release region, where powders are relieved of the stresses and are extruded from the system can be drawn to signify the material has left the unit.

The goal of Johanson's model is to describe the pressure gradients for the slip and nip regions using both the material and roll properties. The equations for the slip and nip region pressure gradients are shown in Equations (2.31) and (2.32), respectively. Three critical

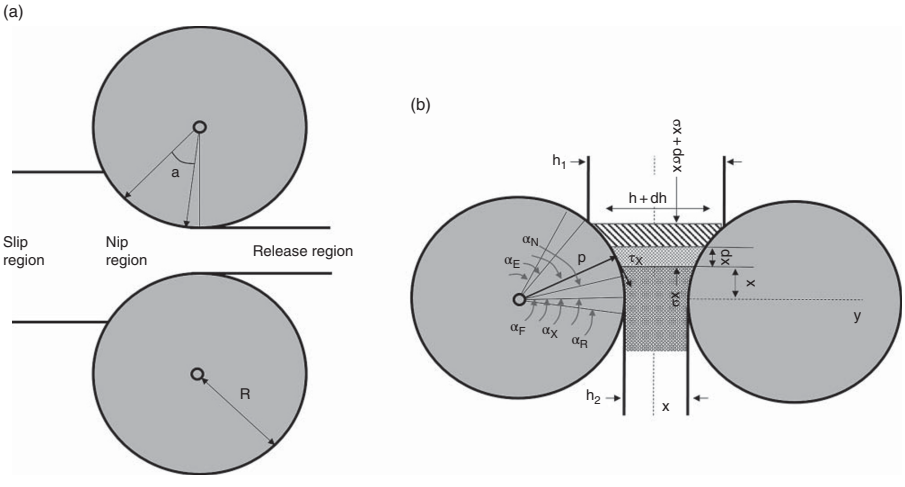


Figure 2.10 *(a) Schematic of counter-rotating rolls in a compaction system. Note the exit roll width is that of the minimum nip width. (b) Schematic of the stress acting on a slab element undergoing compression between two rolls according to the slab method.*

powder property values are required model inputs: the effective angle of internal friction, the angle of friction, and the relationship between pressure and density for the powder of interest (i.e., a Heckel plot analysis). These values can be found experimentally using a punch–die system similar to that found in a tablet press [60].

$$\frac{d\sigma_{Slip}}{dx} = \frac{4\sigma\left(\frac{\pi}{2} - \theta - v\right)\tan\delta_E}{\frac{D}{2}\left(1 + \frac{S}{D} - \cos\theta\right)\left[\cot(A-\mu) - \cot(A+\mu)\right]} \tag{2.31}$$

$$\frac{d\sigma_{Nip}}{dx} = \frac{K\sigma_\theta\left(2\cos\theta - 1 - \frac{S}{D}\right)\tan\vartheta}{\frac{D}{2}\left(1 + \frac{S}{D} - \cos\theta\right)\cos\theta} \tag{2.32}$$

In both equations, σ represents the normal stress applied to the powder, S the roll gap, θ the roll angle, D the roller diameter, μ the friction coefficient between the roll and the powder, δ_E the effective angle of internal friction, and K the material compressibility constant. The roll gap, angle, and diameter can be determined from the equipment geometry. The roll force is determined experimentally as a function of the hydraulic pressure set point for the equipment. The A parameter is an experimentally determined parameter that can be calculated from Equation (2.33):

$$\begin{aligned} A &= \frac{\theta + v + \frac{\pi}{2}}{2} \\ 2v &= \pi - \arcsin\left(\frac{\sin\emptyset_W}{\delta_E}\right) - \emptyset_W \end{aligned} \tag{2.33}$$

where $\emptyset_W$ is the angle of wall friction for the powder.

The compression nip angle (α) is calculated based on the assumption that pressure gradients at the boundary between the no-slip and nip regions are equal. Based on this assumption, the roll angle becomes the nip angle ($\theta = \alpha$). To solve for the nip angle, Equations (2.31) and (2.32) must be set equal to one another and numerically solved for the roll angle. The relative density of the material exiting the process can be calculated from Equation (2.34), where γ_0 is the pre-consolidation relative density, R_f the roll force, and W the roll width. The roll force can be calculated based on the roll diameter and width, the roll gap, the peak pressure, the angle θ and the compressibility K.

$$\gamma = \gamma_0\left(\frac{2R_f}{WD\int_{\theta=0}^{\theta=\alpha}\left[\frac{S}{D}\left\{\left(1 + \frac{S}{D} - \cos\theta\right)\cos\theta\right\}\right]^K\cos\theta d\theta}\right)^{\frac{1}{K}} \tag{2.34}$$

Roller compaction equipment with pressure sensing devices have been used to empirically obtain pressure profiles and torque information. From these results, researchers computed friction coefficients and roll forces during operation [170]. These obtained pressure profiles were also used to verify the pressures predicted by Johanson's model.

Extensions of Johanson's model for simulation and optimization purposes were presented by Hsu *et al*. [71]. The authors proposed a dynamic model as a combination of Johanson's steady state model and a material balance to account for the variability in roll gap as a function of powder feed rate. Roll gap changes in time were assumed to be based in the variability of material input density. Boukouvala *et al*. [171] incorporated a set of delay differential equations to account for the time dependent response of the system and its controller effects. These models were used in the simulation of a continuous tablet manufacturing processes using dry granulation. Rogers and Ierapetritou [172] used the model developed by Boukouvala *et al*. [171] as part of a case study for dynamic feasibility and flexibility analysis.

Katashinskii developed a model for roll compaction of powder materials based on the slab method adapted from metal powders works [168, 173]. The model is based on a force balance around the rolls' nip region and predicts the pressure distribution along the ribbon's length and the separating forces on the rolls. Model formulation was based on a 2-D stress calculation on the system's axial and width directions. This dimensionality makes the model more complex than Johanson's, but has the advantage that it predicts the two principal stresses in roller compaction, rather than just describing the mean stress. It also has potential to include characteristics of powders such as cohesion and global friction between particles. Based on the diagram presented in Figure 2.10b, the equilibrium force balance equation in the feeding direction (i.e., the x direction) is shown in Equation (2.35):

$$\frac{d(h\sigma_x)}{dx} - 2(P\tan\alpha_i - \tau_f) = 0 \tag{2.35}$$

where h is the thickness of the slab, σ_x the stress along the x direction, P the normal pressure acting on the layer, α_i the instantaneous angle, and τ_f the frictional stress. The frictional stress (τ_f) varies based on the magnitude of the friction coefficient $\mu(P)$ and the pressure applied in the system. Equation (2.36) shows the relationship between the frictional stress and the coefficient:

$$\begin{aligned} \tau_f &= Y(\rho) \quad \text{For } P\mu(P) \geq Y(\rho) \\ \tau_f &= P\mu(P) \quad \text{For } P\mu(P) \leq Y(\rho) \end{aligned} \tag{2.36}$$

where $Y(\rho)$ is the effective shear stress and $\mu(P)$ the coefficient of friction. The effective shear stress $Y(\rho)$ is a function of the slab density. Once this relationship has been established and assuming both of principal stresses acting in the x and y directions do not change with respect to time, equilibrium Equation (2.37) can be formulated.

$$Y(\rho) = \sqrt{{\sigma_x}^2 + {\sigma_y}^2 - 2\nu(\rho)\sigma_x\sigma_y} \tag{2.37}$$

In Equation (2.37), $\nu(\rho)$ is the ratio between the powder's transverse contraction strain and the longitudinal extension strain in the direction of stretching force. Further information of this model can be found in [94].

2.4.5 Wet Granulation

Wet granulation is one of the most difficult to model pharmaceutical process, given the number of variables and phases present in the system at any time. In order to understand

wet granulation processes the different subprocesses in granulation, such as nucleation, aggregation, and breakage need to be described in reference to major operational parameters and equipment geometry [174]. Several modeling techniques have been applied as stand alone or in combination (i.e., model hybrids) in order to model this complex phenomena [65]. Hybrid models have intend to either capture the transient behavior of the system (e.g., DEM-PBM) [115, 175] or reduce the dimensionality of the system (e.g., PBM-ANN) [69]. Given the vast literature of these models, they will be briefly presented in this section, primarily focusing on PBMs given their application in this area. Readers are encouraged to follow the review by Kumar et al. [67] for further information about wet granulation modeling.

2.4.5.1 Mechanistic Models

Changes in both particle number and properties, add a dimension to the modeling of wet granulation systems that was not well captured in many mechanistic models. Thus, these models were not initially used to simulate the behavior occurring in wet granulation systems. However, mechanistic models are capable of modeling multiphase systems and capture critical information relevant to the rate kernel used in PBMs simulating wet granulation systems. This model interconnectedness led to the development of hybrid mechanistic–population balance models where results from both model types are iteratively exchanged to one another to simulate the system dynamics [115, 175]. Mechanistic models, such as DEM, take unit-specific geometry information and forces to calculate the trajectories for a given number of particles with specific properties. Results from DEM, such as particle velocity, collision frequency, shear forces, and coalescence of liquid droplets, are computed for a time period and then transferred as inputs to a PBM. The PBM collects the DEM data and computes the changes in particle properties, specifically the change in number, density and size of particles. The results from the PBM are then transferred back to the DEM, where new particle trajectory information is computed for the new particle population. This process is then repeated until a termination criteria is met. The hybrid DEM-PBM framework brings added value to the simulation of wet granulation by coupling the high level of detail from the DEM with a method of predicting the particle changes on those populations. Figure 2.11 shows a schematic of the framework developed by Barraso and Ramachandran [175].

Despite the added value of using mechanistic models to inform kernels of particle level information, empirical or semi-empirical kernels are still often used in simulations. Mechanistic kernels need to be detailed enough to accurately model the process without becoming too computationally expensive to evaluate as this would undermine the effort of the simulation. The coupling of discrete element and population balance models also adds another modeling consideration: the discretization grid used for the DEM and PBM. Barraso *et al.* [69] have proposed a methodology to select the discretization grids of the models in order to reduce computational time and retain model accuracy using artificial neural networks (ANN).

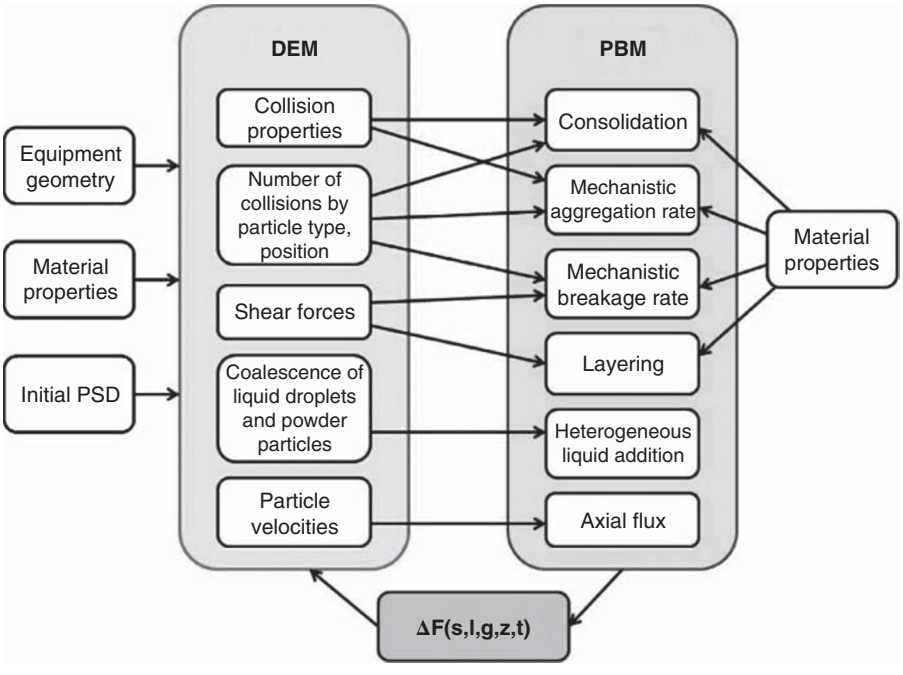


Figure 2.11 *DEM-PBM coupled framework developed by Barraso and Ramachandran [115, 175].*

2.4.5.2 Population Balance Models

Population balance models are primarily used for wet granulation since they model the change in PSD in both time and space as a function of the phases (i.e., liquid, solid and gas) present in the system. Three-dimensional population balances are used to model the population distribution in systems with respect to three phases: solid (s), liquid (l), and gas (g) as a function of time. The solid represent the powder or blend being granulated, liquid the biding solution, and gas the porosity of the particles. The rates of change for the populations typically include a nucleation kernel, a coalescence or aggregation kernel and may also include a breakage kernel; describing granule birth (nucleation), granule growth and attrition, respectively. An overall 3-D population balance is shown in Equation (2.38).

$$\begin{aligned}&\frac{\partial}{\partial t}F(s,l,g,t)+\frac{\partial}{\partial s}\left[F(s,l,g,t)\frac{\mathrm{d}s}{\mathrm{d}t}\right]\\&+\frac{\partial}{\partial l}\left[F(s,l,g,t)\frac{\mathrm{d}l}{\mathrm{d}t}\right]+\frac{\partial}{\partial g}\left[F(s,l,g,t)\frac{\mathrm{d}g}{\mathrm{d}t}\right]\\&=R_{\mathrm{nuc}}(s,l,g,t)+R_{\mathrm{agg}}(s,l,g,t)+R_{\mathrm{break}}(s,l,g,t)\end{aligned}\tag{2.38}$$

In this equation s, l, and g represent the solid, liquid and gas volumes in the granule. The nucleation, aggregation, and attrition rates are represented by the three rate terms on the right hand side of the equation, respectively. The set of population balance equations are solved using ordinary differential equation (ODE) solvers after applying the numerical schemes for discretization of the PBM [176]. Because of the complex geometry of the wet granulation units, the geometry is often viewed in a variety of "blocks", to be modeled according to the function happening in the section (e.g., liquid addition region, shearing, massing). This methodology also reduces the computational time of the model given that less equations need to be written in space. Furthermore, four dimensional PBMs, shown in Equation (2.39), can be formulated to include the granule composition with respect to specific components in the system (e.g. API, excipient) as a fourth dimension.

$$\begin{aligned}&\frac{\partial}{\partial t}F(s_1,s_2,l,g,t)+\frac{\partial}{\partial s_1}\left[F(s_1,s_2,l,g,t)\frac{\mathrm{d}s_1}{\mathrm{d}t}\right]+\frac{\partial}{\partial s_2}\left[F(s_1,s_2,l,g,t)\frac{\mathrm{d}s_2}{\mathrm{d}t}\right]\\&+\frac{\partial}{\partial l}\left[F(s_1,s_2,l,g,t)\frac{\mathrm{d}l}{\mathrm{d}t}\right]+\frac{\partial}{\partial g}\left[F(s_1,s_2,l,g,t)\frac{\mathrm{d}g}{\mathrm{d}t}\right]\\&=R_{\mathrm{nuc}}(s,l,g,t)+R_{\mathrm{agg}}(s,l,g,t)+R_{\mathrm{break}}(s,l,g,t)\end{aligned}\tag{2.39}$$

where s_1 and s_2 represent the two solid phases in the granule with varying composition.

From a practical computational approach, it is preferable to solve lower dimensional PBMs. Reduced dimensionality can be achieved by making assumptions of the internal coordinates and lumping them into other distributions. Several of these types of model reduction options were evaluated by Barrasso and Ramachandran [177], who determined that the best performance was given when one of the material properties was lumped to the other material properties. For example, the authors investigated a model which assumed that granules with the same solid (s) and liquid (l) content had the same gas content in order to describe the 4-D population balance in Equation (2.39) as a set of two 3-D PBMs: a reduced PBM for liquid and solid fractions and a gas balance equation. The gas balance equation relates the total gas volume $G(s_1,s_2,l,t)$ in a discretization bin to the volume of gas in each particle $g(s_1,s_2,l,t)$. The reduction of the 4-D PBM in Equation (2.39) to a 3-D PBM and the gas balance is shown in Equations (2.40) and (2.41), respectively.

$$\frac{\partial}{\partial t}F(s_1,s_2,l,t)+\frac{\partial}{\partial l}\left[F(s_1,s_2,l,t)\frac{\mathrm{d}l}{\mathrm{d}t}\right]=R_{\mathrm{agg}}+R_{\mathrm{break}}\tag{2.40}$$

$$\frac{\partial}{\partial t}G(s_1,s_2,l,t)=F(s_1,s_2,l,t)\frac{\mathrm{d}g}{\mathrm{d}t}+R_{\mathrm{agg,gas}}+R_{\mathrm{break,gas}}\tag{2.41}$$

The reduced dimensionality of the PBMs in Equations (2.40) and (2.41) gave the closest performance compared to the full 4-D population balance model in Equation (2.39) with a computational time reduction around two order of magnitude [177].

2.4.5.3 Engineering or Phenomenological Models

Experimental process parameters, phenomena, and scale up properties are often characterized using engineering models, given their degree of complexity. Two engineering models widely used in wet granulation are the droplet penetration and nucleation regime equations,

presented by [174, 178]. These models are used to predict scale up requirements for wet granulation process, taking into account process information such as equipment size and liquid spray rate. These models also require basic particle properties such as density, mean particle size, and wetting angles.

Phenomenological models are also used for developing rate kernels along with results provided from experiments and/or mechanistic models. Often a combination of multiple approaches kernels can be determined semi-empirically, with parameters fitted based on both sets of data. Development of nucleation, aggregation and breakage kernels is a major research area in population balance modeling for wet granulation given its importance to the process. Aggregation kernels have been studied most overall given the direct association with the wet granulation process. Several authors have summarized the equations for all the kernels, to which readers are encouraged to pursue for information regarding rate kernels [179–182].

2.4.6 Drying

Drying is a process performed after wet granulation, which aims at reducing the excess moisture in granules to avoid caking. Although drying can be achieved through several methods (e.g., convection, radiation, vacuum), in continuous manufacturing it is important to have a method that allows for effective liquid removal in a short residence time. For this reason, drying in continuous pharmaceutical manufacturing processes is typically carried out in a fluidized bed, which incorporates both convective mass and heat transfer to dry the materials. Mathematical models for granule drying in a fluidized bed vary in their level of detail from lumped parameter (i.e., engineering) models to more detailed distributed parameter models such as CFD and DEM.

2.4.6.1 Mechanistic Models

Distributed models include continuum and discrete first principle models such as CFD and DEM. Computational fluid mechanic (CFD) models use macroscopic laws to describe the heat and mass transfer phenomena occurring in the system due to the air-solid interaction and discrete models to describe the microscopic behavior (e.g., pore network development). Discrete models based on CFD can be used to describe granule fluidization within the dryer and also model the boundary layer where convective transport occurs in the system [24, 89]. CFD models often involve a set of assumptions about the granular material, in order to pose the discrete system as a continuous system. Sen *et al.* [117] proposed a methodology for fluidized bed granulation using DEM and PBM coupled frameworks in order to avoid this assumption. More detailed fluidized bed mechanistic models are described in comprehensive reviews by De Beer *et al.* [183] and Van Daele *et al.* [184].

2.4.6.2 Population Balance Models

Distributed PBMs have been used to represent the distribution of liquid content coupled with experimental or simulated data by Mortier *et al.* [185]. The authors presented a 1-D population balance model for granule drying that incorporates information obtained from

a more detailed mechanistic model. The PBM, shown in Equation (2.42), contains a single internal coordinate, the wetted radius R_w, and a negative growth term, G_r, associated with the reduction in particle size due to granule drying.

$$\begin{aligned} \frac{\partial}{\partial t} n(R_w, t) + \frac{\partial}{\partial t} G_r n(R_w, t) = 0 \\ G_r = R_w(R_w, Y) \end{aligned} \tag{2.42}$$

Semi-empirical relations for drying rate or granule size as a function of dryer parameters were developed from mechanistic drying model who accounted for process parameters like gas temperature and velocity. The growth term in equation, can be determined empirically as a function of the drying gas temperature [185].

2.4.6.3 Engineering or Phenomenological Models

Lumped parameter models for drying process have been widely used to assess experimental process efficiency and properties. Mass balances around water content of the granules can be performed by measuring the relative humidity of the air entering and leaving the fluidized bed dryer. Energy balances for particle drying based on convective transport have also been developed [26].

2.4.7 Milling/Co-milling

Milling is a required process in product development where the desired particle size distribution of particles, needed for meeting dissolution and flowability specification, can be attained. Models used for milling are often discrete in nature, given the changes in particle size and number as a function of time.

2.4.7.1 Mechanistic Models

Particle trajectory and forces inside mills have been the primary focus for using first principle models. Several authors have evaluated the forces acting on particles as during their residence time inside of mills, in order to determine the breaking probability of particles in the system. The effect of shear rate, characterized by the change in the rate of impeller rotation, has been extensively modeled using DEM for both milling and co-milling [186]. Coupled DEM-PBM simulations for milling operations have been proposed by Sen *et al.* [187].

2.4.7.2 Population Balance Models

PBMs are used in milling processes, given the changes in particle size and number. Size populations are tracked in a mill based on a discretized spatial and time coordinate depending on the unit's design. Both 1-D and multi-dimensional population balance models for milling have been described in the literature for a variety of industries [159, 188, 189]. For pharmaceutical applications multi-dimensional PBMs are preferred as the materials being milled are typically granules, which may consist of multiple solid phases, as well as

a gas phases [151]. A multi-dimensional population balance helps consider variations in the composition with respect the internal coordinates. A general form of a multi-dimensional population balance used for milling processes is given in Equation (2.43):

$$\begin{aligned} &\frac{\partial}{\partial t}F(s_1, s_2, g, t) = R_{\text{break}}(s_1, s_2, g, t) \\ &R_{\text{break}}(s_1, s_2, g, t) = R_{\text{break}}^{\text{formation}} - R_{\text{break}}^{\text{depletion}} \end{aligned} \tag{2.43}$$

where $F(s_1,\ s_2,\ g,\ t)$ represents the population distribution in which s_1 and s_2 are the two different solid phases or components, g the gas phase, and t is time. For a wet milling process an added internal coordinate, the liquid phase, needs to be included. The breakage term represents the likelihood or probability that a particle in a size class will break into smaller ones and the distribution of sizes into which the particle will fragment. A general form of the breakage term is given in Equation (2.44). In this equation, the triple integral represents the formation of particles in smaller size classes due to breakage of larger particles into smaller fragments. This term yields the changes in each population due to breakage. The second term represents the number balance accounting for loss of particles from a larger size class due to breakage:

$$\begin{aligned} &R_{\text{break}}(s_1, s_2, g, t) \\ &= \int_{s_1}^{\infty}\int_{s_2}^{\infty}\int_{g}^{\infty} k_{\text{break}}(s_1', s_2', g')b(s_1, s_2, g, s_1', s_2', g') \times F(s_1', s_2', g', t)ds_1'ds_2'dg' \\ &- k_{\text{break}}(s_1, s_2, g)F(s_1, s_2, g, t) \end{aligned} \tag{2.44}$$

where the breakage kernel k_{break} and breakage function b account for the rate at which particles break and the size distribution into which they fragment.

2.4.7.3 Engineering or Phenomenological Models

As mentioned previously during the discussion on wet granulation, semi-empirical models are often used to model the rate kernels. In this case, the breakage kernels are modeled using different semi-empirical equations based on the system conditions. Semi-empirical breakage functions in which parameters are estimated from experimental data are common in the literature [190–194].

2.4.8 Flowsheet Modeling

In an integrated process, individual pieces of equipment (i.e., unit operations) are connected in series. In such a process, a train of multiple units, one after the next, is connected via piping to sequentially perform powder to tablet manufacturing without isolation of intermediates. The output of a preceding unit becomes the input of a subsequent one with material continuously flowing between them. Mathematically, process integration follows the same logic. Individual equipment models, presented previously, are combined by taking the results from a preceding model and using it as the inputs of a subsequent one. The integrated process models are labeled *flowsheet models* as the flow of information between the

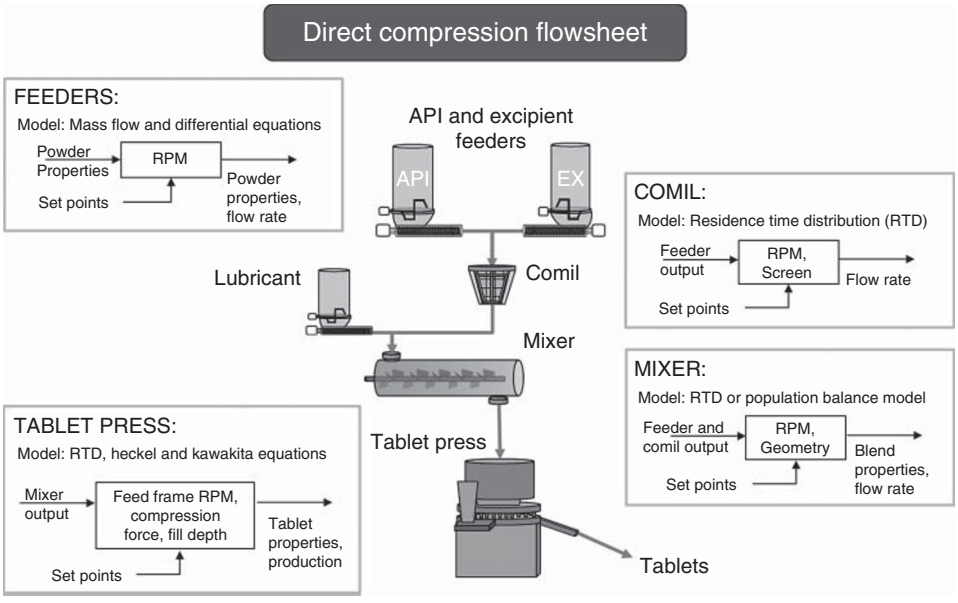


Figure 2.12 *Flowsheet models for a continuous direct compression system. The output from each unit operation model (represented as a schematic) is the input for the subsequent unit.*

unit models, resembles the flow of material(s) between unit operations. Therefore, flowsheet models are defined as equation-based representations of the series of interconnected unit operations that describe a complete manufacturing process. These types of models have long been used in fluid-based chemical processes for process simulation, design, control and optimization applications [195–197]. Several flowsheet modeling software packages (e.g., ASPEN Plus®, ChemCAD®, gPROMS™) have been effectively demonstrated for predictive modeling and design of fluid-based processes and are already widely used across the chemical and petrochemical industries [198]. However, the development of comparable tools for solids handling processes is challenging due to a lack of available first principles and constitutive models to describe many solids-based processes [199–201]. Current flowsheet simulation software packages are not capable of modeling first principle models effectively and require long times to evaluate multidimensional models. If flowsheet models are to be used for optimization, control, and case–scenario evaluation; less complex models need to be developed and implemented for the unit operations. Figure 2.12 shows an illustrative example of flowsheet models for a continuous direct compression system.

These types of models have long been used in fluid-based chemical processes for process simulation, design, control and optimization applications [195–197]. The recent development of the modeling tools previously presented for solids handling units coupled with the commercial availability of platforms for modeling and simulation of solids-based processes have facilitated the development of flowsheet models in the pharmaceutical industry [199–201]. These models can be implemented in commercially available development environments including gPROMS™ ModelBuilder and Aspen Custom Modeler, which just recently incorporated SolidSim® into their portfolio of modeling tools. The flowsheet

models described in the case studies following this section are developed and simulated using gPROMS™ ModelBuilder due to the relative ease of building custom models in this environment. The governing equations describing individual unit operations are those in the population balance, engineering and phenomenological, and empirical sections for the units previously presented.

2.4.8.1 Units Model Integration

Model integration is a process that requires consideration at all stages of model development. In an integrated model it is important to transfer the relevant information between unit models in order to accurately represent the effects preceding units have on subsequent ones. In the existing flowsheet model development environment, each unit operation can accept process inputs from upstream operations and transfer information to downstream operations via information channels and ports. Information channels are assigned connection types, which indicate the types of variables that can be transmitted within them. These information channels, carry variable information (e.g., bulk density, flow rate, particle size distribution, component concentration) between units even if for one unit those variables are irrelevant. For instance, a *powder movement* connection might transmit the mass flow rate of a bulk powder stream as well as its bulk material properties. In order for a unit operation to accept a connection, it must have a port that matches said connection type. Thus, in order for one unit operation to connect to another, the first must be transmitting information that is consistent with the type data that the second seeks. For instance, if a blender model requires information about the mass flow rate, bulk density, and particle size for a powder stream, the feeders, which are connected to this blender, must be sending information not only about material flow rate, but also about the powder properties of the materials exiting the feeders.

Once model integration begins, it may be necessary to define additional variables for certain models if only to pass this information to subsequent operations. In addition to connection types, each variable in a process model also has a variable type. Each variable type is associated with certain unit of measure. For instance, the variable *bulk density* might have variable type *density* and units of g/cm^3. Errors in units may lead to erroneous results, which may lead to problems in connectivity between units. For this reason, it is recommended that a single variable type library be developed prior to the outset of unit operation model development. If all models are generated using the same set of variable types and units, the process of model integration can be greatly simplified.

2.4.8.2 Case Study: Refill of API Feeder During Operation

As previously mentioned, model integration gives us a way to simulate the production line's performance. The simulation can provide information on how the process reacts and absorbs disturbances. With an integrated flowsheet model, we can carry out design iterations on the whole process, for optimal design problems, sensitivity analysis, feasibility analysis, and so on. Figure 2.13 presents the flowsheet model of a continuous direct compression (CDC) line in the process modeling software gPROMS™. The process modeled is shown as following: API and excipient are fed to a co-mill to delump the particles. Then together with a lubricant, the three materials are sent to the blender for mixing. The outlet mixed

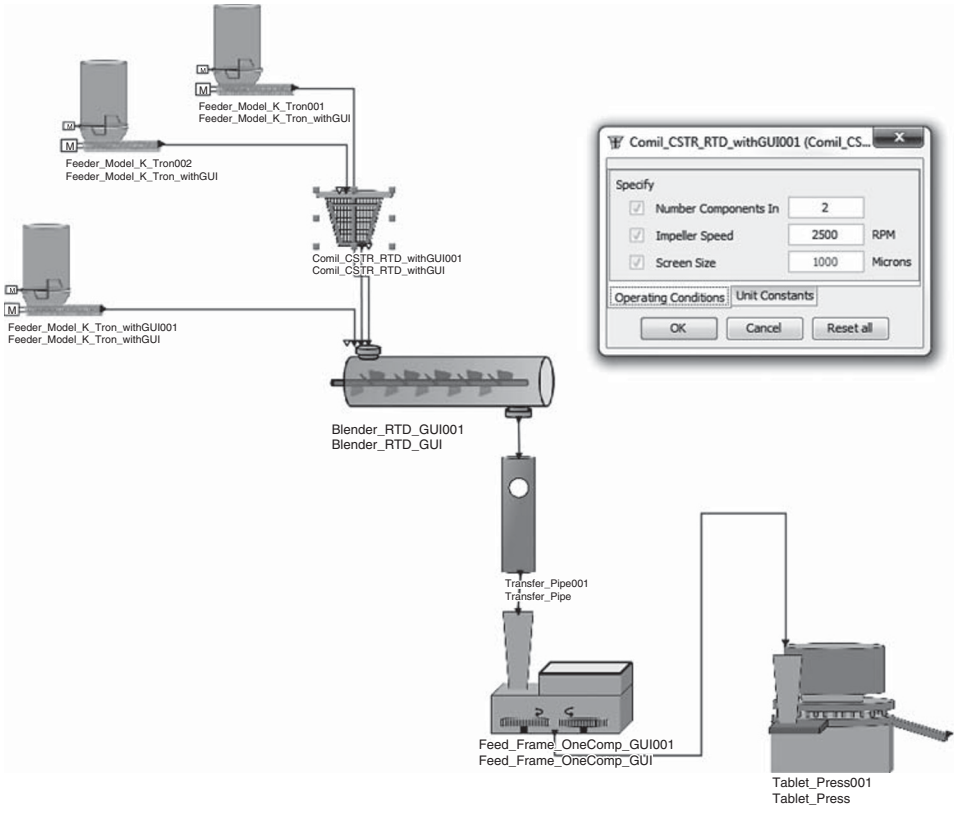


Figure 2.13 *Direct compaction flowsheet model. A GUI will pop up by double clicking a unit model. This will help users to easily set the parameters for the unit model.*

powders then go through transfer pipe, after which the mixed powders will be sent to tablet press's feed frame via a pipe. The feed frame then transfers the materials into the tablet press, where tablets are the output of the system. A three-component formulation (96% Excipient, 3% API, 1% lubricant) was arbitrarily chosen for the simulation.

The results from running this simulation are shown in Figure 2.14, parts (a) to (j). Initially, the outlet flow rate of API feeder is set as 0.9 kg/h (a); outlet flow rate of excipient feeder is set as 28.8 kg/h (b); outlet flow rate of lubricant feeder is set as 0.3 kg/h (c). At $t = 150$ s, a refill in API feeder is introduced as a disturbance to the process. The refill continues for 5 s with a speed of 3600 kg/h. From Figure 2.14a, a small spike of flow rate increase at outlet of API feeder is observed. A sudden change of concentration is also found in the co-mill (d). A time delay is introduced in the blender (e), as it takes time for powders to be mixed and transferred from the inlet to the outlet of the blender. In Figure 2.14f, we can see the blender dampens the API concentration disturbance. Figure 2.14g shows the material height gradually gets to the steady state in the transfer pipe. In Figure 2.14h, we can also observe a time delay of feed frame, which represents the time it takes for powders to move from inlet to outlet of the feed frame. Figure 2.14, parts (i) and (j) show the properties of tablets coming out of the tablet press.

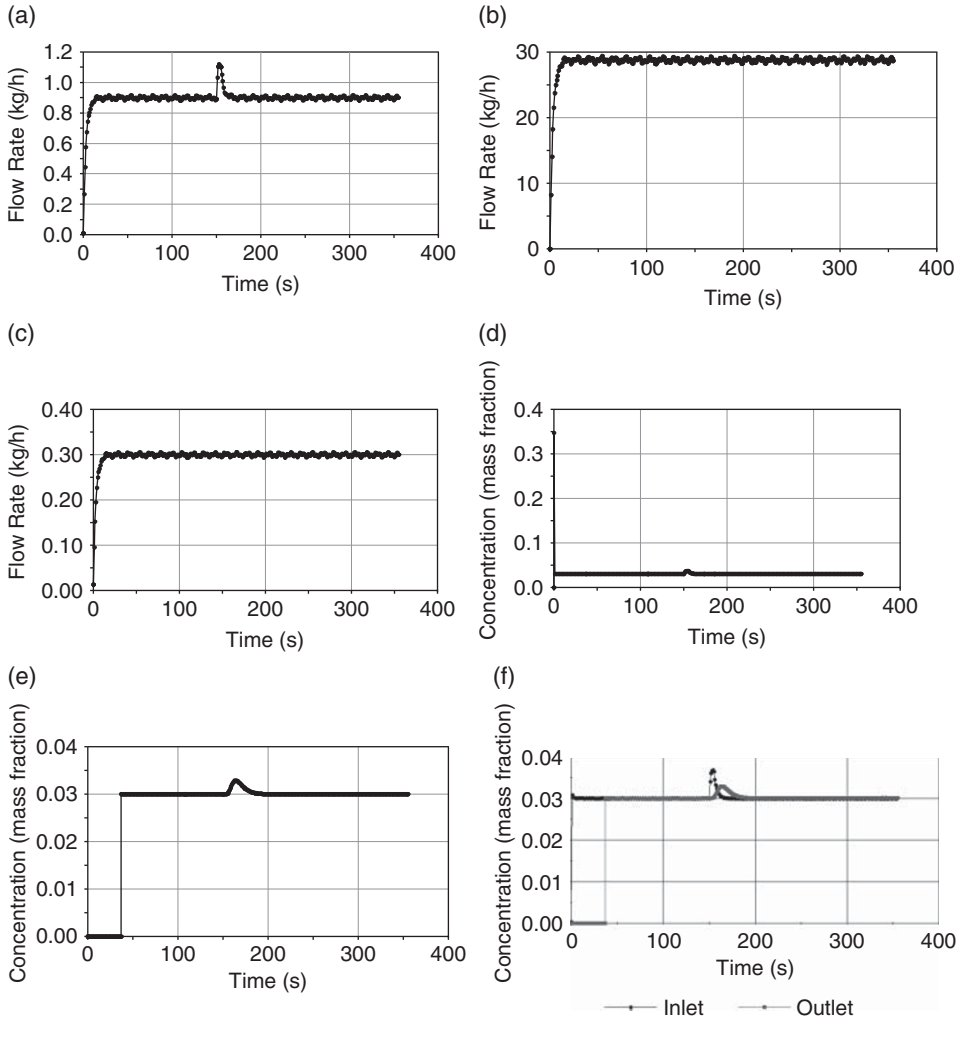


Figure 2.14 *Simulation of the direct compression line modeled in Figure 2.13. For the case study of refilling the a feeder unit. (a) API feeder mass flow rate (kg/h). (b) Excipient feeder mass flow rate (kg/h). (c) Lubricant feeder mass flow rate (kg/h). (d) Concentration of API at the outlet of Comill. (e) Concentration of API at outlet of blender. (f) Concentration of API at inlet and at outlet of blender. Black and gray lines are inlet and outlet concentrations of API, respectively. (g) Material height inside transfer pipe (m). (h) Mass flow rate of feed frame (kg/h). Black represents inlet. Gray represents outlet. (i) Tablet weight (kg). (j) Tablet hardness (Pa).*

2.5 Process Control of Continuous Solid-based Drug Manufacturing

The pharmaceutical processes are desired to be properly controlled in order to achieve the desired critical quality attributes as mandated by regulators. Different authors have suggested the control strategy for different continuous pharmaceutical processes. Lakerveld

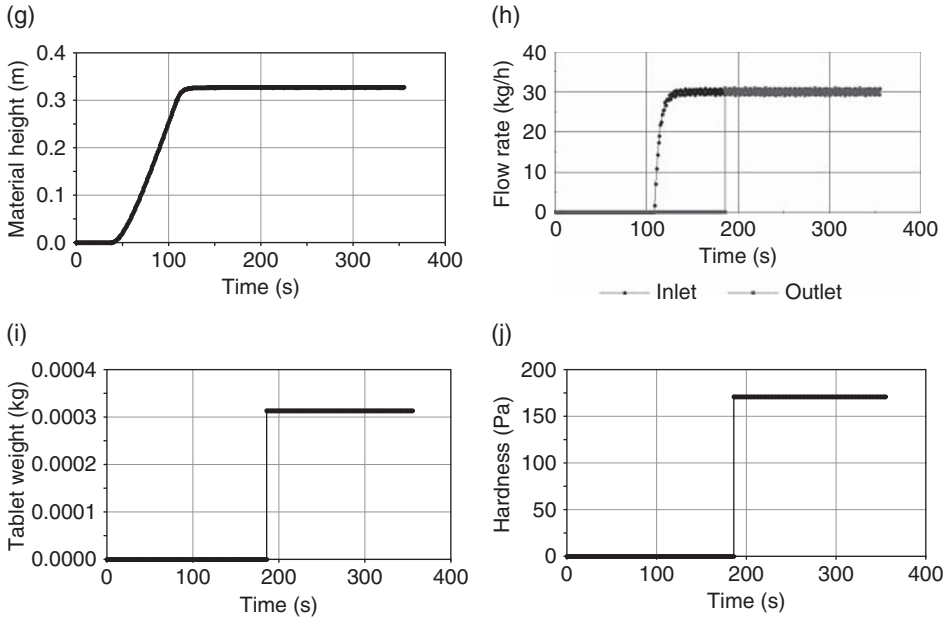


Figure 2.14 *(Continued)*

et al. [202] have suggested a control system for end to end continuous pharmaceutical manufacturing process. Icten *et al.* [203] have proposed a control system for a continuous pharmaceutical manufacturing involving drop on demand (DoD) technology. The control of a continuous pharmaceutical manufacturing via twin screw hot melt extrusion has been proposed by Baronsky-Probst *et al.* [204]. Few attempts have been also made toward design of control system for individual unit operations involved in pharmaceutical manufacturing processing. Hsu *et al.* suggested a control system for a roller compactor, an important unit operation used for a dry granulated continuous tablet manufacturing process [71]. A detailed review on the control of a fluid bed granulation process has been performed by Burggraeve et al. [205], and a discussion has been provided by Bardin *et al.* [206] on the control aspects for efficient operation of a high shear mixer. Sanders *et al.* have performed extensive control studies using proportional integral derivative (PID) and model predictive control (MPC) methods on an experimentally validated fluidized bed granulation model [207]. An MPC strategy has been proposed for a wet drum granulation process [208, 209]. Extensive work has been done to control the downstream continuous tablet manufacturing process involving powders to tablets. Singh *et al.* have developed an advanced MPC system for a direct compaction continuous tablet manufacturing process [44]. A control system for the roller compaction route of the continuous tablet manufacturing process has been also developed [52]. The control system for wet granulation route has been proposed as well [41]. Singh *et al.* have demonstrated the implementation of the control system into the direct compaction continuous tablet manufacturing pilot plant using NIR as a real time monitoring tool [40, 43]. A combined feedforward/feedback control system has been also developed [48]. The control of direct compaction continuous tablet manufacturing process is described in following sections.

2.5.1 Process Control Basics

Process models developed in previous sections are very important tools for the design of control system. The process flowsheet model has been used to understand the continuous tablet manufacturing process in order to design an efficient control system. The critical control variables that have significant effects on CQAs have been identified through sensitivity analysis coupled with scientific process understanding. Subsequently, the control variables have been paired with suitable actuators via relative gain array and dynamic sensitivity analysis methods. Furthermore, the process flowsheet model has been employed to tune the controller parameters and finally to analyze the closed-loop process performance before implementing it into the pilot plant.

2.5.1.1 PID Controller

Proportional integral derivative (also known as a regulatory controller) is the most commonly used controller in the manufacturing industry because of its simplicity. Proportional (P), integral (I) and derivative (D) terms can be used individually or in any combination as per requirement of the control loops. In PID controllers, the manipulating variable is calculated as follows [210]:

$$u(t) - u_0(t) = K_C e(t) + \frac{1}{\tau_I}\int_0^t e(t)\,\mathrm{d}t + \tau_D \frac{\mathrm{d}e(t)}{\mathrm{d}t} \qquad (2.45)$$

$$e(t) = Y_{sp}(t) - Y(t)$$

where $u(t)$ is the manipulating variable, $u_0(t)$ is the nominal value of the manipulating variable, $e(t)$ is the deviation of the control variable from the set point, $Y_{sp}(t)$ is the set point, $Y(t)$ is the control variable, K_C is the proportion gain, τ_I is the integral time constant, τ_D is the derivative time constant. K_C, τ_I, and τ_D are tuning parameters that impact the control performance of the system [210].

2.5.1.2 Model Predictive Controller

Model predictive controller uses linear/non-linear plant models and optimization tools to generate the control actions [38, 39]. MPC has several advantages over the simpler PID controller. For example, MPC is better in handling multivariable control problems (multi inputs multi outputs system), process constraints (e.g., actuator limitations, constraints on controlled variable, system constraints), process delays, system disturbances, process variable interactions and equipment (sensor/actuator) failures. The major limitation of MPC includes its design complexity, computationally expensive optimization-based control algorithm (requires optimization tool), and necessity of additional (linear/nonlinear) process model. The performance of MPC depends on the process model, hence poor process models may lead to poor controller performance [210].

Depending on a specific process, either a linear or a non-linear model can be used in MPC. In case of linear MPC, a time invariant model (e.g., state space) can be employed. Together with the model, MPC uses the current plant measurements and dynamic state of

the process, and the process variable targets and limits to calculate future changes in the independent variables. These changes are calculated to hold the dependent variables close to the target while honoring constraints on both independent and dependent variables. The MPC typically sends out only the first change in each independent variable to be implemented and repeats the calculation when the next change is required. The optimization function can be formulated as follows [44]:

$$J = \sum_{i=1}^{P}\sum_{j=1}^{n_y}\{w_j^y[y_j^{\text{set}}(k+i) - y_j(k+i)]\}^2 + \sum_{i=1}^{M}\sum_{j=1}^{n_u}\{w_j^{\Delta u}\Delta u_j(k+i-1)\}^2 + \sum_{i=1}^{M}\sum_{j=1}^{n_u}\{w_j^u[u_j(k+i-1) - \overline{u}_j]\}^2 \quad (2.46)$$

The various MPC algorithms may use different cost functions for obtaining the control law [211]. The first term in the objective function represents the weighted sum of squared deviations [$S_y(k)$]. The second term represents the weighted sum of controller adjustments [$S_{\Delta u}(k)$]. The third term represents the weighted sum of manipulated variable deviations [$S_u(k)$]. k: current sampling interval, $k + i$: future sampling interval (within the prediction horizon). y_j: jth control variable, y_j^{set}: set point of jth variable, u_j: actuator for jth control variable. P: number of control intervals in the prediction horizon. n_y: number of plant outputs. M: is the number of intervals in the control horizon. n_u: number of manipulated variables. $\Delta u_j(k+i-1)$: predicted adjustment in manipulated variable j at the future (or current) sampling interval k + i – 1. w_j^y: weight for output j (the output weights let you dictate the accuracy with which each output must track its set point. $w_j^{\Delta u}$: rate weight (it penalizes the incremental change rather than the cumulative value and increasing this weight forces the controller to make smaller, more cautious adjustments). w_j^u: input weight (this weight helps to avoid large deviation from the nominal value of actuators). The optimization based method Integral of Time Absolute Error (ITAE [210]) can be employed for tuning of MPC parameters (weights). $\overline{u}_j$: nominal value of actuator for input j. Prediction (P) and control (M) horizons should be selected such that $P\text{–}M \gg td_{\max}/\Delta t$, where $td_{\max}$ is the maximum process delay, and Δt is the control interval [44].

2.5.2 Control Design of Continuous Pharmaceutical Manufacturing Process

A systematic methodology for design of control system is shown in Figure 2.15. As shown in the figure, the design of a process control system involves the identification of critical controlled variables, coupling of the controlled variables with suitable actuators (manipulated variables), selection of suitable real time monitoring tools, selection of control strategy followed by tuning of controller parameters, and finally, model-based, closed-loop performance assessment [42, 52]. The knowledge base consists of information related to the critical process variables, corresponding actuator candidates, sensors and controllers [212]. A control expert can also provide such information. The model library consists of the process model of the continuous tablet manufacturing process as described in Sections 2.3 and 2.4. The design control system can then be implemented in the manufacturing plant through standard control hardware and software [44]. In the past, the pharmaceutical processes were considered to be frozen and therefore very limited or no real time control systems were

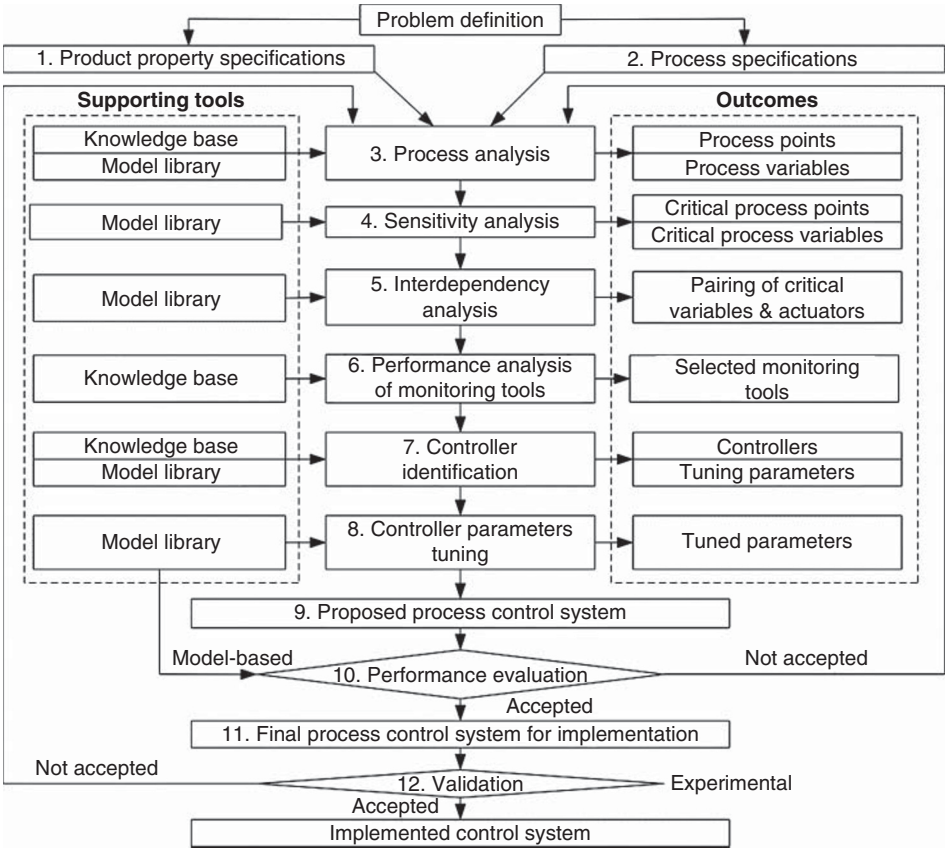


Figure 2.15 *Systematic methodology for design of control system (adapted from Singh* et al. *[42, 52]).*

used. But, currently there is a growing interest to control the pharmaceutical processes in real time using suitable control algorithms and real time monitoring tools. As a result, both unit operation levels, as well as plant-wide control strategies, have been developed. Few examples of pharmaceutical process control are given in the following paragraphs.

A plant-wide control strategy for continuous downstream tablet manufacturing process (powders to tablet) has been developed at Rutgers University as part of C-SOPS project [41, 44, 52]. This process consist of different unit operations needed to convert powder raw materials in form of tablets. The number of unit operations depends on whether the tablet is produced via direct compaction, roller compaction or wet granulation routes. The systematic methodology shown in Figure 2.15 has been used to design the control architecture for this process. A control strategy for continuous tablet manufacturing via tumble mixer has been developed at University of Puerto Rico as part of C-SOPS project [213]. This process consists of continuous tumble mixer in place of convective mixer.

A plant-wide control strategy for end to end continuous pharmaceutical manufacturing process has been developed as part of MIT-Novartis project [214]. This process consists of several reactions and separations for synthesis and purification of intermediates and the

final active pharmaceutical ingredient (API) followed by a sequence of downstream units that produce a pharmaceutical product in tablet form. A combination of a bottom-up and hierarchical top-down approach was used to structure and prioritize the control objectives for this process. A bottom-up approach has been used to stabilize the process followed by a top-down hierarchical approach to develop control strategies at different representations of the process. Level 1 focuses on the input and output streams of the plant, which are decomposed in Level 2 into separate sections for the synthesis and purification of intermediates and the formulation of the API. Recycle structures are revealed during Level 3 of the decomposition. Finally, control strategies at the most detailed level are developed during Level 4 of the approach. The control strategies developed at higher levels constrain the control strategies at lower levels. The hierarchical nature of the approach aims to satisfy both plant-wide and local control objectives with minimum interference.

A control strategy for continuous drop on demand pharmaceutical manufacturing process has been developed at Purdue University as part of C-SOPS project. This process is an alternative to conventional pharmaceutical manufacturing methods. This mini manufacturing process for the production of personalized pharmaceutical products utilizes drop on demand (DoD) printing technology for the deposition of active pharmaceutical ingredient (API) onto edible substrates. The dropwise additive manufacturing system consists of a precision positive displacement pump, *xy*-staging, a hot air based heating system, on-line imaging and sensing, and temperature, pump and stage controllers. A supervisory control strategy to achieve the critical quality attributes of solid oral dosages produced with the DoD system was proposed. The supervisory control strategy consists of two main parts: an automated low-level control system and a surrogate model based supervisory control layer. The low level control system provides effective control of the drop on demand manufacturing process, whereas the surrogate model based supervisory control layer demonstrates the indirect control of drug dissolution on-line and enables model-based real time release of solid oral dosages [203].

2.5.2.1 Critical Control Variables

The critical control variables of direct compaction continuous tablet manufacturing process have been identified based on process understanding and sensitivity analysis. These critical control variables include API composition at blender outlet, powder level of instrumented hopper placed in between blender and tablet press, tablet weight and tablet hardness at tablet press. Powder flow rate from each feeder is controlled through an in-built controller. API composition at blender outlet needs to be controlled in order to assure the drug concentration. Powder level of instrumented hopper needs to be controlled to ensure the presence of powder in front of the NIR sensor. The main compression force is controlled through an in-built controller. The tablet weight and hardness are the critical quality attributes (CQAs) as these affects tablet dissolution.

For end to end continuous pharmaceutical manufacturing process, the importance of the selected CPPs at each level of the hierarchical decomposition was evaluated by computing the parametric sensitivities of the CQAs with respect to the CPPs. The influences of the CPPs on the CQAs that are visible at the input-output level are evaluated to establish constraints that will propagate to lower levels. The process is further decomposed in the

second step of the top-down approach where the sections involving synthesis and purification of the first intermediate and API and formulation steps are visualized separately. The influence of the properties of the intermediate streams on the final CQAs are evaluated using parametric sensitivities. For this process, the main control variables are the temperature, pressure, holdup, and composition at different unit operations [202, 214]. For drop on demand process, the main control variables are temperature and dissolution [203].

2.5.2.2 *Control Variables and Actuators Pairing*

The best actuator for each control variable needs to be selected. The relative gain array (RGA) method [215] or dynamic sensitivity analysis method (also called interdependency analysis) [52] can be used to identify suitable actuators. In RGA method, an array of relative gain needs to be prepared. The relative gain is defined as the ratio of open-loop gain and closed-loop gain and can be calculated as follows [210]:

$$\lambda_{ij} = \frac{(\partial y_i/\partial u_j)_u}{(\partial y_i/\partial u_j)_y} = \frac{\text{open-loop gain}}{\text{closed-loop gain}} \tag{2.47}$$

$$\text{RGA} \begin{bmatrix} & u_1 & u_2 & \dots & u_n \\ & \lambda_{11} & \lambda_{12} & \dots & \lambda_{1n} \\ & \lambda_{21} & \lambda_{22} & \dots & \lambda_{2n} \\ & \cdot & \cdot & \cdot & \cdot \\ & \lambda_{n1} & \lambda_{n2} & \dots & \lambda_{nn} \end{bmatrix} \begin{matrix} \\ y_1 \\ y_2 \\ \cdot \\ y_n \end{matrix} \tag{2.48}$$

where y_i is the ith control variable and u_j is the jth actuator candidate. Open-loop gain is obtained by partial differentiation of y_i with respect to u_j while assuming that other actuator candidates are constant. The closed-loop gain is obtained by partial differentiation of y_i with respect to u_j while assuming that other control variables are constant. The values in the relative gain array (RGA) describe the relationship between the input (actuator) and output variables (control variables). Negative values indicate an unstable relationship. A value of zero indicates no relationship. A value of 1 indicates that specific input variable is the only influence on that output variable. A value between 0 and 1 indicates interactions among the control loops. A dynamic sensitivity analysis method can be also used for pairing of control variables with the actuators. In a dynamic sensitivity analysis method, the actuator candidates are perturbed (e.g., –3% to +3%) and the absolute percentage change in controlled variable is analyzed [42]. The actuator that results in the highest change in control variable is selected as the final actuator. Actuators for API composition, powder level in the instrumented hopper, tablet weight and tablet hardness are ratio set point, rotary valve speed, main compression force set point and punch displacement, respectively. Main compression force is controlled through a slave PID controller by manipulating the fill depth. Powder flow rate from each feeder is controlled by manipulating the feeder screw rotational speed.

There are other examples available in the scientific literatures where sensitivity analysis has been used for pairing of control variables and actuators of pharmaceutical processes. For example, a sensitivity analysis based approach has been used for pairing of control variables and actuators of end to end continuous pharmaceutical manufacturing process.

Strategies are developed to control the identified key properties by using the CPPs available as manipulated variables. The detail of control variables and actuators pairing for this process is given in Lakerveld *et al.* [214].

2.5.2.3 Selection of Monitoring Tools

The specifications, such as accuracy, precision, response time, operating range, resolution, sensitivity, drift, and cost, are the important factors that need to be taken into account in selection of the sensors [212]. The sensors for real time monitoring of critical control variables have been integrated with the direct compaction continuous tablet manufacturing process. API composition and powder bulk density are measured by the NIR sensor, powder flow rate from feeders are measured by load cells (built within feeders), the powder level is measured by a webcam, tablet weight and hardness are measured by a Checkmaster (Fette) and main compression force is measured via load cell based inbuilt sensor.

Online imaging systems have been also used for monitoring and control of drop on demand continuous pharmaceutical manufacturing process [203]. The drop size has been monitored using a imaging system. The temperature and flow rate were also monitored for this process. NIR is the main technique for monitoring and control of tumble mixer [213]. NIR has been also used for monitoring of ribbon density at roller compaction unit operation. Other spectroscopic techniques have been also employed for feedback control. For example, Simone *et al.* (2014), have used Raman and ATR-UV/Vis spectroscopy for feedback control of crystallization process, an important unit operation of API manufacturing [216]. Raman spectroscopy was used to detect the presence of the undesired crystalline form using a calibration-free approach; ATR-UV/Vis was used to measure the solute concentration and perform super saturation control (SSC) using a calibration-based approach to determine the set point for the temperature controller. Optical coherence tomography technique was used for in-line monitoring of a pharmaceutical pan coating process [217].

2.5.2.4 Selection of Controller and Tuning of Controller Parameters

Selection of appropriate controllers (PID, MPC, or hybrids) is needed for optimal performance. In case of PID, subsequently one needs to decide whether to use a single-loop or a cascade one. In cascade mode, two controllers are used. One controller is called master and the other is called slave. The master controller generates a set point for the slave controller. The cascade control system is preferred when a large time delay is involved in the process or when disturbances affect a measurable intermediate that directly affects the controlled variable. Also, cascades are preferred when the gain of the secondary process, including the actuator, is nonlinear. The major limitations of the cascade controller includes the need of more sensors and that it is harder to tune the controller parameters. The controller parameters need to be properly tuned. Heuristic methods [218] or optimization based methods (e.g. Integral of Time Absolute Error; ITAE) can be employed to tune the controller parameters [210].

A combination of MPC and PID controllers has been proposed for continuous downstream (powder to tablet) pharmaceutical manufacturing process [43]. The controller configuration for direct compaction continuous tablet manufacturing process is shown

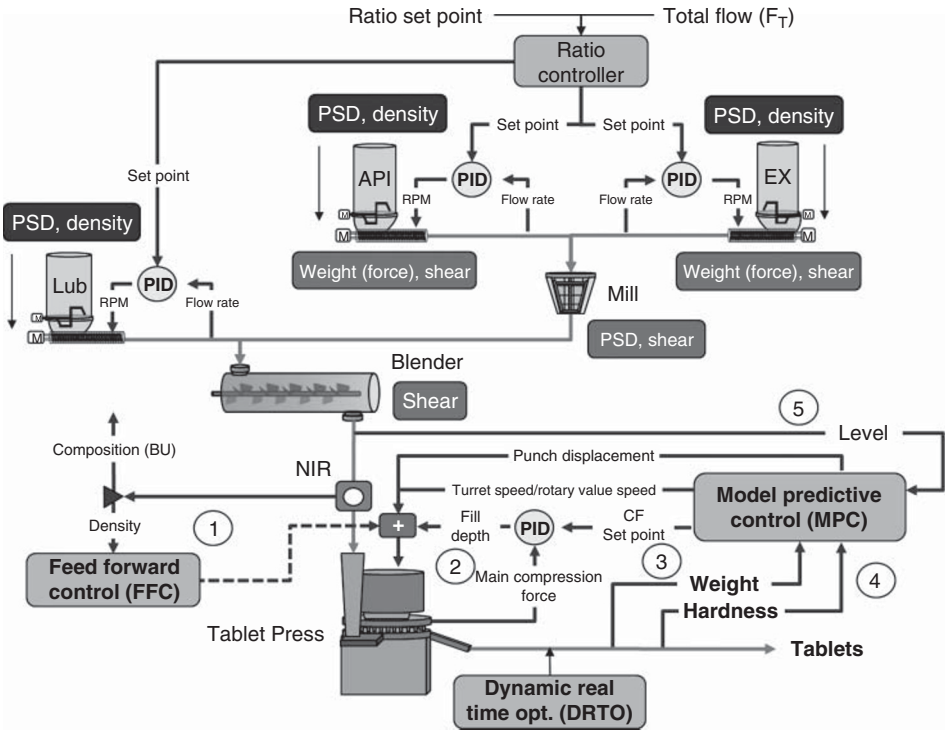


Figure 2.16 *Closed-loop process flowsheet of direct compaction tablet manufacturing process. PSD: Particle size distribution; MPC: model predictive control; PID: proportional integral derivative; FFC: feedforward control; DRTO: dynamic real time optimization.*

in Figure 2.16. As shown in the figure, a hybrid MPC-PID control scheme in which MPC is placed at supervisory level and PID is placed under MPC as a slave controller has been used. The PID controller parameters are tuned using the Ziegler and Nichols [218] method and the ITAE optimization-based method [210]. MPC parameters (prediction horizon, control horizon, output weight, rate weight, input weight) are specifically tuned using the ITAE method. The control system for tumble mixer is based on PID controller. The drop on demand manufacturing process was controlled via PID control logic [203].

The control architecture of end to end continuous pharmaceutical manufacturing process is based on PI and proportional (P) controllers [214]. The tuning of the controllers was achieved using various criteria as described next. All the level controllers were set to P-only controller since the residence time of the controllers were not needed to control very tightly. This controller resulted in more gradual changes in the outlet flow rate in comparison to PI controller but at the expense of steady state offset. A sluggish tuning of P-controller can help to attenuate the propagation of disturbances in flow throughout the process. The main idea was to exploit buffering capacity of the tanks by employing P-only controller to reject the short-term disturbances and to employ a PI controller for the outer flow-rate control loop established at a higher level of the control strategy to reject long-term disturbances. The tuning of the remaining control loops was accomplished by generating initial guesses

for the tuning parameters using the internal model control by assuming a first order plus time delay process and then manually adjusting those initial parameters if needed.

2.5.2.5 Designed Control System

The designed control architecture of direct compaction continuous tablet manufacturing process is shown in Figure 2.16. A combination of MPC and PID has been used to utilize the advantages of both control algorithms. Drug concentration has been measured using NIR sensor. The measured drug concentration is the input for the master controller, which generates the feeder ratio set point. Based on this ratio set point and the total powder flow rate, the individual flow rate set points for API, excipients and lubricant feeders are calculated and then controlled by manipulating the respective feeder RPMs using built-in feeder controllers. The powder level in the chute has been controlled by manipulating the rotary valve speed. In the tablet press, the tablet weight is controlled through a cascade control arrangement using one master loop and one slave loop. The master loop is used to control the tablet weight that provides the set point of slave controller which has been designed to control the main compression force. Main compression force has been controlled by manipulating the fill depth. A feedforward control loop has been also shown in the figure. The real time measured powder bulk density is the input to a feedforward controller (FFC) that manipulates the fill depth. FFC has been added to take proactive actions to mitigation the effects of variations in powder bulk density. The tablet hardness has been controlled by manipulating the punch displacement. The control system for roller compactor has been described in Singh *et al.* (2012). The control system for wet granulation has been reported in Singh *et al.* (2014). The designed control system for tumble mixer [213], drop on demand manufacturing process [203] and end to end pharmaceutical manufacturing process [214] are available in the literature.

2.5.2.6 Model-based Performance Evaluation

The performance of the designed control system can be evaluated using the process model prior to implementation into the plant. The direct compaction continuous tablet manufacturing process has been considered here as a demonstrative example. The model-based closed-loop performance of the control system for critical quality attributes is shown in Figure 2.17. Two control scenarios have been compared in the figure. In scenario one, feedback only control scheme has been used while in scenario two, a combined feedforward/feedback control scheme has been used. The set point tracking and disturbances rejection ability of the control system has been assessed. A random disturbance in the powder bulk density has been introduced. A step change in the powder bulk density has been also introduced at 2500 s in order to analyze its effects on control system. A step change in the hardness set point has been introduced to analyze the set point tracking ability of the control system. Figure 2.17a shows that under combined feedforward/feedback control scheme the hardness has been controlled better in comparison to feedback only control scheme. Similarly, Figure 2.17b shows that the tablet weight is controlled better under combined control scheme. This is essentially because the effects of density variations have been proactively mitigated through the feedforward controller. A small deviation can be seen at the points where the step changes in hardness and powder bulk density have been made.

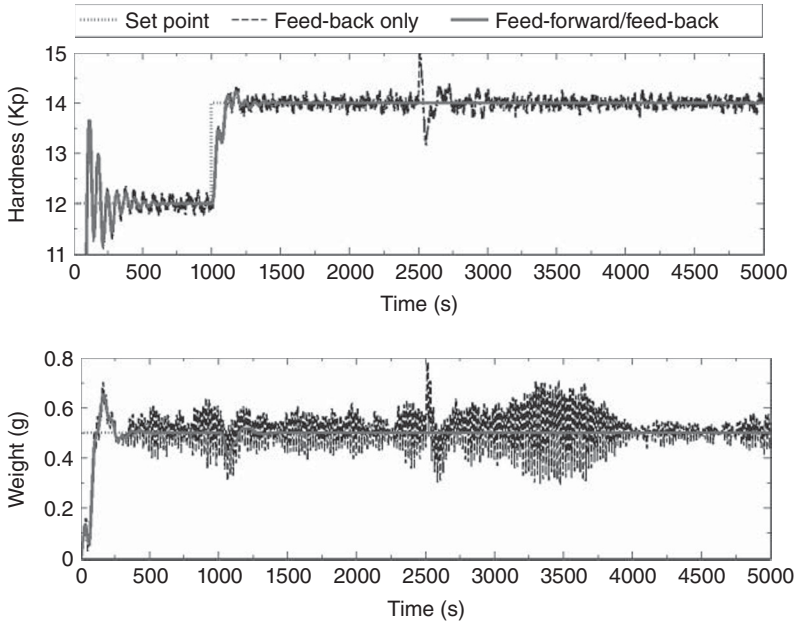


Figure 2.17 *Model based performance evaluation of closed-loop continuous tablet manufacturing process.*

The performance of control architecture of end to end continuous pharmaceutical manufacturing process has been evaluated using process model in scientific literatures [202, 214]. The model based performance evaluation of continuous downstream tablet manufacturing process via roller compaction [52] and wet granulation routes [41] have been also previously performed.

2.5.2.7 Implementation of Control System

A systematic procedure to implement the control system into the continuous direct compaction tablet manufacturing process has been previously reported [219]. The online/inline monitoring tools for all control variables, the appropriate control platform (e.g., DeltaV, Emerson) in which the control strategy can be implemented, the control hardware needed to communicate data with the plant and the software tools needed to close the loop have been integrated with the plant. Spectroscopic techniques are the preferred option for monitoring the pharmaceutical tablet manufacturing processes because of their non-destructive nature and fast-acquisition times. An interface (chute) is needed to integrate the inline measuring probe. After constructing and mounting the interface (chute), the sensor and its respective data acquisition software are integrated into the manufacturing line and the control architecture. The measured signal is then sent to the control platform. For spectroscopic sensors, this step includes the development of a calibration model [108], the integration of the sensor operating software with the online prediction tools, the integration of the online prediction tools with the PAT data management tool and the integration of the PAT data management

tool with the control platform via the OPC communication protocol. Through this step, the measured signal and any other signals (e.g., alarms, warnings, etc.) can be sent to the control platform to be recorded in the historian, and any data from the control platform can be sent back to the PAT data management tool for data storage, inspection and auditing purposes. A multivariate data analysis tool (e.g., Unscrambler X, CAMO) was used to compute principal component analysis (PCA) and partial least square (PLS) models to further develop a calibration model required for prediction of desired variable from the spectra. PLS is a quantitative regression method that looks for correlation between spectral data (X matrices) and the independent variable of interest (Y vector). The integration of other type of sensors (e.g., webcam) is easier and can be directly connected with the control platforms. Standard industrial communication protocols such as Fieldbus or EtherNet/IP have been used to connect the unit operations with the control platform [220]. Feeders are connected via device net, blender is connected via serial ports, and tablet press is connected via OPC. The control software communicates with the control hardware, which communicates with the plant via fieldbus/serial ports. To connect the plant input (actuators) with the plant output (control variable), the control strategy is implemented in the control platform. The input for the controller comes from the sensors and the output from the controller goes to the plant. The control studio (toolbox) of the control platform has been used to add the controller. The linear process model needed for MPC has been identified. Finally, the performance of the control system is evaluated through closed-loop operation. The selection of control hardware, software and sensors depends on its availability and the specific process to be controlled. For example, in order to control tumble mixer SIMCA tool was used in place of CAMO tools for real time prediction of NIR signal [213]. In the case of drop on demand manufacturing process, LABVIEW control platform was used [203]. The control system in crystallization process was implemented using the Crystallization Process Informatics System (CryPRINS) platform [216].

2.5.2.8 Closed-loop Operation of a Direct Compaction Continuous Tablet Manufacturing Process

The control of the API composition through MPC has been considered here as a demonstrative example. There is a cascade control arrangement where the master controller is MPC and the slave controllers are in-built PIDs. The plant has been run in closed-loop scenario to validate the different integrations and proposed control framework. API (APAP (acetyl-para-aminophenol)) has been placed in one feeder and excipient [silicified microcrystalline cellulose (SMCC)] mixed with 1% magnesium stearate is placed in a second feeder. A micro NIR sensor (JDSU) 1700 model has been used to measure the API composition at the blender outlet. A PLS model developed in UnscramblerX is used for the NIR prediction. Unscrambler Process Pulse and a prediction engine (OLUPX) are used for real time the NIR prediction. The API composition is then sent to DeltaV using the MATLAB OPC communication protocol. The linear model for MPC has been developed through step and pulse experiments. An inbuilt feature in DeltaV has been used to build the MPC model [43]. The blender speed is kept at 30% of the maximum speed. The closed-loop response of API composition is shown in Figure 2.18 [43]. The performance of the hybrid MPC-PID control system has been compared with the performance of base level PID controller. The set point tracking ability of the control system has been assessed. The auto-tuning capability

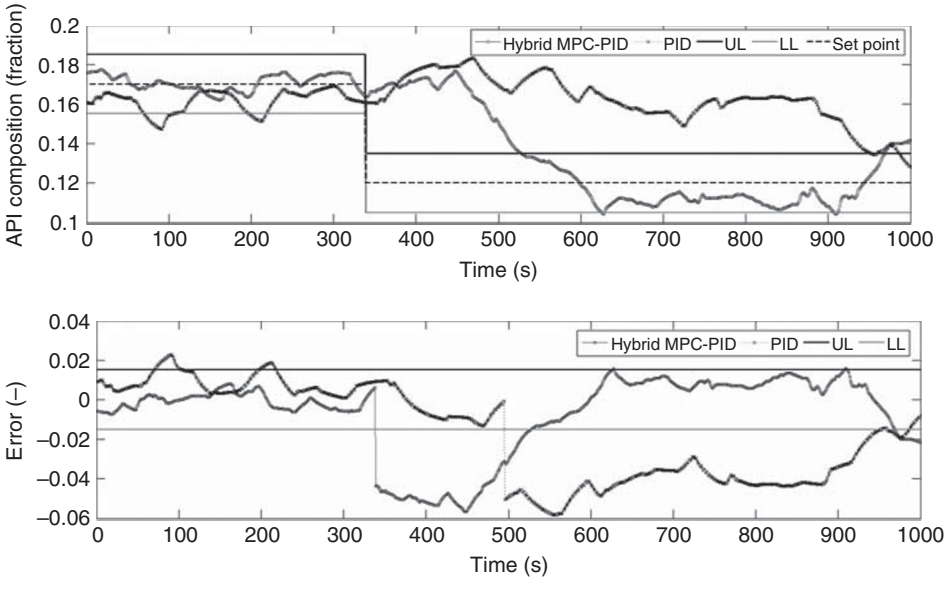


Figure 2.18 *Comparison of MPC with PID controller.*

of DeltaV has been used to tune the PID controller parameters [220]. The acceptable control limits was specified to be of set point ±0.15. The figure shows that at 17% API composition, the MPC response is within the control limits while the PID response violates the control limits. On step change from 17 to 12% API composition, the MPC brings the signal faster to the new set point in compare to PID controller meaning that MPC has less rise time in compare to PID. At the new set point, the MPC response is within the control limits except very minor violation at two points while the PID response is outside the control limits. PID controller has been selected for comparison to analyze the advantages of advanced hybrid MPC-PID control scheme in compare to basic level controller. Note that the performance of both hybrid MPC-PID and PID control schemes can be further improved by integrating the other performance improvement techniques and tools and by reducing the measurement noise.

The results presented here validate that the NIR sensor can be successfully integrated with the continuous tablet manufacturing plant. The sensor output is communicated with the control platform (DeltaV) via OPC. In this way real time monitoring of drug concentration using NIR sensor can been accomplished [40, 43].

2.6 Summary

The use of modeling tools in pharmaceutical processes has been increasingly reported in the literature in recent years given the proven benefits for process design. This review focused specifically on process modeling tools related to the production of tablets via continuous processing. An overview of continuous tableting processes, including direct compaction, wet granulation and dry granulation manufacturing routes was provided and a discussion of

the unit operations, involved was included. A discussion of the equations involved in unit operation models was presented, focusing primarily in lower dimensional models given the applicability with integrated process models. Computational tools, including those related to detailed process modeling, reduced-order modeling and integrated flowsheet simulation have been discussed in some detail. The control system of continuous pharmaceutical manufacturing processes has been reviewed. End to end continuous pharmaceutical manufacturing, drop on demand manufacturing process, and different downstream continuous pharmaceutical manufacturing processes (DC, RC, WG, tumble mixer) were considered in this review. The control system design, tuning, control hardware and software integration, and control system implementation into the pilot plant has been demonstrated in detail via direct compaction continuous tablet manufacturing case study.

Acknowledgments

This work is supported by the National Science Foundation Engineering Research Center on Structured Organic Particulate Systems (ERC-CSOPS) through grant NSF-ECC 0540855.

References

[1] Muzzio, F.J. (2006)Engineering approaches for pharmaceutical processes, in *Pharmaceutical Process Scale-Up* (ed.) M. Levin, 2006, Taylor and Francis: Boca Raton, pp. 57–69.
[2] US FDA (2002) *Pharmaceutical cGMPs for the 21st Century: A Risk-based Approach*, FDA, Rockville.
[3] Plumb, K. (2005) Continuous processing in the pharmaceutical industry: changing the mind set. *Chemical Engineering Research and Design.* **83**(6): 730–738.
[4] Kaufman, B. and G.D. Novack (2003) Compliance issues in manufacturing of drugs. *The Ocular Surface*, **1**(2): 80–85.
[5] Ting, N. (2006) *Dose Finding in Drug Development*, Springer, New York.
[6] Makrydaki, F.G., C; Saranteas, K. (2010) Dynamic optimization of a batch pharmaceutical reaction using the design of dynamic experiments (dode): the case of an asymmetric catalytic hydrogenation reaction, in *Dynamics and Control of Process Systems*. Leuven, Brussels.
[7] Toulouse, C.E.A. (1996) Optimisation and scale-up of batch chemical reactors: impact of safety constraints. *Chemical Engineering Science*, **51**(10).
[8] Raaymakers, W.H. (2000) Scheduling multipurpose batch process industries with no-wait restrictions by simulated annealing. *European Journal of Operational Research*, **2000**: 126.
[9] PwC (2008) La R&D virtuelle, in *Pharma 2020*, Industrie Pharmaceutique et des Sciences de la Vie, PricewaterhouseCoopers, Paris.
[10] PwC (2012) From vision to decision, in *Pharma 2020*, Global Pharmaceuticals and Life Sciences Industry Group, PricewaterhouseCoopers, London.
[11] Gernaey, K.V., A.E. Cervera-Padrell, and J.M. Woodley (2012) A perspective on PSE in pharmaceutical process development and innovation. *Computers and Chemical Engineering*, **42**: 15–29.
[12] Gernaey, K.V. and R. Gani (2010) A model-based systems approach to pharmaceutical product-process design and analysis. *Chemical Engineering Science*, **65**(21): 5757–5769.
[13] Lee, S., *et al.* (2015) Modernizing pharmaceutical manufacturing: from batch to continuous production. *Journal of Pharmaceutical Innovation*, **10**(3): 191–199.

[14] Leuenberger, H. (2001) New trends in the production of pharmaceutical granules: batch versus continuous processing. *European Journal of Pharmaceutics and Biopharmaceutics*, **52**(3) 289–296.

[15] Mascia, S., *et al.* (2013) End-to-end continuous manufacturing of pharmaceuticals: integrated synthesis, purification, and final dosage formation. *Angewandte Chemie International Edition*, **52**(47): 12359–12363.

[16] Ooi, S.M., *et al.* (2013) Continuous processing and the applications of online tools in pharmaceutical product manufacture: developments and examples. *Therapeutic Delivery*, **4**(4): 463–470.

[17] Rantanen, J. and J. Khinast (2015) The future of pharmaceutical manufacturing sciences. *Journal of Pharmaceutical Sciences*, **2015**:1–10.

[18] Stephanopoulos, G. and G.V. Reklaitis (2011) Process systems engineering: from Solvay to modern bio- and nanotechnology. A history of development, successes and prospects for the future. *Chemical Engineering Science*, **66**(19): 4272–4306.

[19] Himmelblau, D. and K. Bischoff (1968) *Process Analysis and Simulation: Deterministic Systems*. John Wiley & Sons, Inc., New York.

[20] Sargent, R. (2010) Verification and validation of simulation models. in *Proceedings of the 2010 Winter Simulation Conference*. pp. 20–10.

[21] Rajalahti, T. and O.M. Kvalheim (2011) Multivariate data analysis in pharmaceutics: a tutorial review. *International Journal of Pharmacology.* **417**(1/2): 280–290.

[22] Kremer, D.M. and B.C. Hancock (2006) Process simulation in the pharmaceutical industry: a review of some basic physical models. *Journal of Pharmacology Science*, **95**(3): 517–529.

[23] Perry, R.H.G. and Don W. (2005) *Perry's Chemical Engineering Handbook*. 5th edn., McGraw-Hill, New York.

[24] Keshani, S., *et al.*, (2015) Spray drying: An overview on wall deposition, process and modeling. *Journal of Food Engineering*, **146**: 152–162.

[25] Wörner, M. (2012) Numerical modeling of multiphase flows in microfluidics and micro process engineering: a review of methods and applications. *Microfluidics and Nanofluidics* **12**(6): 841–886.

[26] Sahni, E.K. and B. Chaudhuri (2012) Contact drying: A review of experimental and mechanistic modeling approaches. *International Journal of Pharmaceutics*, **434**(1/2): 334–348.

[27] Rathore, A.S. and H. Winkle (2009) Quality by design for biopharmaceuticals. *Nature Biotechnology*, **27**(1) 26–34.

[28] Cervera-Padrell, A.E., *et al.* (2012) Active pharmaceutical ingredient (API) production involving continuous processes – A process system engineering (PSE)-assisted design framework. *European Journal of Pharmaceutics and Biopharmaceutics*, **82**(2): 437–456.

[29] McKenzie, P., *et al.* (2006) Can pharmaceutical process development become high tech? *AIChE Journal*, **52**(12): 3990–3994.

[30] Ketterhagen, W.R., M.T. am Ende, and B.C. Hancock (2009) Process modeling in the pharmaceutical industry using the discrete element method. *Journal of Pharmaceutical Sciences*, **98**(2): 442–470.

[31] Agatonovic-Kustrin S., B.R. (2000) Basic concepts of artificial neural network (ANN) modeling and its application in the pharmaceutical research. *Journal of Pharmaceutical and Biomedical Analysis*, **2000**: 22.

[32] Bezerra, M.A., *et al.* (2008) Response surface methodology (RSM) as a tool for optimization in analytical chemistry. *Talanta*, **76**(5): 965–977.

[33] Boukouvala, F., F.J. Muzzio, and M.G. Ierapetritou (2011) Dynamic data-driven modeling of pharmaceutical processes. *Industrial and Engineering Chemistry Research*, **50**(11): 6743–6754.

[34] Horstemeyer, M.F. (2010) Multiscale modeling: a review, in *Practical Aspects of Computational Chemistry* (eds) J. Leszczynski and M.K. Shukla, Springer, Dordrecht. pp. 87–135.
[35] Balci, O. (2010) Golden rules of verification, validation, testing, and certification of modeling and simulation applications. *SCS M&S Magazine*, **2010**: 4.
[36] Tolsma, J.E., J.A. Clabaugh, and P.I. Barton (2002) Symbolic Incorporation of External Procedures into Process Modeling Environments. *Industrial Engineering Chemical Research*, **41**: 3687–3876.
[37] Morari, M. (1983) Flexibility and resiliency of process systems. *Computers and Chemical Engineering*, **7**(4): 423–437.
[38] Swaney, R.E., Grossmann, I.E. (1985) An index for operational flexibility in chemical process design part I: formulation and theory. *AIChE Journal*, **1985**: 36.
[39] Floudas, C.A., Gümüs, Z.H., Ierapetritou, M.G. (2001) Global optimization in design under uncertainty: feasibility test and flexibility index problems. *Industrial and Engineering Chemistry Research*, **40**: 4267–4282.
[40] Singh, R., *et al.* (2014) A systematic framework for onsite design and implementation of a control system in a continuous tablet manufacturing process. *Computers and Chemical Engineering*, **66**: 186–200.
[41] Singh, R., *et al.* (2014) Closed-loop feedback control of a continuous pharmaceutical tablet manufacturing process via wet granulation. *Journal of Pharmaceutical Innovation*, **9**(1): 16–37.
[42] Singh, R., K.V. Gernaey, and R. Gani (2009) Model-based computer-aided framework for design of process monitoring and analysis systems. *Computers and Chemical Engineering*, **33**(1): 22–42.
[43] Singh, R., *et al.* (2014) Implementation of an advanced hybrid MPC-PID control system using PAT tools into a direct compaction continuous pharmaceutical tablet manufacturing pilot plant. *International Journal of Pharmaceutics*, **473**(1/2): 38–54.
[44] Singh, R., M. Ierapetritou, and R. Ramachandran (2013) System-wide hybrid MPC–PID control of a continuous pharmaceutical tablet manufacturing process via direct compaction. *European Journal of Pharmaceutics and Biopharmaceutics*, **85**(3, part B): 1164–1182.
[45] Singh, R., M. Ierapetritou, and R. Ramachandran (2013) Hybrid advanced control of flexible multipurpose continuous tablet manufacturing process via direct compaction, in *Computer Aided Chemical Engineering*, (eds) K. Andrzej and T. Ilkka, Elsevier, London,pp. 757–762.
[46] US FDA (2004) *Challenge and Opportunity on the Critical Path to New Medical Products*. US Food and Drug Administration, Rockville.
[47] US FDA/CDER (2005) *Process Analytical Technology – (PAT) Initiative*. US Food and Drug Administration/ Center for Drug Evaluation and Research, Rockville.
[48] Singh, R., *et al.* (2015) A combined feed-forward/feed-back control system for a QbD based continuous tablet manufacturing process. *Processes*, **3**: 339–356.
[49] Singh, R., *et al.* (2015) Real time monitoring of powder blend bulk density for coupled feed-forward/feed-back control of a continuous direct compaction tablet manufacturing process. *International Journal of Pharmaceutics*, **495**(1): 612–625.
[50] Singh, R., Sen, M., Ierapetritou, M., Ramachandran, R. (2015) Integrated moving horizon based real time optimization and hybrid MPC-PID control of a direct compaction continuous tablet manufacturing process. *Journal of Pharmaceutical Innovation*, **10**(3): 233–253.
[51] Ierapetritou, M., *et al.* (2013) Model-predictive design control and optimization. *PharmTech*, **2013**: 40–41.
[52] Singh, R., Ierapetritou, M., and Ramachandran, R. (2012) An engineering study on the enhanced control and operation of continuous manufacturing of pharmaceutical tablets via roller compaction. *International Journal of Pharmaceutics*, **2012**: 49–56.

[53] Gibson, M. (2009) *Pharmaceutical Preformulation and Formulation: A Practical Guide from Candidate Drug Selection to Commercial Dosage Form*, Informa Healthcare, New York.

[54] Castle, B.C. and R.A. Forbes (2013) Impact of quality by design in process development on the analytical control strategy for a small-molecule drug substance. *Journal of Pharmaceutical Innovation*, **8**(4): 247–264.

[55] Challa, S. and R. Potumarthi (2013) Chemometrics-based process analytical technology (PAT) tools: applications and adaptation in pharmaceutical and biopharmaceutical industries. *Applied Biochemistry and Biotechnology*, **169**(1): 66–76.

[56] Ende, D., *et al.* (2007) API quality by design example from the torcetrapib manufacturing process. *Journal of Pharmaceutical Innovation*, **2**(3/4): 71–86.

[57] Saraswat, M., *et al.* (2013) Preparative purification of recombinant proteins: current status and future trends. *Biomedical Research International*, **2013**: 312709.

[58] Norioka, T., *et al.* (2013) A novel approach to establishing the design space for the oral formulation manufacturing process. *Chemical and Pharmaceutical Bulletin*, **61**(1): 39–49.

[59] Norioka, T., *et al.* (2011) Optimization of the manufacturing process for oral formulations using multivariate statistical methods. *Journal of Pharmaceutical Innovation*, **6**(3): 157–169.

[60] Rogers, A., A. Hashemi, and M. Ierapetritou (2013) Modeling of particulate processes for the continuous manufacture of solid-based pharmaceutical dosage forms. *Processes*, **1**(2): 67–127.

[61] Zhu, H.P., *et al.* (2008) Discrete particle simulation of particulate systems: A review of major applications and findings. *Chemical Engineering Science*, **63**(23): 5728–5770.

[62] Wu, C.Y., *et al.* (2005) Modelling the mechanical behaviour of pharmaceutical powders during compaction. *Powder Technology*, **152**(1/3): 107–117.

[63] Jajcevic, D., *et al.* (2013) Large-scale CFD-DEM simulations of fluidized granular systems. *Chemical Engineering Science*, **98**: 298–310.

[64] Verkoeijen, D., *et al.* (2002) Population balances for particulate processes — a volume approach. *Chemical Engineering Science*, **57**(12): 2287–2303.

[65] Barrasso, D. and R. Ramachandran (2012) A comparison of model order reduction techniques for a four-dimensional population balance model describing multi-component wet granulation processes. *Chemical Engineering Science*, **80**: 380–392.

[66] Sen, M., *et al.* (2012) Multi-dimensional population balance modeling and experimental validation of continuous powder mixing processes. *Chemical Engineering Science*, **80**: 349–360.

[67] Kumar, A., *et al.* (2013) Model-based analysis of high shear wet granulation from batch to continuous processes in pharmaceutical production – A critical review. *European Journal of Pharmaceutics and Biopharmaceutics*, **85**(3, part B): 814–832.

[68] Sen, M., *et al.* (2013) Mathematical development and comparison of a hybrid PBM-DEM description of a continuous powder mixing process. *Journal of Powder Technology*, **2013**: 11.

[69] Barrasso, D., A. Tamrakar, and R. Ramachandran (2014) A reduced order PBM-ANN model of a multi-scale PBM-DEM description of a wet granulation process. *Chemical Engineering Science*, **119**: 319–329.

[70] Kremer, D.M. and B.C. Hancock (2006) Process simulation in the pharmaceutical industry: A review of some basic physical models. *Journal of Pharmaceutical Sciences*, **95**(3): 517–529.

[71] Hsu, S.H., G.V. Reklaitis, and V. Venkatasubramanian (2010) Modeling and control of roller compaction for pharmaceutical manufacturing. Part I: Process dynamics and control framework. *Journal of Pharmaceutical Innovation*, **5**: 14–23.

[72] Bindhumadhavan, G., *et al.* (2005) Roll compaction of a pharmaceutical excipient: Experimental validation of rolling theory for granular solids. *Chemical Engineering Science*, **60**: 3891–3897.

[73] Johanson, J.R. (1965) A rolling theory for granular solids. *ASME Journal of Applied Mechanics*, **E32**(4): 842–848.

[74] Reynolds, G., *et al.* (2010) Practical application of roller compaction process modeling. *Computers and Chemical Engineering*, **34**: 1049–1057.
[75] Kuentz, M. and H. Leuenberger (2000) A new model for the hardness of a compacted particle systems, applied to tablets of pharmaceutical polymers. *Powder Technology*, **111**: 145–153.
[76] Gao, Y., *et al.* (2011) Characterizing continuous powder mixing using residence time distribution. *Chemical Engineering Science*, **66**(3): 417–425.
[77] Gao, Y., F.J. Muzzio, and M.G. Ierapetritou (2012) A review of the residence time distribution (RTD) applications in solid unit operations. *Powder Technology*, **228**: 416–423.
[78] Danckwerts, P.V. (1953) Continuous flow systems: Distribution of residence times. *Chemical Engineering Science*, **2**(1): 1–13.
[79] Froment, G., K. Bischoff, and J. Wilde (2011) *Chemical Reactor Analysis and Design*. John Wiley & Son, Inc., Hoboken.
[80] Shvartsman, S.Y., *et al.* (2000) Order reduction for nonlinear dynamic models of distributed reacting systems. *Journal of Process Control*, **10**(2/3): 177–184.
[81] Boukouvala, F., *et al.* (2013) Reduced-order discrete element method modeling. *Chemical Engineering Science*, **95**: 12–26.
[82] Lang, Y.D., *et al.* (2009) Reduced order model based on principal component analysis for process simulation and optimization. *Energy and Fuels*, **23**(3): 1695–1706.
[83] Rogers, A. and M. Ierapetritou (2014) Challenges and opportunities in pharmaceutical manufacturing modeling and optimization, in *Computer Aided Chemical Engineering*, (eds) J.D.S. Mario R. Eden and P.T. Gavin, Elsevier, New York,pp. 144–149.
[84] Ammarcha, C., *et al.* (2012) Predicting bulk powder flow dynamics in a continuous mixer operating in transitory regimes. *Advanced Powder Technology*, **23**(6): 787–800.
[85] Benyahia, B., R. Lakerveld, and P.I. Barton (2012) A plant-wide dynamic model of a continuous pharmaceutical process. *Industrial and Engineering Chemistry Research*, **51**(47): 15393–15412.
[86] Boukouvala, F., *et al.* (2012) An integrated approach for dynamic flowsheet modeling and sensitivity analysis of a continuous tablet manufacturing process. *Computers and Chemical Engineering*, **42**: 30–47.
[87] Duchaine, F., T. Morel, and L.Y. M. Gicquel (2009) Computational-fluid-dynamics-based kriging optimization tool for aeronautical combustion chambers. *AIAA Journal*, **47**(3): 631–645.
[88] Wendt, J. (2009) *Computational Fluid Dynamics*. Springer, New York.
[89] Xia, B. and D.-W. Sun (2002) Applications of computational fluid dynamics (CFD) in the food industry: a review. *Computers and Electronics in Agriculture*, **34**(1/3): 5–24.
[90] Engisch, W. and F. Muzzio (2015) Loss-in-weight feeding trials case study: pharmaceutical formulation. *Journal of Pharmaceutical Innovation*, **10**(1): 56–75.
[91] Engisch, W.E. and F.J. Muzzio (2012) Method for characterization of loss-in-weight feeder equipment. *Powder Technology*, **228**: 395–403.
[92] Engisch, W.E. and F.J. Muzzio (2015) Feedrate deviations caused by hopper refill of loss-in-weight feeders. *Powder Technology*, **283**: 389–400.
[93] Jia, Z., *et al.* (2009) Predictive modeling for pharmaceutical processes using Kriging and response surface. *Journal of Pharmaceutical Innovation*, **4**(4): 174–186.
[94] Yu, Y. (1997) Theorical modelling and experimental investigation of the performance of screw feeders, in *Mechanical Engineering*. University of Wollongong, Darwin.
[95] Bortolamasi, M. and J. Fottner (2001) Design and sizing of screw feeders, *International Congress for Particle Technology*, pp. 12–14.
[96] Cleary, P.W. (2007) DEM modelling of particulate flow in a screw feeder model description. *Progress in Computational Fluid Dynamics*, **7**(2): 128–138.

[97] Guoming, H., *et al.* (2010) Modeling and simulation of transportation system of screw conveyors by the discrete element method, *Mechanic Automation and Control Engineering 2010 International Conference*. MACE, Adelaide, PP 20–30.

[98] Owen, P.J. and P.W. Cleary (2010) Screw conveyor performance: comparison of discrete element modelling with laboratory experiments. *Progress in Computational Fluid Dynamics*, **10**(5): 327–333.

[99] Owen, P.J. and P.W. Cleary (2009) Prediction of screw conveyor performance using the discrete element method (DEM). *Powder Technology*, **193**(3): 274–288.

[100] Fernandez, J.W., P.W. Cleary, and W. McBride (2011) Effect of screw design on hopper drawdown of spherical particles in a horizontal screw feeder. *Chemical Engineering Science*, **66**(22): 5585–5601.

[101] US FDA (2004) *Guidance for Industry: PAT - A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance*, FDA, Rockville.

[102] US FDA (2014) *Guidance for Industry Current Good Manufacturing Practice*, FDA, Rockville.

[103] Escotet-Espinoza, M.S., *et al.* (2014) Modeling of residence time distribution in continuous solid oral dose manufacturing processes. in *American Institute of Chemical Engineering Annual Meeting*. AIChE, Atlanta.

[104] Falk, J., *et al.* (2015) Mass flow and variability in screw feeding of biomass powders - Relations to particle and bulk properties. *Powder Technology*, **276**: 80–88.

[105] Boukouvala, F., F.J. Muzzio, and M.G. Ierapetritou (2010) Design space of pharmaceutical processes using data-driven-based methods. *Journal of Pharmaceutical Innovation*, **5**(3): 119–137.

[106] Pernenkil, L. and C.L. Cooney (2006) A review on the continuous blending of powders. *Chemical Engineering Science*, **61**(2): 720–742.

[107] Osorio, J.G., *et al.* (2015) Continuous Powder Mixing. *Pharmaceutical Blending and Mixing*, Springer, Heidelberg, pp. 101–127.

[108] Vanarase, A.U., *et al.* (2010) Real-time monitoring of drug concentration in a continuous powder mixing process using NIR spectroscopy. *Chemical Engineering Science*, **65**(21): 5728–5733.

[109] Vanarase, A.U., J.G. Osorio, and F.J. Muzzio (2013) Effects of powder flow properties and shear environment on the performance of continuous mixing of pharmaceutical powders. *Powder Technology*, **246**: 63–72.

[110] Vanarase, A.U. and F.J. Muzzio (2011) Effect of operating conditions and design parameters in a continuous powder mixer. *Powder Technology*, **208**(1): 26–36.

[111] Ketterhagen, W.R., M.T.A. Ende, and B.C. Hancock (2009) Process Modeling in the Pharmaceutical Industry using the discrete element method. *Journal of Pharmaceutical Sciences*, **98**(2): 442–470.

[112] Bertrand, F., L.-A. Leclaire, and G. Levecque (2005) DEM-based models for the mixing of granular materials. *Chemical Engineering Science*, **60**: 2517–2531.

[113] Gao, Y.J., M. Ierapetritou, and F. Muzzio (2012) Periodic section modeling of convective continuous powder mixing processes. *AIChE Journal*, **58**(1): 69–78.

[114] Gao, Y., Muzzio, F.J., Ierapetritou, M.G. (2012) Optimizing continuous powder mixing processes using periodic section modeling. *Chemical Engineering Science*, **80**: 70–80.

[115] Barrasso, D., *et al.* (2015) A multi-scale, mechanistic model of a wet granulation process using a novel bi-directional PBM–DEM coupling algorithm. *Chemical Engineering Science*, **123**: 500–513.

[116] Florian-Algarin, M. and R. Méndez (2015) Blend uniformity and powder phenomena inside the continuous tumble mixer using DEM simulations. *AIChE Journal*, **61**(3): 792–801.

[117] Sen, M., *et al.* (2013) Multi-scale flowsheet simulation of an integrated continuous purification–downstream pharmaceutical manufacturing process. *International Journal of Pharmaceutics*,**445**(1/2): 29–38.
[118] Rogers, A., *et al.* (2013) Dynamic reduced-order modeling of particulate systems for pharmaceutical unit operations, in *AIChE Annual Meeting*. AIChE, San Fransisco.
[119] Rogers, A. and M.G. Ierapetritou (2014) Discrete element reduced-order modeling of dynamic particulate systems. *AIChE Journal*, **60**(9): 3184–3194.
[120] Portillo, P.M., Vanarase, A.U., Ingram, A., Seville, J.K. (2010) Investigation of the effect of impeller rotation rate, powder flowrate, and cohesion on powder flow behavior in a continuous blender using PEPT. *Chemical Engineering Science*, **65**: 5685–5668.
[121] Portillo, P.M., M.G. Ierapetritou, and F.J. Muzzio (2008) Characterization of continuous convective powder mixing processes. *Powder Technology*, **182**(3): 368–378.
[122] Levenspiel, O. (1999) *Chemical Reaction Engineering*. John Wiley & Sons, Inc., New York.
[123] Portillo, P.M., Ierapetritou, M.G., Muzzio, F.J. (2009) Effects of rotation rate, mixing angle, and cohesion in two continuous mixers – A statistical approachwder. *Powder Technology*, **194**: 217–227.
[124] Marikh, K., *et al.* (2006) Flow analysis and markov chain modelling to quantify the agitation effect in a continuous powder mixer. *Chemical Engineering Research and Design*, **84**(11): 1059–1074.
[125] Marikh, K., *et al.* (2008) Influence of stirrer type on mixture homogeneity in continuous powder mixing: A model case and a pharmaceutical case. *Chemical Engineering Research and Design*, **86**(9A): 1027–1037.
[126] Marikh, K., *et al.* (2005) Experimental study of the stirring conditions taking place in a pilot plant continuous mixer of particulate solids. *Powder Technology*, **157**(1/3): 138–143.
[127] Berthiaux, H., K. Marikh, and C. Gatumel (2008) Continuous mixing of powder mixtures with pharmaceutical process constraints. *Chemical Engineering and Processing*, **47**(12): 2315–2322.
[128] Portillo, P.M., Muzzio, F.J., Ierapetritou, M.G. (2008) Using compartment modeling to investigate mixing behavior of a conituous mixer. *Journal of Pharmaceutical Innovation*, **3**: 161–174.
[129] Portillo, P.M., F.J. Muzzio, and M.G. Ierapetritou (2007) Hybrid DEM-compartment modeling approach for granular mixing. *AIChE Journal*, **53**(1): 119–128.
[130] Boukouvala, F. and M. Ierapetritou (2013) Surrogate-based optimization of expensive flowsheet modeling for continuous pharmaceutical manufacturing. *Journal of Pharmaceutical Innovation*, **8**(2): 131–145.
[131] Boukouvala, F., F.J. Muzzio, and M.G. Ierapetritou (2010) Predictive modeling of pharmaceutical processes with missing and noisy data. *AIChE Journal*, **56**(11): 2860–2872.
[132] Mendez, R., F. Muzzio, and C. Velazquez (2010) Study of the effects of feed frames on powder blend properties during the filling of tablet press dies. *Powder Technology*, **200**(3): 105–116.
[133] Ward, H.W., *et al.* (2013) Monitoring blend potency in a tablet press feed frame using near infrared spectroscopy. *Journal of Pharmaceutical and Biomedical Analysis*, **80**: 18–23.
[134] Šašić, S., *et al.* (2015) Detailed analysis of the online near-infrared spectra of pharmaceutical blend in a rotary tablet press feed frame. *Journal of Pharmaceutical and Biomedical Analysis*, **103**: 73–79.
[135] Mateo-Ortiz, D., F.J. Muzzio, and R. Méndez (2014) Particle size segregation promoted by powder flow in confined space: The die filling process case. *Powder Technology*, **262**: 215–222.
[136] Mateo-Ortiz, D. and R. Méndez (2015) Relationship between residence time distribution and forces applied by paddles on powder attrition during the die filling process. *Powder Technology*, **278**: 111–117.

[137] Boukouvala, F. (2013) Integrated simulation and optimization of continuous pharmaceutical manufacturing, in *Chemical and Biochemical Engineering*. Rutgers, The State University of New Jersey, New Brunswick.
[138] Govedarica, B., *et al.* (2012) The use of single particle mechanical properties for predicting the compressibility of pharmaceutical materials. *Powder Technology*, **225**: 43–51.
[139] Razavi, S.M., M. Gonzalez, and A.M. Cuitiño (2015) General and mechanistic optimal relationships for tensile strength of doubly convex tablets under diametrical compression. *International Journal of Pharmaceutics*, **484**(1/2): 29–37.
[140] Jerier, J.F., *et al.* (2011) Study of cold powder compaction by using the discrete element method. *Powder Technology*, **208**(2): 537–541.
[141] Zavaliangos, A., *et al.* (2008) Temperature evolution during compaction of pharmaceutical powders. *J Pharm Sci*, **97**(8): 3291–3304.
[142] Jackson, S., I.C. Sinka, and A.C. Cocks (2007) The effect of suction during die fill on a rotary tablet press. *European Journal of Pharmacology and Biopharmaceutics*, **65**(2): 253–256.
[143] Koynov, A., I. Akseli, and A.M. Cuitiño (2011) Modeling and simulation of compact strength due to particle bonding using a hybrid discrete-continuum approach. *International Journal of Pharmaceutics*, **418**(2): 273–285.
[144] Siiriä, S., *et al.* (2011) 3D simulation of internal tablet strength during tableting. *AAPS PharmSciTech*, **12**(2): 593–603.
[145] Patel, S., A.M. Kaushal, and A.K. Bansal (2007) Effect of particle size and compression force on compaction behavior and derived mathematical parameters of compressibility. *Pharmaceutical Research*, **24**(1): 111–124.
[146] Mehrotra, A., *et al.* (2009) A modeling approach for understanding effects of powder flow properties on tablet weight variability. *Powder Technology*, **188**(3): 295–300.
[147] Heckel, R.W. (1961) Density pressure relationships in powder compaction. *Transactions of the Metallurgical Society AIME*, **221**: 671–675.
[148] Heckel, R.W. (1961) An analysis of powder compaction phenomena. *Transactions of the Metallurgical Society AIME*, **221**: 1001–1008.
[149] Kawakita, K., Lüdde, K.H. (1971) Some considerations on powder compression equations. *Powder Technology*, **4**: 61–68.
[150] Mazel, V., Busignies, V., Duca, S., Leclerc, B., Tchoreloff, P. (2011) Original predictive approach to the compressibility of pharmaceutical powder mixtures based on the Kawakita equation. *International Journal of Pharmaceutics*, **410**: 92–98.
[151] Frenning, G., Nordström, J., Alderborn, G. (2009) Effective Kawakita parameters for binary mixtures. *Powder Technology*, **189**: 270–275.
[152] Kuentz, M., Leuenberger, H. (1999) Pressure susceptibility of polymer tablets as a critical property: a modified Heckel equation. *Journal of Pharmaceutical Sciences*, **88**(2): 174–179.
[153] Kuentz, M., Lunenberger, H. (2000) A new model for the hardness of a compacted particle systems, applied to tablets of pharmaceutical polymers. *Powder Technology*, **111**: 145–153.
[154] Juban, A., *et al.* (2015) Predictive model for tensile strength of pharmaceutical tablets based on local hardness measurements. *International Journal of Pharmaceutics*, **490**(1/2): 438–445.
[155] Shang, C., *et al.* (2013) Break force and tensile strength relationships for curved faced tablets subject to diametrical compression. *International Journal of Pharmaceutics*, **442**(1/2): 57–64.
[156] Singh, R., K.V. Gernaey, and R. Gani (2010) ICAS-PAT: A software for design, analysis and validation of PAT systems. *Computers and Chemical Engineering*, **34**(7): 1108–1136.
[157] Reynolds, G., *et al.* (2010) Practical application of roller compaction process modeling. *Computers and Chemical Engineering*, **34**(7): 1049–1057.
[158] Peter, S., R.F. Lammens, and K.-J. Steffens (2010) Roller compaction/Dry granulation: Use of the thin layer model for predicting densities and forces during roller compaction. *Powder Technology*, **199**(2): 165–175.

[159] Barrasso, D., *et al.* (2013) Population balance model validation and prediction of CQAs for continuous milling processes: toward QbDin pharmaceutical drug product manufacturing. *Journal of Pharmaceutical Innovation*, **8**(3): 147–162.
[160] Michrafy, A., *et al.* (2011) Experimental and numerical analyses of homogeneity over strip width in roll compaction. *Powder Technology*, **206**(1/2): 154–160.
[161] Michrafy, A., *et al.* (2011) Analysis of strain stress state in roller compaction process. *Powder Technology*, **208**(2): 417–422.
[162] Dec, R.T., A. Zavaliangos, and J.C. Cunningham (2003) Comparison of various modeling methods for analysis of powder compaction in roller press. *Powder Technology*, **130**(1/3): 265–271.
[163] Guigon, and O. Simon (2003) Roll press design—influence of force feed systems on compaction. *Powder Technology*, **130**(1/3): 41–48.
[164] García-Muñoz, S., S. Dolph, and H.W. Ward II, (2010) Handling uncertainty in the establishment of a design space for the manufacture of a pharmaceutical product. *Computers and Chemical Engineering*, **34**(7): 1098–1107.
[165] Dec, R.T., Zavaliangos, A., Cunningham, J.C. (2003) Comparison of various modeling methods for analysis of powder compaction in roller press. *Powder Technology*, **130**: 265–271.
[166] Johanson, J.R. (1965) A rolling theory for granular solids. *AMSE Journal of Applied Mechanics*, **E32**(4): 842–848.
[167] Bindhumadhavan, G., *et al.* (2005) Roll compaction of a pharmaceutical excipient: Experimental validation of rolling theory for granular solids. *Chemical Engineering Science*, **60**(14): 3891–3897.
[168] Katashinskii, V.P. and M.B. Shtern (1983) Stress–strain state of powder being rolled in the densification zone. *Soviet Powder Metallurgy and Metal Ceramics*, **22**(12): 972–976.
[169] Yu, S. (2012) Roll compaction of pharmaceutical excipients, in *Chemical Engineering*. University of Birmingham, Birmingham.
[170] Souihi, N., *et al.* (2013) Design space estimation of the roller compaction process. *Industrial and Engineering Chemistry Research*, **52**(35): 12408–12419.
[171] Boukouvala, F., Niotis,V., Ramachandran, R. Muzzio, F.J., Ierapetritou, M.G. (2012) An integrated approach for dynamic flowsheet modeling and sensitivity analysis of a continuous tablet manufacturing process. *Computers and Chemical Engineering*, **42**: 30–47.
[172] Rogers, A. and M. Ierapetritou (2016) Mathematical tools for the quantitative definition of a design space, in *Process Simulation and Data Modeling in Solid Oral Drug Development and Manufacture*, (eds) M.G. Ierapetritou and R. Ramachandran, Springer, New York. pp. 225–279.
[173] Katashinskii, V.P. and M.B. Shtern (1983) Stressed-strained state of powder being rolled in the densification zone. I. Mathematical model of rolling in the densification zone. *Soviet Powder Metallurgy and Metal Ceramics*, **22**(11): 882–885.
[174] Faure, A., York, P., Rowe, R.C. (2001) Process control and scale-up of pharmaceutical wet granulation processes: a review. *European Journal of Pharmaceutics and Biopharmaceutics*, **52**: 269–277.
[175] Barrasso, D. and R. Ramachandran (2015) Multi-scale modeling of granulation processes: Bi-directional coupling of PBM with DEM via collision frequencies. *Chemical Engineering Research and Design*, **93**: 304–317.
[176] Chaudhury, A., *et al.* (2014) Population balance model development, validation, and prediction of CQAs of a high-shear wet granulation process: towards QbD in drug product pharmaceutical manufacturing. *Journal of Pharmaceutical Innovation*, **9**(1): 53–64.
[177] Barasso, D. and R. Ramachandran (2012) A comparison of model order reduction techniques for a four-dimensional population balance model describing multi-component wet granulation process. *Chemical Engineering Science*, **80**: 380–392.

[178] Kayrak-Talay, D., *et al.* (2013) Quality by design for wet granulation in pharmaceutical processing: Assessing models for a priori design and scaling. *Powder Technology*, **240**: 7–18.
[179] Gannt, J.A., Cameron, I.T., Litster, J.D., Gatzke, E.P. (2006) Determination of coalescence kernels for high-shear granulation using DEM simulations. *Powder Technology*, **170**: 53–63.
[180] Gantt, J.A. and E.P. Gatzke (2006) A stochastic technique for multidimensional granulation modeling. *AIChE Journal*, **52**(9): 3067–3077.
[181] Liu, L.X., Litster, J.D. (2002) Population balance modelling of granulation with a physically based coalescence kernel. *Chemical Engineering Science*, **57**: 2183–2191.
[182] Ramachandran, R. and P.I. Barton (2010) Effective parameter estimation within a multi-dimensional population balance model framework. *Chemical Engineering Science*,**65**(16): 4884–4893.
[183] Mortier, S.T.F.C., De Beer, T., Gernaey, K.V., Remon, J.P., Vervaet, C., Nopens, I. (2011) Mechanistic modelling of fluidized bed drying processes of wet porous granules: A review. *European Journal of Pharmaceutics and Biopharmaceutics*, **79**: 205–225.
[184] Mortier, S.T.F.C., Van Daele, T., Gernaey, K.V., De Beer, T., Nopens, I. (2013) Reduction of a single granule drying model: An essential step in preparation of a population balance model with a continuous growth term. *AIChE Journal*, **59**(4): 1127–1138.
[185] Mortier, S.T.F.C., Gernaey, K.V., De Beer, T. Nopens, I. (2013) Development of a population balance model of a pharmaceutical drying process and testing solution methods. *Computers and Chemical Engineering*, **50**: 39–53.
[186] Deng, X., *et al.* (2015) Discrete element method simulation of a conical screen mill: A continuous dry coating device. *Chemical Engineering Science*, **125**: 58–74.
[187] Sen, M., *et al.* (2013) Multi-scale flowsheet simulation of an integrated continuous purification-downstream pharmaceutical manufacturing process. *International Journal of Pharmaceutics*, **445**(1/2): 29–38.
[188] Akkisetty, P.K., Lee, U., Reklaitis, G.V., Venkatasubramanian, V. (2010) Population balance model-based hybrid neural network for a pharmaceutical milling process. *Journal Pharmaceutic Innovations*, **5**: 161–168.
[189] Bilgili, E., Scarlett, B. (2005) Population balance modeling of non-linear effects in milling processes. *Powder Technology*, **153**: 59–71.
[190] Tsoy, E.N. (2012) A modelling approach for derivation of the breakage functions. *Chemical Engineering Science*, **80**: 361–364.
[191] Ramachandran, R., *et al.* (2009) A mechanistic model for breakage in population balances of granulation: Theoretical kernel development and experimental validation. *Chemical Engineering Research and Design*, **87**(4A): 598–614.
[192] Pandya, J.D. and L.A. Spielman (1983) Floc breakage in agitated suspensions: Effect of agitation rate. *Chemical Engineering Science*, **38**(12): 1983–1992.
[193] Majumder, A., *et al.* (2012) Lattice Boltzmann method for population balance equations with simultaneous growth, nucleation, aggregation and breakage. *Chemical Engineering Science*, **69**(1): 316–328.
[194] Bilgili, L.C., M. (2011) Quantitative analysis of multi-particle interactions during particle breakage: A discrete non-linear population balance framework. *Powder Technology*, **213**: 162–173.
[195] Foss, B.A., Lohmann, B., Marquardt, W. (1998) A field study of the industrial modeling process. *Journal of Process Control*, **8**(5/6): 325–338.
[196] Cameron, I.T. and G.D. Ingram (2008) A survey of industrial process modelling across the product and process lifecycle. *Computers and Chemical Engineering*, **32**(3): 420–438.
[197] Papadopoulous, A.I., Seferlis, P. (2009) Generic modelling, design and optimization of industrial phosphoric acid production processes. *Chemical Engineering and Processing: Process Intensification*, **48**(1): 493–506.

[198] Othman, M.R., *et al.* (2010) A modular approach to sustainability assessment and decision support in chemical process design. *Industrial and Engineering Chemistry Research*, **49**(17): 7870–7881.
[199] Boukouvala, F., *et al.* (2012) An integrated approach for dynamic flowsheet modeling and sensitivity analysis of a continuous tablet manufacturing process. *Computers and Chemical Engineering*, **42**: 30–47.
[200] Toebermann, J.-C., Rosenkranz, J., Werther, J., and Gruhn, G. (2000) Block-oriented process simulation of solids processes. *Computers and Chemical Engineering*, **23**: 1773–1782.
[201] Hartage, E.U., Pogodda, M., Reimers, C., Schwier, D., Gruhn, G., Werther J. (2006) Flowsheet simulation of solids processes. *KONA*, **24**: 146–156.
[202] Richard, L., *et al.* (2013) Averaging level control to reduce off-spec material in a continuous pharmaceutical pilot plant. *Processes*, **1**: 330–348.
[203] Içten, E., Z.K. Nagy, and G.V. Reklaitis (2015) Process control of a dropwise additive manufacturing system for pharmaceuticals using polynomial chaos expansion based surrogate model. *Computers and Chemical Engineering*, **83**: 221–231.
[204] Baronsky-Probst, J., *et al.* (2011) Process design and control of a twin screw hot melt extrusion for continuous pharmaceutical tamper-resistant tablet production. *European Journal of Pharmaceutical Sciences*, **4**: 46–56.
[205] Burggraeve, A., *et al.* (2012) Development of a fluid bed granulation process control strategy based on real-time process and product measurements. *Talanta*, **100**: 293–302.
[206] Bardin, M., P.C. Knight, and J.P.K. Seville (2004) On control of particle size distribution in granulation using high-shear mixers. *Powder Technology*, **140**(3): 169–175.
[207] Sanders, C.F.W., M.J. Hounslow, and F.J. Doyle III, (2009) Identification of models for control of wet granulation. *Powder Technology*, **188**(3): 255–263.
[208] Gatzke, E.P. and F.J. Doyle III, (2001) Model predictive control of a granulation system using soft output constraints and prioritized control objectives. *Powder Technology*, **121**(2/3): 149–158.
[209] Pottmann, M., *et al.* (2000) Model-based control of a granulation system. *Powder Technology*, **108**(2/3): 192–201.
[210] Seborg, D.E., T.F. Edgar, and D.A. Mellichamp (2003) *Process Dynamics and Control*, 2nd edn. John Wiley & Sons, Inc., New York.
[211] Trierweiler, J.O. and L.A. Farina (2003) RPN tuning strategy for model predictive control. *Journal of Process Control*, **13**(7): 591–598.
[212] Singh, R., K.V. Gernaey, and R. Gani (2010) An ontological knowledge-based system for the selection of process monitoring and analysis tools. *Computers and Chemical Engineering*, **34**(7): 1137–1154.
[213] Valencia, A.F. (2015) *Modeling and Control of Continuous Tumble Mixing of Granular Materials*. University of Puerto Rico, Mayagüez.
[214] Richard, L., *et al.* (2013) Model-based design of a plant-wide control strategy for a continuous pharmaceutical plant. *AIChE J.*, **59**(10): 3671–3685.
[215] Bristol, E. (1966) On a new measure of interaction for multivariable process control. *IEEE Transactions on Automatic Control*, **11**(1): 133–134.
[216] Edwardo, S., *et al.* (2014) Active polymorphic feedback control of crystallization processes using a combined Raman and ATR-UV/Vis spectroscopy approach. *Crystal Growth and Design*, **14**: 1839–1850.
[217] Markl, D., *et al.* (2015) In-line monitoring of a pharmaceutical pan coating process by optical coherence tomography. *Journal of Pharmaceutical Sciences*, **104**(8): 2531–2540.
[218] Ziegler, J.G. and B. Nichols (1942) Optimum settings for automatic controllers. *Transactions of the ASME*, **64**: 759–765.

[219] Singh, R., *et al.* (2014) A systematic framework for onsite design and implementation of a control system in a continuous tablet manufacturing process. *Computers and Chemical Engineering*, **66**: 186–200.
[220] Wojsznis, W., *et al.* (2003) Practical approach to tuning MPC*. *ISA Transactions*, **42**(1): 149–162.
[221] Engisch, W.E. and F.J. Muzzio (2012) Method for characterization of loss-in-weight feeder equipment. *Powder Technology*, **228**: 395–403.
[222] Cunningham, J.C., D. Winstead, and A. Zavaliangos (2010) Understanding variation in roller compaction through finite element-based process modeling. *Computers and Chemical Engineering*, **34**(7): 1058–1071.
[223] Reynolds, G., Ingale, R., Roberts, R., Kothari, S., Gururagan, B. (2010) Practical application of roller compaction process modeling. *Computers and Chemical Engineering*, **34**: 1049–1057.
[224] Schaber, S.D., *et al.* (2011) Economic Analysis of Integrated Continuous and Batch Pharmaceutical Manufacturing: A Case Study. *Industrial and Engineering Chemistry Research*, **50**(17): 10083–10092.
[225] Paavola, M.E.A. (2013) 3D population balance model for continuous twin screw granulator. *Chemical Engineering Transactions*, **13**: 32.
[226] Sahni, E.K., Chaudhuri, B. (2012) Contact drying: A review of experimental and mechanistic modeling approaches. *International Journal of Pharmaceutics*, **434**: 334–348.
[227] Parrott, E.L. (1974) Milling of pharmaceutical solids. *Journal of Pharmaceutical Sciences*, **63**(6): 813–829.
[228] Khadka, P., *et al.* (2014) Pharmaceutical particle technologies: An approach to improve drug solubility, dissolution and bioavailability. *Asian Journal of Pharmaceutical Sciences*, **9**(6): 304–316.
[229] Ng, K.M. (2002) Design and development of solids processes – a process systems engineering perspective. *Powder Technology*, **126**(3): 205–210.
[230] Norton, T. and D.-W. Sun (2006) Computational fluid dynamics (CFD) – an effective and efficient design and analysis tool for the food industry: A review. *Trends in Food Science and Technology*, **17**(11): 600–620.
[231] Versteeg, H.M., (2007) *An Introduction to Computational Fluid Dynamics*. Pearson Education, New York.
[232] Immanuel, C.D. and F.J. Doyle III, (2005) Solution technique for a multi-dimensional population balance model describing granulation processes. *Powder Technology*, **156**(2/3): 213–225.
[233] Wang, F.Y. and I.T. Cameron (2007) A multi-form modelling approach to the dynamics and control of drum granulation processes. *Powder Technology*, **179**(1/2): 2–11.
[234] Kleijnen, J.P.C. (2009) Kriging metamodeling in simulation: A review. *European Journal of Operational Research*, **192**(3): 707–716.
[235] Lebensztajn, L.E.A. (2004) Kriging: A useful tool for electromagnetic device optimization. *IEEE Transaction on Magnetics*, **40**: 2.
[236] Raymond H.M. (1995) *Response Surface Methodology: Process and Product in Optimization Using Designed Experiments*, John Wiley & Sons, Inc., New York.
[237] Khuri, A.I. and S. Mukhopadhyay (2010) Response surface methodology. *Wiley Interdisciplinary Reviews: Computational Statistics*, **2**(2): 128–149.
[238] Genyuan Li S.-W.W. (2000) High dimensional model representations (HDMR): concepts and applications. *Powder Technology*, **172**: 22–31.
[239] Li G., Wu, S.-W., Rabitz H. (2002) Practical approaches to construct RS-HDMR component functions. *Journal of Physical Chemistry A*, **106**: 37.
[240] Agatonovic-Kustrin, S. and R. Beresford (2000) Basic concepts of artificial neural network (ANN) modeling and its application in pharmaceutical research. *Journal of Pharmaceutical and Biomedical Analysis*, **22**(5): 717–727.

3

Regulatory and Quality Considerations for Continuous Manufacturing

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Continuous Manufacturing of Pharmaceuticals, First Edition.
Edited by Peter Kleinebudde, Johannes Khinast, and Jukka Rantanen.
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3.1 Introduction

In a continuous manufacturing process, input raw materials or mixtures are fed into a process train continuously while the processed output materials are removed continuously. Although the amount of material being processed at any given instance may be relatively small in a continuous manufacturing process, the process may be run over a period of time to generate quantities of finished product with desired product quality. In an end to end continuous pharmaceutical manufacturing process, different process steps are sequenced together to form a continuous production line where product removal can occur concurrently at the same rate as the input of raw materials. There may also be situations where a pharmaceutical manufacturing process consists of a combination of batch and continuous process steps.

Continuous processing provides opportunities for improvements in pharmaceutical manufacturing, including:

1. An integrated process with fewer separate unit operations (e.g., safer, faster response times, more efficient, shorter times, integrated control);
2. Smaller equipment footprint (e.g., potentially small active pharmaceutical ingredient (API) requirements, more flexibility, lower costs, environmental friendly);
3. An enhanced development approach [quality by design (QbD), incorporating process analytical technology (PAT)];
4. Real time product quality information;
5. Potentially easier to scale up/down to accommodate changing supply needs.

3.2 Current Regulatory Environment

The current regulatory environment supports advancing regulatory science and innovation, which may include abandoning some traditional manufacturing practices in favor of *cleaner*, *more flexible*, *and more efficient* continuous manufacturing. Regulatory authorities in the three International Conference on Harmonisation (ICH) regions and an increasing number of non-ICH regulators are encouraging industry to adopt new technology as supported by ICH Q8 (R2), Q9, Q10, and Q11 and the introduction of QbD concepts, emphasizing science- and risk-based approaches to assure product quality.

The regulatory expectation for assurance of reliable and predictive processing, that is technically sound, risk-based, and relevant to product quality in a commercial setting, is the same for batch and continuous processing.

3.3 Existing Relevant Regulations, Guidelines, and Standards Supporting Continuous Manufacturing

3.3.1 ICH Guidelines

The emergence of ICH Q8 (R2), Q9, Q10, and Q11 guidelines and accompanying ICH Q-IWG points to consider (PTC) and Q&A documents emphasized that a prospective science- and risk-based approach to development and lifecycle management could increase the assurance of quality of pharmaceutical products. Collectively, these guidelines reinforce the adoption of risk-based (Q9), systematic and science-based approaches

[Q8 (R2) and Q11], and a robust pharmaceutical quality system (PQS) (Q10), to establish an increased level of process understanding and product knowledge. Although many of the tools described in these ICH guidelines are not, by themselves, new, the implementation of the concepts within a more systematic and integrated framework based on sound science and quality risk management introduce a fundamental paradigm shift in product development and manufacturing.

3.3.2 United States Food and Drug Administration Guidances

The *United States Food and Drug Administration (US FDA) Guidance for Industry PAT-A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance* specifically identifies that the introduction of continuous processing may be one of the outcomes from the adoption of a scientific risk-based approach to process design. Process understanding, control strategies, plus on-line, in-line, or at-line measurement of critical quality attributes (CQA) can provide for control strategies that include real time quality evaluation that is at least equivalent to, or better than, laboratory-based testing on collected samples.

3.3.3 US FDA Guidance on Process Validation

US FDA Guidance To Industry: Process Validation: General Principles and Practices aligns process validation activities with a product lifecycle concept. The guidance encourages the use of modern pharmaceutical development concepts, quality risk management, and quality systems at all stages of the manufacturing process lifecycle. The lifecycle concept links product and process development, qualification of the commercial manufacturing process. (The term *commercial manufacturing process* refers to the manufacturing process resulting in *comercial product*; (i.e., drug that is marketed, distributed, and sold or intended to be sold). In this usage, the term *commercial manufacturing process* does not include clinical trial or treatment IND material), and maintenance of the process in a state of control during routine commercial production. This guidance supports process improvement and innovation, including continuous manufacturing.

3.3.4 American Society for Testing and Materials Standards

The *American Society for Testing and Materials (ASTM) E2537 Validation: Standard Guide for the Application of Continuous Quality Verification to Pharmaceutical and Biopharmaceutical* describes continuous quality verification (CQV) as an approach to process validation where a manufacturing process (or supporting utility system) performance is continuously monitored, evaluated, and adjusted as necessary. It is a science-based approach to verify that a process is capable and will consistently produce product meeting its predetermined CQAs. With real time quality assurance (that CQV will provide), the desired quality attributes are ensured through continuous assessment during manufacture. Data from production batches can serve to validate the process and reflect the total system design concept, essentially supporting validation with each manufacturing batch.

3.3.5 European Union Guidelines

The ICH Guidelines referenced above apply in the European Union (EU). EU guidelines that might be particularly relevant to continuous manufacturing include the *Guidelines for Process Validation* where the concept of continuous process verification (CPV) is introduced; the *Guideline on NIR* as it is often used as a PAT tool for process monitoring and/or control, and the *Guideline on Real Time Release Testing.* Although not required, continuous manufacturing is commonly coupled with real time release testing (RTRT). Additionally, the European Medicines Agency (EMA) set up a Process Analytical Technology Team in 2003 to support PAT and QbD activities in the EU. The team provides a forum for dialogue between the Quality Working Party (QWP), the Biologics Working Party (BWP), and the Good Manufacturing Practice/Good Distribution Practice Inspectors' Working Group.

In summary, global and regional regulations, guidelines, and standards are supportive of innovative pharmaceutical development and manufacturing approaches. Current guidelines may need to be re-evaluated with consideration of continuous manufacturing operations as experience is gained.

3.4 Regulatory Considerations

As the pharmaceutical industry and regulatory agencies gain more experience with continuous manufacturing, several regulatory aspects will need to be explored in order to link the principles and practice. Although the current regulatory framework is adequate to allow for continuous manufacturing, traditional concepts may need to be further explored or challenged to advance the implementation of continuous processes from traditional approaches.

The following aspects are applicable to both batch and continuous processing. In evaluating the differences and similarities between batch and continuous processing, it is important to note that different approaches may be needed for continuous processing:

- As a matter of principle, the definition of a batch should be stated prior to manufacture. Although each continuous process has unique considerations, one may consider a batch definition based on quantity manufactured or duration of the process.
- In-process controls (IPCs) and sampling considerations will be different. For example, continuous unit operations may have different operating principles; therefore, the sampling considerations (e.g., size, frequency, location) may differ. Setting up acceptance criteria considering representative tested sample size (e.g., large N) should be considered.
- Acceptable procedures for handling deviations including detection and removal of non-conforming material in continuous manufacturing processes must be defined.
- The rationale for testing of a continuous batch should be based on considerations of the system dynamics such as time or amount of material impacted by deviation or reaction time for material rejection.
- The importance of the raw material specifications and the lot-to-lot variability of raw materials to the process performance should be considered.
- Sources of variability should be considered during development and controlled during validation and continuous verification.

- The evaluation of manufacturing changes and their impact on product quality should reflect relevant risks associated with continuous manufacturing which may be different from batch processes.

Early and frequent communication between manufacturers and regulators is encouraged to ensure alignment and clarify continuous manufacturing requirements. Some regulatory agencies have the opportunity for site visits prior to submission of a regulatory application (US FDA ORA Field Management Directive No. 135; http://www.fda.gov/ICECI/Inspections/FieldManagement Directives/ucm096042.htm).

3.4.1 Development Considerations for Continuous Manufacturing

3.4.1.1 Process Development

Pharmaceutical companies can use a variety of manufacturing strategies in developing continuous processes for drug substance and drug product manufacture. Possible options include:

1. A fully continuous process where all drug substance and/or drug product unit operations are sequenced together to form a single production line;
2. A fully continuous process as above, but with two or more production lines in parallel;
3. A "hybrid" of batch and continuous mode unit operations.

A continuous manufacturing process emphasizing key design and control aspects would be described in sufficient detail in regulatory submissions similar to traditional/batch manufacturing processes.

The regulatory submission could include a general description of the overall manufacturing strategy. This general description could consist of a brief outline of each unit operation and its mode of operation (i.e., batch or continuous), including interfaces between unit operations, the material flow, proposed flow rate and total process operation time, critical process parameters, and their ranges and IPC points.

The pharmaceutical development section of the regulatory submission can also include information specific to development and modeling of the continuous process. These aspects may include residence time distributions, system dynamics, disturbance propagation, information on model set up, maintenance, and model improvement.

The definition of a batch or lot has significant regulatory implications, particularly with respect to cGMPs, product recalls, and other regulatory or enforcement actions. Although the definition of a batch or lot could differ for individual continuous manufacturing operations, the underlying regulatory expectation is that the batch or lot is of "uniform character and quality within specified limits." The manufacturing process should include a clear definition of a batch or lot.

Additional considerations for the continuous manufacturing process include:

- Flow rate of material through the process.
- Factors affecting "scale" of the continuous manufacturing process. For example, "scale out" plans (i.e., multiple lines operated in parallel considered to be the same lot), flow rate ranges, and operation time ranges.
- IPC points.

- Control systems integral to the control strategy. For example, feedback or feedforward controls utilized for maintaining a state of control in the system or automated valves used for rejecting material deemed to be out of specification, and diverting non-conformance materials.

3.4.1.2 Control Strategy

The same regulatory requirements apply for continuous manufacturing as for batch manufacturing, specifically in that a control strategy should be developed that ensures that the manufacturing process produces product of the intended quality in a reproducible way. Similar to any other mode of manufacturing, a control strategy is unique for different products and manufacturing processes. A control strategy developed for a batch process may not be appropriate when the same unit operation is operated in continuous mode. Therefore, the control strategy should be re-examined if a unit operation that was operated in a batch mode is replaced by a unit operation in a continuous mode.

Aspects unique to a continuous operation should be assessed in developing the overall control strategy of a continuous process. As material flows through the system and product is formed continuously over a long period of time, the process, product, or environmental conditions could potentially vary over time resulting in product of variable quality. A robust control strategy is essential to ensure the consistent quality of product formed over the total operation time.

3.4.2 Special Considerations for Control Strategy in Continuous Manufacturing

Some aspects to consider in establishing the control strategy for a continuous process are listed below:

State of control: A continuous manufacturing process maintaining a state of control provides assurance that the desired product quality is consistently met. There may be situations such as sudden or uncontrolled changes in a process variable such as at startup and shutdown, where assurance is needed that the product is homogeneous and of acceptable quality. However, the process is expected to reach and maintain a state of control after some time. Startup, shutdown, and transient states should be considered. The control strategy could establish criteria for determining that the process is under a state of control and procedures for handling process startup, shutdown, or process variables change. The control strategy could include appropriate process attributes or ranges for monitoring or a multivariate process control approach. The ability to detect process upsets and institute corrective actions to bring the process back into conformance, such as feedback control, help ensure the consistency of a continuous manufacturing process over the production time.

Raw materials and intermediates: Continuous processing may require additional raw material control, if multiple lots of a raw material are used in a single continuous manufacturing batch. Control approaches should be based on product and process understanding and may include use of PAT tools. The determination of the characteristics of an intermediate product that may or may not be isolated may be more difficult in a continuous process due to the limited sampling ports and high sampling frequencies. The quality

attributes of raw materials and excipients should be linked to the product CQAs and the needs of the process.

Equipment: It is important to consider equipment control aspects for continuous processes. Equipment such as chemical reactors, loss in weight feeders, twin screw blenders, extruders, and tablet presses may need to run for long periods of time and may require special maintenance, calibration, and periodic review to ensure their performance.

Uniform quality and character of product: The criteria for determining that the product manufactured is of uniform quality and character, the robustness of the process to produce product of desired quality in the presence of variability, and the ability of the system to detect non-conforming product should be established.

Product collection or rejection: Although the continuous process is expected to maintain a state of control, there may be temporary process upsets or disturbances over the total operation time. There may be situations where product made during the disturbance is removed, whereas the remainder of the product is retained. Other situations may warrant rejection of the entire batch instead of a portion of a batch. Establishing a priori criteria, based on the level of risk, for product collection, product rejection, rejection of an entire batch, and indicating how or who makes those decisions prevent ad hoc decisions by manufacturing personnel and helps to ensure the desired quality and consistency of the collected product. The disposition strategy of product obtained during start up and shut down should also be established.

Traceability: Traceability of incoming materials to the final product should be understood and documented. Traceability can be supported by data on system dynamics such as residence time distributions. Planned disturbances such as feeder refills and how those disturbances propagate through the system should also be considered.

Process monitoring and sampling: The purpose of the monitoring system is to manage planned changes and respond to unplanned disturbances. Samples (whether analyzed inline or extracted) should be representative and the frequency of measurement or sample acquisition time should consider material flow rate, system dynamics, and unit dose. Potential failure modes of any sampling devices employed should be understood. Flow rate, frequency of sampling, time constants, and residence time distributions: all of these have impact on how to test for quality at any point (raw material attributes, IPCs, final quality) and also how to achieve feedback and feed forward control. Consideration can be given to define a flexible monitoring frequency where more monitoring is expected in periods where there is a greater risk of variability (e.g., following addition of a new lot of input material, or following process parameter adjustments based on feedforward/feedback loops).

Risk assessment and failure modes: Process robustness is an important factor for consistent operation of a continuous process, which in turn helps to ensure the product formed is of uniform quality and character. A thorough understanding of the risks and failure modes of the process and its associated measurement and control systems allows the development of effective risk mitigation strategies and helps support manufacturing changes and process improvements that may occur over the lifecycle of a product. Knowledge of risks and failure modes is also useful to make risk-based decisions.

Scaleup: Scaleup can be achieved in several ways including running longer time, increasing throughput, or parallel units (scale out). Increasing throughput at fixed size units can have effects on residence time distributions and time constants. These effects should be

considered during development. Representative sampling may be affected. Physical and physicochemical conditions may be affected by throughput, and criticality of parameters may change following change in throughput.

Specifications: Specifications will be required as part of the control strategy. Continuous processes may include an RTRT approach for some quality attributes, but it is possible to foresee traditional end product testing on offline samples. RTRT approaches may require an enhanced sampling plan compared to traditional release testing and may involve a larger sample size.

3.4.3 Stability Considerations for Continuous Manufacturing

Regulatory requirements for having adequate stability data do not change between batch manufacturing and continuous processing. There are some differences that should be considered when developing the stability plan.

3.4.3.1 Representative Stability Batches

As scale may not be a significant risk to stability when using continuous manufacturing, deciding how to determine a representative batch may be different than when using a batch process. Current ICH stability criteria for process scaleup provide a good starting point for consideration. A risk assessment can be used to understand the potential risks of the proposed lot sizes and determine a representative lot that has similar characteristics to the lots being manufactured.

3.4.3.2 Considerations for Stability

Stability data should fulfil the initial filing requirements where data are generated on the critical to quality and stability-indicating attributes on representative batches. Representative batches for annual stability requirements will also need to be defined.

3.4.3.3 Stability Considerations at Scaleup

The risks arising from batch scaleup are different for continuous manufacturing. These potential risks may include heat buildup over time, material buildup in the equipment, events occurring at the interface between unit operations, different surface area/volume rations, and other risks that may be product specific. These risks are usually easily manageable for continuous manufacturing so change in scale might not need additional stability testing.

A change in scale for a continuous process could include volume, time, and/or multiple manufacturing trains that run in parallel. Each of these has its own potential risks to stability that should be considered when determining the type of stability testing needed to assess the impact, if any, of scaleup on product stability.

3.4.3.4 Stability Considerations for Site Change/Technology Transfer

When transferring a continuous process from one site to another, the impact on stability should be considered. Considerations can include equipment changes, scale changes,

and potential location impacts such as different raw material suppliers, and/or different environmental conditions.

3.4.3.5 Location of Information in Regulatory Submissions

The development of a continuous manufacturing process is likely to include information obtained from enhanced process development approaches. ICH Q11 and ICH Q8(R2) recommend that process development information be submitted in section 3.2.S.2.6 of the CTD for drug substance and 3.2.P.2 (Pharmaceutical Development) of the CTD for drug product. The two guidance documents also contain specific suggestions for the provision of information from development studies.

In general, the recommendations of ICH Q11 and ICH Q8(R2) could be adopted for placement of information supporting a continuous manufacturing application. ICH Q11 and Q8(R2) recommend the control strategy information be summarized in the specification sections, 3.2.S.4.5 and 3.2.P.5.6, for the drug substance and drug product, respectively. The ICH Q8 and ICH Q11 suggestions for placement of information in a regulatory filing could also be used for continuous manufacturing applications. As in other regulatory submissions, the applicant could clearly indicate where the different information is located in the application. Similar to batch processes, certain aspects of the control strategy are handled under the applicant's PQS (see ICH Q10). As with other QbD approaches, the current CTD format does not provide an optimum platform to present the regulatory development story.

3.5 Quality/GMP Considerations

Current good manufacturing practices do not preclude the introduction of new manufacturing technologies and embody the flexibility needed to support continuous manufacturing. Points to consider when implementing continuous manufacturing in a cGMP environment are noted below.

3.5.1 Pharmaceutical Quality Systems

To implement continuous manufacturing in an existing PQS, a site should evaluate its PQS and associated elements to determine if design and content of the PQS should be modified. In addition to the areas described in Q10 (e.g., pharmaceutical development, manufacturing, quality, regulatory affairs, and medical), the manufacturing site should establish continuous manufacturing expertise in the quality organization. As with traditional batch processes, change management for continuous processes should incorporate an assessment of potential risks.

3.5.2 Batch Release

Current regulatory cGMP guidance considers a "batch" as a defined quantity of product processed in one process or series of processes so that it is expected to be uniform character and quality, within specified limits, and is produced according to a single manufacturing order during the same cycle of manufacture. This principle applies equally to continuous

processes where the amount of material subject to a quality disposition decision could be defined as:

- Process time when all of the material is discharged from the process between two specific time points
- Product quantity when a specific quantity of material is produced
- Process event when all of the material is produced between two specific process events
- Raw material quantity input when all of the material that is "intended" to contain a specific lot or quantity of a specified input material.

If continued state of control operation is demonstrated, it could be possible to designate large quantities of material as "homogenous" even though different lots of raw materials and different processing conditions may have been used. The key is to have clearly defined criteria, which describe state of control operation, and to establish the product and process data, which demonstrate continued conformance with these criteria.

Continuous manufacturing within a controlled and reproducible operation may have periods of process perturbation. Therefore during development, these perturbations should be considered and criteria developed to define the state of control. Procedures should be established to define a process of diversion of waste should adverse perturbations occur.

Material traceability is vital in the event of problems with product quality such as contamination, raw material, recalls, or other GMP failures. An understanding of material flow in the system is essential to track or divert the potentially affected material. Close monitoring of product and process data could support further decisions to be made, such as bringing the process back to target via process control measures, which could help to minimize the impact of process failures.

3.5.3 Startup and Shutdown Procedures

During periods of startup, shutdown, and processing of material, it is possible that not all unit operations within a continuous production line will be in a state of control at the same time. For example:

- During shutdown, material may not be fed and discharged simultaneously. Material will continue to be processed and discharged after the feeding operation has stopped.
- Where small amounts of material are produced, the first unit operation could already be shut down while the material is processed further.

The start from which onward material gets collected for later can be defined relative to the time point when the process is in a state of control, and significant process parameters, in-process material attributes, CPPs, and CQAs are all within their specified criteria, needs to be defined. The same determination can be made for shutdown periods and for transient adverse perturbations requiring material diversion.

The ability of the process to reach and detect the period of normal production is normally demonstrated during process verification.

The time available for a given process transformation can be determined by the residence time of the material in a specific process environment and can be used to accommodate the necessary reaction time for completion. As the material flows through the system, rate-limiting elements within the process can be considered to ensure that the end point

conditions are met within the time available (e.g., required process to complete a chemical reaction or drying operation).

An understanding and subsequent verification of the various time constants of the process is specifically important in determining the expected behavior of the process during startup and shutdown and hence the impact on quality decisions regarding the disposition of material manufactured during this period.

3.5.4 State of Control: Product Collection and In-process Sampling

A state of control provides assurance of continued process performance and product quality, as described in ICH Q10.

Acceptance criteria based on monitoring at an adequate frequency can be established to ensure that the entirety of the material subjected to the release decision is compliant to the applicable specifications. Decisions of diversion and/or rejection of material that does not meet acceptance criteria should be based on reliable data and understanding of process dynamics.

Consideration should be given to confirm the ability of the system to produce consistent product over extended operation and to understand potential mechanisms of failure and degradation of performance together with the methods of detection. Risk analysis techniques including practical tests and/or modeling tools can be employed to ensure that any impact on product quality is understood and appropriately managed overall operating states, including during normal operations.

In order to define the period of product collection, the process residence time and residence time distribution is typically quantified during start up and normal operation conditions as well as during shutdown conditions. In particular, an understanding and quantification of the residence time distribution can be used to determine which material may have been affected by a deviation in process conditions and hence the range of product within the scope of any investigation or disposition decision.

In some cases, the maximum length of time over which the process is run could be determined by monitoring specific product attributes or process parameters and equipment capability rather than by validating a single fixed length of run time.

Sampling, testing, quality control procedures, and equipment mechanisms to detect and reject materials which are out of specification are typically necessary. In order to ensure that a process parameter or product attribute cannot move outside the predefined acceptable process window or acceptable range without being detected, it is important to ensure that the control and monitoring system is able to take measurements at a frequency which is appropriate to the dynamic response time of the parameter or attribute. Measurement frequency considerations include the intrinsic process risk (e.g., higher risk at lower API dose), the known process variability, and the required residence time in the equipment to complete transformation (e.g., higher risk at faster throughput).

3.5.5 Process Validation and CPV

Within process validation and continued process verification, process robustness and reproducibility is typically evaluated. The development of a continuous process can

follow established principles which are applied generally within pharmaceutical process development. Existing guidances and standards can also be consulted for process validation and when applicable, CPV. In general, the requirements for including process validation and lifecycle management information in the regulatory submission can be expected to be the same as that for batch processes.

In verifying the ability of the system to control and achieve the specified performance, the following should be considered for continuous processes:

1. Are the process conditions, which determine that the system is under normal state of control including verification that CPPs and CQAs within target range?
2. Is the process control system able to reach and detect the start of acceptable product production? In order to demonstrate this ability as part of the process verification, a set of startup and shutdown activities could be included. The number of startups and shutdowns included in the verification activities could be determined based on a risk analysis for a given process and the unique critical considerations for that process including process robustness, and number and interrelationship of CPPs/CQAs.
3. Is the system able to reach and maintain the intended process conditions over the entire process? The expected process run time and worst case (longest) process run time could be considered as a component of the process validation activities.
4. What is the ability to detect excursions from the target CPP or CQA values? These excursions can require the diversion of non-conforming material based on understanding of process dynamics or shutdown of the process.
5. What is the impact of changes in the process production rate and/or equipment scale changes on the process dynamics?
6. Does the process remain in a state of control (the validated state) during commercial manufacture? This is one goal of the final validation stage.
7. Is the validation data statistically trended and reviewed by trained personnel? The information collected can help to verify that the quality attributes are being appropriately controlled throughout the process.

    a. Quantitative, statistical methods are recommended whenever appropriate and feasible.
    b. Scrutiny of intra-batch as well as inter-batch variation should be considered.

Continuous process verification as an alternative validation approach may be particularly well suited to the evaluation of continuous manufacturing processes. It can utilize in-line, on-line, or at-line monitoring or controls to evaluate process performance. These are based on product and process knowledge and understanding. Monitoring can also be combined with dynamic control systems in order to adjust the process to maintain output quality. This capability also provides the advantage of enhanced assurance of intra-batch uniformity, fundamental to the objectives of process validation. Some process measurements and controls in support of RTRT can also play a role in CPV.

Using this approach, data from production batches can often serve to validate the process and demonstrate processing in accordance with the total system design concept, essentially supporting validation with each manufacturing batch replacing a conventional process validation approach (e.g., three-batch validation at set-point) that was historically used.

As with traditional batch manufacturing, system qualification of commercial equipment and other supporting systems, including PAT and/or automation, is necessary. This may be especially critical if some systems are providing real-time monitoring and control of a continuous manufacturing process.

3.5.6 Material Traceability in Continuous Manufacturing

For any specific quantity of product produced from a continuous processing system and released to the market, it may be necessary to reliably link the relevant process information to the specific quantity of product in a timely manner and to identify the lots of raw materials from which it has been manufactured. This typically includes an understanding of residence time and residence time distribution at relevant flow rates and operating conditions. An appropriately reliable and timely link between relevant product quality information and any specifically identified product can be decisions related to later release, including considerations such as diversion of unacceptable product during the process.

Other traceability considerations include the overall flow of product in the system or subsections of the system, and the ability to account for material which may be removed deliberately from the system for sampling or unintentionally lost from the system due unforeseen events, or diverting.

3.5.7 Handling of Raw Material and In-process Material

Continuous processing may pose challenges due to behaviors of both equipment and material, for example starting materials in a hopper, or intermediates in process which occur gradually over a long period and which are not easily observed during batch processing or short tests runs. Determining the handling and flow properties of materials to be processed as early as possible within the development of the product can greatly aid in appropriate design of the process equipment. Transport processes may cause some degree of transformation (e.g., segregation and/or attrition of powders) and therefore careful consideration should be given.

Risk analysis, practical tests, and modeling techniques should be considered in order to determine and evaluate potential challenges in maintaining stable process conditions during the operation of a continuous process over the full length of the production run. Consideration should be given to the potential for undesirable buildup of material due to physical and chemical processes, stability of starting materials, or intermediates being held in buffer tanks.

3.5.8 Detection and Treatment for Non-conformity

A key consideration in any quality system is handling non-conformities and/or deviations. Although process and product understanding are extremely important, unexpected discrepancies will undoubtedly occur during the product lifecycle. These issues may raise questions regarding the existing process and product understanding and may require additional process development. A robust corrective action and preventive action (CAPA)

system is integral to product and process improvement. The methodology used can aid in product and process improvements and enhanced product and process understanding.

There are some key elements for consideration in a continuous manufacturing process. The process control/monitoring system should be adequately developed to recognize a normal process, and be able to identify when the data are divergent enough to represent a departure that could have direct impact on quality. In these cases, the product should be diverted for further determination and potential rejection/waste. As a consequence, it is possible that not all of the materials that were originally fed into the process, as part of the original single manufacturing order, will be in the finished product intended for release to the market.

Continuous manufacturing could also have more complex IPCs and monitoring that could include the potential for unintended failure modes. Such failure modes should be considered in setting a robust control system.

Handling of non-conformities for continuous manufacturing and batch manufacturing are generally similar. Some key differences for consideration are described in sections *Personnel Procedures and Training*, *Material Carry-Over*, *Material Diversion*, *Production Floor Product Monitoring*, and *Raw Material Variability*.

3.5.9 Personnel Procedures and Training

In a robust PQS, when new technology such as continuous manufacturing and PAT tools are implemented, it is important to evaluate the impact, if any, on existing quality, production, and engineering procedures. Procedures that define who is responsible for halting and resuming operations, how non-conformities are documented, investigating discrepancies, and taking remedial action may need to be modified based on the new technology. New procedures and/or modifications will typically require additional personnel training.

3.5.10 Material Carry-over

It is important to ensure that any investigations are properly extended to other batches of the same drug product as appropriate. Thus, understanding how the facility defines a batch is critical to ensuring that the investigation is properly extended to related batches. The amount of allowable carryover volume should be considered.

3.5.11 Material Diversion

Establishing thorough procedures to describe handling of non-conformances including out-of-specification or out-of-trend results that requires product stream diversion during manufacturing is critical. Procedures describing when the product stream is to be diverted and when collection is to be reinitiated should be established prior to the occurrence of non-conformance. If non-conforming material is detected it should be diverted at the next appropriate point. If the in-process monitoring detects that a certain amount of material needs to be diverted, this diverted material should be investigated before determining the disposition of the batch.

3.5.12 Production Floor Product Monitoring

Process analytical technology tools are more likely to be implemented in continuous manufacturing processes on the production floor (in-line, at-line, or on-line). As with batch manufacture, if a discrepancy is identified on the production floor, it should be investigated prior to material disposition. For example, if in-line testing results are trending towards failure, end product testing is not sufficient to release associated material; an associated investigation should be performed.

Breakdown in the monitoring equipment should also be investigated. A procedure can often be established for the use of alternative testing or monitoring approaches in cases of equipment failure. The alternative approach could involve use of end product testing or other options, while maintaining an acceptable level of quality.

3.5.13 Raw Material Variability

For continuous manufacturing processes, it is important to consider raw material variability as a potential root cause when performing an investigation. In a batch process, multiple raw material batches are typically mixed at the start of manufacturing. This may not be true for continuous manufacturing, where different lots of raw material can be used during the production campaign. Multiple raw material lots used in a single product batch, though they might meet specification, could introduce variability into the finished product.

3.5.14 Cleaning Validation

Cleaning and cleaning validation considerations for continuous manufacturing equipment and systems are primarily the same as those for non-continuous manufacturing equipment and systems. As continuous unit operations may be smaller than those in batch processing, the surface area to volume ratios will differ. For continuous manufacturing, either dedicated or non-dedicated equipment could be utilized. Principles for determining acceptance criteria for cleaning agent, bioburden, endotoxin, and degradation products for cleaning validation of dedicated equipment are essentially the same as for non-dedicated equipment.

If dedicated equipment is utilized for continuous manufacturing, cross-contamination of the active ingredient from the previous product to the next product is not an issue. Therefore, cleaning validation related to the active itself is generally not considered a requirement for dedicated equipment. However, cleaning validation should be considered for dedicated equipment if carryover of the cleaning agent or the contribution of bioburden or degradation byproducts to the next manufactured batch is a concern. Manufacturers should conduct risk assessments for all cleaning scenarios in order to ensure that manufactured product using that equipment complies with quality expectations (e.g., residue removal, lot integrity and regulatory expectations). It is considered to be best practice to document effectiveness of a cleaning process for dedicated equipment even if “visually clean” is the only criteria.

The cleaning process and frequency of cleaning should be defined and the effectiveness verified periodically.

Considerations for the design and verification of the cleaning process include:

1. Material holdup and buildup. on equipment, piping, instruments (e.g., on-line analyzers, sensors), filters
2. Degradation of the material within the process
3. Microbiological growth
4. Formation of chemical films
5. Cleaning agent removal, if applicable
6. Product change-over, if applicable
7. Equipment size and complexity, for example, equipment used for continuous manufacturing may be smaller in size and may have more intricate parts and components that maybe more difficult to clean.

The cleaning frequency for continuous manufacturing equipment and systems could be defined in terms of:

1. Elapsed operating time
2. Quantity of material processed
3. History of process conditions or deviations
4. Product change-over, if applicable

Cleaning strategies employed for continuous manufacturing can include:

1. Stopping production or diverting or tagging material as non-releasable material (e.g., if reliant on a single analyzer that requires attention)
2. Providing a second, duplicate piece of equipment or instrument (e.g., analyzer)
3. In process cleaning of instruments such as sensors (e.g., air washes)

3.5.15 Equipment Failure

Continuous processing may pose challenges due to degrading performance of the equipment, which could occur gradually over a long period and hence might not be easily observed during batch processing or short tests runs. The control system should consider how equipment performance is to be detected and addressed.

Risk analysis, practical tests, and modeling techniques can be beneficial to determine and evaluate potential challenges in maintaining stable process conditions during the operation of a continuous process over the full length of the required production run.

Control systems can be designed to address where one unit operation within a process line is determined to be disproportionally vulnerable (for example, due to degradation or lack of robustness) or prone to equipment failure. Such considerations could include rapid change over or redundancy/parallelization/duplication of critical equipment elements.

3.6 Quality Considerations for Bridging Existing Batch Manufacturing to Continuous Manufacturing

Situations could arise where a continuous manufacturing process is proposed after using a different process, such as a batch process, to make the clinical, bioequivalence, or registration stability batches. A company could also wish to introduce a continuous process as a post-approval manufacturing change.

In such situations, a risk-based approach can be useful to determine the type of bridging information to support continued product quality.

A change from batch to continuous is likely to result in changes to equipment, process parameters, control strategy, and facility or manufacturing area. A comparison of the two processes and the input materials (or formulation) can be a starting point for assessing the risk of the process change. In addition to differences within individual unit operations and equipment, a holistic assessment of the overall processes can be beneficial to evaluate risks due to differences in system dynamics.

Factors such as dosage form, strength, drug load, potency, release profile, and route of administration can also impact risk to product quality. For example, the risk of a high drug load immediate release tablet is likely to be less than that of a low drug load extended release tablet. A discussion of the proposed change and the bridging strategy with the respective Regulatory Agency is advisable to gain agreement prior to conducting the studies.

Some aspects to consider when bridging batch and continuous processes are discussed below.

3.6.1 Physicochemical Equivalence Considerations

A change from batch to continuous manufacturing typically necessitates establishing physicochemical equivalency. Evaluation of a change from batch to continuous operation could include a comparison of individual unit operations, process parameters, equipment, CQAs, and the control strategy. Comparative batch data, particularly with respect to physical properties, impurity profiles, and drug release profiles, and bridging stability data can be helpful to support chemical equivalency.

3.6.2 Bioequivalence Considerations

When the risk of change to product quality attributes (e.g., polymorphicity, dissolution, impurities, stability, etc.) is low, demonstration of chemical equivalence could be sufficient to support the change from batch to a continuous process. In many instances, this could be when the continuous process is based on the same unit operations and formulation as used for the batch process. However, there could be situations, albeit rare, when significant changes or novel approaches are used in moving from batch to a continuous process. For example, the continuous process could incorporate a novel crystallization method that changes crystal form or a significant formulation change. Also, the drug product characteristics (e.g., a dosage form with a complex release profile or a very low drug load) may need to be considered in evaluating risk. Significant changes or high-risk products are more likely to require bridging by bioequivalence studies.

3.7 Glossary and Definitions

3.7.1 Batch Definition

An important aspect of continuous manufacturing is the definition of a batch. There are specific references to “batch” and “lot” in the US Code of Federal Regulations, which are applicable and need to be considered.

3.7.2 21CFR 210.3

> "The definition of a *batch* is a specific quantity of a drug or other material that is intended to have uniform character and quality, within specified limits and is produced according to a single manufacturing order due the same cycle of manufacturer. Therefore, batch refers to the quantity of material and does not specific the mode of manufacture.
>
> *Lot: a batch*, or a specific identified portion of a batch, having uniform character and quality within specified limits; or, in the case of a drug product *produced by continuous process*, it is a specific identified amount produced in a *unit of time or quantity* in a manner that assures its having uniform character and quality within specified limits."

The 21 CFR definitions for both "batch" and "lot" are applicable to continuous manufacturing.

3.7.3 CFR 211

Documentation of manufacturing 21CFR 211.188

> "Batch product and control records shall be prepared for each batch of drug product produced and shall include complete information relating to the production and control of each batch."

Although the regulations in the CFR provide flexibility in the area of documentation, the definition of a batch/lot at collection is not specifically described.

3.7.4 ICH Q7

A batch or lot is defined as:

> "A specific quantity of material produced in a process or series of processes so that it is expected to be homogeneous within specified limits. In the case of *Continuous production*, a batch may correspond to a defined fraction of the production. The batch size can be defined either by a fixed quantity or by the amount produced in a fixed time interval."

The batch definition is a fundamental element of continuous processes. It is linked to in-process testing, specifications, batch disposition, and many critical aspects of cGMP compliance.

3.7.5 ICH Q10

State of control: A condition in which the set of controls consistently provides assurance of continued process performance and product quality.

3.8 General Regulatory References

ICH Quality documents Q3, Q7, Q8 Q8(R2),Q9, Q10, Q11

2004 FDA Guidance for Industry PAT. *A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance.*

3.8.1 cGMP Guidance

Woodcock J, FDA, AAPS Annual Meeting. October 2011; http://www.fda.gov/Science Research/AboutScience ResearchatFDA/ucm342928.htm.

PhRMA White Paper Implementation and Application of Quality by Design Feb 2013; http://www.ema.europa.eu/docs/en GB/document library /Scientific guideline/ 2014/02/WC500162136.pdf.

EU Guidelines for Process Validation Guideline on NIR Guideline on Real Time Release testing ASTM Standards E2537 21CFR references are in the Glossary section 21CFR210.3 21CFR211.118

2011 FDA Guidance for Industry: *Process Validation: General Principles and Practices*.

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Note

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4

Continuous Manufacturing of Active Pharmaceutical Ingredients via Flow Technology

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4.1 Introduction

The pharmaceutical industry continuously investigates, discovers, develops and delivers new treatments to existing and emerging diseases [1]. Meanwhile, pharma also faces challenges such as slower success rate, expirations of patents, intense price competition with generics, and tighter constraints due to environmental concerns [2]. This brings about the incentive to modify the way active pharmaceutical ingredients (APIs) are manufactured.

In 2005, continuous processing and process intensification were defined as key green engineering research areas for sustainable manufacturing by the American Chemical Society (ACS) Green Chemistry Institute (GCI) Pharmaceutical Roundtable [3]. The main drivers to implement continuous manufacturing are aspects related to logistics, quality of the final product, chemistry to be implemented, process and safety concerns [4, 5]. Flow technology offers a platform to realize those drivers [6]. It represents a set of equipment with typical internal dimensions lower than one millimeter. The flow technology equipment used within the lab to design and develop a process can be scaled out to ensure the same quality of the final product. Thus, "right first time" performance of the process is more

Continuous Manufacturing of Pharmaceuticals, First Edition.
Edited by Peter Kleinebudde, Johannes Khinast, and Jukka Rantanen.
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attainable than in scaling up batch processes. Moreover, due to the modularity of flow equipment the construction and installation of plants can be accounted as operational expenditures rather than capital expenditures. Due to the same scale equipment used in laboratory, pilot and plant scale, the process development time is shortened. Contrary to batch processing, where batch determines the size of the production campaign, continuous processing allows production to meet exact demands, thus minimize long-term storage of large stocks of material. Operating temperatures below −40 °C or above +200 °C are outside of most standard batch reactors in pharmaceutical industry [7]. Flow reactors allow safe operation in that thermal range along with the creation of novel environments for the molecules to react in the most efficient way with minimization of energy input, reaction time and waste due to decomposition or side reactions [8, 9]. Higher safety associated with flow synthesis enables acceleration of the batch processes, slowed down due to the safety concerns. Moreover, reactions involving hazardous gas (CO, H_2, O_2) when run in large volume pressure reactors pose a safety issue due to the possible leakages. In flow technology, due to the smaller dimensions and intensified transport those processes become possible and safe [10–13]. Finally, the footprint of a continuous manufacturing plant is much smaller than a batch operation-based plant [14].

This chapter introduces the reader to a relatively new operating platform of flow chemistry [8, 15–20]. First, it discusses the principles of micro reaction engineering, followed by the novel process windows available within the operating platform. Subsequently, it presents downstream processing of the product stream and its analytical characterization. Finally, it gives a top view on multi-step processes leading to important APIs.

4.2 Micro Flow Technology

As mentioned in the introduction, flow technology represents a set of equipment with typical internal dimensions lower than one millimeter. Micro dimensions minimize transport limitations due to the increased surface to volume ratio [21]. This brings about three types of intensification:

- *Flow intensification*. Smaller dimensions of the reactor result in a well-defined laminar flow regime. Typical for that is the parabolic flow profile with a broad residence time distribution [22]. Yet, dependent on dimensions and flow specifications as well as by active stimulation (see below), radial diffusion can set in and transform that to a quasi-plug flow. Quasi-plug flow is characterized by narrow residence time distribution (RTD) and minor back-mixing, which is desired. Studies performed in chip-based reactors demonstrate a minor tailing of the RTD curve, indicating axial dispersion [23, 24]. Liauw *et al*. studied the effect of coiled geometries on the axial dispersion behaviour in small-scale capillary reactors with integrated optic sensors for mid-infrared spectroscopy [25]. Straight tube and coiled tubular reactors were compared. It was shown that due to the presence of secondary flows in a coiled reactor, axial dispersion could be decreased by a factor of four. Axial dispersion can be further minimized by the addition of gas as an inert phase, which separates liquid slugs and enhances mixing within them [26]. The uniformity of the environment assures that every molecule experiences the same operating conditions during its residence within the reactor. Thus, selectivities of fast reactions that take place in milliseconds to seconds, involving unstable or reactive species can be maximized. Finally, multiphase flows benefit from a regular pattern and well-defined interface.

- *Mass transfer intensification*. Decreasing channel size significantly decreases the diffusion path and increases the specific exchange area [27]. This, in turn, accelerates mass transfer in flows, improves mixing and interfacial mass transfer, resulting in a more homogeneous reactant distribution, when reactive species meet.
- *Heat transfer intensification*. Another benefit of decreasing channel size is an increased heat-transfer coefficient and temperature gradient, which in combination with increased surface area maximizes heat transfer [28, 29]. In this way, formation of hot spots is minimized and thermal overshooting is avoided.

There has been extensive research, incorporating an innovative approach, performed to develop tools that would make intensification in micro flow possible. This section discusses the main units/aspects comprising a micro flow platform with impressive single-step transformations.

4.2.1 Micromixing

Flow within a confined space can be viewed on two levels: molecular and continuum [30]. Molecular transport takes place within the nanometer scale, while for continuum it ranges across microns and centimeters. Thus, micro flow is considered to be a continuum, which can be described by a set of conservation equations given in Chapter 1, with the assumption of a complete uniformity of space.

In general, hydrodynamics of flow can be either laminar or turbulent. Due to the small length scale within the microchannel, viscous forces dominate over inertial forces resulting in laminar flow. In laminar flow there is a constant unidirectional flow of fluid elements moving at a constant velocity at any location with respect to the stream axis. This results in a very well-defined streamline flow, leading to a convective mass transfer solely along the stream axis, while mixing on the molecular level takes place due to diffusion [31]. The flow hydrodynamics can be characterized by the Reynolds number (Re), while the mass transfer can be characterized by the Peclet number (Pe). The Reynolds number represents the ratio of convective to viscous forces, while the Peclet number is the ratio of mass transfer due to convection to that occurring due to diffusion. Mixing extent can be estimated using these dimensionless numbers by using related correlations [30]. Mixing can become convective when the flow is brought to intermediate regime (Re > 100), which is governed by inertial forces. Then recirculations enable a stretching and disruption of fluid segments which lead to an ever finer dispersion of them until diffusion becomes effective.

$$\mathrm{Re} = \frac{uD_h}{\nu} \tag{4.1}$$

$$Pe = \frac{uL}{D} \tag{4.2}$$

Mixing within micro reactors is enhanced by micro mixers, designed as separate modules or embedded within a micro reaction system [32]. There are two types of micro mixers based on the means utilized to facilitate the mixing, such as active and passive [33]. Active micro mixers require an external disturbance source in addition to the flow energy [34] Those disturbances can be set via electrical, magnetic or acoustic forces. Active mixers are mostly used in zero-flow bioanalytical applications that take place on so-called lab chips. In synthetic applications, however, use of passive mixers is usually sufficient. Passive mixers

use flow energy provided by a pumping action to facilitate chaotic advection and promote molecular diffusion via either special channel geometry or the introduction of a secondary flow [33].

4.2.2 Flow Reactors

Flow reactors are fabricated from various materials depending on the particular application. Chemical compatibility and physical robustness are two main factors determining the choice of the material. Reactors can be constructed from glass, quartz, diamond, polymethylmethacrylate (PMMA), polydimethylsiloxane (PDMS), polytetrafluorine (PTFE), perfluoroalkoxy alkane (PFA), fluorinated ethylene propylene (FEP), ethylene tetrafluoroethylene (ETFE), ceramic, silicone, copper, stainless steel, nickel and Hastelloy [35]. Based on the phase of process development and/or production rate requirements, reactors can range in scale:

- *Micro scale flow reactors* are based on a channel with dimensions lower than a millimeter, as mentioned above. They can be fabricated as chips, straight tube, coiled tube or packed bed reactors. Micro scale flow reactors are mainly used for process optimization and/or to prepare small amounts of material. Macchi and Roberge *et al*. presented a toolbox approach in transferring batch processes to continuous, where reactors are selected based on reaction rates and reacting phases [36]. Knowledge of the kinetics of a particular reaction determines the choice of a particular reactor [36]. Very fast, exothermic reactions benefit from smaller dimensions, high mass and heat transfer, and therefore are usually performed in chips [37]. Meanwhile, slower reactions are carried out in coil or tubular reactor of larger dimensions and volumes [38]. Reactions requiring heterogeneous catalysts are performed in packed bed reactors [39]. Figure 4.1 shows three types of reactors along with the commercially available setups incorporating the corresponding reactors.
- *Mesoscale flow reactors* have higher production rates when compared to micro scale flow reactors. The increase in productivity comes either due to the stacking of micro scale flow reactors or due to increase in a channel diameter up to 10 mm.
- *Large sale flow reactors* that can deliver more than 100 Mt year^{-1} and can be fabricated upon demand by companies such as Chemineer, Alfa Laval, Chemtrix and Sulzer Chemtech.

4.2.3 Reaction Activation Tools

Usually micro flow process development starts off with the transfer of batch conditions to flow and continues with optimization and intensification of the reaction outcome via manipulation of process variables. Multiple reviews summarizing reactions performed and improved in micro flow environment have been published [15, 40]. The most extensive description of organic synthesis in flow was compiled in a book by Wiles and Watts [35].

Micro flow technology allows tighter control over process variables and affords safer operation, which meanwhile enlarges the safe region of the process windows. Hessel introduced the concept of novel process windows (NPW) into the field of micro reaction technology [19, 21, 41, 42]. NPW reside on two mutually connected aspects of process

Figure 4.1 *Overview of commercially available micro flow reactors.*

design and development. First is the chemical intensification, where harsher operating conditions, when compared to batch, intensify the process with the target of maximizing the productivity. A side product of this application is a discovery of new chemical transformations, since an *entirely different environment* than in batch is accessible in micro flow [43]. Second pillar of NPW is the process design intensification, which forces the integration of intensified step changes into an existing process or to rethink the whole sequence of

connected step processes with the aim to simplify and intensify the process as a whole, end to end process design. Thus, NPWs stimulate a new perspective within synthetic chemists and chemical process engineers. Chemical intensification has been observed in multiple cases, where a batch procedure was translated and later optimized in flow. However, the most striking examples are the ones that cannot be traditionally performed in batch due to the harsher conditions, bringing about instability of the reagents/intermediates, explosive nature of the reaction or due to the toxicity and higher concentration of the reagents used. Temperature, pressure and/or concentration are usually increased with the aim to intensify the reaction kinetics.

4.2.3.1 Intensification via Increase in Operating Temperature

Multiple processes have benefitted when reactions were performed at high temperatures [7, 44–47]. Increasing temperature in the system, where thermally sensitive reagents are used or formed *in situ* can be dangerous on a large scale in batch, where heat removal is not as efficient as in micro flow reactors. On the contrary, micro reactors offer a great platform to maintain isothermal conditions throughout the operation and minimize the formation of local hot spots [48]. Thus, reactions that are normally performed at cryogenic conditions speed up and result in higher selectivities when performed in micro reactors at room temperature [49, 50]. Examples to those are formation of triflates, lithium–halogen exchange and swern–moffat oxidation carried out at room temperature rather than at cryogenic conditions [49–51]. In addition to facilitation of reaction and higher safety, processes brought from cryogenic conditions to ambient require less energy input, normally used for cooling down the reactors. Yoshida *et al.* demonstrated how fast chemistry, coined as "flash", can maximize the selectivity of fast reactions utilizing highly reactive species or even intermediates, due to the precise control of operating conditions in micro reactors [37]. NPWs are the process counterpart of Yoshida's flash chemistry relying on chemical species. One of the examples is the lithiation reaction to synthesize alkynes and alkenes starting from trans-1,2-dichloroethene [48]. The deprotonation reaction to synthesize 1,2-dichlorovinylihium, normally performed at −78 °C in batch conditions, was carried out at 0 °C in 0.055 s. Subsequently, the lithium-bearing intermediate reacted with an electrophile to generate alkenes in good yields, ranging between 85 and 93%. A second lithium–halogen exchange of formed alkenes lead to the subsequent electrophile addition. Allowing longer residence time brought about lithium chloride elimination and resulted in the formation of chloroacetylenes, which could further react with *n*-butyl lithium, and then with elctrophile to generate disubstituted alkynes in 48–89% yield (Figure 4.2). Thus, Yoshida's chemistries are good example of flash chemistry activation combined with process design intensification.

Another class of reactions that can benefit from high temperatures are those with slower kinetics. Reaction rates can be accelerated when carried under superheated conditions. There are different ways to have been applied to micro flow systems.

Convective heating usually takes place in a hot medium, filled with air or oil. Both tubular and metal chip reactors are usually heated in this manner. One of the first examples of chemical intensification due to superheated conditions was a Kolbe–Schmitt reaction and was published by Hessel *et al*. in 2005 [33]. Carboxylated phenols, obtained via the

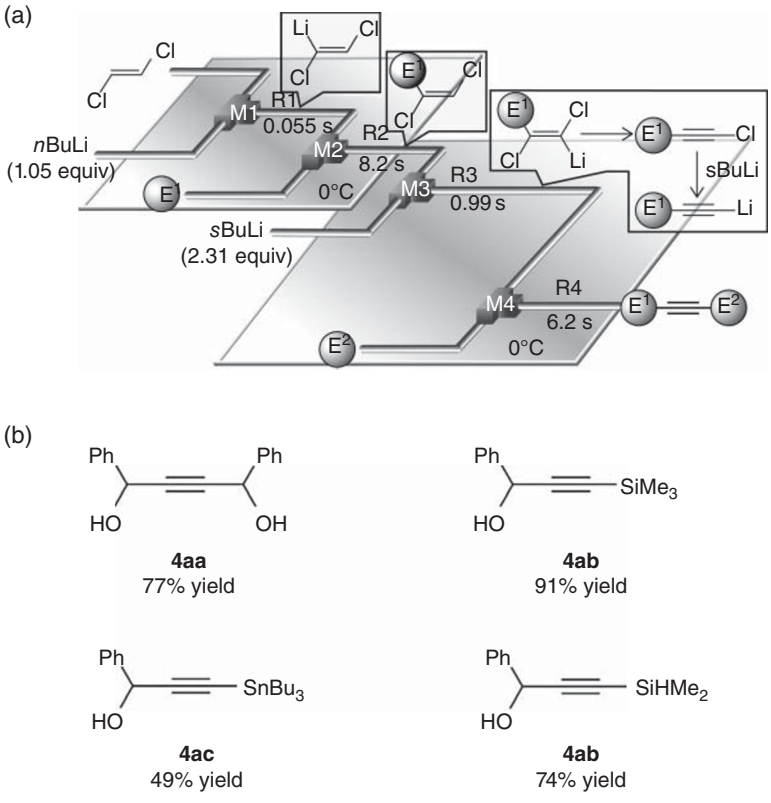

Figure 4.2 *(a) Microreactor sequence for continuous synthesis of asymmetric di-substituted alkynes. (b) The structures and the yields of the di-substituted alkynes synthesized. Reproduced from Ref. [48] with permission of John Wiley & Sons.*

Kolbe–Schmitt reaction, need strong base to form phenolate with electron pair stabilized at the ortho-position that attacks CO_2, usually under 100 atm pressure and temperatures around 125 °C [54]. When resorcinol is used, the Kolbe–Schmitt reaction proceeds to completion in 2 h at 100 °C under reflux and batch conditions in the presence of bicarbonate as base. A significant reduction in residence time down to 4 s at a yield of 40% under mildly basic superheated conditions of 200 °C and 40 bar was achieved in micro reactor [55]. Raising the temperature up to 220 °C further shortened the reaction time resulting in a space–time yield of circa 18.20 t $(h\ m^3)^{-1}$, which is about 1000× more than can be gained from a 1 L flask. Another example is the synthesis of 1,2,3-triazole moiety in an intermediate to rufinamide [52]. The reaction consists of sluggish cycloaddition of 2,6-difluorobenzyl azide to (E)-methyl 3-methoxyacrylate, which takes 28 h at 135 ° under solvent-free conditions in batch. The reaction cannot be performed at higher temperature in batch due to the instability of 2,6-difluorobenzyl azide. A micro flow tubular reactor offers a safe alternative, allowing the reaction to be intensified at 210 °C and reaction time to be brought down to 10 min with the resulting yield of 83% and an initial productivity of 9 g h^{-1} (Figure 4.3). Jia *et al*. synthesized a variety of 2,4,5-trisubstituted

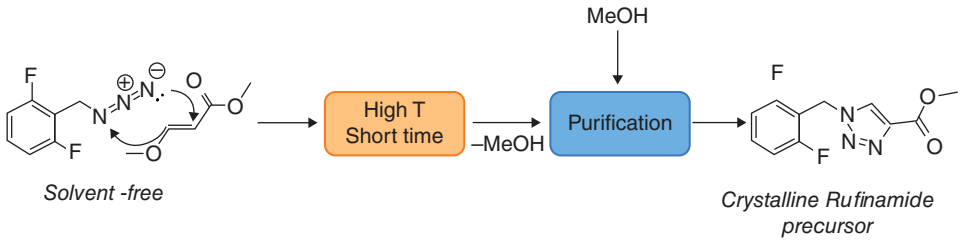

Figure 4.3 *Solvent-free intensified synthesis of rufinamide precursor in capillary reactor. Reproduced from Ref. [52] with permission of Wiley-VCH Verlag GmbH & Co. KGaA.*

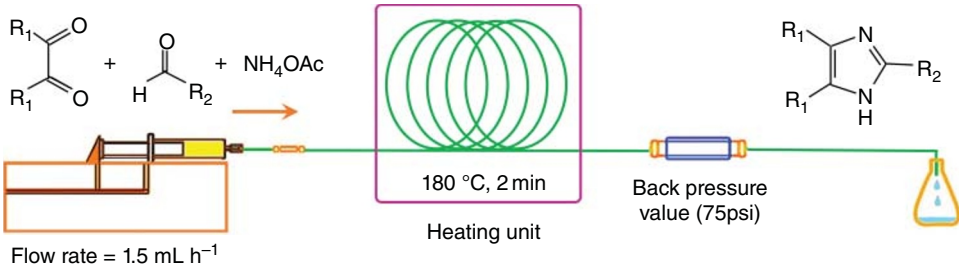

Figure 4.4 *Intensified synthesis of 2,4,5-tri-substituted imidazoles. Reproduced from Ref. [53] with permission of the American Chemical Society.*

imidazoles, where good to excellent yields were reached in only 2 min residence time in a tubular reactor (Figure 4.4) heated within an oil bath to 180 °C [53]. More examples of superheated conditions are compiled in past reviews [19].

Conductive heating is usually incorporated in micro chips assemblies, where electric cartridges heat up a metallic block, which heats up the micro reactor. Jensen *et al*. constructed a silicon/Pyrex micro reactor, shown in Figure 4.5, that can be heated to temperatures up to 400 °C and 300 bar [56]. Silicon etching techniques in fabrication of micro reactors combined with bonding to Pyrex allows tight thermal control, good chemical compatibility and visibility. Due to the scarcity of connections capable of withstanding high temperature and pressure, authors incorporated a "mild" conditions platform that is separate from the high temperature zone platform. The heat was provided by an aluminium block (Figure 4.5 bottom right) equipped with electric heating cartridges. One of the applications was the oxidation of methanol by hydrogen peroxide in supercritical water at 250 bar and 400 °C. At a fixed residence time of 2 s conversion increased from 36.5% at 20 MPa and 300 °C to 87% at 25 MPa and 380 °C. The cyclization and benzannulation reactions to synthesize heterocyclic ketones (pyridopyrimidinones, naphthyridinones) were carried out in X-cube Flash setup at temperatures ranging from 300 to 370 °C and pressure of 100–160 bar [58]. The reactions proceeded best at high tempratures and short residence time (0.45–4.5 min), while the side reactions increased at longer residence times. The flow system allowed the rapid optimization of the synthetic procedures for the library of 11 heterocyclic biphenyls.

Dielectric heating is possible in microwave operating platforms and gives an insight to the possibility of reaction rate acceleration. Kappe *et al*. demonstrated multiple

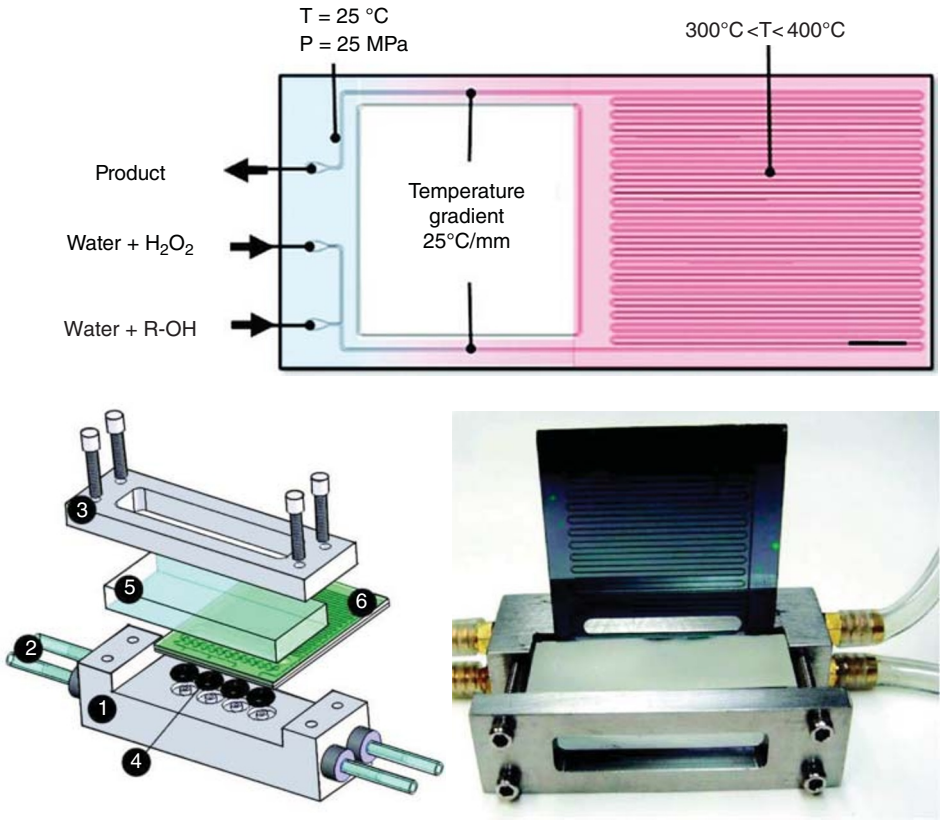

Figure 4.5 *Top: HP/HT microreactor with a single channel microreactor. Bottom left: HP/HT microreactor assembly: (1) and (3)compression parts, (2) cooling fluid pathway, (4) O-rings and grooves, (5) Pyrex plate for optical access, (6) single channel microreactor; Bottom right: Photograph of the final assembly. Reproduced from Ref. [56] with permission of the American Chemical Society.*

examples, where reactions accelerated under superheated conditions on a small scale in a microwave batch reactor could later be transferred into convectively heated flow reactor [59]. In addition, several continuous microwave reactors have been developed with a commercially relevant scale [60]. Morschhauser *et al*. described the design of the industrial scale single-mode microwave flow reactor with high temperature (310 °) and high pressure (50 bar) process windows with a throughput of 20 l h^{-1}. The reactor was tested on synthesis of amides and esters from carboxylic acids. The reactions were highly accelerated and took place within typical residence times of 28–48 s, while resulting in good yields (>89%) [61].

Electric heating was applied to a tubular mini reactor by Kunz *et al*. (Figure 4.6) [57]. Electric current was applied on two ends of the tube by a low voltage/high current power supply that was controlled by a temperature controller. The overall efficiency of the power supply was determined to be 80%. The system was used to perform kinetic measurements of acid catalyzed hydrolysis of methyl formate. Even though the values

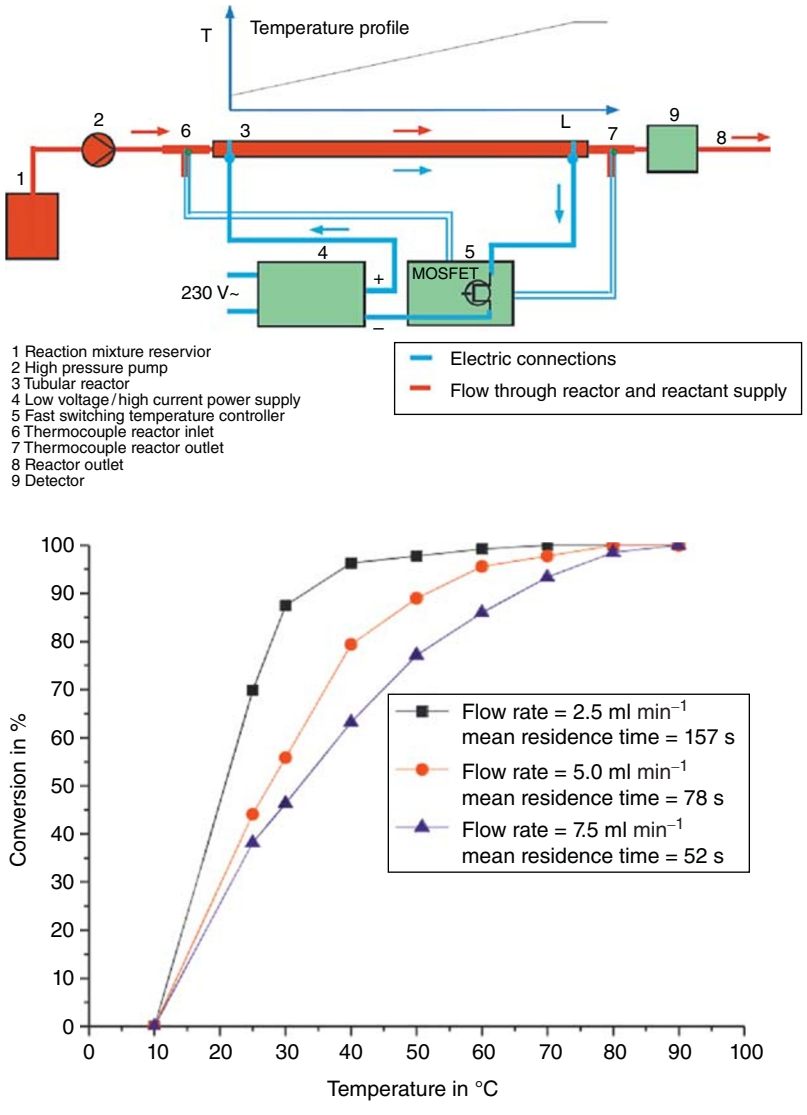

Figure 4.6 *Top: Experimental setup for electrically heated tubular flow reactor, along with temperature profile. Bottom: Conversion of methyl formate as a function of temperature for three different residence times. Reproduced from Ref. [57].*

of the reaction rate constants are scattered when data is converted into an Arrhenius plot, the built system demonstrates the potential of electric heating applicable on fast reactions and high volumetric flow rates.

Inductive heating has generally been employed for surface hardening, melting, brazing, soldering and welding. It is used in medicinal applications for thermal destruction of tumors, by means of application of magnetic field onto a magnetic particle which heats up to relatively high temperatures [62]. Application of inductive heating within

organic synthesis is relatively recent, however already proven to give enhanced yields in intensified ways [63, 64]. The basic principle is similar to that used in medical treatments using superparamagnetic particles coated with silica gel or conductive particles heated up within an applied electromagnetic field. Kirschning *et al*. demonstrated how reactions can benefit when inductive heating is applied to mesofluidic fixed bed-type reactors packed with ferromagnetic materials, such as steel beads, copper metal and superparamagnetic nanostructured particles [63]. Very high temperatures, up to 400 °C, are rapidly reached within the reaction medium when inductive heating is applied. The results of Claisen rearrangement with highly deactivated substrate, performed in conventional batch reactors, heated in an oil bath, by microwave and induction were compared. High frequency inductive heating 0.4 mm steel beads (magsilica) worked the best at an optimal temperature of 205 °C. Surprisingly, the residence time decreased sixfold with only 5 °C higher temperature than that tried in oil bath and microwave setups. This is explained by the fact that high-frequency inductive heating seems to create a much hotter surface, that leads to higher reaction rates at the surface of the nanostructured particles [65, 66].

4.2.3.2 Intensification via Increase in Operating Pressure

High pressure increases the rate of reactions with negative activation volume. Those reactions result in a smaller volume of transition state when reactants come together. Examples are reactions such as cycloadditions, condensations, reactions proceeding via cyclic transition state, such as Cope and Claisen rearrangements, reactions involving the formation of dipolar transition states, such as electrophilic aromatic substitutions, and reactions with steric hindrance. In addition to acceleration, product distribution if more than one product is possible may also be varied when pressure is applied. Several investigations were performed in flow. Verboom *et al*. studied nucleophilic aromatic substitution reaction among p-halonitrobenzenes with cyclic amines in micro capillary under stop–flow, that is non-stirred batch, conditions under pressures up to 600 bar [45, 67]. The rates of reactions for pyrrolidine, piperidine and morpholine were increased by a factor of 2.7, 1.7 and 1.5, respectively. When high pressure was applied to Diels–Alder reaction of 2- and 3-furylmethanol with maleimides, pressure increased the rate of the reaction with 2-furylmethanol, which is less reactive than 3-furylmethanol under atmospheric conditions. Due to the larger negative change in the reaction volume of exo-product when compared to endo-product, formation resulted in a slight increase in the formation of exo-product. An increase of the reaction rate of the Diels–Alder reaction, between cyclopentadiene and phenylmaleimide, by a factor of 14 was observed upon increasing the pressure to 150 bar in a high-pressure glass micro reactor [67]. Kappe *et al*. reported multiple high-pressure, high-temperature accelerations in reaction rates of Newman–Kwart and Claisen rearrangements, a Fischer indole synthesis and nucleophilic substitution in flow [7, 68, 69]. Another type of cycloaddition, [3+2]-Huisgen azide-alkyne cycloaddition, was studied by Hessel *et al*. in batch and flow capillary reactor, which could be pressurized up to 1800 and 400 bar, respectively [70]. Cycloaddition of benzyl azide and methyl propiolate was on the order of several days when carried out in a round bottom flask under non-catalyzed atmospheric conditions, resulting in 60% yield after 6 days. A yield increase of 13% over a pressure gap of 1300 bar was observed indicating the

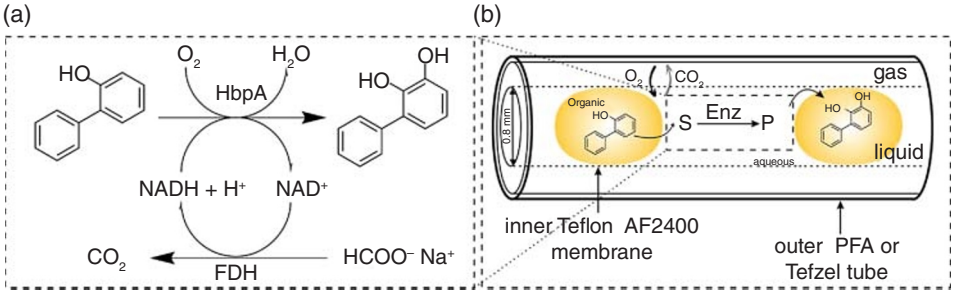

Figure 4.7 *(a) Scheme of catalyzed hydroxylation of 2-hydroxybiphenyl to 3-phenylcatechol accompanied with NADH regeneration by formate dehydrogenase (FDH). (b) Schematic representation of a tube-in-tube reactor (TiTR) with an aqueous–organic two-liquid segmented flow within porous Teflon AF-2400 tubing and oxygen on the shell side. Reproduced from Ref. [77] with permission of the American Chemical Society.*

intensification by pressure, that is speed-up of the reaction kinetics and improvement in regioselectivity. Yield of the desired 1,4-regioisomer rose to 84% in 24 h, and resulted in a 1,4:1,5-cycloadduct ratio of 6.3 at 1800 bar with no catalyst present. Operation in a capillary flow reactor allowed temperature increases up to superheated conditions, and safe work at higher concentrations and pressures than in batch. A yield of 81% of the desired 1,4-cycloadduct in 30 min residence time was observed at 400 bar. Gas-liquid reactions benefit from continuous operation under high pressure in flow [71–73]. 3-Phenyl catechol was synthesized within the tube in tube reactor from 2-hydroxybiphenyl by an enzyme catalyst coupled to enzymatic regeneration of NADH by FDH (Figure 4.7). Pure oxygen was used in the shell of the tube while the inner tube was a Teflon AF-2400 tubing permeable to oxygen and carbon dioxide. After manual batch purification of the product 35% yield was obtained, corresponding to 14.5 g $(L\ h)^{-1}$ space time yield. More reactions have been performed in tube in tube reactors, demonstrating their high applicability with continuous synthesis [13, 74–76].

4.2.3.3 Intensification via Increase in Operating Concentration and Change of Solvent Properties

Concentration is another parameter that can be varied in optimization of reaction conditions. The highest concentration value is achieved when no solvent is used. However, due to the abundance of solid reactants or products, clogging can easily take place within the micro dimensions of the reactors. One solution is to work at temperatures higher than melting point of the solids used. Jamison *et al*. performed neat nucleophilic substitution of chlorodiphenylmethane with dimethylaminoethanol to form Benadryl salt [78]. The incorporation of isopropanol at the outlet of the reaction zone prevented crystallization of the salt until cooling down, whereupon it precipitated in its pure form. Similar work has been done by Hessel *et al*., where [3+2]-Huisgen cycloaddition was carried out to synthesize a 1,2,3-triazole precursor for an antiepileptic drug, rufinamide [52]. The alternative, less expensive, less toxic and also less reactive, dipolarophile was used. Operation under solvent-free conditions and high temperature afforded the product, with a

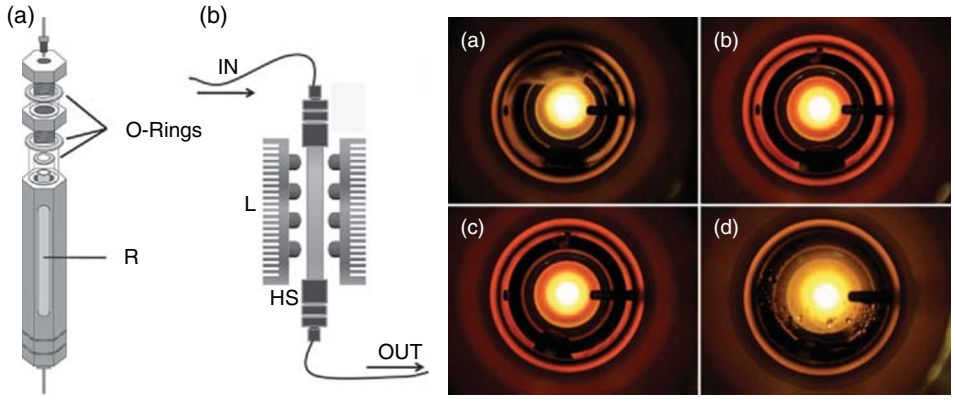

Figure 4.8 *Left: (a) Schematic exploded view of the reactor assembly used in photo-oxidation of citronellol with singlet oxygen; (b) Positioning of LED lamp array around the reactor. Right: Photographs of phase behavior at 55 °C for starting compounds at (a) 120 bar, (b) 140 bar, (c) 180 bar and (d) a biphasic mixture of scCO$_2$ and peroxide product. Reproduced from Ref [81] with permission of Wiley-VCH Verlag GmbH & Co. KGaA.*

melting point of 136 ° in liquid state. The product was carried out from the reactor by the addition of methanol as antisolvent, and resulted in pure triazole precipitate upon cooling.

Alternative solvents can be created under supercritical conditions [79, 80]. Supercritical solvents have high solvating power, which diminishes mass transfer limitations among normally immiscible and insoluble species [7]. Although possible, supercritical processes pose a strong safety concern when their scaleup is considered, especially when a flammable solvent is used in combination with oxygen. Continuous flow synthesis of Rose oxide by photo-oxidation of citronellol with singlet oxygen was carried out in isopropanol under supercritical conditions with 3000× scaleup compared to previous work [81]. The reactor (Figure 4.8) was based on a sapphire tubular reactor surrounded by high-power visible light emitting diodes (LED). The internal diameter of the tube was 7.8 mm, the wall thickness was 1.2 mm, resulting in internal volume of 4.1 mL. In a typical experiment, liquid CO_2 was pumped at 2 mL min^{-1} (−10 °C, 48 bar), while the organic reactant containing 5,10,15,20-tetrakis(pentafluorophenyl)porphyrin was pumped at 0.2 mL min^{-1} and oxygen was introduced into the stream of CO_2 at a rate of two molar equivalents with respect to the organic substrate. Greater than 99% conversion was achieved after a single run. The reactor was allowed to continuously run for 8 h, which yielded 96 mL of the product with less than 0.5% of the starting material.

4.2.4 Downstream Processing

The development of reactions in flow brings about the need for the development of continuous equipment that would lead to an isolation and purification of the desired products. Manufacturing pharmaceuticals usually involves cost- and time-consuming work-up steps. In order to fully benefit from flow technology, continuous reactions need to be followed by appropriate separation techniques such as in-line chromatography, extraction, distillation,

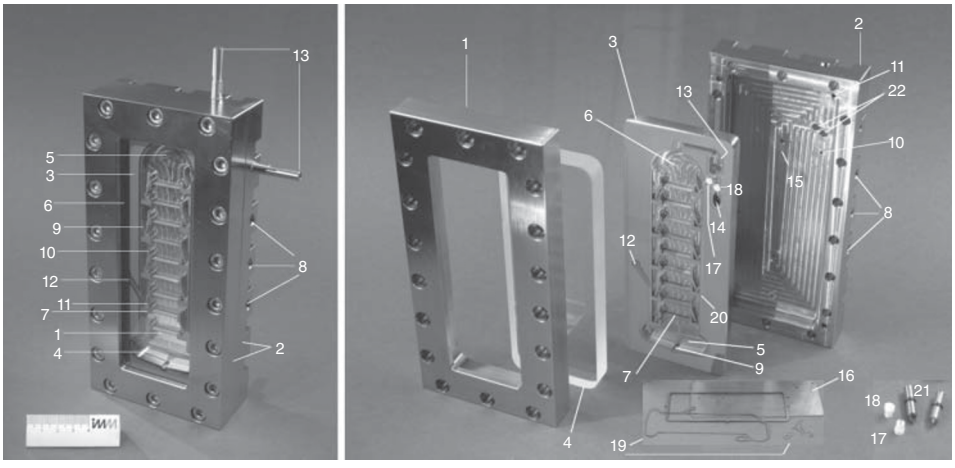

Figure 4.9 *Micro-sieve tray based micro-distillation device to separate binary mixtures. Left: Compact view. Right: Exploded view. For a more detailed description of components please refer to the original reference. Reproduced from Ref. [84] with permission of Wiley-VCH Verlag GmbH & Co. KGaA.*

adsorption and crystallization. Moreover, a step by step approach needs to be reconsidered in favor of telescoped processes, where the product of one reaction would become a reactant for the next. In this manner, work-up steps would be minimized resulting in a more efficient process. Finally, entrapment techniques for moisture and hazardous compounds removal prior to the subsequent step should be developed. Herein, we briefly describe examples of separation techniques used in flow. More information regarding the progress of separation and purification technology in micro flow chemistry is available in related reviews [82].

Distillation relies on a separation based on the difference in volatility of components within a given mixture. Continuous distillation is a well-established separation technique in industry. Meanwhile, in micro flow technology it is relatively new. The domination of surface forces makes it hard to control the evaporation behaviour within the mixture of components. Moreover, heat losses due to the excellent heat transfer have to be controlled to maintain a tight temperature control. A recent overview of the progress in micro scale distillation is given by Sundberg *et al*. [83]. Figure 4.9 shows a micro- sieve tray based micro-distillation device developed by Hessel *et al*. [84]. The device worked effectively in separating binary mixtures with a throughput of 0.5 mL min^{-1}. A theoretical separation stage number of 12 was attained, along with a height equivalent to one theoretical plate of 1.08 cm.

Gavriilidis *et al*. developed a multistage micro distillation chip with incorporated arrays of micro-pillars along the side walls of the micro-channel [85]. The liquid flow was forced to flow through micro-pillars zones close to the micro-channel walls due to the effect of capillary forces thus avoiding flooding and maintaining stable liquid–vapour interface (Figure 4.10). A temperature gradient was applied along the micro-channel by heating and cooling the two ends of the micro-channel, while the liquid mixture was introduced from the middle position of the micro-channel. Three configurations were tested in their efficiencies in separation, straight, zig-zag and serpentine shaped micro channels. The last had micro pillars on both sides of the microchannel, resulting in the most stable liquid–vapour

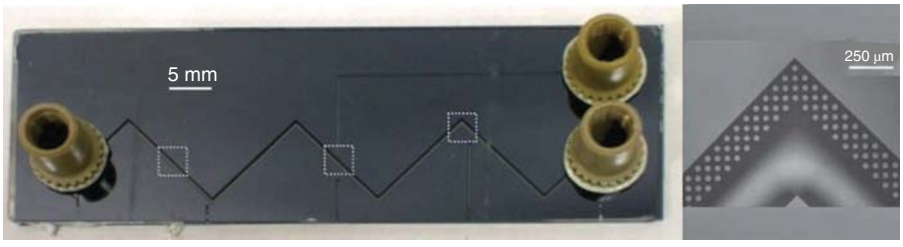

Figure 4.10 *Zig-zag micro-distillation device to separate binary mixtures. Left: Micro chip. Right: Close-up of the channel with incorporated micro-pillars. Reproduced from Ref. [85] with permission of the Royal Society of Chemistry.*

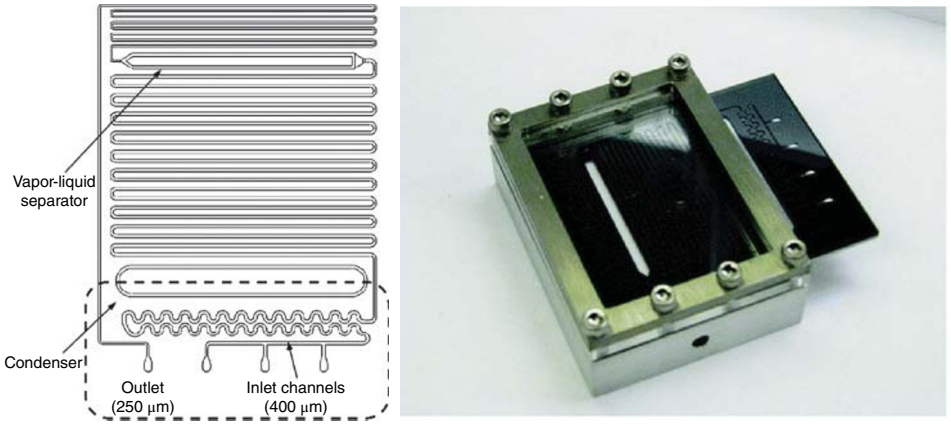

Figure 4.11 *Single-stage distillation device with integrated condenser and membrane-based vapor–liquid separator. Reproduced from Ref. [89] with permission of the Royal Society of Chemistry.*

interface and no flooding. A 50 mol% acetone–water mixture was almost completely separated at 95 °C, leading to separation equivalent to at least four equilibrium stages. Membrane-based micro distillation presents another way of separation [86–89]. One of the examples is shown in Figure 4.11, where single-stage micro distillation is performed by introducing a carrying gas along with a mixture of components. The process is based on the difference between the partial vapour pressures of the mixture components and takes place below the boiling points of the individual components. Components with higher volatility evaporate into a carrying gas phase. Second stage of the separation takes place within a membrane separator, where gas phase is separated along with volatile compounds, while components with low vapour pressure pass through a membrane in a liquid phase. Due to having only one equilibration stage possible, the efficiency of the process as such is relatively low and could be increased by connecting several devices in series. Buchwald and Jensen *et al*. integrated the membrane based distillation within a multi-step synthesis [86]. The product stream of the first reaction, the synthesis of an aryl triflate in dichloromethane, was coupled with 2.0 M hydrochloric acid to extract the excess of diisopropylethylamine. The aqueous phase was removed, while the organic phase containing triflate was mixed with pure toluene (or DMF) and nitrogen gas prior to

entering the distillation device, which was kept at 70 °C. Dichloromethane was evaporated and left the subsequent membrane based separator, while the product dissolved in toluene exited the separator and was coupled to a palladium-catalyzed Heck reaction.

Adsorptive and desorptive techniques (catch–release) have been used within the multi-step synthetic sequences to yield natural products and APIs by Let *et al.* [90, 91] Although it is difficult to quantify and optimize the extent of the separation this technique could be employed on a larger scale. In-line evaporation was implemented within a multi-step synthesis of Imatinib shown in Figure 4.12, by heating up the collected from the first reactor sequence amide product in DCM in N-methyl piperazine and DMF [92]. The mixture was heated to 50 °C and nitrogen was flushed over the mixture to remove DCM vapours into the exhaust. The evaporation of approximately 2 ml of solution took 30 min, after which the amide and *N*-methyl piperazine in DMF were pumped into a second reactor.

In the micro environment, surface forces dominate over gravity, thus complicating density-based separation of two immiscible liquid phases upon extraction. The difference in the surface tension of two liquids can be used instead of gravimetric separation. Membrane-based separators present a great tool in separating two liquids with different surface tension. In the case of a hydrophobic membrane, the organic phase is retained and the aqueous phase (along with gas, if present) flows over the membrane towards the device exit. Thus, two phases exit at separate outlets of the membrane containing device. Breakthrough of the phases can occur when the given limits of the device are forced. Maintaining the "right" pressure difference over the membrane provides the solution. The commercially available FLLEX membrane-based separator, developed by Syrris, incorporates an adjustable pressure difference over the membrane. A homogeneous copper catalyst used in click reaction was scavenged by the device when organic product stream was mixed with EDTA-containing aqueous stream [93]. Jensen *et al*. designed a membrane-based separator with integrated pressure control, realized by adding a PTFE diaphragm, which accommodates the pressure fluctuations and allows breakthrough-free separation [94]. The device was used in counter-current extraction, where a total extraction of acetone in toluene–water system was reached in three stages. Applications within synthesis of APIs were demonstrated by Gernaey *et al*. [95], where hydrolyzed intermediate to zuclopenthixol was separated from magnesium salts of the Grignard alkylation reaction. The pressure at the outlets was applied by in-line back-pressure regulator. Total flow rates up to 2.4 L h^{-1} were tested and shown to be sufficient for an efficient separation.

4.2.5 Process Analytical Technology and Automation

Process analytical technology (PAT) is a system for designing, analyzing and controlling a manufacturing process [96]. The aim of PAT is to understand and control a given process. FDA supports the PAT use with the aim to attain higher process understanding and control, higher safety and higher efficiency in process development. The in situ measurement of reaction parameters leads to a faster response and thus more information regarding the process. In addition it also minimizes difficult or hazardous techniques in acquiring samples from the operating equipment. Thus, development stage PAT provides an understanding of the process and its fast optimization due to the known sensitive variables of the system. On the manufacturing level PAT assures control and safety. Therefore, equipment as

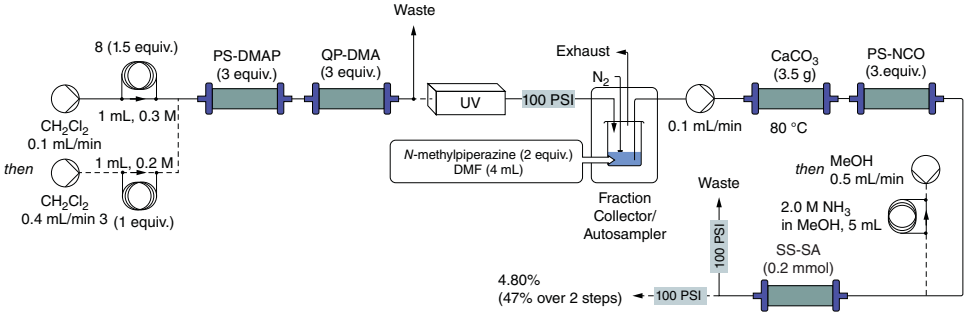

Figure 4.12 *Multi-step synthesis of Imatinib with in-line scavengers and evaporation. Reproduced from Ref. [92] with permission of the Royal Society of Chemistry.*

well as information of use is different for development and manufacturing levels. A recent review by the IQ Consortium of branded pharmaceutical manufacturers summarizes the recent developments within in situ analytical equipment along with the accommodation of PAT within different stages of a given process [97]. Figure 4.13 shows API process work flow with analytical needs along with the equipment used. The opportunities presented by micro flow technology concentrate on the reactor stage and slowly are moving towards workup. Determining and monitoring concentration *in situ* remains a challenge. Without in situ analytical techniques the process parameters remain trapped in a black box, which makes translation of the laboratory-scale process to a commercial scale harder. Figure 4.14 shows the factors playing role in choice of the particular analytical technique within a continuous process. The time scale of the analysis and reaction has to be compatible to allow an adequate feedback time. Moreover, the reaction platform should be compatible with the technique used in terms of the material compatibility. Finally, the complexity of the chemical process, such as the formation of several by-products or the presence of multiple phases may complicate the choice of the analytical technique. The progress in the development of analytics with subsequent integration and automatization is an ongoing with developing micro flow technology. Up to now, spectroscopic tools such as NIR [98], FTIR [99–104], Raman [105–109], UV [110–112], NMR [113–117] and MS [118, 119] have been used to monitor the appearance or disappearance of certain functional groups within continuous reactive system. For more examples, please see the related references, meanwhile one example per technique integrated with flow reaction will be presented here.

4.2.5.1 Near-infrared Spectroscopy

Gernaey *et al*. implemented a feedforward-feedback control loop in a continuous Grignard reaction in the production of an intermediate towards the production of zuclopenthixol [98]. The reaction between 2-chlorothioxantone with allylmagnesium chloride in THF took place in the setup shown in Figure 4.15. An inline NIR spectroscopic method was developed in order to determine the remaining concentration of 2-chlorothioxantone in real time. The feedforward control loop measured: the flow rate of chlorothioxantone, the temperature within the reactor and the concentration of Grignard reagent within a stock solution. The reaction is sensitive towards stoichiometric ratio of Grignard reagent to the substrate. The excess of the reagent leads to the formation of undesired by-products. Therefore, the response of the reaction system to the disturbances in Grignard reagent flow was used to model the reactor dynamics that is required to develop the reactor control system. The model was used to tune a PI controller and simulate the process control performance, which assisted in choosing the right analyzer for the system to minimize the formation of impurities.

4.2.5.2 FTIR Spectroscopy

Mettler Toledo developed an IR flow cell, which allows non-intrusive *in situ* analysis of the flowing stream [120, 121]. The instrument is based on FTIR spectroscopy (mid-IR range) coupled to an ATR sensor, therefore allowing monitoring the appearance and disappearance of a wide range of functional groups. Once the plateau is reached in the measurement response, a steady state is reached. This eliminates a common waiting period of “several

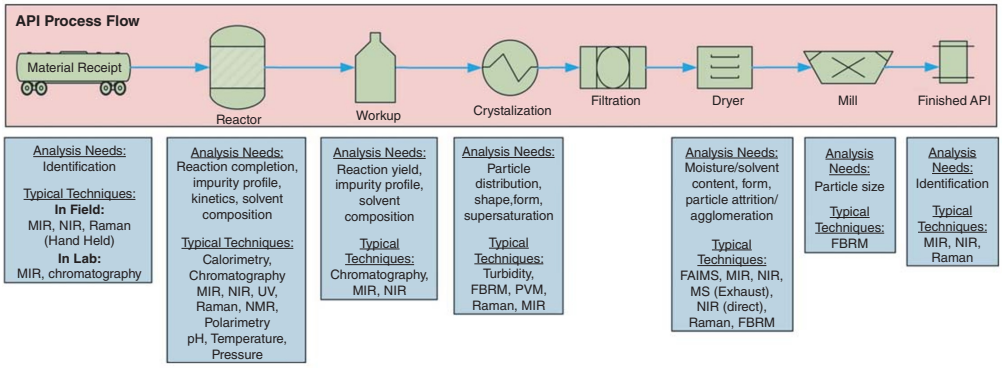

Figure 4.13 *API process work flow along with analytical needs and typical equipment used to meet those needs. Reproduced from Ref. [97] with permission of the American Chemical Society.*

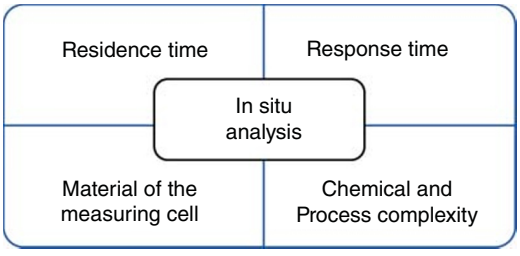

Figure 4.14 *Aspects to consider during the design of in-line analytical equipment for continuous flow processes.*

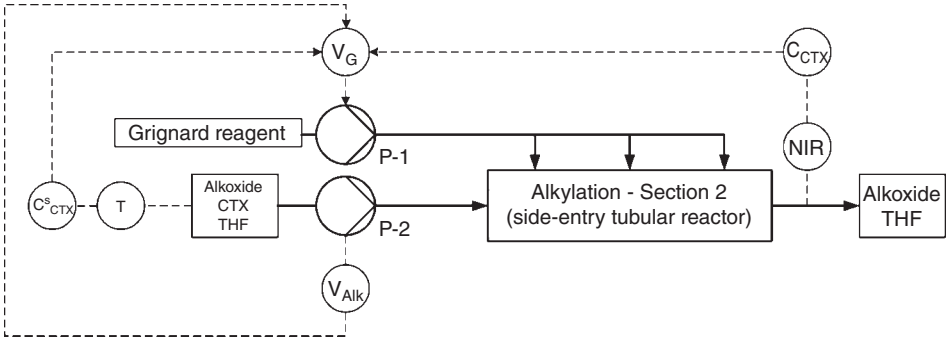

Figure 4.15 *Control loop scheme for a Grignard reaction monitored by NIR. Reproduced from Ref. [98] with permission of the American Chemical Society.*

reactor volumes" length in flow experiments, therefore reducing the material use during the optimization of experiments. Several examples benefiting from the device are published, among those is the optimization of a Paal-Knorr reaction by Jensen *et al*. [100]. Figure 4.16 shows the IR spectrum of the main reaction components, based on which the reaction progress could be assessed. The authors relied on DOE and three different algorithms to find the optimal conditions. All three algorithms lead to a similar optimum point as expected, due to the convex nature of the objective within the parameter space. Similar technique could be applied within the optimization of more complex and multi-parameter based systems.

4.2.5.3 Raman Spectroscopy

Gavriilidis *et al*. designed a device and a technique to monitor the catalytic gas–liquid oxidation of alcohols in a micro reactor by using a 90° extension arm (Figure 4.17) from a Raman microscope [105]. Consequently, the micro reactor could be installed along side the microscope. Authors studied the reaction in the temperature range of 80–120 °C and pressures up to 5 bar. Increasing pressure from 0.7 to 3.7 bar improved selectivity toward benzadehyde over toluene, that is the formation of toluene decreased from 36 to 12% at higher pressure.

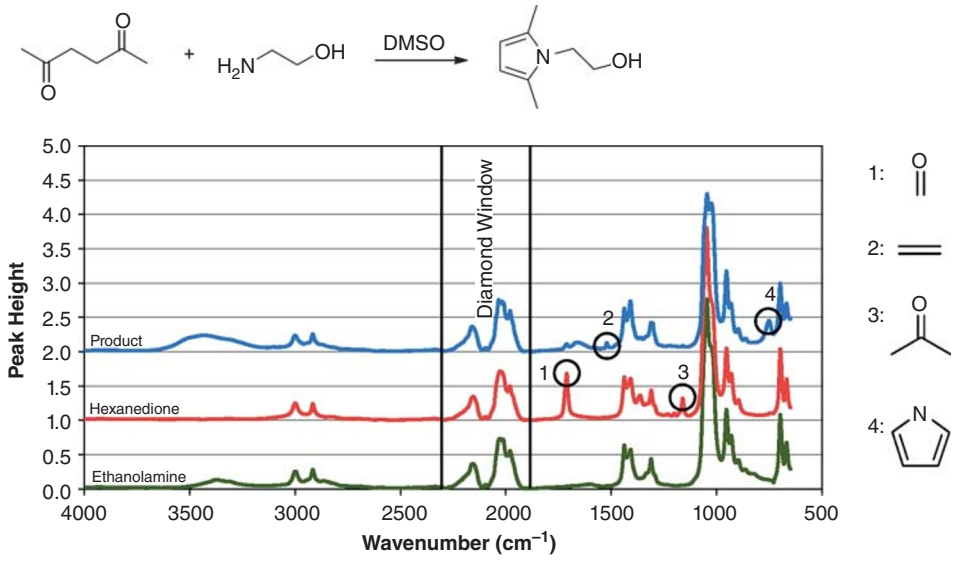

Figure 4.16 *IR spectrum of the Paal–Knorr reaction components along with their characteristic peaks. Reproduced from Ref. [100] with permission of the American Chemical Society.*

4.2.5.4 UV-vis Spectroscopy

Welch and Gong *et al*. integrated online UV-vis spectroscopy via an Eksigent Express RT system onto the outlet of stainless steel tubular reactor, where the selectivity of the thermal equilibrium of Diels–Alder reaction (Figure 4.18) was studied [112]. The setup consisted of a controllable HPLC pump that would introduce *endo*-1 reactant into a reactor of 1 mL internal volume, which was heated within a GC oven. Sampling was performed every 4 min, while the analysis time was 3 min, allowing the subsequent change in operating conditions. Screening temperature and residence time effects resulted in the response surface plot, which indicated that the best isomer ratio was observed when residence time was 5 min and reaction temperature was 240 °C.

4.2.5.5 Nuclear Magnetic Resonance Spectroscopy

Nuclear Magnetic Resonance (NMR) spectroscopy is one of the most used characterization and quantification techniques in organic synthetic chemistry. One of the few drawbacks of using NMR is its low sensitivity to mass-limited samples. Miniaturization of the detection coil to improve the sensitivity and resolution has been widely investigated. One of the early integrations of NMR with flow technology was accomplished by Gardeniers *et al*. [116]. A NMR micro coil was directly coupled to a microchip reactor. Imine formation from benzaldehyde and aniline served as a model reaction. The authors showed the speed of the reaction doubled due to the better mixing in the micro chip and confirmed that the kinetic data obtained via monitoring with NMR complied with the findings measured by Raman spectroscopy.

However, the fragile design and inhomogeneity of the magnetic field remained as a barrier for larger applications. Subsequently, Kentgens *et al*. devised a microfluidic probe

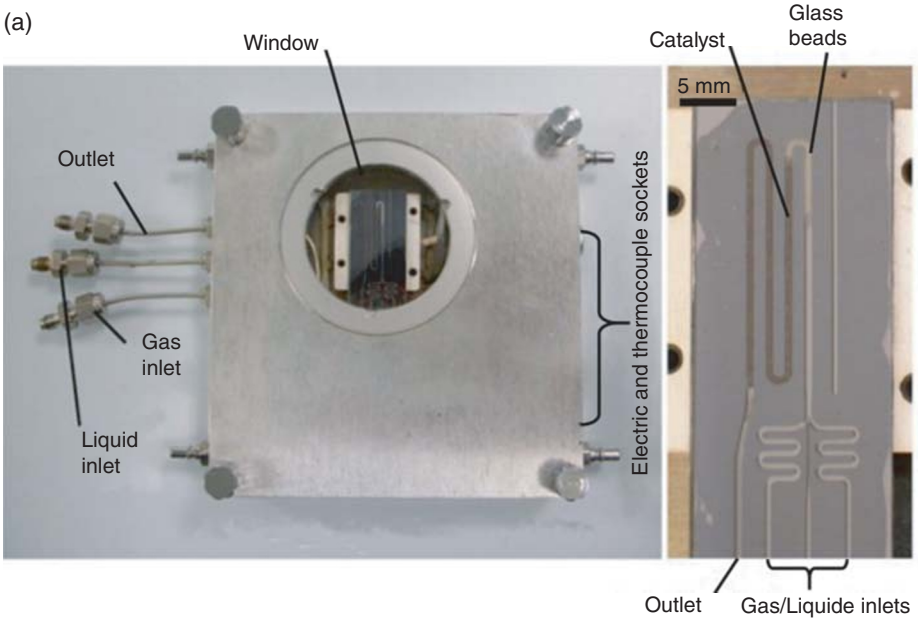

Figure 4.17 *(a) Micro reactor used in oxidation of benzyl alcohol with a window for reaction-monitoring. (b) Raman microscope positioned on top of the micro reactor. Reproduced from Ref. [105] with permission of Elsevier B.V.*

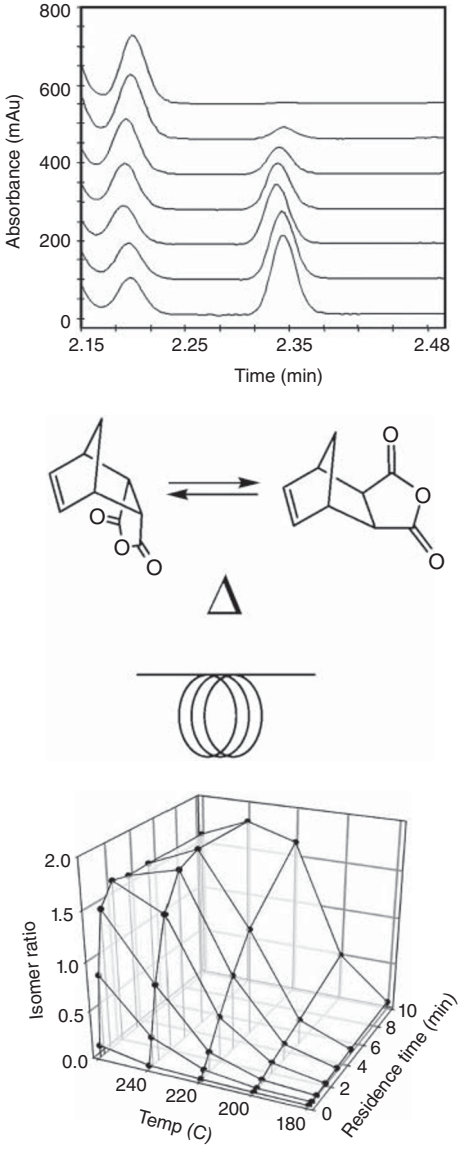

Figure 4.18 *Top: UV-absorbance of thermal isomerization of endo-1 to exo-1. Bottom: Response surface showing the effect of temperature and residence time on the thermal isomerization of* endo*-1. Reproduced from Ref. [112] with permission of the American Chemical Society.*

for in situ monitoring of the acetylation of benzyl alcohol [116]. A flow probe is based on a resonator, where the chip is positioned vertically in an aluminium tube and is connected to a rf circuit, thus overcoming the problem of field distortion. Meanwhile, the micro reactor is placed on top of the probe and connected to the NMR chip via fused silica

capillary (ID- 100 μm, L-200 mm). Syringe pumps delivered reactants via FEP tubing into the micro reactor. Since then Magritek devised several benchtop NMR spectrometers that can easily be connected to a flow setup. Cronin *et al*. integrated the Spinsolve (42.5 MHz Proton, 40.1 MHz Fluorine and 10.8 MHz Carbon) device in the synthesis of imine, fluorination of phenylpropanoate and Diels-Alder cycloaddition [115]. Self-optimization using Nelder-Mead algorithm was employed in optimization of the reaction between benzaldehyde and aniline. The volumetric fraction of aldehyde and the residence time were used as variables.

4.2.5.6 Mass Spectroscopy

Ley *et al*. showed how the unsafe, and therefore avoided, procedure of benzyne generation could be optimized and safely performed in flow reactor integrated with a 3500 MiD miniature electrospray ionization (ESI) mass spectrometer (Microsaic Systems plc, Woking, UK) [122]. Diazotization of anthranlic acid was carried out to generate benzyne as a desired product with its subsequent cycloaddition to furan to yield 1,4-endoxide-1,4-dihydronaphtalene. Upon diazotization the highly explosive benzenediazonium-2-carboxylate is formed. Subsequently, benzyne is generated upon loss of N_2 and CO_2. A mass spectrometer was connected at the outlet of a FlowSyn reactor and the sample was extracted by passing thorugh a sample loop within a six-port valve. The content of the valve was diluted approximately 130-fold and then was pumped to the mass spectrometer. The total delay after the collection was only 10 s, while the reaction residence time was 20 min. Mass spectra showed that when the reaction was performed at temperatures below 50 °C, unreacted benzenediazonium-2-carboxylate was one of the major components at the outlet of the stream. Increasing temperature facilitated the desired reaction, as well as other side reactions. The authors propose that triazines and nitrocarbazole form, along with other products of diazo coupling reactions. The relative area of the product peak allowed the optimization of the system, to maximize its yield at 50 °C and 3–5 min residence time.

4.3 Multi-step Synthesis of Active Pharmaceutical Ingredients in Micro Flow

To demonstrate the ability of micro flow technology to deliver active pharmaceutical ingredients, this section presents a compilation of continuous syntheses of active pharmaceutical ingredients that result after more than two bonds have formed in an uninterrupted fashion. Uninterrupted in this case means that a particular intermediate does not undergo any batch unit operations or manual handling, apart from being collected in a reservoir with the inserted stream line for the next reactor, on its way to the subsequent reaction. Syntheses of natural compounds present an interesting and promising area for drug discovery class of compounds. Due to space considerations, we invite the reader to read a recently written review by Ley *et al*. on the continuous synthesis of natural compounds along with other multi-step syntheses with interrupted synthetic sequence [40, 123–125]. Finally, another requirement on micro flow processes is that reactants are introduced into a reaction platform continuously and not based on loops, which contain a limited amount of reactants and thus result in a limited amount of operating time.

4.3.1 Aliskiren

The most extensive and complete end to end synthesis performed in micro flow reactors was developed by Trout *et al*. in collaboration with Novartis International AG [127]. The target API in this process was aliskiren hemifumarate, shown in Figure 4.19, existing under the brand name of Tekturna (US) or Rasilez (UK). The API is used in the management of hypertension. An end to end integrated continuous manufacturing plant was built to manufacture tablets containing 112 mg of the free base form of aliskiren with a total nominal throughput of 45 g h^{-1}, which corresponds to 2.7×10^6 tablets $year^{-1}$. The capacity can range between 20 and 100 g h^{-1}. The plant fits into a conventional university building and occupies a 2.4×7.3 m^2 area. The synthesis started off with a melted intermediate, which was pumped at 100 °C into a tubular reactor to result in amide formation under neat conditions. The first step was intensified in flow, where reaction time was decreased from 72 h needed in batch down to 4 h in flow. The product stream was extracted in the in-line membrane based liquid–liquid extractor with addition of water and ethyl acetate. The typical recrystallization and filtration was translated by addition of heptane and cooling the suspension to 5 °C. Subsequently the slurry was filtered on a rotating porous plate while vacuum was applied to the back of the plate. The slurry was then washed with ethanol and ethyl acetate, prior to being scraped off and sent to another vessel. A density flow cell was integrated to adjust the flow rate of the ethyl acetate into the vessel containing slurry to deliver the outlet stream with 26 wt% concentration of four. The stream was then sent to a second reactor for an acid-catalyzed deprotection of the amine. The reaction is quenched with sodium hydroxide which proceeds in an isothermal manner in a flow reactor. The product stream is worked up by the addition of additional ethyl acetate to dilute the product to the concentration of 6 wt%. Sodium chloride formed upon the neutralization of hydrochloric acid precipitates within the flow, which is than filtered via a microfiltration membrane and the concentration is measured with an inline UV flow cell. Finally the flow passes through a column packed with molecular sieves in order to remove traces of water. The final product is obtained by performing reactive crystallization with fumaric acid. Once again the addition of fumaric acid is controlled by an inline UV detector to maintain 0.55 equivalents of the acid with respect to amine. The crystallization takes place in two stages, first crop is obtained at 20 °C and the additional crystallization takes place when the temperature is decreased to −10 °C. The crystals are then washed and mixed with the first excipient (SiO_2). The mixed slurry was then dried in two convection-heated drums, scraped off and sent into a vacuum chamber. Further, the dried flakes were transported through the heated tubes with the aim of final solvent removal. Later, the dried matter is mixed with PEG and melted at 60 °C to provide a good mixing and create tablets with a predefined geometry. The final tablets go through a quality testing. One major impurity was detected and was kept to within the specification limits.

4.3.2 Artemisinin

Malaria poses a serious threat on undeveloped regions, where the underpaid infected are in a desperate need for a cure [129]. Currently, the most effective treatment is offered by artemisinin. It is extracted from the plant *Artemisisa annua* (sweet wormwood); however

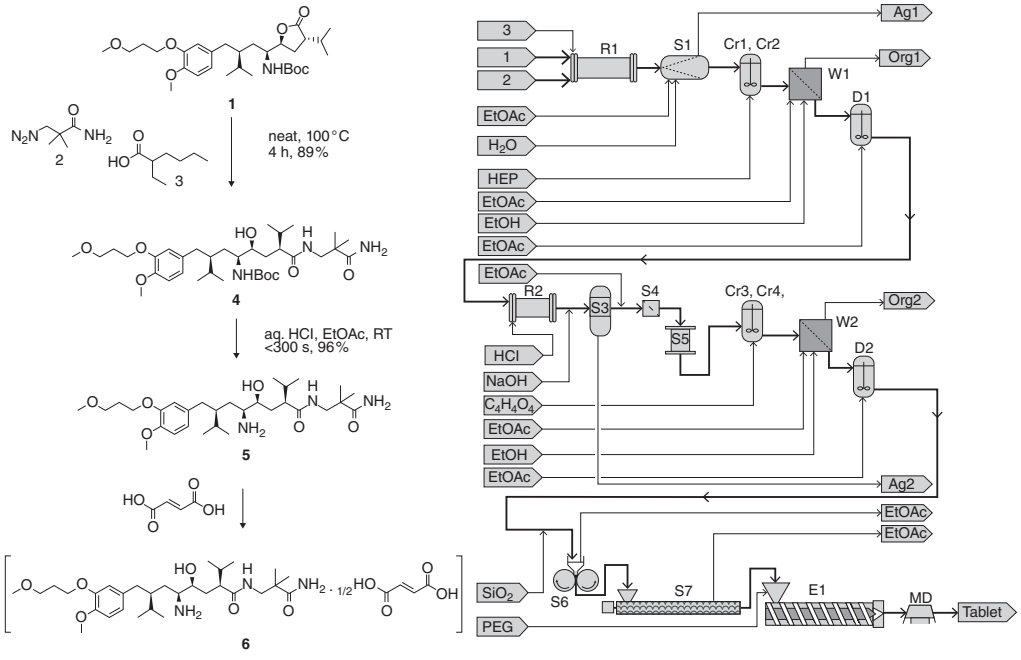

Figure 4.19 *Left: Synthetic steps from intermediate 1 to aliskiren hemifumarate. Right: Process flow diagram including the major unit operations. R – reactor, S – separation, Cr – crystallization, W – filter/wash, D – dilution tank, E – extruder, MD – mold. Reproduced from Ref. [126] with permission of WILEY-VCH Verlag GmbH & Co. KGaA.*

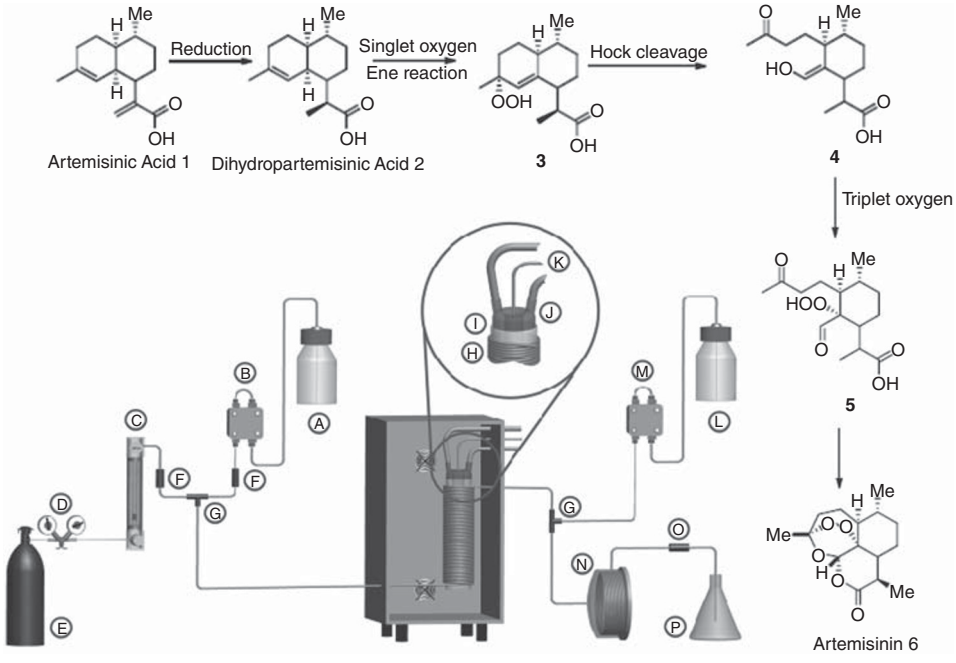

Figure 4.20 *Synthetic pathway toward Artemisinin performed in continuous flow reactor. For a detailed description of the setup components, please refer to the original reference. Reproduced from Ref. [128] with permission of WILEY-VCH Verlag GmbH & Co. KGaA.*

the high demand and limited supply results in the elevated cost of the drug [131]. The precursor to artemisinin, artemisinic acid is a simplex structure and can be extracted from the same wood in higher yields. The challenge is to convert available artemisinic acid to highly desired artemisinin (Figure 4.20). Seeberger *et al*. developed a simple, fast, efficient and inexpensive continuous process of converting the reduction product of artemisinic acid, dihydroartemisinic acid into the target compound, Artemisinin [128, 131]. By wrapping transparent FEP tubing around a Schenk photochemical reactor containing a 450 W mercury lamp that was cooled to 25 °C, the authors afforded generation of singlet oxygen in the presence of tetraphenylporphyrin. The ene reaction of artemisinic acid and singlet oxygen resulted in generation of tertiary allylic hydroperoxide (91% conversion, 75% yield). Hock cleavage was afforded by treating the product with trifluoroacetic acid in the first 16 mL of reactor at room temperature and then raising the temperature of the last 10 mL to 60 °C. Hock cleavage was followed by the addition of triplet oxygen and condensation reactions to completion, and afforded 39% yield after chromatographic purification. Authors calculated that at the current capacity 1500 of photochemical flow setups will be needed to meet the estimated annular demand of 225 million artemisinin doses.

4.3.3 Ibuprofen

Jamison *et al*. reduced the total synthesis of Ibuprofen down to 3 min with 72% overall yield and initial productivity 8.1 g h^{-1} [130]. The first step of the Fridel–Crafts acylation takes

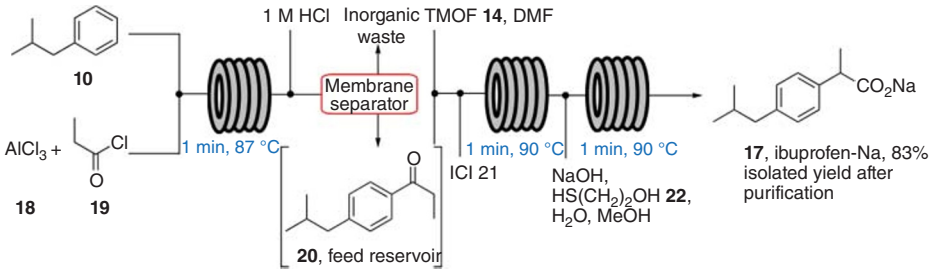

Figure 4.21 *Multi-step synthesis of Ibuprofen. Reproduced from Ref. [130] with permission of Wiley-VCH Verlag GmbH & Co. KGaA.*

place under neat conditions in 1 min yielding 95% yield of the product. Quenching of the reaction occurs when HCl is introduced into the reacting stream (Figure 4.21). The organic and aqueous phases are then separated within a membrane-based liquid–liquid separator. The organic outlet is immersed into a reservoir, where the product is collected and pumped into the subsequent reactor with a separate pump (144 µl min^{-1}) to mix with trimethylorthoformate in DMF (630 µl min^{-1}). Iodine chloride used in the following step was pumped in its neat melted form (109 µl min^{-1}). The absence of a solvent prevented the formation of iodine precipitate. Finally, the product stream of the second reactor is diluted by a factor of four upon meeting with the stream of sodium hydroxide and 2-mercaptoethanol in water–methanol mixture (3 ml min^{-1}).

4.3.4 Gleevec

Gleevec (imatinib mesylate) was developed by Novartis AG and is used for the treatment of chronic myeloid leukaemia and gastrointestinal stromal tumors [132]. The synthesis of the target molecule in flow by Ley *et al*. started with the formation of the amide core via a reaction of 4-(chloromethyl)benzoyl chloride and aniline. Polystyrene-supported DMAP within a glass column was followed by a column with supported dimethylamine in order to facilitate the reaction and neutralize the hydrochloric acid formed as a by-product. Connecting the outlet stream to the next step of nucleophlic substitution of chloride by *N*-methyl piperazine turned out to be problematic due to the dispersion of the product within the stream, and changing concentration, as was indicated by in-line monitoring through a UV spectrometer. An automated fraction collector was then attached to the UV spectrometer and programmed to collect the output of the reaction with a pre-defined UV absorption threshold. A highly concentrated fraction of 4 mL (75% isolated yield) was then premixed with *N*-methyl piperazine. The second reaction was optimized when the concentration of the collected product was increased, by evaporating the DCM from the collected 4 mL of product solution. The output of the first reaction was combined with the *N*-methyl piperazine in DMF, after that nitrogen was aspirated over the solution heated to 50 °C and the evaporated DCM was removed from the headspace to an exhaust. Evaporation of the volume took 30 min, and was followed by the injection of the reactant mixture into the calcium carbonate containing column heated to 80 °C. To scavenge unreacted *N*-methyl piperazine polystyrene-supported isocyanate followed the calcium carbonate column. In order to catch the product silica-supported sulfonic acid was used. Later, the product was released into the

mixture of ammonia in methanol resulting in 80% yield and >90% purity. The final step on the way to the target molecule is Buchwald–Hartwig amination, which was achieved by using 10 mol% of a BrettPhos Pd precatalyst and 4.0 equivalents of amine and sodium ter-butoxide. Thus, three three-step synthesis of Gleevec was afforded with 32% overall yield and >95% purity.

4.3.5 Nabumetone

Kappe *et al*. connected aldol condensation and hydrogenation reaction to produce 4-aryl-3-butenones [133]. One of compounds, 4-(6-methoxy-2-naphtalenyl)-2-butanone (nabumetone), synthesized in two separate steps is a nonsteroidal anti-inflammatory drug. It was first launched in 1985 by Beecham under the brand names of Relafen and Noracet. Aldol condensation was first optimized in microwave batch setup. After confirming the benefits of superheating, the reaction was performed under continuous conditions in commercially available flow platform, Uniqsis FlowSyn. The aldol condensation is spontaneous under room temperature, while increasing the reaction temperature to 70 °C resulted in the full conversion and 94% isolated yield within a 7.5 min residence time. Hydrogenation, as a subsequent step was optimized in the commercially available H-Cube setup. The connection of the steps was performed for the 4-(4-methoxyphenyl)-3-buten-2-one rather than the nabumetone precursor. In case of 4-(4-methoxyphenyl)-3-buten-2-one, the hydrogenation step performed at 55 °C and connected to aldol condensation resulted in 93% crude yield and 75% after chromatographic purification. No information was given regarding the residence time during the hydrogenation step, nor the volume of the filled catalyst carrying cartridge, to be able to calculate it.

4.3.6 Quinolone Derivative as a Potent $5HT_{1B}$ Antagonist

A potent $5HT_{1B}$ antagonist developed by AstraZeneca was synthesized by Horchler *et al.* via seven steps with an overall yield of 7% [134]. Ley *et al*. employed a commercially available Vapourtec $R2^{+}$/R4 reactor, ThalesNano H-Cube reactor, polymer-supported reagents and scavengers to deliver the final molecule in six steps with overall 18% yields and 98% purity. The synthesis presents an advantage of using flow techniques within the medicinal chemistry department, where variety is important and small quantities are sufficient. Six steps were incorporated with three scavenging resins and two resins for "catch and release" purposes. Due to the fact that information about the quantity of caught and concentration of the released product is missing it is difficult to evaluate the scale of the process.

4.3.7 Rufinamide

Rufinamide, used in the treatment of Lennox–Gastaut syndrome, exists under the brand names of Inovelon and Banzel and is produced by Eisai [52]. Recently the total synthesis of rufinamide in flow was published by Jamison *et al*. [135]. 2,6-difluorobenzyl bromide dissolved in DMSO was mixed with sodium azide solution to yield a final 0.29 M concentration of 2,6-difluorobenzyl bromide within the reactor, with 1.3 equivalents of sodium azide [135]. Nucleophilic substitution took place in 1 min at room temperature. Dipolarophile

needed to construct 1,2,3-trizole moiety in rufinamide was synthesized from neat methyl propiolate and ammonia in 5 min at 0 °C. Finally, 2,6-difluorobenzyl azide and propiolamide were combined in copper tubing to facilitate a catalyzed [3+2]-Huisgen cycloaddition at 110 °C and given 6.2 min residence time. Thus, the total synthesis took 11 min and resulted in 92% overall yield. Product was purified by addition of two equivalents of water with respect to reaction mixture, filtering off the precipitate and drying. The productivity of the sequence was 217 mg h^{-1}.

4.3.8 Thioquinazolinone

Dong-Pyo Kim *et al*. synthesized a library of multifunctionalized thioquinazolinones using a multi-injection one flow reaction system [136]. The total residence time for three subsequent reactions is 10 s. The sequence consisted of a Br-Li exchange reaction, an intramolecular cyclization to thioquinazolinone ring, upon which a lithium thiolate intermediate was formed, which was later coupled to benzylic bromides. Thus, a library of S-benzylic thioquinazolinones derivatives with high yields (75–98%) has been delivered. First, a Br-Li exchange reaction is carried out at −78 °C in batch, while in flow it was successfully delivered at RT and short resindence time of 16 ms. Second step needs heating in batch, while in flow the reaction proceeded to completion in 2.3 s at RT. This example, once again demonstrates the benefits of tight control over reaction time and heat and mass transfer offered by micro flow technology.

4.4 Larger-scale Syntheses

4.4.1 Hydroxypyrrolotriazine (Bristol–Myers–Squibb)

LaPorte *et al*. described the design of the process for manufacturing of an intermediate in the synthesis of brivamib alaninate [137]. Hydrogen peroxide is used as the oxidant in a benzylic hydroperoxide rearrangement. However, its combination with an acid catalyst brings about the thermal runaway potential at ambient conditions. Chemical hazard analysis concluded that the reaction was unsafe for operating at more than 0.5 kg of starting material in batch. Alternative chemistries were not sufficient for the quality expected, therefore the engineering solution of transferring batch process into continuous was devised. In order to to prevent the decomposition of hydrogen peroxide and minimize side reactions, the mixing section of the compounds was kept at −5 °C. Process simulation showed that operating the reactor in two temperature regimes was the safest, that is first low temperature (0 °C) prevented the thermal runaway, while a second higher temperature zone (12–15 °C) drove the reaction to completion. The laboratory-scale setup proves to operate in a stable manner and therefore was further scaled-up to kilo-laboratory and pilot-plant scale. Figure 4.22 shows a portable pilot plant rack reactor, which operated at 400 mL min^{-1} with a productivity of 22.4 kg day^{-1}.

4.4.2 2,2-Dimethylchromenes (Bristol–Myers–Squibb)

2,2-Dimethylchromenes represent a highly interesting class of compounds due to their biological acitivity in plants and animals [138]. Multi-step synthesis of the compound involves

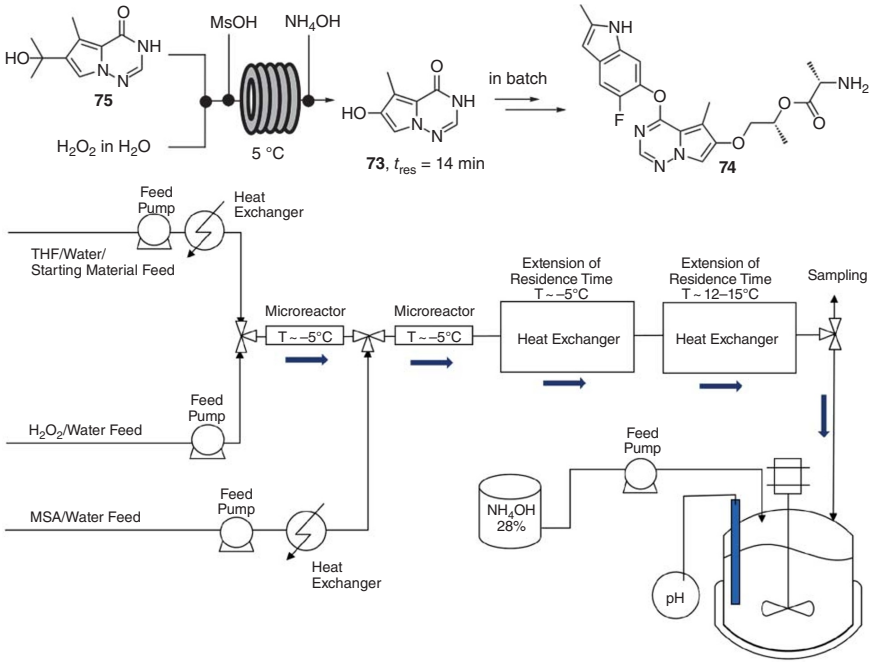

Figure 4.22 *Top: Reaction scheme for the synthesis of hydroxypyrrolotriazine. Bottom left: Laboratory-scale continuous setup. Bottom right: Pilot plant assembly on a portable rack. Reproduced from Ref. [137] with permission of the American Chemical Society.*

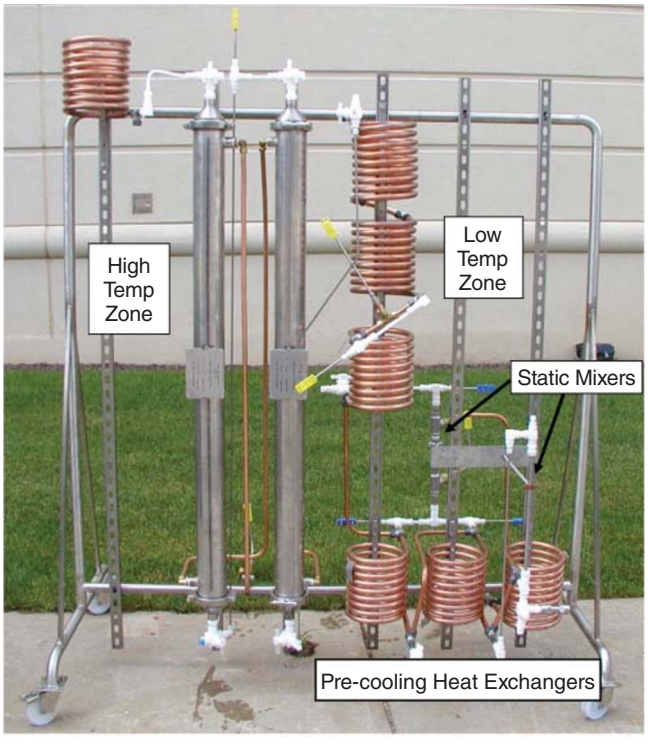

Figure 4.22 *(Continued)*

a thermal Claisen rearrangement. Its execution at large scale in batch poses a safety risk, in addition to decomposition of the product. Therefore, Polomski and Soundararajan *et al*. performed a DSC study and subsequently developed a mathematical model that could identify the key parameters in the optimization of the reaction outcome as well as maximizing the safety [138]. A stainless steel capillary reactor (80 ml) of one-eighth inch (0.32 mm) ID dimensions was heated within an oil bath to 195–200 °C. A flow of 20 mL min^{-1} allowed 4 min residence time and resulted in 98% yield with a productivity of 7 kg h^{-1}.

4.4.3 Fused-Bycyclic Isoxazolidines (Eli Lilly and Company)

Process intensification in synthesyzing bicyclic isoxazolidines via 1,3-dipolar cycloaddition of nitrone was achieved when a flow reactor could be heated up to much higher temperatures than a conventional batch reactor [139]. The process was realized in a stainless steel tubular coil (0.32 mm OD, 343 mL) at 210 °C in 10 min residence time. The concentration of the reactant in toluene was 0.24 M, which was pumped with 34.3 ml min^{-1} and resulted in a productivity of 120 g h^{-1} (50% yield).

4.4.4 7-Ethyltryptophol on the Way to Etodolac

Indole moiety is often found in natural products and biologically active compounds [140]. 7-Ethyltryptopol is a key intermediate for the anti-inflammatory drug etodolac. Etodolac

proved to be safe with respect to gastrointestinal and renal tract and to slow down the progression of skeletal changes in rheumatoid arthritis [141]. The benchmark method consists of hydrozone formation, followed by the [3+3]-sigmatropic rearrangement. The instability of hydrozones poses a safety concern on large scale calling for one-pot procedures. Su *et al*. developed a continuous one-pot procedure in micro flow reactor constructed from a Hastelloy tubing (ID 6 mm) [142]. Two reacting streams of 2-ethylphenylhydrazine and 4-hydroxybutyraldehyde were mixed at a total flow rate of 230 mL min^{-1} within a mixing T (ID 7 mm). The tubular reactor was heated within an oil bath. It was observed that decomposition of hydrozone could be minimized by shortening the reaction time to 20 s, after which sulfuric acid was added to promote [3+3]-sigmatropic rearrangement to the final product. In total, the one-pot process took 280 s, including cooling of 20 s. On 10 kg-scale the developed procedure afforded 74% yield of the final product with 83% purity. Authors state that during the manufacturing the isolation of 7-ethyltryptopol would not be necessary and the process could go on to the synthesis of etodolac.

4.4.5 6-Hydroxybuspirone (Bristol-Myers-Squibb)

LaPorte *et al*. designed a process in line with PAT to deliver a safer and more efficient continuous process on production scale [143]. The process consisted of converting buspirone to 6-hydroxybuspirone via hydroxylation in three steps, first enolization with sodium bis(trimethylsilylamide) in THF at or below −70 °C in the presence of excess of triethylphosphite (Figure 4.23). Once enolization is complete, air is introduced to afford oxidation, which is followed by reduction of formed hydroperoxy anion to hydroxide. Equivalents of base govern the formation of the by-product, diol. Moreover, premature introduction of oxygen leads to the formation of residuals of unreacted sodium bis(trimethylsilylamide) and unreacted buspirone enolate, which may result in the

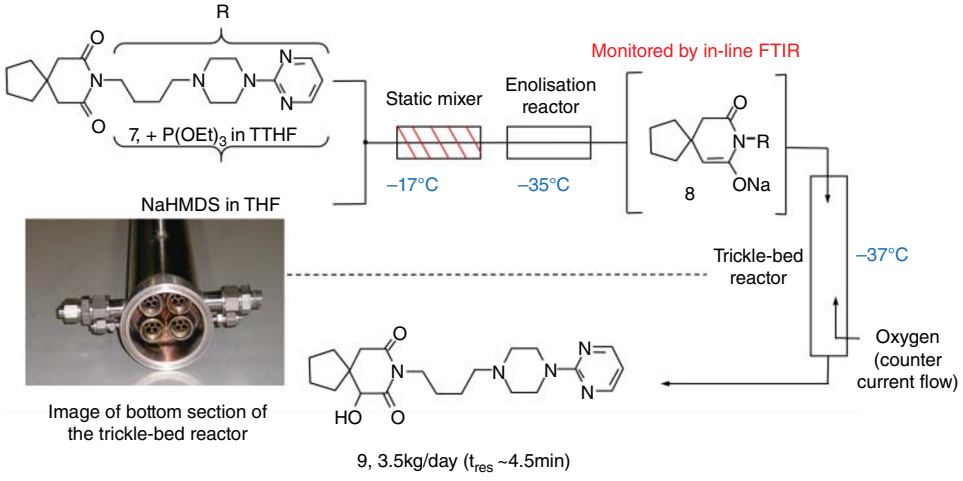

Figure 4.23 *Top: Reaction scheme for the synthesis of 6-hydroxybuspirone. Bottom left: Laboratory-scale continuous setup and bottom of the Quad oxidation reactor. Bottom right: Internal reaction tubes and extra-tubular baffles of the Quad trickle-bed reactor. Reproduced from Ref. [143] with permission of the American Chemical Society.*

deprotonation of the intermediate that can be oxidized to diol impurities. A high excess (3.5–5.0 eq.) of triethylphosphite is needed to maintain sufficient progress in the reduction and prevent formation of amino acids and other impurities. Apart from possible waste generation, there is a danger coming from the exothermic oxidation within flammable solvent in the presence of oxygen. Therefore, headspace of the reactor is continuously diluted with nitrogen. The complications listed above lead to the design of a continuous process. The reactant and base were mixed within a T-mixer with internal dimensions of three-eighth inch (0.95 mm), followed by one static mixer [0.5 in (1.27 mm) ID with 27 elements] at room temperature to avoid sudden precipitation of base and second mixer that was cooled with a jacket containing glycol to −15 °C. Enolization was allowed to reach completion within the heat exchanger. A React-IR DiComp probe was installed at the outlet of the enolatation reactor to perform on-line FTIR measurements. The product stream was then split in four streams that entered a trickel bed reactor containing four columns. Oxygen was fed in a counter-current fashion, since it lead to a higher selectivity. Oxidation reactor (600 mL) was cooled down to −37 °C with the same fluid used to cool heat exchanger used in enolation. Unreacted oxygen flowed out the top of the reactor, where it was diluted with nitrogen and sent to the plant's thermal oxidizer, while product flowed by gravity along the reactor into a tank with a level control system. When a certain level was reached the level output signal would make the valve on the outlet of a piston pump open and allow the product stream to flow into the quench tank. The product flow rate into the quench tank was 168 ml min^{-1} and the pH was kept constant by continuous addition of HCl. In total, the continuous process took 4 min as total residence time, while the batch process took 8 h in laboratory and 16–24 h on a pilot plant scale. In three continuous process pilot-plant campaigns, more than 100 kg of API was produced. Thus, the current process benefited from speeded-up kinetics, higher safety due to no accumulation and limited reactive species in handling, higher selectivity and thus less generation of waste delivering 74% yield of the final product with 83% purity. Authors state that during the manufacturing the isolation of 7-ethyltryptopol would not be necessary and the process could go on to the synthesis of etodolac.

4.5 Current Industrial Applications

At the initial stages in drug discovery, when a wide variety of drug candidates is investigated for initial testing, it is acceptable to synthesize small quantities by the fastest synthetic way with minimal regard to the final yield, or sustainability of the synthetic route. However, a new approach is to deliver products with an already planned efficient, safe and reliable synthetic route. Thus, a new utopia is the design of the drug along with its end to end continuous process. The process should be seen as a whole without segmentation to upstream, production and downstream processing. In this setting, flow technology provides opportunities on multiple levels. Reactions that can benefit from chemical intensification can be optimized within laboratory-scale flow setups or microwave-based batch units that allow the screening of dozens of conditions at once. Medicinal chemists knowing how to operate these platforms may consider and try chemistries they would not normally propose [144]. Thus, new chemical transformations with accompanying benefits may arise. Moreover, reduced handling and the automatization of technlology makes the work of developers

safer and faster. At this stage, commercial equipment designed for general use such as platforms offered by Chemtrix, Syrris, Vapourtec, Uniqsis and FutureChemistry would suit and suffice for most applications. However, when it comes to the implementation of continuous technology within existing industrial processes a tighter collaboration in between technology providers and users is required.

According to the recent news given in C&EN, over the past decade pharma industry has invested over US$ 1 billion in development of continuous manufacturing [145]. The majority of investments were made independently by companies with no extensive collaboration. Moreover, the companies adopting the technology seldomly share the information regarding success or failure, which slows down the theoretically possible spread of technology. Drug manufacturers having exisiting batch processes are risk-averse and not willing to switch to still less known flow technology. Contract manufacturing organizations, however, are faster to adopt the technology with the incentive to implement new chemistries and provide a process that would not be possible in batch. One result revealed to public is the synthesis of an arthritis drug, naproxcinod, which is the first in a new class of cyclooxygenase-inhibting nitric oxide donators. Naproxcinod developed by NicOx involves a nitration reaction, highly dangerous on a large scale [146]. In collaboration with DSM Pharma Chemicals and using the Corning glass microreactor system, a process based on three key process steps, such as the nitration reaction, neutralization and workup, was implemented to deliver a few hundred tonnes of product per year.

Scaleup of the micro technology process presents a hurdle and has yet to be set in a standardized procedure. On the production scale micro chips are substituted by micro plates, which are numbered up to scaleup a given process. In this context, Chemtrix is now collaborating with DSM Pharma to design and evolve the technology [145]. Lonza has developed a large number and variety of plate reactors licensed to Ehrfeld Mikrotechnik BTS owned by Bayer. According to Dominique Roberge (Lonza) the challenges of scaleup are an even and constant distribution of the flow among multiple plate reactors, as well as ensuring that all of the channels are clean. Moreover, downstream equipment for isolation and purification, especially for crystallization and filtration is still not available. However, several pioneers have developed end to end processes incorporating continuous work-up. One of the examples, synthesis of aliskiren hemifumarate developed by Novartis-MIT Center for continuous manufacturing, is described above. The equipment used is not yet available for pharma manufacturers, and was designed and constructed in-house. Thus, a collaboration between academia and technology developers is needed to move the implementation of flow technology forward. With this incentive, MIT and Continuous Manufacturing and Crystallisation (which is the result of collaboration among GSK, AstraZeneca, Novartis and the UK National Centre for Innovative Manufacturing) organized an international symposium on the continuous manufacturing of pharmaceuticals. A series of white papers, unveiling the current state and open gaps, are now available to the public [147].

4.6 Conclusion and Outlook

Continuous flow technology offers the pharmaceutical industry a great platform to develop continuous manufacturing processes. The technology can and should be adopted at an early stage of the development to realize all its potential until the manufacturing is established.

Easy integration of PAT techniques allows a deeper understanding of the process kinetics, its fast optimization and tighter control [148, 149]. Flow technology allows safe operation under normally explosive and thermal runaway regimes. High pressure processes are also easier to apply, opening a way to use of greener solvents under superheated and supercritical conditions. Thus, processes can be chemically intensified to maximize selectivity and productivity. The modularity of the equipment allows building a sequence of reactions and thus, completing the whole process at one location with a possible switch to different processes based on the specific demand of the production. Ongoing development of work-up equipment and its integration with continuous reactions leads to process design intensification.

Despite being a very useful tool, flow technology is sill in its development and evolvement stage. There are a number of non-technological barriers to innovation for flow chemistry – actually those seem to have more impact than the technological hurdles. Recently, those were discussed for green chemistry and engineering to which flow chemistry belongs. The barriers listed included economic and financial, regulatory, systemic, organizational, sociocultural, definitions and metrics [150]. Tighter collaboration among manufacturers and academia, as well as transparency about lessons learned is needed to bring the development further. Solutions to handling solids and the minimization of solvents used needs to be found. Moreover, equipment manufactures are to provide relevant equipment, such as pumps, valves and reactors with high chemical resistance. Cost analysis schemes developed for evalution of flow processes can help current manufacturers to rethink their strategies and implement step by step changes from batch to flow. This, hopefully, will lead to more sustainable applications, while meeting the needs of society.

References

[1] M. Abou-Gharbia and W. E. Childers (2014) *J. Med. Chem.*, **57**, 5525–5553.
[2] L. Malet-Sanz and F. Susanne, (2012) *J. Med. Chem.*, **55**(9), 4062–4098.
[3] C. Jiménez-González, P. Poechlauer, Q. B. Broxterman, B.-S. Yang, D. am Ende, J. Baird, C. Bertsch, R. E. Hannah, P. Dell'Orco, H. Noorman, S. Yee, R. Reintjens, A. Wells, V. Massonneau, and J. Manley (2011) *Org. Process Res. Dev.*, **15**, 900–911.
[4] P. Poechlauer, J. Colberg, E. Fisher, M. Jansen, M. D. Johnson, S. G. Koenig, M. Lawler, T. Laporte, J. Manley, B. Martin, and A. O'Kearney-McMullan (2013) *Org. Process Res. Dev.*, **17**, 1472–1478.
[5] M. C. Bryan, B. Dillon, L. G. Hamann, G. J. Hughes, M. E. Kopach, E. A. Peterson, M. Pourashraf, I. Raheem, P. Richardson, D. Richter, and H. F. Sneddon (2013) *J. Med. Chem.*, **56**, 6007–6021.
[6] N. Kockmann, M. Gottsponer, B. Zimmermann, and D. M. Roberge (2008) *Chem. – A Eur. J.*, **14**, 7470–7477.
[7] T. Razzaq, T. N. Glasnov, and C. O. Kappe (2009) *European J. Org. Chem.*, **2009**, 1321–1325.
[8] R. L. Hartman and K. F. Jensen (2009) *Lab Chip*, **9**, 2495–2507.
[9] A. Nagaki, Y. Tomida, H. Usutani, H. Kim, N. Takabayashi, T. Nokami, H. Okamoto, and J. Yoshida (2007) *Chem. Asian J.*, **2**(12), 1513–1523.
[10] E. Colombo, P. Ratel, L. Mounier, and F. Guillier (2011) *J. Flow Chem.*, **1**, 68–73.
[11] X. Fan, M. Gonzalez, K. Wilson, S. Tennison, A. Kozynchenko, A. A. Lapkin, and P. K. Plucinski (2009) *J. Catal.*, **267**, 114–120.
[12] P. W. Miller, N. J. Long, A. J. de Mello, R. Vilar, H. Audrain, D. Bender, J. Passchier, and A. Gee (2007) *Angew. Chem. Int. Ed. Engl.*, **46**, 2875–2878.

[13] P. D. Hampton, M. D. Whealon, L. M. Roberts, A. A. Yaeger, and R. Boydson, (2008) *Org. Process Res. Dev.*, **12**(5), 946–949.
[14] I. Dencic, V. Hessel, M. H. J. M. De Croon, J. Meuldijk, C. W. J. Van Der Doelen, and K. Koch (2012) *ChemSusChem*, **5**, 232–245.
[15] J. Wegner, S. Ceylan, and A. Kirschning (2012) *Adv. Synth. Catal.*, **354**, 17–57.
[16] R. L. Hartman, J. P. McMullen, and K. F. Jensen (2011) *Angew. Chem. Int. Ed. Engl.*, **50**, 7502–7519.
[17] J. Wegner, S. Ceylan, and A. Kirschning (2011) *Chem. Commun. (Camb).*, **47**, 4583–4592.
[18] L. Vaccaro, D. Lanari, A. Marrocchi, and G. Strappaveccia (2014) *Green Chem.*, **16**, 3680.
[19] V. Hessel, D. Kralisch, N. Kockmann, T. Noël, and Q. Wang (2013) *ChemSusChem*, **6**, 746–789.
[20] K. Geyer, J. D. C. Codée, and P. H. Seeberger (2010) *Chem. – A Eur. J.*, **12**, 8434–8442.
[21] S. Borukhova and V. Hessel (2013) *Process Intensification for Green Chemistry*, John Wiley & Sons, Ltd, London, pp. 91–156.
[22] K. D. Nagy, B. Shen, T. F. Jamison, and K. F. Jensen (2012) *Org. Process Res. Dev.*, **16**, 976–981.
[23] D. Bošković and S. Loebbecke (2008) *Chem. Eng. J.*, **135** (Suppl.), S138–S146.
[24] S. Lohse, B. T. Kohnen, D. Janasek, P. S. Dittrich, J. Franzke, and D. W. Agar (2008) *Lab Chip*, **8**, 431–438.
[25] C. B. Minnich, F. Sipeer, L. Greiner, and M. A. Liauw (2010) *Ind. Eng. Chem. Res.*, **49**, 5530–5535.
[26] F. Trachsel, A. Günther, S. Khan, and K. F. Jensen (2005) *Chem. Eng. Sci.*, **60**, 5729–5737.
[27] T. Illg, P. Löb, and V. Hessel (2010) *Bioorg. Med. Chem.*, **18**, 3707–3719.
[28] J. Yoshida, A. Nagaki, and T. Yamada (2008) *Chemistry*, **14**, 7450–7459.
[29] O. Benali, G. Davies, M. Deal, E. Farrant, D. Guthrie, J. Holden, and R. Wheeler (2008) *J. Comb. Chem.*, **10**, 52–55.
[30] N.-T. Nguyen (2008) *Micro Mixers: Fundamentals, Design and Fabrication*., William Andrew, Norwich.
[31] A. Gunther and K. F. Jensen (2006) *Lab Chip*, **6**, 1487–1503.
[32] K. Sato, A. Hibara, M. Tokeshi, H. Hisamoto, and T. Kitamori (2003) *Anal. Sci.*, **19**, 15–22.
[33] V. Hessel, H. Löwe, and F. Schönfeld (2005) *Chem. Eng. Sci.*, **60**, 2479–2501.
[34] M. Rahbar, L. Shannon, and B. L. Gray (2014) *J. Micromechanics Microengineering*, **24**, 25003.
[35] C. Wiles and P. Watts (2011) *Micro Reaction Technology in Organic Synthesis*, Taylor and Francis, London.
[36] P. Plou, A. Macchi, and D. M. Roberge (2014) *Org. Process Res. Dev.*, **18**(11), 1286–1294.
[37] J. Yoshida, Y. Takahashi, and A. Nagaki (2013) *Chem. Commun.*, **49**, 9896–9904.
[38] N. Krasberg, L. Hohmann, T. Bieringer, C. Bramsiepe, and N. Kockmann (2014) *Processes*, **2**, 265–292.
[39] M. Irfan, T. N. Glasnov, and C. O. Kappe (2011) *ChemSusChem*, **4**(3), 300–316.
[40] J. C. Pastre, D. L. Browne, and S. V Ley (2013) *Chem. Soc. Rev.*, **42**, 8849–69.
[41] T. Illg, V. Hessel, P. Löb, and J. C. Schouten (2011) *Chem. Eng. J.*, **167**, 504–509.
[42] V. Hessel (2009) *Chem. Eng. Technol.*, **32**, 1655–1681.
[43] V. Hessel, D. Kralisch, and U. Krtschil (2008) *Energy Environ. Sci.*, **1**, 467.
[44] T. Razzaq and C. O. Kappe (2010) *Chem. Asian J.*, **5**, 1274–1289.
[45] F. Benito-Lopez, R. M. Tiggelaar, K. Salbut, J. Huskens, R. J. M. Egberink, D. N. Reinhoudt, H. J. G. E. Gardeniers, and W. Verboom (2007) *Lab Chip*, **7**, 1345–51.
[46] B. Reichart, G. Tekautz, and C. O. Kappe (2013), *Org. Process Res. Dev.*, **17**(1), 152–157.
[47] D. Cantillo and C. O. Kappe (2013) *J. Org. Chem.*, **78**, 10567–10571.

[48] A. Nagaki, C. Matsuo, S. Kim, K. Saito, A. Miyazaki, and J. Yoshida (2012) *Angew. Chemie Int. Ed.*, **51**, 3245–3248.
[49] K. Kurahashi, Y. Takemoto, and K. Takasu (2012) *ChemSusChem*, **5**, 270–273.
[50] T. Kawaguchi, H. Miyata, K. Ataka, K. Mae, and J.-I. Yoshida (2005) *Angew. Chem. Int. Ed. Engl.*, **44**, 2413–2416.
[51] R. L. Hartman, J. R. Naber, S. L. Buchwald, and K. F. Jensen (2010) *Org. Process Res. Dev.*, **75**(3), 911–915.
[52] S. Borukhova, T. Noël, B. Metten, E. de Vos, and V. Hessel (2013) *ChemSusChem*, **6**, 2220–5.
[53] L. Kong, 4. Lv, Q. Lin, 4. Liu, Y. Zhou, and Y. Jia (2010) *Org. Process Res. Dev.*, **14**, 902–904.
[54] V. Hessel, C. Hofmann, H. Löwe, A. Meudt, S. Scherer, F. Schönfeld, B. Werner (2004) *Org. Process Res. Dev.*, **8**(3), 511–523.
[55] F. Benaskar, V. Hessel, U. Krtschil, and P. Lo (2009) *Org. Process Res. Dev.*, **13**(5), 970–982.
[56] S. Marre, A. Adamo, S. Basak, C. Aymonier, and K. F. Jensen (2010) *Ind. Eng. Chem. Res.*, **49**(22), 11310–11320.
[57] U. Kunz and T. Turek (2009) *Beilstein J. Org. Chem.*, **5**, 1–7.
[58] L. Lengyel, T. Z. Nagy, G. Sipos, R. Jones, G. Dormán, L. Ürge, and F. Darvas (2012) *Tetrahedron Lett.*, **53**, 738–743.
[59] M. Damm, T. N. Glasnov, and C. O. Kappe (2010) *Org. Process Res. Dev.*, **14**, 215–224.
[60] F. Bergamelli, M. Iannelli, J. A. Marafie, and J. D. Moseley (2010) *Org. Process Res. Dev.*, **14**, 926–930.
[61] R. Morschhäuser, M. Krull, C. Kayser, C. Boberski, R. Bierbaum, P. a. Püschner, T. N. Glasnov, and C. O. Kappe (2012) *Green Process. Synth.*, **1**, 281–290.
[62] D.-L. Zhao, H.-L. Zhang, 4.-W. Zeng, Q.-S. Xia, and J.-T. Tang (2006) *Biomed. Mater.*, **1**, 198.
[63] J. Wegner, S. Ceylan, C. Friese, and A. Kirschning (2010) *Eur. J. Org. Chem.*, **2010**(23), 4372–4375.
[64] T. K. Houlding and E. V. Rebrov (2012) *Green Process. Synth.*, **1**, 19–31.
[65] S. Ceylan, L. Coutable, J. Wegner, and A. Kirschning (2011) *Chem. Eur. J.*, **17**(6), 1884–1893.
[66] S. Ceylan, C. Friese, C. Lammel, K. Mazac, and A. Kirschning (2008) *Angew. Chemie Int. Ed.*, **47**, 8950–8953.
[67] W. Verboom (2009) *Chem. Eng. Technol.*, **32**, 1695–1701.
[68] T. Razzaq, T. N. Glasnov, and C. O. Kappe (2009) *Chem. Eng. Technol.*, **32**, 1702–1716.
[69] U. Tilstam, T. Defrance, T. Giard, and M. D. Johnson (2009) *Org. Process Res. Dev.*, **13**, 321–323.
[70] S. Borukhova, A. D. Seeger, T. Noël, Q. Wang, M. Busch, and V. Hessel (2015) *ChemSusChem*, **8**, 504–512.
[71] A. Leclerc, M. Alamé, D. Schweich, P. Pouteau, C. Delattre, and C. de Bellefon (2008) *Lab Chip*, **8**, 814–817.
[72] Y. Zhao, G. Chen, C. Ye, and Q. Yuan (2013) *Chem. Eng. Sci.*, **87**, 122–132.
[73] D. Cantillo, H. Sheibani, and C. O. Kappe (2012) *J. Org. Chem.*, **77**, 2463–73.
[74] A. Polyzos, M. O. Brien, T. P. Petersen, I. R. Baxendale, and S. V Ley (2011) *Angew. Chem. Int. Ed.*, **50**(5), 1190–1193.
[75] P. B. Cranwell, M. O'Brien, D. L. Browne, P. Koos, A. Polyzos, M. Peña-López, and S. V Ley (2012) *Org. Biomol. Chem.*, **10**, 5774–9.
[76] S. Newton, S.V. Ley, E. C. Arcé, and D. M. Grainger (2012) *Adv. Synth. Catal.*, **354**(9), 1805–1812.
[77] B. Tomaszewski, A. Schmid, and K. Buehler (2014) *Org. Process Res. Dev.*, **18**, 1516–1526.
[78] D. R. Snead and T. F. Jamison (2013) *Chem. Sci.*, **4**, 2822–2827.
[79] J. Fraga-Dubreuil and M. Poliakoff (2006) *Pure Appl. Chem.*, **78**, 1971–1982.
[80] P. E. Savage, S. Gopalan, T. I. Mizan, C. J. Martino, and E. E. Brock (1995) *AIChE J.*, **41**, 1723–1778.

[81] R. A. Bourne, 4. Han, M. Poliakoff, and M. W. George (2009) *Angew. Chemie*, **121**, 5426–5429.
[82] E. Y. Kenig, Y. Su, A. Lautenschleger, P. Chasanis, and M. Grünewald (2013) *Sep. Purif. Technol.*, **120**, 245–264.
[83] A. T. Sundberg, P. Uusi-Kyyny, and V. Alopaeus (2012) *Russ. J. Gen. Chem.*, **82**, 2079–2087.
[84] A. Ziogas, V. Cominos, G. Kolb, H.-J. Kost, B. Werner, and V. Hessel (2012) *Chem. Eng. Technol.*, **35**, 58–71.
[85] K. F. Lam, E. Cao, E. Sorensen, and a Gavriilidis (2011) *Lab Chip*, **11**, 1311–1317.
[86] R. L. Hartman, J. R. Naber, S. L. Buchwald, and K. F. Jensen (2010) *Angew. Chemie Int. Ed.*, **49**, 899–903.
[87] Y. Zhang, S. Kato, and T. Anazawa (2010) *Lab Chip*, **10**, 899–908.
[88] Y. Zhang, S. Kato, and T. Anazawa (2009) *Chem. Commun. (Camb).*, 2750–2752.
[89] R. L. Hartman, H. R. Sahoo, B. C. Yen, and K. F. Jensen (2009) *Lab Chip*, **9**, 1843–1849.
[90] R. J. Ingham, E. Riva, N. Nikbin, I. R. Baxendale, and S. V Ley (2012) *Org. Lett.*, **14**, 3920–3923.
[91] M. O'Brien, R. Denton, and S. Ley (2011) *Synthesis (Stuttg).*, **2011**, 1157–1192.
[92] M. D. Hopkin, I. R. Baxendale, and S. V. Ley (2013) *Org. Biomol. Chem.*, **11**, 1822–39.
[93] I. Vural Gürsel, F. Aldiansyah, Q. Wang, T. Noël, and V. Hessel (2015) *Chem. Eng. J.*, **270**, 468–475.
[94] A. Adamo, P. L. Heider, N. Weeranoppanant, and K. F. Jensen (2013) *Ind. Eng. Chem. Res.*, **52**, 10802–10808.
[95] A. E. Cervera-Padrell, S. T. Morthensen, D. J. Lewandowski, T. Skovby, S. Kiil, and K. V. Gernaey (2012) *Org. Process Res. Dev.*, **16**, 888–900.
[96] L. L. Simon, H. Pataki, G. Marosi, F. Meemken, K. Hungerbühler, A. Baiker, S. Tummala, B. Glennon, M. Kuentz, G. Steele, H. J. M. Kramer, J. W. Rydzak, Z. Chen, J. Morris, F. Kjell, R. Singh, R. Gani, K. V Gernaey, M. Louhi-Kultanen, J. O'Reilly, N. Sandler, O. Antikainen, J. Yliruusi, P. Frohberg, J. Ulrich, R. D. Braatz, T. Leyssens, M. von Stosch, R. Oliveira, R. B. H. Tan, H. Wu, M. Khan, D. O'Grady, A. Pandey, R. Westra, E. Delle-Case, D. Pape, D. Angelosante, Y. Maret, O. Steiger, M. Lenner, K. Abbou-Oucherif, Z. K. Nagy, J. D. Litster, V. K. Kamaraju, and M.-S. Chiu (2015) *Org. Process Res. Dev.*, **19**, 3–62.
[97] A. Chanda, A. M. Daly, D. A. Foley, M. A. LaPack, S. Mukherjee, J. D. Orr, G. L. Reid, D. R. Thompson, and H. W. Ward 2015) *Org. Process Res. Dev.*, **19**, 63–83.
[98] A. E. Cervera-Padrell, J. P. Nielsen, M. Jønch Pedersen, K. Müller Christensen, A. R. Mortensen, T. Skovby, K. Dam-Johansen, S. Kiil, and K. V Gernaey (2012) *Org. Process Res. Dev.*, **16**, 901–914.
[99] M. Rueping, T. Bootwicha, and E. Sugiono (2012) *Beilstein J. Org. Chem.*, **2012**(8), 300–307.
[100] J. S. Moore and K. F. Jensen (2012) *Org. Process Res. Dev.*, **16**, 1409–1415.
[101] S. (Bas) A. M. W. van den Broek, J. R. Leliveld, R. Becker, M. M. E. Delville, P. J. Nieuwland, K. Koch, and F. P. J. T. Rutjes (2012) *Org. Process Res. Dev.*, **16**, 934–938.
[102] A. Friebe and H. W. Siesler (2007) *Vib. Spectrosc.*, **43**, 217–220.
[103] U. Bentrup, L. Küpper, U. Budde, K. Lovis, and K. Jähnisch (2006) *Chem. Eng. Technol.*, **29**, 1216–1220.
[104] Z. Qian, I. R. Baxendale, and S. V Ley (2010) *Chem. Eur. J.*, **16** (41), 12342–12348.
[105] E. Cao, M. Sankar, S. Firth, K. F. Lam, D. Bethell, D. K. Knight, G. J. Hutchings, P. F. McMillan, and A. Gavriilidis (2011) *Chem. Eng. J.*, **167**, 734–743.
[106] S.-A. Leung, R. F. Winkle, R. C. R. Wootton, and A. J. deMello (2005) *Analyst*, **130**, 46–51.
[107] E. Cao, S. Firth, P. F. McMillan, and A. Gavriilidis (2007) *Catal. Today*, **126**, 119–126.
[108] M. Lee, J.-P. Lee, H. Rhee, J. Choo, Y. Gyu Chai, and E. Kyu Lee (2003) *J. Raman Spectrosc.*, **34**, 737–742.
[109] A. Urakawa, F. Trachsel, P. R. von Rohr, and A. Baiker (2008) *Analyst*, **133**, 1352–1354.

[110] V. Sans, S. Glatzel, F. J. Douglas, D. A. Maclaren, A. Lapkin, and L. Cronin (2014) *Chem. Sci.*, **5**, 1153–1157.
[111] A. S. Rathore, M. Yu, S. Yeboah, and A. Sharma (2008) *Biotechnol. Bioeng.*, **100**, 306–316.
[112] C. J. Welch, 4. Gong, J. Cuff, S. Dolman, J. Nyrop, F. Lin, and H. Rogers (2009) *Org. Process Res. Dev.*, **13**, 1022–1025.
[113] S. S. Zalesskiy, E. Danieli, B. Blümich, and V. P. Ananikov (2014) *Chem. Rev.*, **114**, 5641–5694.
[114] H. Wensink, F. Benito-Lopez, D. C. Hermes, W. Verboom, H. J. G. E. Gardeniers, D. N. Reinhoudt, and A. van den Berg (2005) *Lab Chip*, **5**, 280–284.
[115] V. Sans, L. Porwol, V. Dragone, and L. Cronin (2015) *Chem. Sci.*, **6**, 1258–1264.
[116] J. Bart, A. J. Kolkman, A. J. O. De Vries, K. Koch, P. J. Nieuwland, H. J. W. G. Janssen, J. P. J. M. Van Bentum, K. a M. Ampt, F. P. J. T. Rutjes, S. S. Wijmenga, H. J. G. E. Gardeniers, and A. P. M. Kentgens (2009) *J. Am. Chem. Soc.*, **131**, 5014–5015.
[117] M. V. Gomez, H. H. J. Verputten, A. Diaz-Ortiz, A. Moreno, A. de la Hoz, and A. H. Velders (2010) *Chem. Commun.*, **46**, 4514–4516.
[118] D. L. Browne, S. Wright, B. J. Deadman, S. Dunnage, I. R. Baxendale, R. M. Turner, and S. V Ley (2012) *Rapid Commun. Mass Spectrom.*, **26**, 1999–2010.
[119] B. V Silva, F. A. Violante, A. C. Pinto, and L. S. Santos (2011) *Rapid Commun. Mass Spectrom.*, **25**, 423–428.
[120] C. F. Carter, H. Lange, S. V Ley, I. R. Baxendale, B. Wittkamp, J. G. Goode, and N. L. Gaunt (2010) *Org. Process Res. Dev.*, **14**(2), 393–404.
[121] C. J. Smith, N. Nikbin, S. V Ley, H. Lange, and I. R. Baxendale (2011) *Org. Biomol. Chem.*, **9**, 1938–1947.
[122] D. L. Browne, S. Wright, B. J. Deadman, S. Dunnage, I. R. Baxendale, R. M. Turner, and S. V Ley (2012) *Rapid Commun. Mass Spectrom.*, **26**, 1999–2010.
[123] T. Schwalbe, D. Kadzimirsz, and G. Jas (2005).
[124] L. Dalla-Vechia, B. Reichart, T. Glasnov, L. S. M. Miranda, C. O. Kappe, and R. O. M. a de Souza (2013) *Org. Biomol. Chem.*, **11**, 6806–6813.
[125] T. Noël, S. Kuhn, A. J. Musacchio, K. F. Jensen, and S. L. Buchwald (2011) *Angew. Chem. Int. Ed. Engl.*, **50**, 5943–5946.
[126] S. Mascia, P. L. Heider, H. Zhang, R. Lakerveld, B. Benyahia, P. I. Barton, R. D. Braatz, C. L. Cooney, J. M. B. Evans, T. F. Jamison, K. F. Jensen, A. S. Myerson, and B. L. Trout (2013) *Angew. Chemie*, **125**, 12585–12589.
[127] S. Mascia, P. L. Heider, H. Zhang, R. Lakerveld, B. Benyahia, P. I. Barton, R. D. Braatz, C. L. Cooney, J. M. B. Evans, T. F. Jamison, K. F. Jensen, A. S. Myerson, and B. L. Trout (2013) *Angew. Chem. Int. Ed. Engl.*, **52**, 12359–12363.
[128] F. Lévesque and P. H. Seeberger (2012) *Angew. Chem. Int. Ed. Engl.*, **51**, 1706–1709.
[129] K. Booker-Milburn (2012) *Nat. Chem.*, **4**, 433–435.
[130] D. R. Snead and T. F. Jamison (2015) *Angew. Chemie Int. Ed.*, **54**, 983–987.
[131] D. Kopetzki, F. Løvesque, and P. H. Seeberger (2013) *Chem. Eur. J.*, **19**(17), 5450–5456.
[132] M. D. Hopkin, I. R. Baxendale, and S. V Ley (2010) *Chem. Commun. (Camb).*, **46**, 2450–2452.
[133] M. Viviano, T. N. Glasnov, B. Reichart, G. Tekautz, and C. O. Kappe (2011) *Org. Process Res. Dev.*, 110601102409070.
[134] Z. Qian, I. R. Baxendale, and S. V. Ley (2010) *Synlett*, **2010**, 505–508.
[135] P. Zhang, M. G. Russell, and T. F. Jamison (2014) *Org. Process Res. Dev.*, **53**, 59–63.
[136] H. Kim, H. Lee, and D. Kim (2015) *Angew. Chem. Int. Ed.*, **54**(6), 1877–1880.
[137] T. L. LaPorte, L. Spangler, M. Hamedi, P. Lobben, S. H. Chan, J. Muslehiddinoglu, and S. S. Y. Wang (2014) *Org. Process Res. Dev.*, **18**, 1492–1502.
[138] R. J. Bogaert-Alvarez, P. Demena, G. Kodersha, R. E. Polomski, N. Soundararajan, and S. S. Y. Wang (2001) *Org. Process Res. Dev.*, **5**, 636–645.

[139] J. A. Rincón, C. Mateos, P. García-Losada, and D. J. Mergott (2015) *Org. Process Res. Dev.*, **19**, 347–351.
[140] G. R. Humphrey and J. T. Kuethe (2006) *Chem. Rev.*, **106**, 2875–2911.
[141] P. Hughes, J. DeVirgilio, L. G. Humber, C. Thuy, B. Weichman, and G. Neuman (1989) *J. Med. Chem.*, **32**, 2134–2137.
[142] Z. Yu, Y. Lv, and C. Yu (2012) *Org. Process Res. Dev.*, **16**, 1669–1672.
[143] T. L. Laporte, M. Hamedi, J. S. Depue, L. Shen, D. Watson, and D. Hsieh (2008) *Org. Process Res. Dev.*, **12**(5), 956–966.
[144] M. Thayer (2012) *Ann. Chem. Eng. News*, **2012**, 12–17.
[145] M. Thayer (2014) *Ann. Chem. Eng. News*, **2014**, 13–21.
[146] M. Thayer (2009) *Ann. Chem. Eng. News*, **2009**, 17–19.
[147] ISCMP (2014) *International Symposium on the Continuous Manufacturing of Pharmaceuticals*. Available at: https://iscmp2014.mit.edu/white-papers (accessed 12 February 2016).
[148] J. P. McMullen and K. F. Jensen (2010) *Org. Process Res. Dev.*, **14**, 1169–1176.
[149] C. Samuel, L. Bourne, P. Koos, M. O. Brien, B. Martin, B. Schenkel, I. R. Baxendale, and S. V Ley (2011) *Synlett*, **2011**(18), 2643–2647.
[150] A. Guenther, E. M. Fritzsche (2013) *CHEManager*, **2013**, 12.

5

Continuous Crystallisation

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5.1 Introduction

Although crystallisation in pharmaceutical manufacturing is traditionally carried out as a batch operation, with the current drive towards implementing continuous manufacturing of pharmaceuticals there is increased interest in developing and applying approaches for continuous crystallisation [1, 2]. Indeed, the potential to directly connect multiple process stages as part of an integrated end to end process chain including a continuous crystallisation step has been demonstrated for the manufacture of aliskiren hemifumarate tablets [3] and in a compact reconfigurable platform for a range of active pharmaceutical ingredients (APIs) for liquid dosage [4]. Crystallisation is a key operation for the purification and isolation of APIs from solution mixtures to produce pure drug substance in a stable, solid form suitable for subsequent formulation and processing. Crystallisation is therefore a critical stage in controlling the physical properties of the solid material [5, 6]. For pharmaceuticals, achieving high levels of chemical purity of crystallised or precipitated particles is an essential requirement. However, a given API can also show a range of variability in crystalline form (polymorph, solvate, salt, co-crystal), crystal size, size distribution and shape that can have significant effects on processing performance and product stability [7]. Consequently, robust continuous crystallisation processes are required that can achieve the target particle attributes consistently and avoid uncontrolled variation in quality and performance. However, despite the widespread application of crystallisation in fine chemical and

Continuous Manufacturing of Pharmaceuticals, First Edition.
Edited by Peter Kleinebudde, Johannes Khinast, and Jukka Rantanen.
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pharmaceutical production, it still remains relatively poorly understood. Hence the development of consistent and robust continuous crystallisation processes requires systematic and rigorous approaches to identify and control the complex physical transformations that take place within a multicomponent, multiphase process environment.

Pharmaceutical materials also frequently display other challenging physical properties that need to be managed during crystallisation. These include the tendency of low symmetry crystals to adopt extreme morphologies [8], the occurrence of attrition during processing [9] due to relatively fragile crystal mechanical properties [10] and a tendency for crystals to agglomerate [11, 12]. Specific process requirements are dictated by the particular physical properties of the system and an overall understanding of the interactions between material properties, process conditions and particle attributes is therefore necessary. In principle, this can be achieved by the implementation of quality by design (QbD) principles during process development to establish a rigorous understanding of the process and acceptable operating ranges to achieve the required performance [13, 14]. Processes must also be designed to meet economic and sustainability requirements.

Continuous crystallisation technologies offer considerable flexibility over the control of crystallisation, allowing each stage of the process to be physically separated and controlled (Table 5.1). This separation of the key transformations along with a relative reduction in the volume of material to be controlled, allows for closer control over the conditions governing the individual transformations at each stage that dictate the final crystal size distribution and product quality. For example, primary nucleation processes typically require higher levels of supersaturation than crystal growth. Thus control can be achieved in multiple vessels, for example, with primary nucleation being driven in a stirred tank operating at

Table 5.1 *Key stages, aims and consideration for selection of conditions during continuous crystallisation*

1. Mixing	2. Nucleation	3. Growth	4. Filter/wash/dry
Required to: • Produce consistent composition • Control crystallisation driving force • Influence flow rate, shear-kinetic effects • Consistent suspension of seed and product	Controlled via: • Supersaturation • High shear • External fields, e.g. ultrasound, non-photochemical laser induced nucleation Seed. Seeds produced via dry milling, wet media milling, precipitation, recycle, dissolution, spray drying or secondary nucleation Controlled to avoid: • Fouling • Agglomeration • Dissolution • Crystalline form transformation(s)	Controlled via: • Supersaturation (typically low) via cooling, anti-solvent, evaporation • Effective heat/mass transfer Ensures: • Efficient desupersaturation Controlled to avoid: • Fouling • Agglomeration • Attrition (particle breakage) • Dissolution Crystalline form transformation(s)	Required to: • Create filter cake • Remove mother liquor and impurities • Maintain particle attributes Controlled to avoid: • Agglomeration • Attrition (particle breakage)

high supersaturation, and subsequent vessels operating at lower supersaturations to achieve controlled growth rates and effective rejection of impurities [15]. Hence a variety of process configurations have been demonstrated on different platforms and systems.

Continuous crystallisation has been implemented for many decades in other manufacturing sectors, typically for large volume commodity chemicals, and offers a range of potential advantages [16, 17] including lower operating and capital costs, reduced down time and more efficient use of energy and materials. Cooling and anti-solvent crystallisation are commonly used in industrial applications and can be readily implemented in continuous. The aim is to follow a controlled trajectory through the solubility phase diagram (Section 5.1.2). Using seeding combined with process analytical technology (PAT) enables a direct supersaturation control approach that allows the system to optimise growth whilst avoiding uncontrolled primary nucleation and broadening of the particle size distribution (PSD) or the unexpected appearance of different crystalline forms. The uncontrolled generation of particles via secondary nucleation and attrition (particle breakage) can also impact on the PSD, though this may be minimised by maintaining control over supersaturation and controlling shear forces across the process stages. Approaches for dealing with fines that involve temperature cycling either in a recycle loop or spatially along the crystalliser may also be applied [15].

Continuous operation of crystallisation processes under a controlled state offers a number of potential advantages for the control of particle attributes:

- Accurate control of purity, yield, crystalline form (polymorph, salt, solvate, co-crystal), particle size distribution (PSD) and particle shape or morphology.
- Control of particle size yielding consistent slurry and powder properties improving filtration, drying and bulk flow/formulation properties.
- Growth of targeted PSD enables opportunity to eliminate post-crystallisation milling.
- Suitability for application of in-line sensors for real-time process monitoring and control.
- Elimination of batch to batch variability.
- Scalability of processes through extending operation times, equipment scale-up as well as scale-out/numbering up approaches.
- Adaptability of technologies for multiple products including ability to reconfigure modular platforms to deal with different physical properties.

Given this range of capabilities to support advanced pharmaceutical manufacturing approaches, it is not surprising that continuous crystallisation has been investigated in a range of platforms [18] including mixed suspension mixed product removal (MSMPR) [19–22] and plug flow reactors (PFRs) [23] including oscillatory flow reactors (OFR; Figure 5.1) [16, 24, 25]. A wide array of implementations and technologies have been successfully demonstrated including impinging jet mixers for reactive crystallisation or precipitation [26] often operated in conjunction with MSMPRs, static mixers for anti-solvent crystallisation [27] and segmented (slug) flow reactors [28]. The operation of continuous crystallisations in supersaturated environments for extended periods can also pose challenges including instabilities introduced by variations in services and fouling or encrustation that need to be managed. Fouling or encrustation of vessels, feed lines, or PAT probes under elevated supersaturation and/or solid loadings is a particular issue where extended operation of the process is required, and can lead to disruption of flow, degradation of heat transfer and blockage of reactor channels. Indeed, it can be expected to

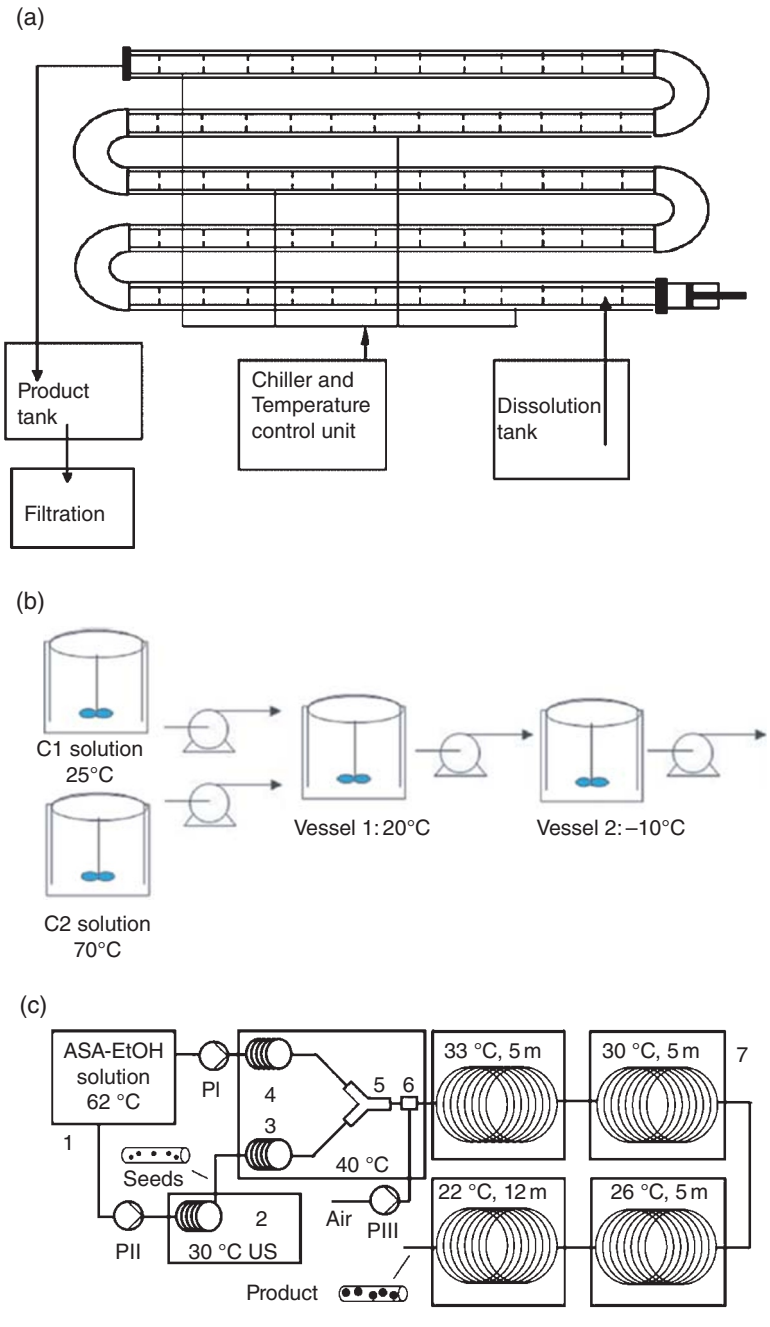

Figure 5.1 *Examples of different platforms for continuous crystallisation of pharmaceutical compounds. (a) Continuous oscillatory flow reactor. Reprinted with permission from: [16], (b) MSMPR cascade. Reprinted with permission from: [33], (c) A seeded segmented tubular flow reactor. Reprinted with permission from: [28], (d) Kenics static mixer with multiple anti-solvent addition. Reprinted with permission from: [27] and (e) Tubular crystalliser with contact secondary nucleation device. Reprinted with permission from: [34]. Copyright American Chemical Society.*

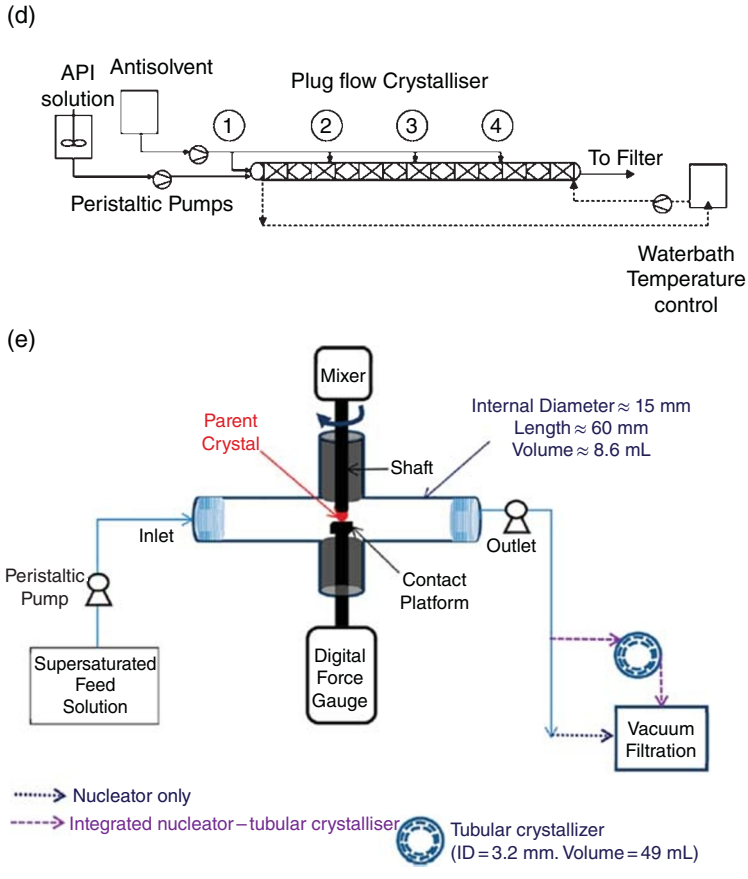

Figure 5.1 *(Continued)*

occur eventually even where crystallisers operated at low supersaturation and approaches to prevent or mitigate accumulation are essential. Localised heating, choice of materials of construction and coatings or the use of ultrasound may be of benefit alongside periodic, scheduled, off line solvent cleanout. Multi-vessel continuous stirred tank reactor (CSTR) cascades can be operated with individual vessel cleanout during continuous operations. The use of ultrasound as an external field, for example, has been shown to be effective in reducing fouling during the continuous crystallisation of adipic acid [29]. For the most part, each of these types of crystalliser is capable of operating with or without seeding and in cooling, anti-solvent and reactive modes. Additional features such as ultrasound, static mixing or flow oscillations and agitated cell and tubular reactor configurations have also been applied to provide additional flexibility [16, 19, 23, 27, 30–32].

5.2 Principles of Crystallisation

5.2.1 Supersaturation

This section provides a general overview of key principles and modes of crystallisation relevant to continuous crystallisation of pharmaceuticals. For a more comprehensive

background of the fundamentals of crystallisation, the interested reader is directed to one of the many detailed and helpful texts on the subject [35–38]. There are various crystallisation approaches that can be used to achieve effective purification and isolation of solids from solution including reactive, evaporative, anti-solvent (or drown-out) and cooling. Crystallisation from melts, where solidification is achieved from molten feed(s) [39–41] is not discussed further as it has more restricted utility for thermolabile organic compounds. Whichever mode of crystallisation is employed, supersaturation must be generated to drive crystallisation and the two main processes involved, nucleation and crystal growth, both depend on supersaturation as the primary driving force.

Supersaturation can be described by the difference between the chemical potential of the solute and the value of the chemical potential at equilibrium:

$$\Delta\mu = \mu - \mu^* \tag{5.1}$$

where μ is the chemical potential of the solute being crystallised and μ^* is the chemical potential of the solute at equilibrium at the same temperature and pressure. For any conditions where $\mu > \mu^*$ the solution is supersaturated and a reduction in the chemical potential through crystallisation of the solute can return the system to equilibrium, $\Delta\mu = 0$. Assuming ideal conditions, the supersaturation, S, can be described in terms of the concentrations of the solute by the expression:

$$\ln S = \ln \frac{c}{c^*} = \frac{\Delta\mu}{RT} \tag{5.2}$$

where R is the gas constant (8.314 J mol^{-1} K^{-1}), T is the temperature (K), c is the solute concentration and c^* is the equilibrium solubility. For practical use, this is often expressed in terms of the supersaturation ratio, S [Equation (5.3)] or as the relative supersaturation, σ [Equation (5.4)]:

$$S = \frac{c}{c^*} \tag{5.3}$$

$$\sigma = \frac{(c - c^*)}{c^*} \tag{5.4}$$

It is therefore essential to know the equilibrium composition of the system under the relevant conditions in order to quantify supersaturation. For example, for a cooling crystallisation of a monomorphic system, a phase diagram in the form of concentration versus temperature can be used (Figure 5.2). Based on this, the driving force for nucleation and growth under any given set of conditions can be determined, in principle providing the basis to select the process conditions that will deliver the required control over each stage of the crystallisation process. In Figure 5.2(a) the solid line shows the equilibrium saturation solubility curve, the dashed line the primary metastable zone limit and the dotted line shows the secondary nucleation metastable zone boundary demarking regions where it is possible to operate with or without nucleation. The arrows show the effect of cooling, evaporation as well as anti-solvent addition to create supersaturation. At point 1, the system is under-saturated, at point 2, the system is minimally supersaturated and would display only growth; at point 3, the system would display growth, secondary nucleation but no primary nucleation and at point 4, new crystals would form from primary nucleation. The metastable zone width (MSZW) illustrates the maximum undercooling before the system enters the labile region

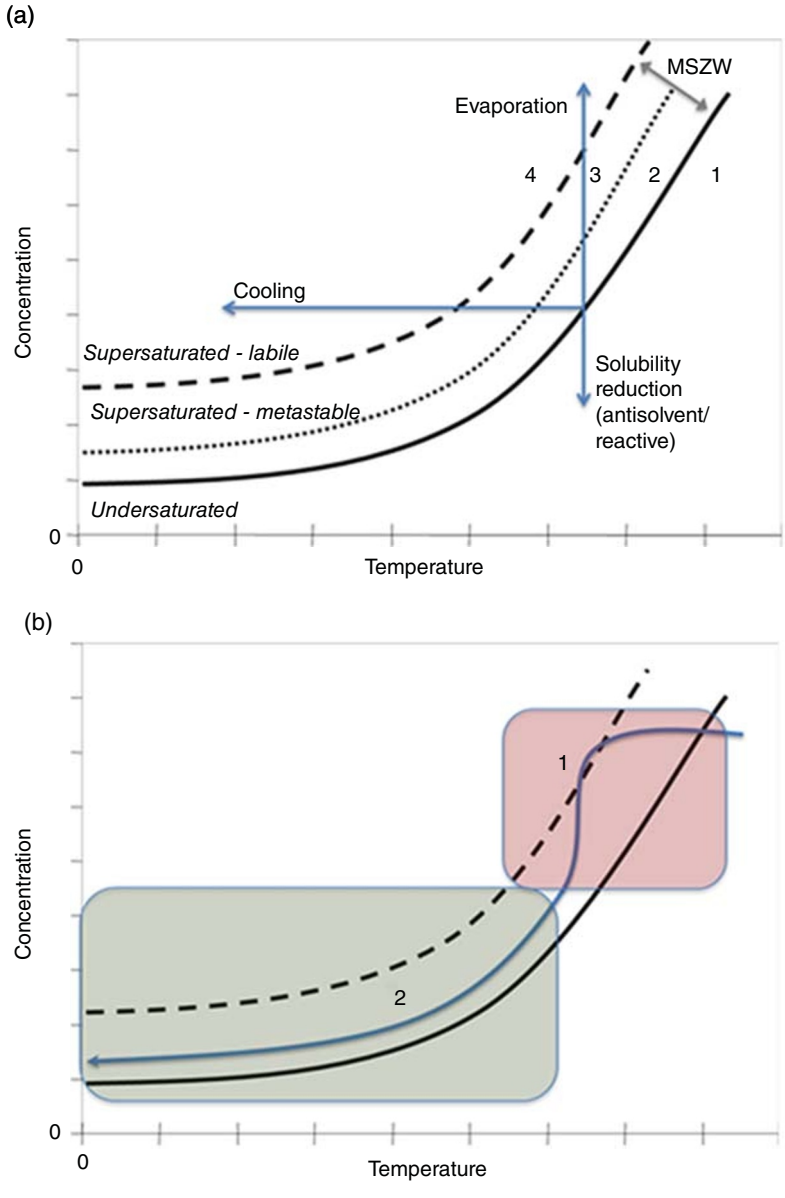

Figure 5.2 *(a) General form of phase diagram for solution crystallisation. (b) Cooling process trajectory through phase diagram.*

and primary nucleation occurs. Figure 5.2(b) gives an example cooling process trajectory through the phase diagram. In region 1, primary nucleation occurs under high supersaturation as the system crosses the MSZW boundary leading to the formation of seed crystals generating growth surface and selecting the polymorphic form. In region 2, a lower level of supersaturation is maintained to allow particles formed to grow whilst avoiding primary

nucleation and minimising secondary nucleation. This scenario also illustrates the potential in a continuous operation to separate out each of the key process stages and utilise different processing units to manage the different process requirements presented for continuous nucleation (seed generation under high supersaturation) and continuous growth (low supersaturation). For example the high supersaturation levels required to achieve nucleation, may be better suited to a short residence time unit minimising the risk of encrustation, with slower, controlled growth best controlled in a longer residence time unit.

Solubility is a thermodynamic property of the system dictated by the solvent and solute and is therefore not affected by process scale or geometry. However, the metastable limits relate to the transformation kinetics and so whilst they are dependent upon the thermodynamic driving force (supersaturation) present at any given stage of the process, they are also influenced by other factors. The MSZW for primary nucleation has been shown to be highly dependent on the hydrodynamic environment within the crystalliser (geometry, stirrer type, flow) as well as on the applied cooling rate and volume and so care is required to ensure that kinetic data are collected under representative conditions.

A controlled crystallisation process involves management of the available growth surface either by primary nucleation or, more commonly by seeding, and subsequently following a trajectory within the MSZW close to the solubility limit to facilitate controlled crystal growth whilst avoiding uncontrolled formation of new particles through nucleation. An understanding of the secondary metastable limit, where new crystals are often generated by attrition, is also valuable for processes where control of the crystal size distribution is important [42].

Anti-solvent can also be used to generate supersaturation in order to drive nucleation and growth [36, 43]. This approach may be the method of choice when the energy utilisation associated with cooling is unfeasible or when cooling alone cannot provide the necessary yield [44] and optimal yields can often be obtained by combining cooling and anti-solvent crystallisation [45, 46]. For anti-solvent addition, as with pH controlled or reactive crystallisations, consideration of rate of addition and concentration or relative addition rates of solvent or reagents requires careful consideration [47, 48]. Evaporative crystallisation generally poses challenges with control and scaling although remains a common approach in the sugar and food industry [35, 49]. Crystallisation from supercritical fluids, where the expansion of a solution is used to create supersaturation [50] can also offer specific advantages over conventional approaches but is not discussed further in this chapter.

5.2.2 Nucleation and Growth

Primary nucleation is used to describe all cases of nucleation (homogeneous [36] and heterogeneous [51]) taking place in systems where no crystalline matter is present, that is, describing the initial formation of crystals within a supersaturated solution. Nucleation can broadly be broken into two categories, primary nucleation is the formation of crystals from solution with no existing solid state of the crystallising solute. In comparison, secondary nucleation is the formation of new crystals initiated by the presence of existing crystals (seeding and attrition) [52, 53]. Primary nucleation can also be broken down further into that of homogeneous and heterogeneous. Much like secondary nucleation, heterogeneous nucleation relies on the presence of a foreign interface for the formation of new crystals, but crucially this interface is different to that of the crystallising solute. Homogeneous nucleation is therefore the unassisted formation of new crystals without the presence

Table 5.2 *A number of empirical nucleation rate expressions*

Nucleation	Expression	References
Primary	$J = k_b S^b$	[55]
Homogeneous	$J = A \exp\left[\frac{-16\pi\gamma^3 v^2}{3k^3T^3(\ln S)^2}\right]$	[36]
Heterogeneous	$J = k_{b\ \text{het}} \exp\left[\frac{-16\pi\gamma^3 v^2 f(\psi)}{3k^3T^3[\ln(\sigma+1)]^2}\right]$	[51]
Secondary	$J = k_b S^b \mu_2$	[52, 53]
	$J = k_b \exp - \frac{\Delta E_G}{T} \sigma_s^b \mu_3^k$	[58]
	$J = k_b \sigma_s^b \mu_3 (L_{\min})^j$	[59]

of a foreign interface or existing crystals. It is however generally accepted that homogeneous primary nucleation, that is, nucleation in a supersaturated solution devoid of any foreign particulates, is of limited practical relevance, particularly in a manufacturing environment. Heterogeneous nucleation, in which various potential nucleation sites are present due to contaminating materials is thought to be the dominant process in most experimental conditions.

The rate at which nuclei are formed, J, that is, the number of nuclei formed, per unit volume, per time, is largely dependent on supersaturation. Modelling and prediction of nucleation is a highly complex process not least in part due to the challenges in measuring rapid processes at the molecular scale. Table 5.2 summarises some of the empirical relationships commonly used in the literature to describe nucleation kinetics. Specific systems will display primary nucleation at varying levels of supersaturation and this physical process is sensitive to a wide range of process conditions including temperature, agitation as well as impurity profiles. For cooling crystallisation the MSZW provides valuable information for developing the controlled operating limits for the process (Figure 5.2). Primary nucleation kinetics have also been deduced from MSZW data, early approaches by Nývlt [54] allowing extraction of a nucleation order, m and rate constant, K, with varying cooling rate but these values generally have no physical significance. Sangwal [36] outlined approaches with the assumption that critical nuclei are formed by the attachment of further molecules to a cluster under supersaturated conditions, with approaches based on classical nucleation theory (CNT) and on a power law relationship between nucleation rate, J, and maximum supersaturation, $\ln S_{\max}$ [55]. Kashchiev also extended Nývlt's early approach deriving an expression relating relative maximum supercooling $\Delta T_{\max}/T_0$ with cooling rate [56] and Kubota demonstrated the importance of avoiding secondary nucleation when deducing accurate primary nucleation parameters [57].

An approach for determining J from a probability distribution of induction time, t_{ind}, has also been proposed [60, 61]. The induction time is defined as the time period between establishing a supersaturated condition to the observation of nucleation. Experimentally determined cumulative probability distributions of t_{ind} at constant S based on at least 80 t_{ind} measurements allowed the determination of J by a best fit of the derived equation to the experimentally obtained distribution. Whilst more labour-intensive than derivation from MSZW the approach has been shown to be more reliable [62].

From a mechanistic perspective, nucleation remains poorly understood. CNT proposes that nucleation occurs via a step wise process, whereby molecules of solute are added to a cluster until a stable critical cluster is formed (ca. 10^{20} molecules) [36]. The critical cluster formation can be interpreted as an activation energy barrier to the formation of

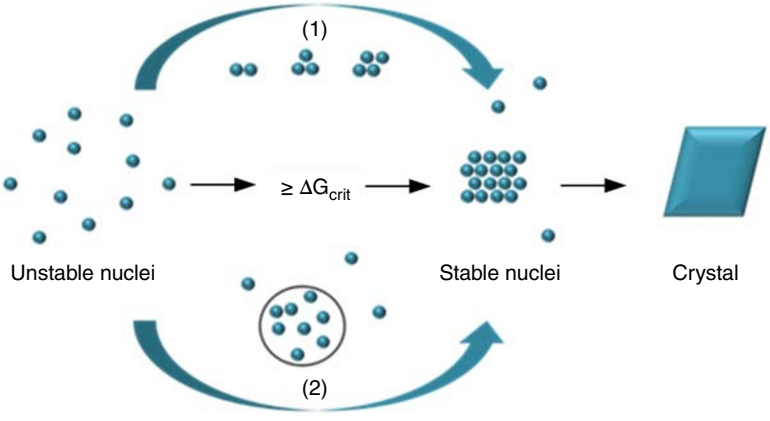

Figure 5.3 *A schematic illustration of: (1) Classical nucleation with growth of clusters until a thermodynamically stable critical nucleus is formed. (2) The two-step nucleation process where the formation of stable crystal nuclei from disordered liquid clusters. Once critical nuclei are formed, growth will occur until a detectable crystal is achieved. Reprinted with permission from [67]. Copyright 2015 N.E.B. Briggs.*

crystals [63, 64]. Whilst improved experimental techniques and the application of molecular modelling methods have provided some progress towards understanding the detailed molecular interactions by which nuclei form and develop into macroscopic crystals this remains an evolving area of science. More recent studies suggest that nucleation occurs via a two-step model where crystalline order is preceded by the separation of a dense, disordered liquid phase [65, 66] (Figure 5.3).

Secondary nucleation occurs when there are parent crystals present in the solution and these can induce the formation of new nuclei through several mechanisms. Crystals can impact with vessel walls, agitators or each other and rupture depositing smaller crystals and/or nuclei into the bulk solution. A summary of the most commonly proposed mechanisms is shown in Figure 5.4. Specifically when a narrow crystal size distribution (CSD) is

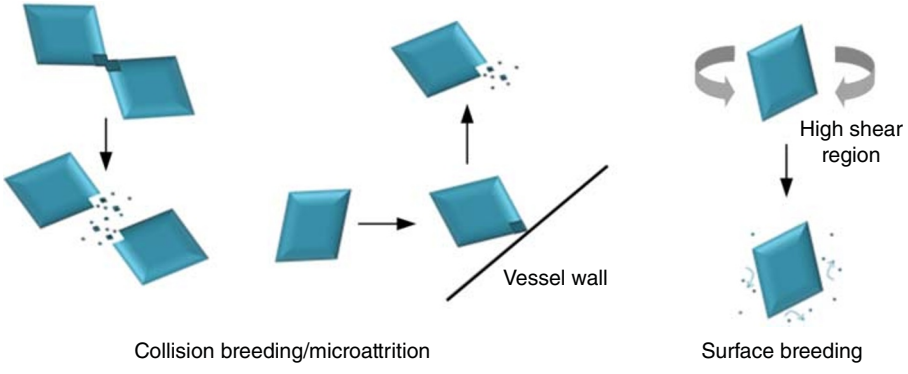

Figure 5.4 *Schematic illustrating the principal mechanisms of secondary nucleation. Reprinted with permission from [67]. Copyright 2015 N.E.B. Briggs.*

a critical quality attribute (CQA) secondary nucleation at different stages of the process can be a cause of significant broadening. Assessing the extent of secondary nucleation for an individual system under different process conditions is a key element of designing a controlled continuous process whether the desire is to minimise (e.g. in a PFR) or to optimise (e.g. in an MSMPR) the overall rate.

Once nucleation has occurred particles can continue to grow into larger, faceted crystals and this process can be either limited by bulk diffusion or surface integration [36]. The effective growth rate is dependent on a number of factors in addition to supersaturation. These include the presence and identity of any impurities, the local mixing or hydrodynamic environment as well as attrition or particle breakage and agglomeration. Agglomeration poses one the largest challenges in interpreting crystal growth as measurement techniques such as focussed beam reflectance measurement (FBRM) and laser diffraction tend to interpret agglomerates as individual particles, leading to overestimation of actual particle size. Similarly the measurement of accurate crystal growth rates using off line techniques such as optical microscopy may not replicate the actual process under the hydrodynamic environment of the crystalliser. A simple expression to describe crystal growth is as a linear growth rate:

$$G = \frac{\mathrm{d}L}{\mathrm{d}t} \tag{5.5}$$

Kinetic growth rate expressions can also incorporate the overall driving force and temperature effects:

$$G = A \exp\left(\frac{-E_G}{RT}\right) \Delta C^g \tag{5.6}$$

where G = growth rate (m s^{-1}), L = crystal length (m), A = constant, E_G = activation energy (J mol^{-1}), g = order of overall crystal growth. A number of variations of this equation have been described to account for different types of growth kinetics (Table 5.3).

Agglomeration represents the process in which crystals adhere and grow together to form larger solid bodies [71]. The primary particles in agglomerates are generally more tightly bound than aggregates which can be redispersed easily using increased shear, for example. Controlled agglomeration can however be a useful way to modify particle attributes to improve performance in downstream processes. However, uncontrolled agglomeration can lead to variability in the product PSD, difficulties in quantifying the growth of primary particles and unexpected particle properties. For example, product can be more difficult to wash because mother liquor and impurities can become entrained inside the intergrown particles. However, larger spherical agglomerates can improve the isolation, flowability and compaction properties of crystalline products [72].

Table 5.3 *Commonly used crystal growth rate expressions*

Mechanism	Expression	Reference
Size-independent growth	$G = k_g S^g$	[68]
Size-dependent growth	$G = k_g S^g (1 + \gamma L)^p$	[69]
	$G = k_g S^g (1 + \gamma L)$	
Power law growth	$G = k_g S^g L^p$	[70]

5.2.3 Conservation Equations

All of the above transformations need to be evaluated for the development of a robust and efficient process. For productivity, the conservation equations (mass, energy and population balance) will be implemented, at least in part, in industrial crystallisation unit operations. Facile calculations of crystal yield indicate only the physical mass obtained but reveal nothing on how the mass is distributed in terms of crystal sizes. Population balance equations (PBEs) account for the latter and can also include additional terms for nucleation, growth, agglomeration and breakage. Early expressions derived by Randolph and Larson [73] describe the population of crystals as a number density function $n(L, t)$:

$$\frac{\partial n}{\partial t} + \frac{\partial (nG)}{\partial L} + \frac{n - n_0}{\tau} = B_{Ag} - D_{Ag} + B_{Br} - D_{Br} + J \tag{5.7}$$

where L = crystal size, t = time, B and D represent birth and death terms for agglomeration and breakage, τ = residence time. Population balance modelling (PBM) can significantly reduce the number of experiments required to develop a crystallisation process and importantly the amount of material required to carry out a full design of experiments. Well designed experiments using equipment which, as far as possible resembles the hydrodynamic environment of the process crystalliser, are essential to provide meaningful kinetic parameter estimates which can be fed into a predictive model. Many examples of the development and application of PBM for crystallisation design have been reported in the literature.

For continuous crystallisation approaches, the optimal temperature or anti-solvent addition profile must be implemented as a spatial distribution that delivers the required supersaturation or driving force at each location in the process to maintain the rate processes within acceptable, controlled ranges to achieve the required product attributes. In a continuous crystalliser the physical volume which requires to be controlled (i.e. heat and mass transfer) is significantly less than the equivalent batch reactor enabling close control. One of the important challenges then becomes managing process start-up procedure [74, 75] which allows a controlled steady state operation to be established whilst minimising waste or off-specification product.

5.3 Crystallisation Process Development

Batch crystallisations are often developed on small-scale laboratory apparatus, to establish thermodynamic parameters and applying various approaches to identify suitable cooling or anti-solvent addition regimes and seeding approaches to manipulate the crystallisation kinetics to deliver the required chemical and physical attributes and yield. This early stage work will then be scaled up to the required manufacturing scale and the challenges of scaling up crystallisation have been well documented. There have also been a number of approaches that provide a systematic approach or workflow for the design and scale-up of crystallisations that can be applied to continuous crystallisation. However, it is also worth noting that the volume of modern potent APIs may be relatively small (e.g. < 1 t year^{-1}), raising the potential to scale process outputs based on extended operation of relatively small scale continuous platforms or numbering up processes to maintain operation under the same conditions used in development.

A workflow for crystallisation process development should support:

- A clear and systematic approach for delivery of the process with data driven decision points;
- Automated data processing steps to minimise repetitive tasks;
- Minimal input of operator and material resources with maximum output of data via design of experiment (DoE) approaches;
- Realistic estimations of campaign timescales.

Bermingham outlined a hierarchical procedure for the conceptual design of solution crystallisation processes including predictive models extracting intrinsic kinetic parameters from experimental data, as well as the analysis and optimisation tasks of the design process [76]. It was highlighted that such models could not be determined purely from first principles and limitations in analysis (e.g. determination of CSD) was an important issue in addition to physical challenges such as crystal agglomeration. Gerogiorgis presented a steady state process model and simulation for the continuous production of ibuprofen [77]. Plug flow reactors and the final purification were designed via systematic kinetic parameter estimation, solvent selection and thermodynamic property modelling. Additionally, economic and environmental factors were included. Vetter investigated the influence of uncertainty in kinetic parameters on the yield and the mean particle size obtained for crystallisation processes [78]. A methodology for uncertainty-adjusted attainable regions was demonstrated, potentially allowing the design of more robust processes. Some additional relevant studies include a generic modelling framework for batch cooling crystallisation processes [79], a practical methodology to assess the feasibility of converting batch processes into continuous [80] and a workflow for managing impurities [81].

A general framework that can be used for the development of a continuous crystallisation process is summarised in Figure 5.5. While the high level inputs required for crystallisation development are generally well known, often the underlying detail at each stage can be quite variable depending on the aims of the study, equipment used, modelling tools available and time, equipment and materials pressures. For example, choice of solvent may be restricted in a pharmaceutical crystallisation process due to environmental/economic factors or indeed based on a fixed synthetic route upstream. Some workflows may feature extensive modelling approaches requiring relevant expertise. However, this may not be available or commercial packages may not handle unusual transformation physics. Yield may also be sacrificed for purity in some cases or downstream processing challenges may dictate residence time.

Characterisation of raw material will include gathering existing physicochemical data from solid-state screening, preformulation or stability trials. Whilst limited data may be available, this step provides initial insight into observed behaviour and can also highlight any associated analytical challenges which may arise. It is essential to carry out chemical characterisation (as even minor impurities can have significant effects on crystallisation) as well as complete early physical reference measurements including at least structural identification. This will be aided by access to crystal structure information and morphology. Understanding variability in raw material supply including water content or composition of solvents, or variable impurities in the crystallisation may also be required. This may be particularly important where composition may not be fixed and input material may feature

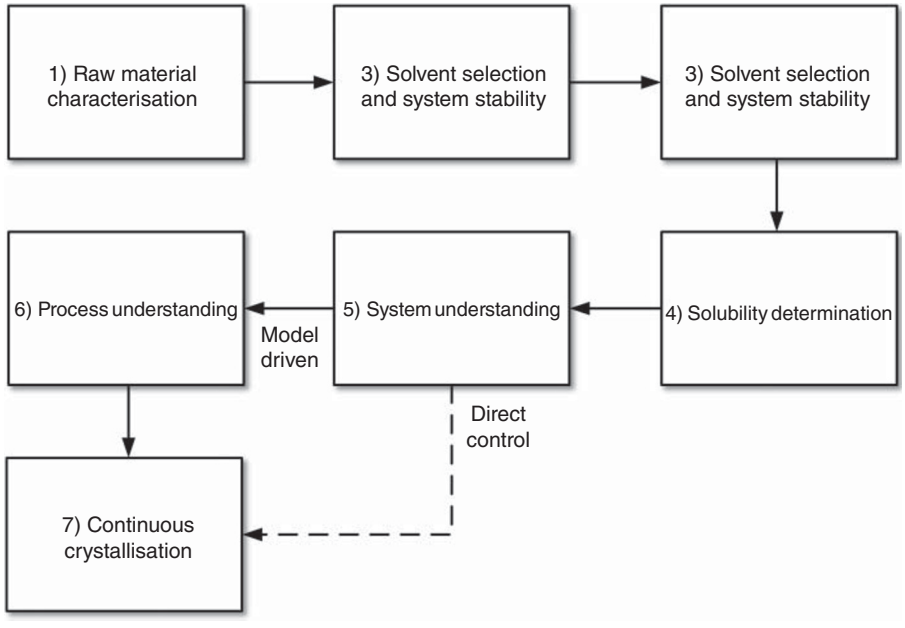

Figure 5.5 *Schematic highlighting key stages in a crystallisation process development workflow.*

variability, for example, based on a synthetic route. It may also be necessary to develop analytical methods to quantify varying levels of impurities.

Where solvent choice is not fixed, as in a recrystallisation, then solvent screening and selection can be influenced by a number of factors (stages 2 and 3 in Figure 5.5). In a manufacturing environment the choice of solvent will often be limited according to safety, cost, environmental impact or ease of disposal. International Conference for Harmonisation (ICH) guidelines categorise solvents in three classes: 1, known to cause unacceptable toxicities; 2, associated with less severe toxicity and 3, less toxic solvents which should ideally be used where practical [82]. However, selection of a good solvent system can help to provide a robust process. In the absence of prior solubility data, a solvent screen allows a first pass at identifying solvent with no, limited or good solubilising ability. These can be readily automated to include liquid and solid dosing, control of temperature and the use of turbidity or imaging to monitor crystal properties as a function of each solvent. Early observation of extreme habits or aspect ratios, fouling or agglomeration can also be helpful. Such automated, small-scale experiments can be optimised for small material amounts and generate data quickly to inform subsequent selection decisions. Advances in computational approaches for solubility prediction may increasingly allow a significantly streamlined approach to solvent selection by reducing the experimental design space required to explore. These approaches can be based on fragment based methods or thermodynamic models though do not tend to include the effect of crystal form. Multi-component solvent mixtures have proved highly challenging in terms of reasonable predictability.

Final solvent selection will primarily depend on the potential recovery, achievable solid loading and throughput in addition to practical handling concerns [44]. Further

considerations may be ease of removal following crystallisation, the crystal habit produced and even physical considerations such as agglomeration. If it is possible to eliminate the latter, this may be advisable as modelling of the overall process becomes less complicated. A stability study at the most extreme conditions of crystallisation (high temperature, hydrodynamic environment) can confirm solvent compatibility and suitability. Once the solvent has been selected based on estimated temperature dependence of the solubility (or solvent/anti-solvent pairs) the solubility phase diagram can be determined. Given this will be a key tool for process development, it should be measured accurately across the accessible temperature range (stage 4 in Figure 5.5). Spectroscopic, in-line techniques are becoming more suitable for such tasks (Figure 5.6). However, it is important to cross validate with additional off line measurements.

Whilst solubility is a thermodynamic parameter and transferrable across crystallisation platforms with varying hydrodynamic environments, the associated kinetic processes – nucleation and growth – can vary significantly, causing challenges in terms of scaling the process. Having established the solubility range of the solute–solvent system, a series of kinetic experiments can be carried out to develop further understanding of the selected system. The results provide assessment criteria for selection of a suitable process platform. These experiments are typically batch in nature, for convenience, but should be designed to be relevant to the expected conditions in continuous equipment. Continuous platforms including microfluidics can also be utilised. An assessment of the primary nucleation limit, growth rate (Figure 5.7) and secondary nucleation rate are key aspects. However, it is also useful to consider practical aspects such as fouling propensity as a function of supersaturation or with different materials of construction as this may impact on the operation of a continuous platform for extended periods. As it would be impractical to perform these kinetic studies in a continuous platform, largely in terms of material

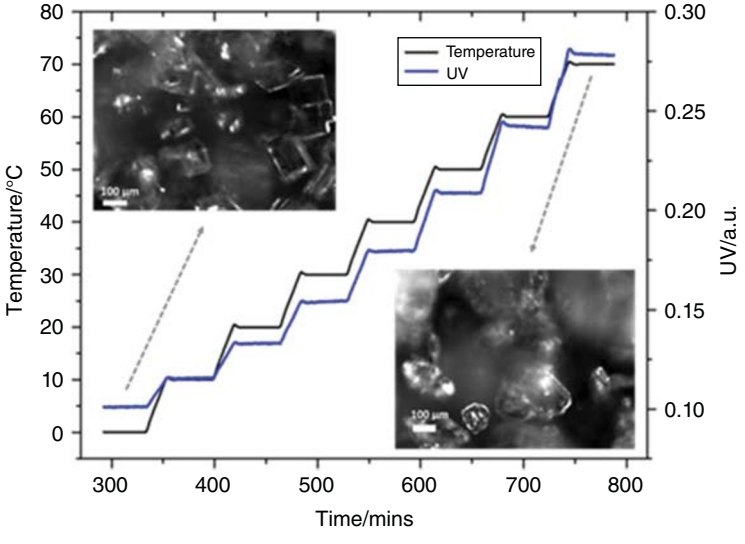

Figure 5.6 *Temperature-dependent solubility measurement in the presence of excess solid material using an ATR-UV method.*

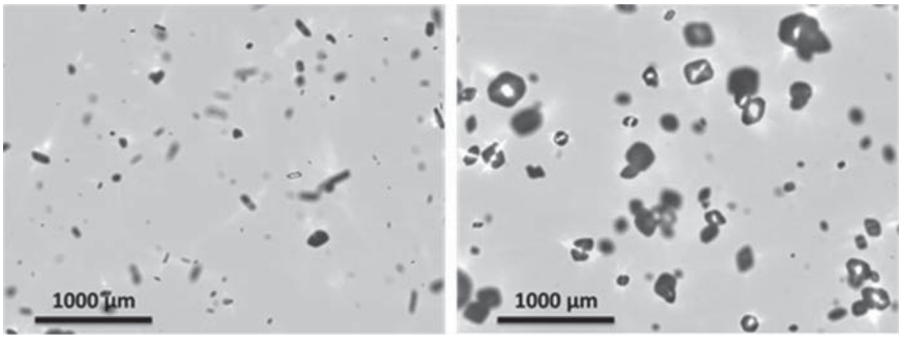

Figure 5.7 *Images of crystal growth using a flow cell.*

consumption, batch equivalent units, which mimic as far as possible continuous conditions can be implemented [16, 18]. To highlight this, Figure 5.8 illustrates some MSZW data collected in various platforms with different mixing mechanisms.

Given a knowledge of the solubility limit and kinetics of the system, sensible choices about the crystallisation platform can be made based on mean residence time, solids loading and particle properties. Direct control and model predictive approaches utilising PAT could also be developed [42, 83]. In many case this may be preferred as attempting to model crystallisation processes from first principles can be extremely challenging as this inherently depends on various assumptions on the rate processes and requires experience to develop, apply and validate the models. In addition real-time direct control may be able to compensate for minor disturbances during the process itself which could not be predicted in advance by a model. However, in addition to a growing number of freeware packages, commercial population balance model platforms such as gCRYSTAL [84] are increasingly allowing improved and practical approaches towards parameter estimation (stage 6 in Figure 5.5) and crystallisation process model development. The potential value of these first principles

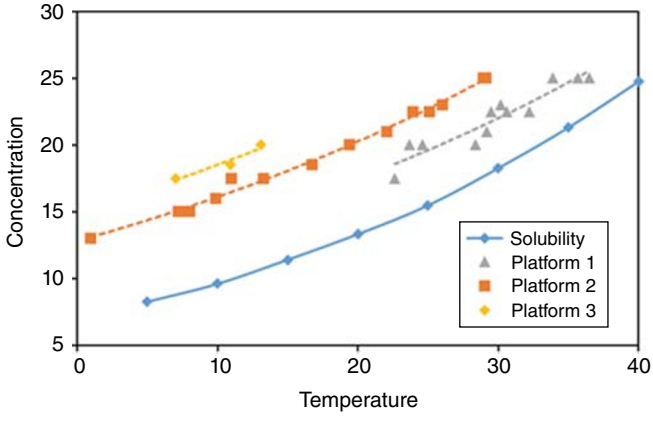

Figure 5.8 *A comparison of MSZW data obtained in crystallisation parameters with different hydrodynamic environments.*

models is to verify any assumptions made on the dominant processes in the system and to allow a more predictive approach to design without the need for extensive, trial and error experimentation. For example to assess the effect of seed loading or size or of alternate temperature profiles to inform the most appropriate experiments to achieve the target product specification.

If kinetic modelling of the process using PBM has been successful and either model based or direct control approaches have been assessed, the final step is to setup and operate the continuous crystallisation process. The aim is to deliver a controlled steady state operation whilst delivering the desired purity, yield, CSD and form. This will include an efficient start-up procedure [74, 75] which minimises wastage as steady state is approached. A practical demonstration for a continuous crystallisation process should be able to operate for extended periods and deliver consistent product throughout. Practical challenges such as fouling must be effectively managed through careful control of supersaturation, clean in place or swap out approaches. Consideration for how to deal with off-specification product, for example, during start-up or shut-down is also required.

5.4 Continuous Crystallisers and Applications

There are a wide variety of platforms that have been documented and described in the literature for continuous crystallisation of molecular systems including single and multistage MSMPRs, PFRs, oscillatory flow reactors (OFRs, COBRs), Taylor Couette reactors, agitated cell reactors (e.g. CoFlore^{TM}), agitated tubular reactors, segmented tubular flow systems, spinning disk reactors, impinging jets, electrospray, spray drying, extrusion systems and microfluidic platforms. The various crystalliser types offer different characteristics relevant to control of crystallisation processes in terms of their mixing performance, heat and mass transfer and accessible mean residence times. Many plug flow type reactors typically have shorter residence times than MSMPR crystallisers as effective mixing in the former is largely dependent on net flow. Crystallisation cycle process times to achieve complete desupersaturation can require hours and so an understanding of maximum growth rate kinetics whilst maintaining purification efficiency is required to design a robust process and inform platform selection. Supersaturation can also be controlled using anti-solvent addition, and rapid and effective mixing afforded by continuous reactors can be useful in this respect. Tubular crystallisers offer a high specific surface area and hence excellent heat transfer which enables the implementation of smoothly controlled cooling profiles, although care is required to prevent encrustation or fouling of heat exchange surfaces. As in batch processes low addition rates into a continuous crystalliser, akin to gradual or dropwise additions in batch, for example, for pH change or for anti-solvent, need to be managed carefully though can be done successfully [27]. The location and rates of multiple addition points along the length of tubular reactions can be optimised and many platforms are fabricated with multiple addition port locations to allow for flexibility over controlling the supersaturation profile for individual crystallisation processes.

Where nucleation rates are relatively slow and the mixing is ideal, MSMPR crystallisers can operate at nearly constant low supersaturation, giving rise to relatively large particles. In flow type crystallisers including tubular reactors and impinging jet crystallisers, supersaturation varies across all positions in the reactor. The optimal strategy to select should

be dictated by the crystallisation process and need to control the relative nucleation and crystal growth rates in order to achieve the required PSD [19, 23, 30–32]. Detailed models of the particle sizes that can be achieved for MSMPR cascades and plug flow crystallisers are available [85]. However, further research is required to demonstrate the full range of control over particle engineering approaches for form, size distribution, crystal shape, microstructure, surface properties and purity and the optimal strategies to achieve these for all cases. In this section we will review the main operating principles of MSMPR and plug flow reactors (PFRs) and present examples of their application for continuous crystallisation processes.

5.4.1 Mixed Suspension Mixed Product Removal

The MSMPR crystalliser is the simplest form of a continuous crystalliser and is analogous to a CSTR or back-mixed reactor [86]. As the MSMPR is a specific implementation of a stirred tank it offers a degree of familiarity to operators when moving from a batch to continuous process as well as lower capital investment as modifications could be made to an existing facility. A simple implementation is shown schematically in Figure 5.9. A detailed explanation of the MSMPR crystalliser can be found in the works by Randolph and Larson [73].

Figure 5.9 shows the typical residence time distribution for a MSMPR subjected to a tracer experiment. Mean residence time, τ, can also be defined as:

$$\tau = \frac{V}{Q} \tag{5.8}$$

For further discussion on the residence time distribution response of an MSMPR, readers are referred to the tanks in series model [86]. It should be noted that the inlet and outlet flow rate, Q, need not be continuous and can be intermittent [87], with the volume, V, varying between minimum and maximum levels. This periodic mode of operation is particularly suited to smaller lab scale MSMPRs where low flow rates can lead to blockage in the outlet line. MSMPRs of course utilise stirred tanks and therefore have the advantage of utilising existing batch equipment and infrastructure to support for continuous operation with minimal adaptation. The following sections list some examples of their utilisation in continuous crystallisations.

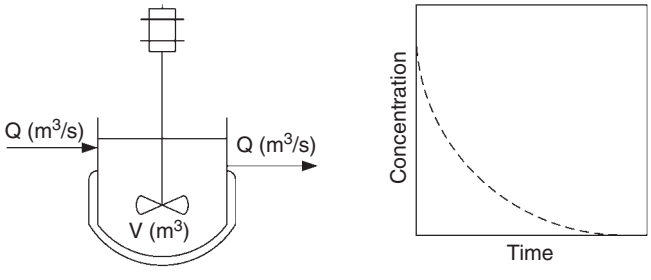

Figure 5.9 *Schematic of MSMPR crystalliser and typical residence time distribution response.*

5.4.1.1 Calcium Lactate

Chemaly and co-workers [88] studied the crystallisation kinetics of calcium lactate pentahydrate in a 300 ml vessel with residence times ranging from 40 to 215 min. Each crystallisation was carried out until steady state was achieved, which was after at least 20 residence times. Crystal D_{50} size was found to initially increase with increasing residence time, before decreasing at residence times longer than 70 min (Figure 5.10). This was due to nucleation rate being controlled by supersaturation at low residence times, where as it was controlled by secondary nucleation (microabrasion) from crystal–crystal collisions at higher residence times.

5.4.1.2 Benzoic Acid

Ferguson and co-workers [23] compared the anti-solvent crystallisation of benzoic acid in batch, plug flow and MSMPR configurations. The MSMPR was operated with a 375 ml volume with a mean residence time of 30 min. Steady state was observed after seven residence times (Figure 5.11). Slurry withdrawal from the MSMPR was preformed intermittently using pneumatics. Most significantly it was found that the continuous modes of operation (MSMPR and plug flow) could obtain crystal size distributions that were both smaller and larger than the equivalent batch, in addition to delivering an increased productivity.

5.4.1.3 Deferasirox

Ferguson and co-workers [89] compared the use of their novel anti-solvent MSMPR setup (shown in Figure 5.12) to an equivalent batch process and current commercial batch process with regards to the level of 4-hydrazinobenzoic acid impurity. This novel setup consisted of recycling the mother liquor from filtration back to the crystallisation to increase yield via a nanofiltration membrane to prevent that build-up of impurity

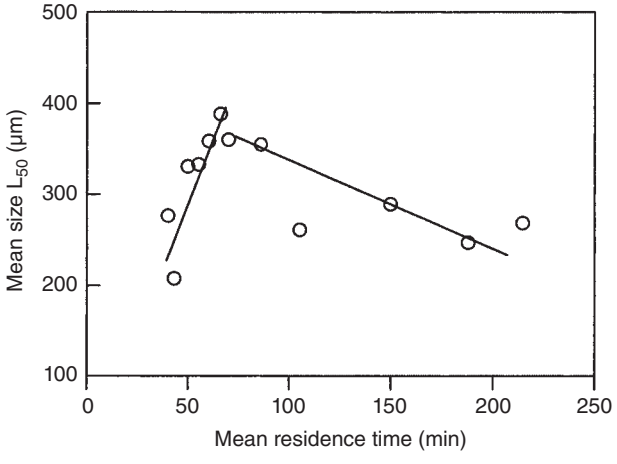

Figure 5.10 *Mean particle size evolution of calcium lactate with residence time. Reprinted with permission from [88]. Copyright 1999 American Chemical Society.*

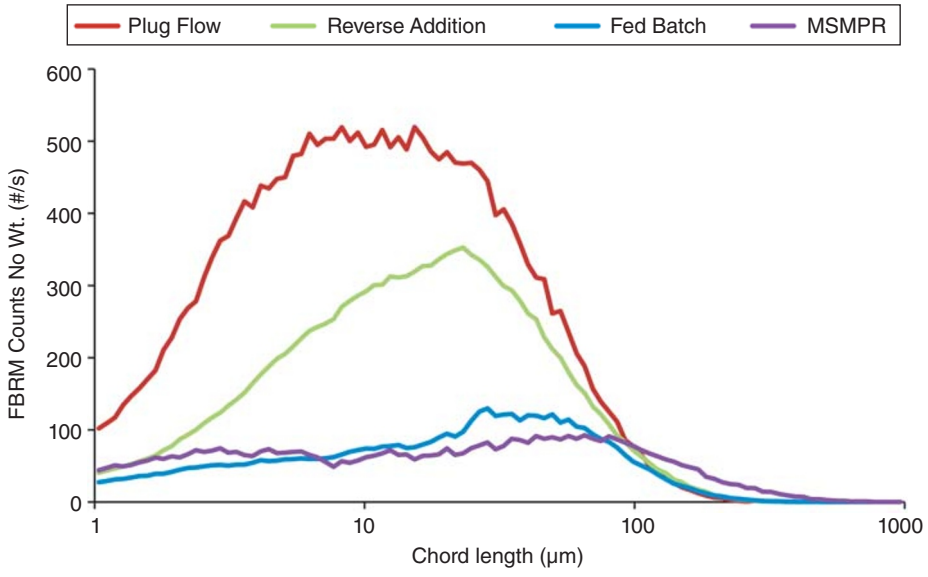

Figure 5.11 *Comparison between chord length distributions from FBRM for fedbatch, reverse addition, plug flow and MSMPR crystallisations. Reprinted with permission from [23]. Copyright 2013 Elsevier.*

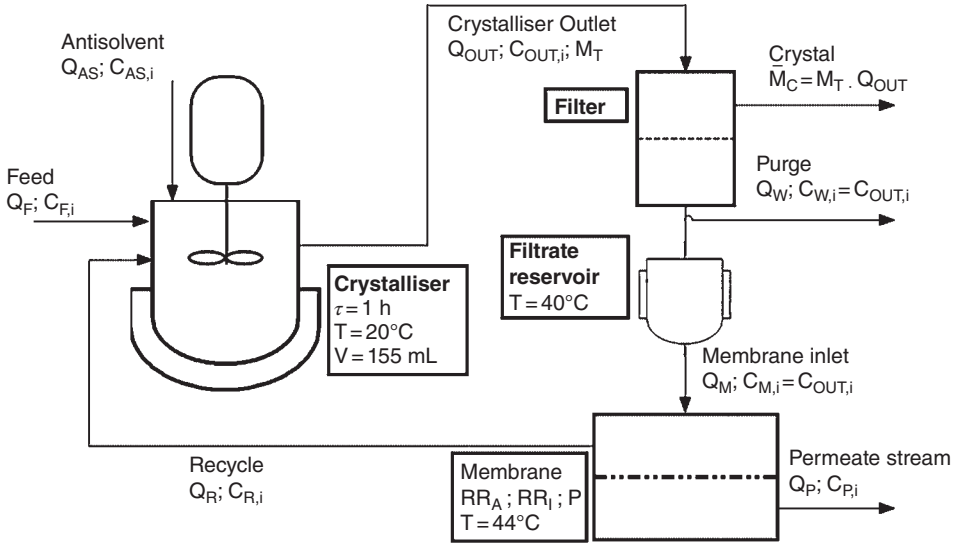

Figure 5.12 *Schematic of MSMPR with recycle and integrated membrane. Reprinted with permission from [89]. Copyright 2014 American Chemical Society.*

Table 5.4 *Comparison of product yield and purity. Summarised from [89]*

	Batch	MSMPR, no membrane	MSMPR, membrane 1	MSMPR, membrane 2	Commercial batch
Yield (%)	89.22	70.29	98.03	98.71	92.0
Impurity in crystals (ppm)	0.32	0.13	0.15	0.22	0.3

(Table 5.4). The MSMPR itself was 155 ml in volume with a 1 h mean residence time and ran for 10 residence times (10 h total running). Wong and co-workers [31] also studied a combined anti-solvent and cooling crystallisation of deferasirox with recycle. In this case the MSMPR was 250 ml with a mean residence time of 1 h but with varying crystalliser temperature.

5.4.1.4 Sodium Bicarbonate

Gerard and co-workers [90] studied the impact of calcium ion addition via different calcium-based additives on the crystallisation of sodium bicarbonate in a 50 l MSMPR with a mean residence time of 73 min. Steady state operation was reached after seven residence times. The identity of the additive used was shown to have a significant impact on crystal morphology, demonstrating the application of a crystal engineering approach in a continuous process to change the morphology from elongated needle to almost spheroidal (Figure 5.13).

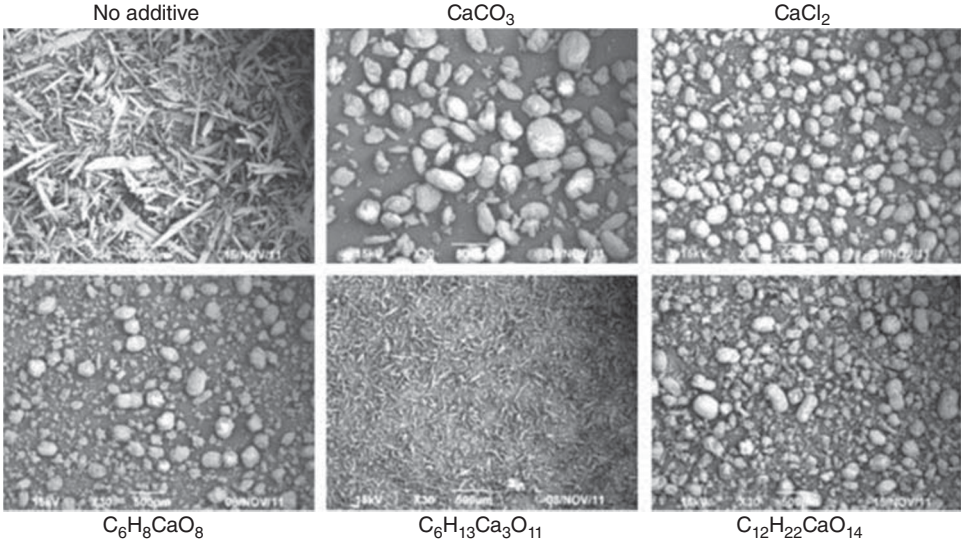

Figure 5.13 *SEM photographs of $NaHCO_3$ crystals with magnification ×30 for various experiments with and without calcium based additives. Reprinted with permission from [90]. Copyright 2014 Elsevier.*

5.4.1.5 Paracetamol

Hou and co-workers [91] operated a continuous single stage 1 l MSMPR with intermittent withdrawal via combined pressure/vacuum. The crystallisation consisted of a cooling recrystallisation of paracetamol from an aqueous 2-propanol solution. The system was operated for over 10 residence times ($\tau = 40$ min). This study also considered different start-up strategies finding that starting continuous operation from a seeded saturated solution obtained from a previous MSMPR run provided the quickest route to steady state operation. Yang and co-workers [92] also demonstrated the crystallisation of paracetamol in an MSMPR, but this time coupled with a wet milling unit, demonstrating the coupling of multiple operations to effect control over the process. The MSMPR was operated at 400 ml with a residence time of 20 min and operated for 12 residence times. Three configurations were evaluated: (1) without wet mill, (2) wet mill in loop around MSMPR and (3) upstream of MSMPR as a nucleation unit. Configurations (2) and (3) are shown in Figure 5.14. When used upstream the wet mill was found to reduce start-up times. Additionally, using the wet mill in a loop around the MSMPR was very effective at reducing particle size and obtaining a narrow size distribution (Figure 5.15). In both configurations with the wet mill an enhancement in yield was recorded in comparison to the no wet mill configuration.

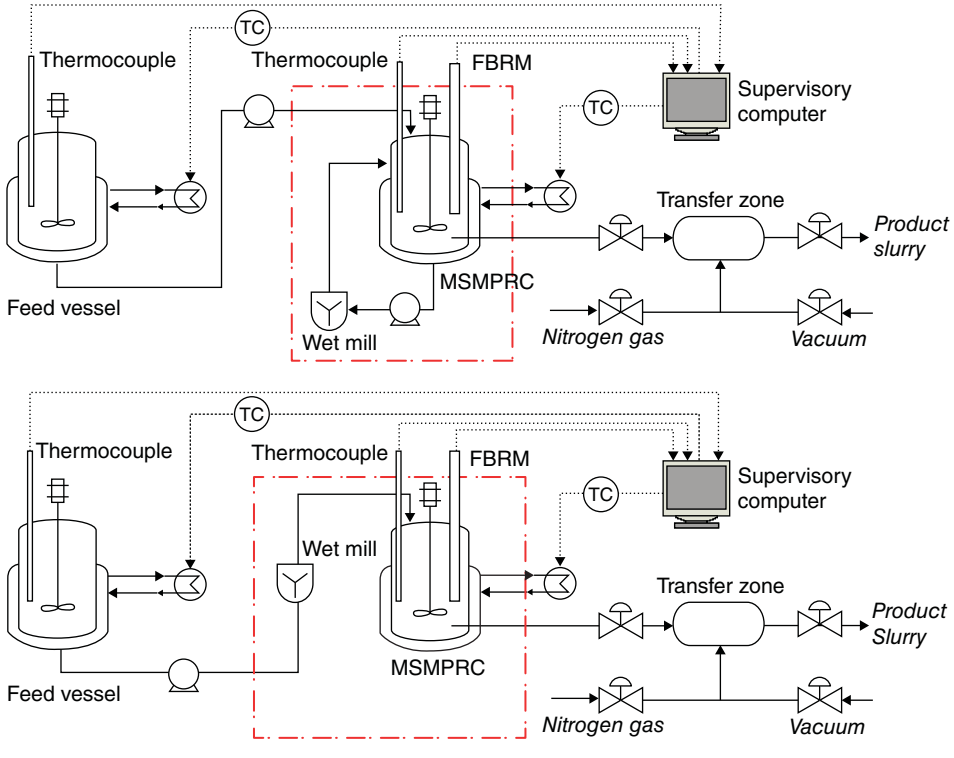

Figure 5.14 *Schematic of MSMPR with wet mill as part of a loop or upstream. Reprinted with permission from [92]. Copyright 2015 American Chemical Society.*

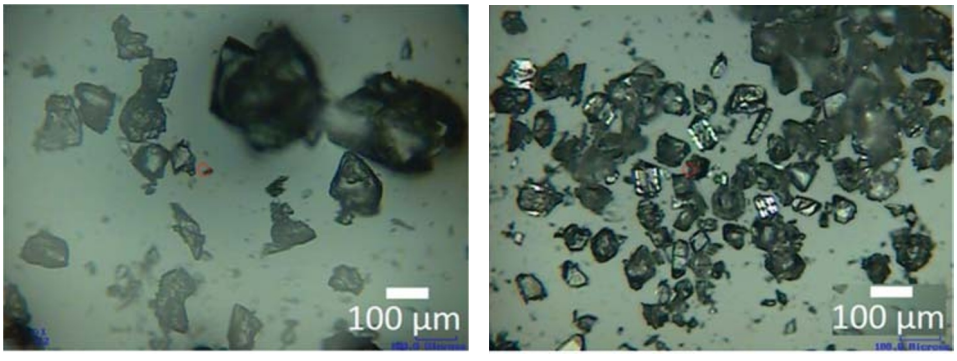

Figure 5.15 *Comparison of steady state product from setup: (a) without and (b) with wet milling loop. Reprinted with permission from [92]. Copyright 2015 American Chemical Society.*

5.4.1.6 Magnesium Ammonium Phosphate (Struvite)

Kozik and co-workers [93] performed a reactive crystallisation of struvite ($MgNH_4PO_4 \cdot 6H_2O$) in a draft tube 1.3 l MSMPR with mean residence times ranging from 15 to 60 min. Influence of pH and mean residence time of the suspension on the product size distribution and process kinetics were investigated. Mean crystal sizes from 19 to 73 µm where obtained with coefficients of variation ranging from 60 to 87%. Providing excess magnesium ions increased the yield of struvite. However, this was at cost of the product crystal quality. Hutnik and co-workers [94] also studied the crystallisation of struvite, this time in a 600 ml draft tube.

5.4.1.7 L-Glutamic Acid

Lai and co-workers [95] studied the polymorphic crystallisation of L-glutamic acid in a 150 ml MSMPR. Withdrawal from the MSMPR was intermittent, removing 10% of the slurry volume every one-tenth of a residence time. Residence times ranged from 30 to 120 min with a total running time up to 140 h. For unseeded crystallisations the MSMPR was first operated as a batch vessel until primary nucleation occurred, after which the feed and withdrawal systems were started. Depending on the startup conditions the initial nuclei were either pure α (25 °C) or a mixture of β and α (45 °C). Experiments with pure α during startup resulted in pure α form when operating at steady state. In comparison, those with a mixture of forms at startup produced pure β at steady state. For seeded crystallisations the MSMPR was started up with a seed mass of either pure α or pure β. However, the crystal form at steady state was always found to be pure α (Figure 5.16). This work concluded that operating conditions could be selected to allow for the production of either polymorphic form at steady state, but that seeding was not a valid strategy to control polymorphic form in this case, highlighting the need to consider not only the thermodynamic driving forces but also the kinetic driving forces of polymorph transformation. Tai and Shei [96] also studied the crystallisation of L-glutamic acid in a MSMPR, but focused on effect of impurities. They concluded that crystal growth and nucleation rates were suppressed by the presence

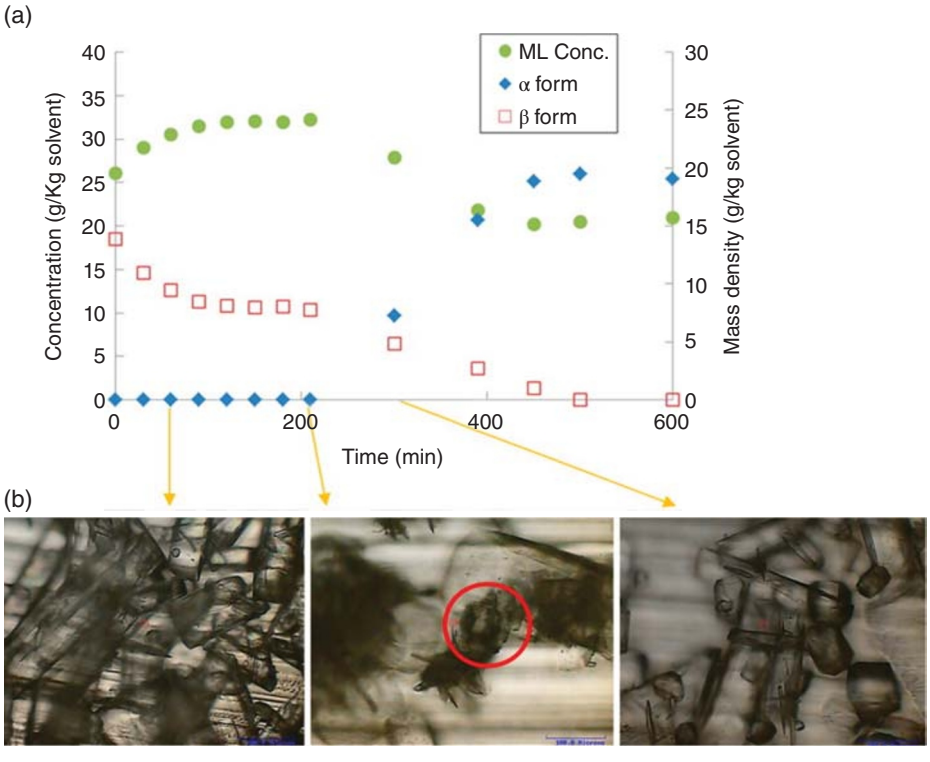

Figure 5.16 *Steady state transition from β to α polymorph in seeded 25 °C MSMPR (120 min residence time): (a) polymorph mass density profiles and (b) optical images of the collected crystal samples. Reprinted with permission from [95]. Copyright 2014 American Chemical Society.*

of impurity. Final crystal product impurity level was also found to correlate with crystal size, supersaturation and impurity concentration in solution.

5.4.1.8 Adipic Acid

Narducci and co-workers [29] also demonstrated a novel implementation of a MSMPR by coupling it with ultrasound technology. A 300 ml vessel was used as the MSMPR with residence times of 10–30 min. The effect of inlet solute concentration and ultrasound power amplitudes where also studied. Continuous ultrasound irradiation resulted in shortening the time required to reach steady state PSD and relative supersaturation. This lead to improved product yields. The ultrasound irradiation was also found to have a significant effect on the crystal habit and PSD (Figure 5.17), with more uniform habits and smaller sizes when compared to operation without ultrasound. In comparison to batch crystallisation a reduction in agglomeration and encrustation was also noted.

5.4.1.9 Ascorbic Acid and L-Sorbose

Over a series of studies Wierzbowska and co-workers investigated the crystallisation of ascorbic acid (vitamin C) in a MSMPR. Most recently [97] they demonstrated the

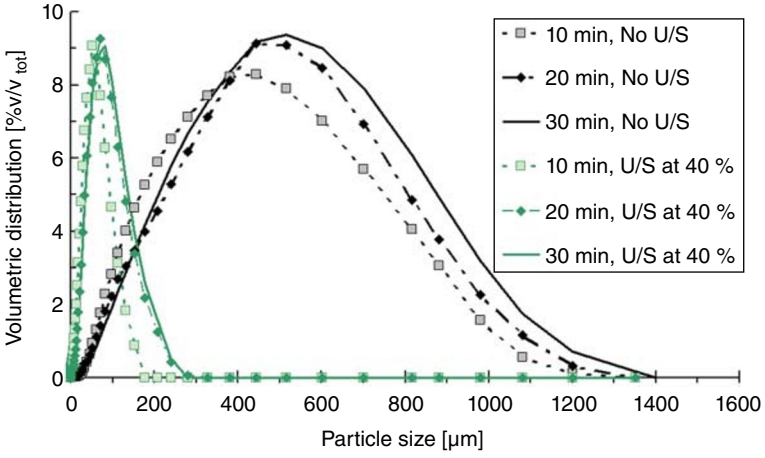

Figure 5.17 *Effect of mean residence time on the crystal size distribution. Reprinted with permission from [29]. Copyright 2011 Elsevier.*

implementation of a L(+)-ascorbic acid/ethanol/water system in a draft tube 600 ml crystalliser. At a fixed residence time of 900 s they investigated the effect of feed solution concentration leading to favourable decreases in particle size and span of particle size distribution. When studying variable residence time (900–3600 s) at a fixed feed solution concentration they noted an increase in solid phase at longer residence times, due to an increase in the levels of desupersaturation. Other studies included crystallisation from a methanol/water system [98, 99]. Wierzbowska and co-workers [100] also studied the crystallisation of L-sorbose in the same 600 ml MSMPR. Similar to their L(+)-ascorbic acid study they investigated the effect of feed solution concentration and residence time (900–3600 s) on production.

5.4.1.10 Cyclosporine

Utilising the same MSMPR configuration as for deferasirox (250 ml volume and 1 h residence time), Wong and co-workers [31] also performed a cooling crystallisation of cyclosporine from acetone. This time the MSMPR was operated with a working volume to 155 ml with a 3 h residence time. To improve yield a recycle of mother liquor, concentrated through evaporation, was also implemented (shown in Figure 5.18). The influence of crystalliser temperature and recycle ratio was recorded on product yield and purity. Wong and co-workers also compared the performance of their setup to a multi-stage MSMPR with and without recycle and a batch processes, noting that this setup produced a higher yield of product with comparable purity and quicker start-up times (Table 5.5).

5.4.2 MSMPR Cascade

If a single vessel, such as in the previously described MSMPR configurations, provides insufficient residence time for the crystallisation, additional vessels can be added downstream to produce a MSMPR cascade or multi-stage MSMPR. As the cascade is an extension of a single MSMPR the same benefits of a MSMPR previously discussed still

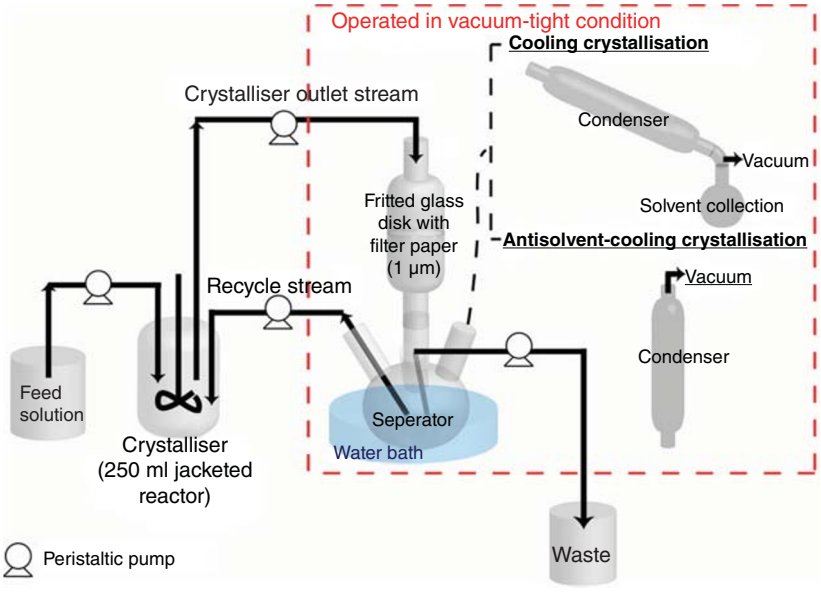

Figure 5.18 *Schematic of MSMPR with recycle and evaporation separator. Reprinted with permission from [31]. Copyright 2012 American Chemical Society.*

Table 5.5 *Comparison of the MSMPR with recycle and three-stage MSMPR cooling crystallisation for cyclosporine [31]*

	MSMPR with recycle (%)	Three-stage MSMPR without/with recycle (%)	Batch (%)
Yield	91.8	71/87	74
Purity	94.0	96/94	95

apply. The potential to vary the conditions in each stage of the cascade provides additional degrees of freedom and flexibility to effect control. A simple implementation is shown schematically in Figure 5.19. A detailed explanation of the MSMPR crystalliser can be found in the works by Randolph and Larson [73] and Mullin [36].

Figure 5.19 also shows the typical residence time distributions for each MSMPR in the cascade subjected to a tracer experiment. Mean residence time can now also be defined to be based on a *per tank* or *all tank* basis [86]. As with a single stage MSMPR the inlet and outlet flow rate, Q, need not be continuous and can be intermittent [101].

5.4.2.1 Paracetamol

Power and co-workers [101] demonstrated the use of a two-stage MSMPR crystallisation with intermittent transfer flow for the cooling crystallisation of paracetamol. The configuration consisted of two 1 l vessels, with residence times from 15 to 60 min. Steady state

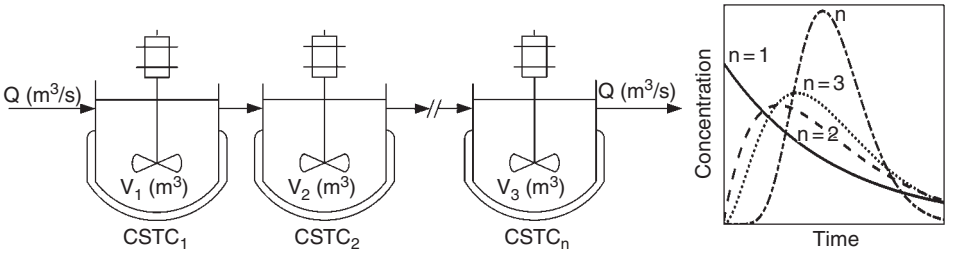

Figure 5.19 *Schematic of MSMPR cascade and typical residence time distribution response.*

was also reached after five to six residence times. Intermittent transfer performed using positive pressure was setup such that <10% of the crystalliser contents was transferred at any one time. Power and co-workers also highlighted the use of modelling to predict the range of product particle sizes that could be achieved for a given MSMPR configuration (Figure 5.20).

5.4.2.2 Benzoic Acid

Peña and Nagy [102] highlighted the use of MSMPRs for specific product attributes, in this case the spherical crystallisation of benzoic acid. This two-stage setup offered the benefit of being able to have different conditions in each vessel, each suited for different stages of the

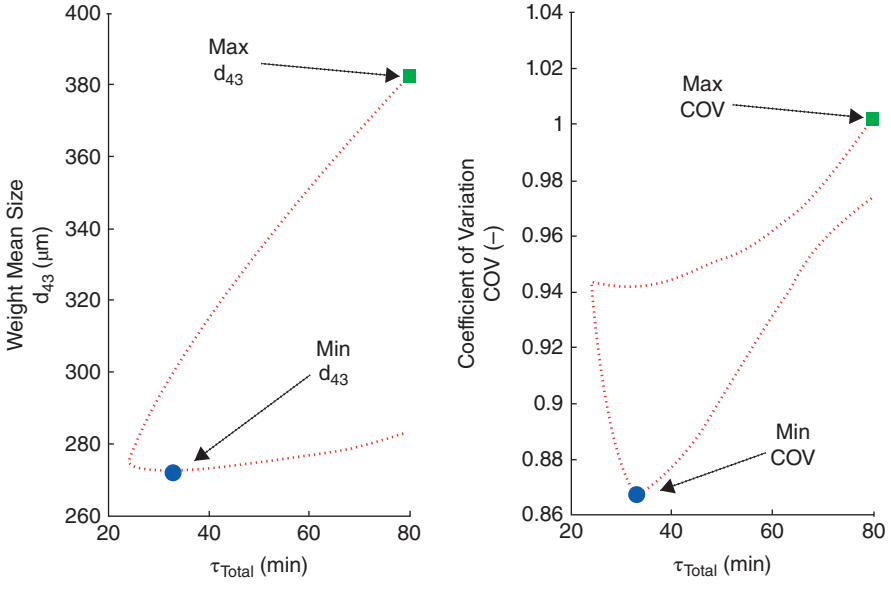

Figure 5.20 *Attainable range of weight mean size and the corresponding range of coefficient of variation for the two-stage MSMPR cascade. Reprinted with permission from [101]. Copyright 2015 Elsevier.*

spherical crystallisation process, in particular agitator speed and vessel volume. Residence time in the first stage was varied from 25 to 60 min and in the second stage from 45 to 100 min. Transfer between stages was via combined vacuum and pressure, transferring no more than 4.2–6.8% of the vessel volume. The flexibility of multiple stages allowing for different processing conditions is reflected in the range of products produced. These ranged from large spheres to small, loosely compact and flakey spheres, as shown in Figure 5.21.

5.4.2.3 p-Aminobenzoic Acid

Lai and co-workers [21] utilised a two-stage MSMPR cascade for the continuous crystallisation of the polymorphic compound, *p*-aminobenzoic acid. An intermittent withdrawal scheme (10% of vessel volume) was implemented between the two 150 ml vessels. Residence time in each vessel was 60 min. Steady state was achieved in two to three residence times and the system operated for a further four residence time from achievement of steady state. Under steady state conditions pure α form was detected in both vessels. To investigate

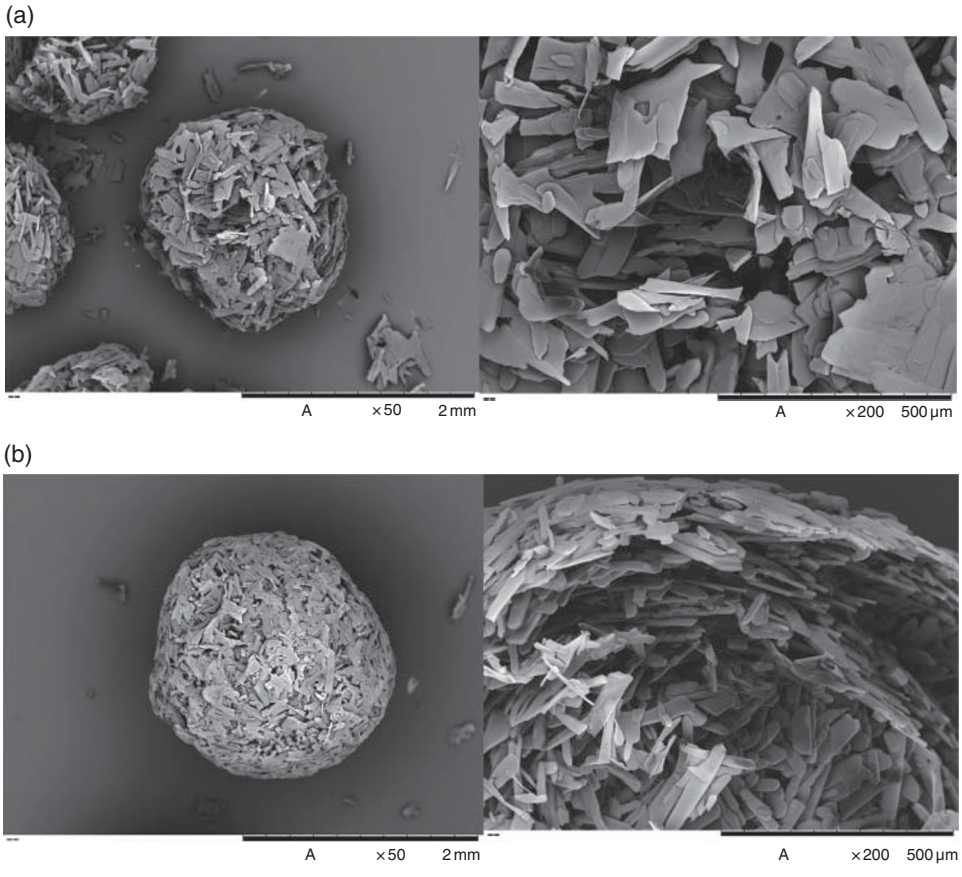

Figure 5.21 *SEM images of agglomerates ranging from (a) irregular shaped to (b) uniform spheres. Reprinted with permission from [102]. Copyright 2015 American Chemical Society.*

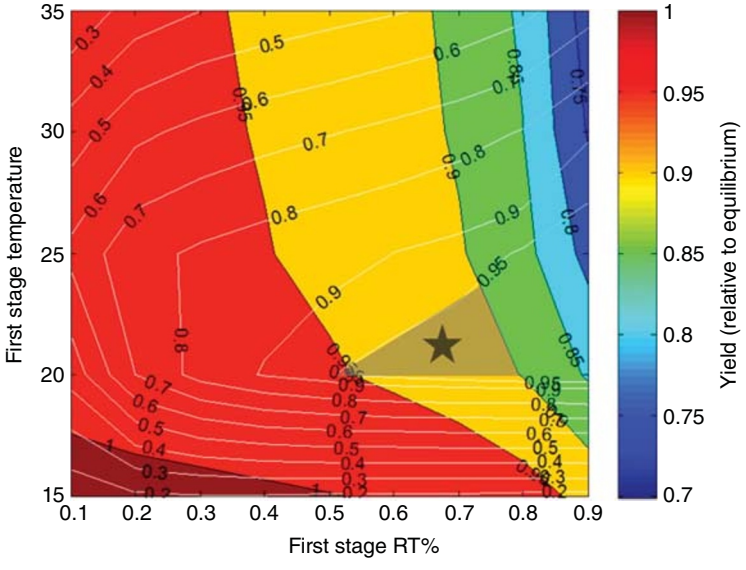

Figure 5.22 *Overlapping contour plots of yield and α polymorph purity to identify the operational window. Reprinted with permission from [21]. Copyright 2015 American Chemical Society.*

the stability of polymorph production, β form crystals were added to each vessel at steady state as a disturbance. Stage 1 returned to pure α form, whereas stage 2 resulted in a 75/25% α/β mixture. Based on these experimental results, kinetic parameters were estimated for a population balance model which was used to identify the operational window for stage temperature and residence time which achieved high polymorph purity and product yield (Figure 5.22).

5.4.2.4 L/D-Threonine

Galan and co-workers [103] implemented a two-stage MSMPR setup for the crystallisation of the enantiomeric threonine. Each vessel had a working volume of 450 ml and residence time was either 70 or 46.5 min and ran for 10 residence times to ensure achievement of steady state. The feed solution to both stages was saturated racemic mixture. To achieve preferential crystallisation each stage was seeded with a different enantiomer. In addition continuous exchange of filtered solution was performed between stages. Slurry product from each stage was filtered and the solution recycled back to the feed vessel, shown schematically in Figure 5.23. This setup demonstrated that ability to harvest both enantiomers simultaneously at high purity is possible.

5.4.2.5 Aliskiren Hemifumarate

Quon and co-workers [33] implemented a two-stage MSMPR cascade for the crystallisation of aliskiren hemifumarate. In this case each MSMPR stage was a 50 ml vessel operating at 20 °C and –10 °C, resulting in yields of 85% and 92.3%, respectively. Transfer between

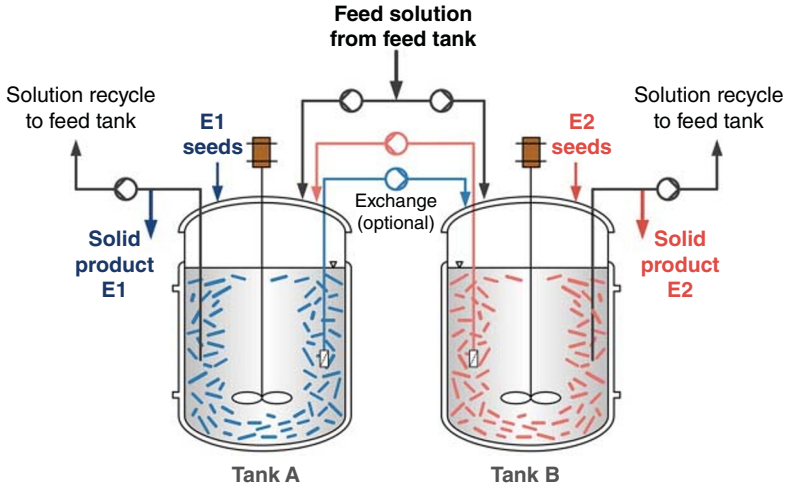

Figure 5.23 *Schematic of an MSMPR cascade for preferential chiral crystallisation. Reprinted with permission from [103]. Copyright 2015 American Chemical Society.*

stages was through peristaltic pumps at a flow rate (0.17 ml min^{-1}) such that each stage had a 4 h residence time. This work also highlights a number of technical challenges when operating at this scale, predominantly the risk of clogging the transfer tubing between stages with such low flow rates. To mitigate this the pumps were operated in an intermittent manner. Operating at such low flow rates also increasing the risk of primary nucleation occurring in the transfer lines due to heat losses reducing the temperature below the saturation point. In this example transfer lines were replaced with metal ones and trace heated to maintain an appropriate temperature. Once these technical issues were overcome continuous crystallisations were run for 48 h with purities >99%.

5.4.2.6 Cyclosporine

Alvarex and co-workers [19] performed a cooling crystallisation of cyclosporine in a three-stage MSMPR cascade. Each stage consisted of a 50 ml glass reactor with intermittent transfer between stages. Total residence time was 8 h 50 min and operated for 35 h 20 min (four residence times). This study also highlighted the potential application of recycle loops to achieve increased crystallisation yields. Each of the recycle loops employed in the cyclosporine study made provision for impurity removal and/or supersaturation regeneration. Without recycle product yield and purity were found to be 71% and 96% respectively. Recycle of the mother liquor was also considered, which improved the yield to 87% but at the cost of product purity, which fell to 94%. Increasing the recycle ratio further increased the yield but with further reduction in purity.

5.4.3 Plug Flow Reactors

In contrast to the back-mixed vessels of the MSMPR and MSMPR cascade, plug flow crystallisers (analogous to plug flow reactors, see [86]) operate without significant back mixing

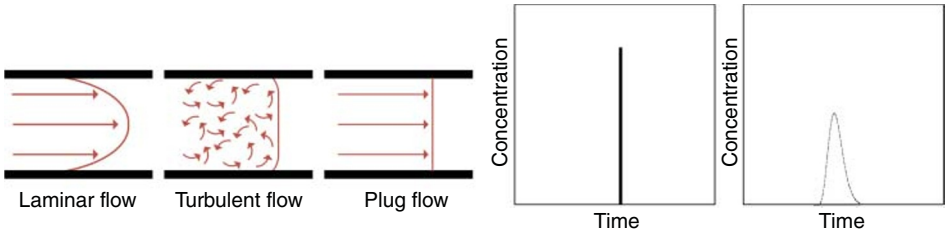

Figure 5.24 *Representation of plug flow in comparison to laminar and turbulent flow. Residence time distribution response for true plug flow and typical plug flow response.*

(Figure 5.24). This can ensure that ideally every particle experiences the essentially same process conditions for a consistent residence team as it proceeds along the length of the crystalliser. As true plug flow is impossible to achieve in reality, plug flow crystallisers tend to operate with a minimal distribution of residence time, often measured by the axial dispersion, Peclet or Bodenstein numbers. Due to this very low distribution of residence time, plug flow crystallisers can generally produce narrower particle size distributions than MSMPR crystallisers. In comparison to MSMPRs or MSMPR cascades, plug flow crystallisers are typically more suited to faster crystallisations with short residence times, due to limitations on the length of reactor available. Plug flow crystallisers are not heavily in operation throughout pharmaceutical industry. This is potentially due to the high capital cost for a new installation (versus modification of an existing batch to a MSMPR setup) and the nonfamiliarity of the equipment to operators.

Mixing behaviour close to plug flow can be achieved through high fluid velocities in a tubular pipe. However, for the velocities typically required to achieve this the length of pipe would be unmanageable for all but very fast crystallisations. Therefore, a secondary mechanism is usually employed for the attainment of plug flow like behaviour but at lower net velocities. These include the addition of twisted baffles as in static mixers, periodic orifices with oscillatory flow or the addition of an immiscible fluid to generate segmented flow. As plug flow crystallisers are generally tubular in geometry they exhibit a much higher surface area to volume ratio for heat transfer in comparison to stirred vessels used in MSMPR setups. This makes them particularly favourable for systems with high heats of crystallisation requiring rapid removal of excess heat. Continuous oscillatory flow reactors (COFRs) offer near plug flow where mixing is decoupled from net flow through the use of oscillatory fluid flow over baffles. This design allows longer mean residence times to be achieved in near plug flow at low residence times making them potentially well suited to slower processes such as crystallisation [16]. These crystallisers also tend to produce lower maximum shear rates compared with stirred tanks operating at similar power densities, making them suitable for suspending fragile crystals.

5.4.3.1 Lipoic Acid–Nicotinamide

Zhao and co-workers [104] demonstrated the use of a 25 m long, 15 mm diameter continuous oscillatory baffled crystalliser with 4.2 l volume for the crystallisation of a novel thermally stable α-lipoic acid–nicotinamide co-crystal. Continuous production allowed for the production of over 1 kg of co-crystals at a throughput of 350 g h^{-1} with a purity of 99%.

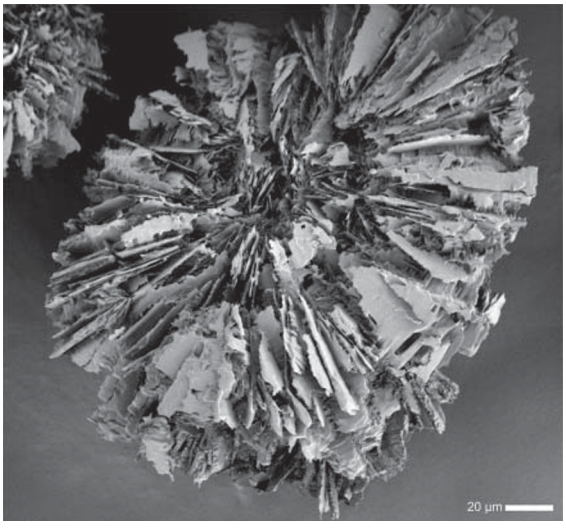

Figure 5.25 *SEM images of dried lipoic acid–nicotinamide co-crystals from continuous.*

Initial control of nucleation for the co-crystal was through the addition of co-crystal seeds for the first 10 s of operation with the system subsequently self-seeding. Product crystals were large spherical agglomerates of pure co-crystalline product comprising of multiple small thin plates (Figure 5.25).

5.4.3.2 Salicylic Acid

Brown [105] utilised a similar 15 mm diameter oscillatory baffled crystalliser as Zhao [104] but configured to have a shorter length (1.7 m) for the anti-solvent crystallisation of salicylic acid from 2-propanol with water. Solute concentration and particle size were monitored both spatially along the length of the crystalliser as well as with operating time. With short residence times (1.0–1.5 min) to complete the crystallisation the crystalliser was operated for >100 residence times. An extended operation of 6.25 h (250 residence times) was also performed to produce 1 kg of product crystals with a minimal variation in mean crystal size of ±3 µm (Figure 5.26).

5.4.3.3 Benzoic Acid

In their characterisation study Ferguson and co-workers [106] employed a Roughton-type vortex mixer to rapidly mix solvent and anti-solvent streams for the crystallisation of benzoic acid. The plug flow section of the crystalliser comprised of 5 m of 2.9 mm tube connected to the outlet of the Roughton mixer (Figure 5.27). Total volume was 33 ml with an approximate mean residence time of 2 s. In this study the batch and plug flow configuration were found to reach equilibrium, allowing for the maximising of yield. To illustrate the benefit of continuous crystallisers, to produce 15.8 t $year^{-1}$ of isolated product would require 43.2 × 10 000 l batch crystallisation versus a 33 ml plug flow crystalliser or a 9 l MSMPR crystalliser operating for 300 days $year^{-1}$.

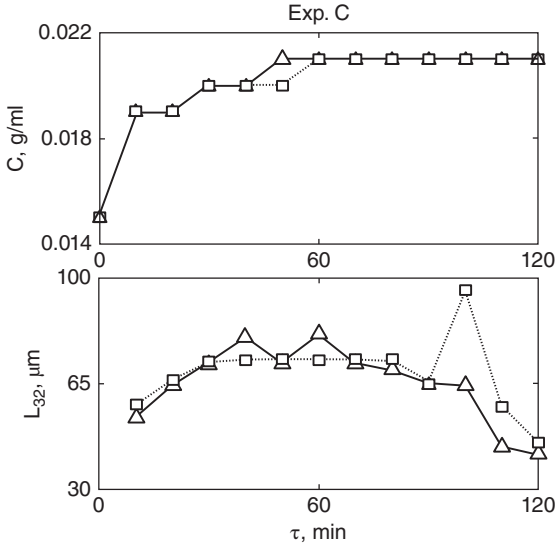

Figure 5.26 *Measurements of solute concentration, C, and particle size, L, for extended operation. Reprinted with permission from [105]. Copyright 2015 Elsevier.*

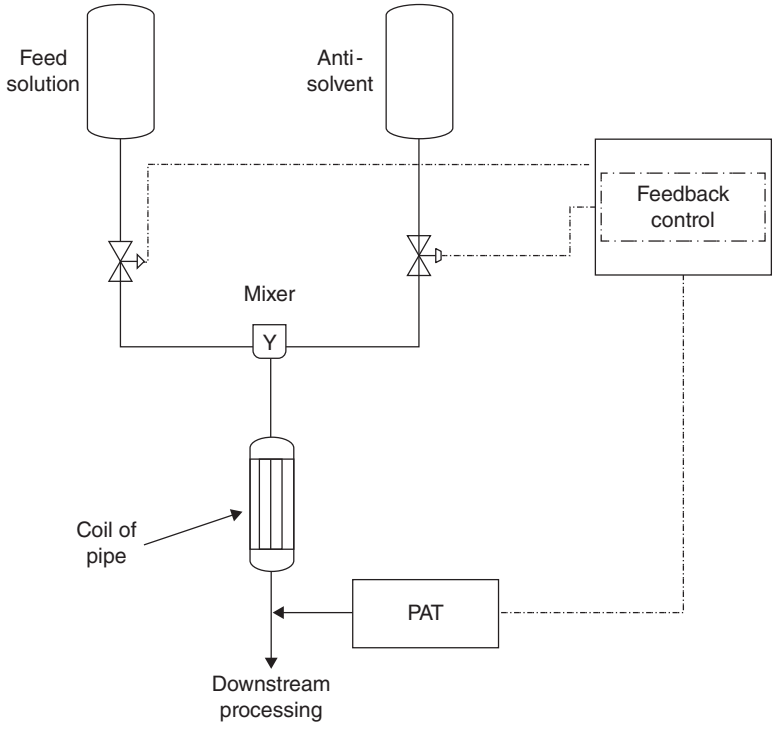

Figure 5.27 *Schematic diagram of the Roughton mixer plug flow crystalliser setup. Reprinted with permission from [106]. Copyright 2012 Elsevier.*

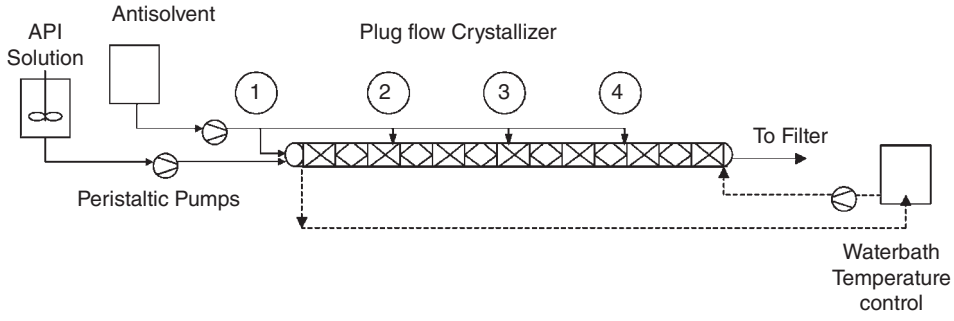

Figure 5.28 *Schematic process flow diagram of the kenics continuous crystallisation system with multistage anti-solvent addition. Reprinted with permission from [27]. Copyright 2010 American Chemical Society.*

5.4.3.4 Ketoconazole, Flufenamic Acid, L-Glutamic Acid

Alvarez and Myerson [27] demonstrated in a series of studies the use of Kenics-type static mixers, Figure 5.28, for the anti-solvent crystallisations of ketoconazole (from methanol with water), flufenamic acid (from ethanol with water) and L-glutamic acid (from water with acetone). The crystalliser consisted of up to four static mixer sections, each 600 mm long, 12.7 mm internal diameter with a volume of 76 ml. Solvent solution was employed as the main flow with the anti-solvent injected between each section. Number of injection points for the anti-solvent was investigated with the volume of anti-solvent split evenly between each point. Residence times studied ranged from 15 to 60 s with each experiment operating for seven residence times. The results of this study highlighted the ability to produce small size and narrow size distributions with the capability of using multiple points along the crystalliser for anti-solvent addition to control the mean size of the crystals (Figure 5.29).

For L-glutamic acid, Briggs and co-workers [107] also performed seeded and unseeded cooling crystallisation in a 25 m long, 15 mm diameter continuous oscillatory baffled crystalliser with 4.2 l volume (Figure 5.30). In the unseeded experiments they highlighted one of the drawbacks of the high surface area to volume ratio tubular crystallisers in that the combination of high surface area and high supersaturation needed for primary nucleation leads to unwanted nucleation on the walls, commonly referred to as fouling or encrustation. Supplying seed crystals to the system provides a more attractive surface (the crystal faces) for growth rather than primary nucleation on the walls, leading to uninterrupted operation. For the seeded crystallisations steady state was reached by the second residence time with total operation for eight residence times (10 h).

5.4.3.5 Acetylsalicylic Acid

Over a series of studies Eder and co-workers demonstrated the crystallisation of acetylsalicylic acid (aspirin) in a tubular plug flow crystalliser. First, for seeded crystallisation the effect of seed crystal size and loading was investigated [108]. Solution and seed streams were mixed in a y-mixer before entering a 15 m long, 2 mm inner diameter tube to provide sufficient residence time for growth. The main conclusions were that a steady state

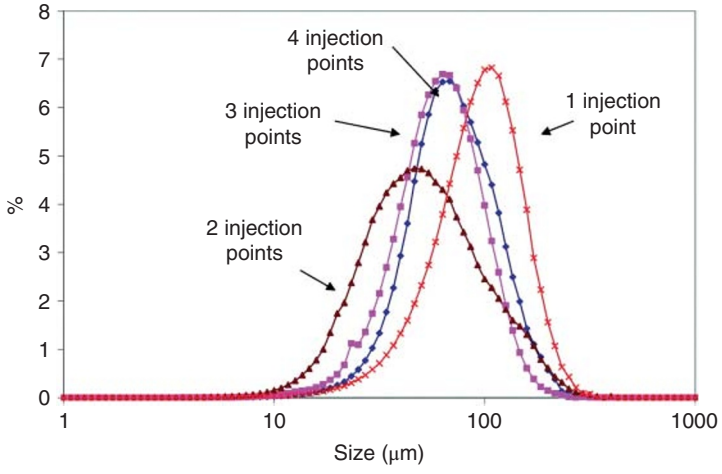

Figure 5.29 *Crystal size (volume based) for L-glutamic acid as a function of the number of points of addition of anti-solvent. Reprinted with permission from [27]. Copyright 2010 American Chemical Society.*

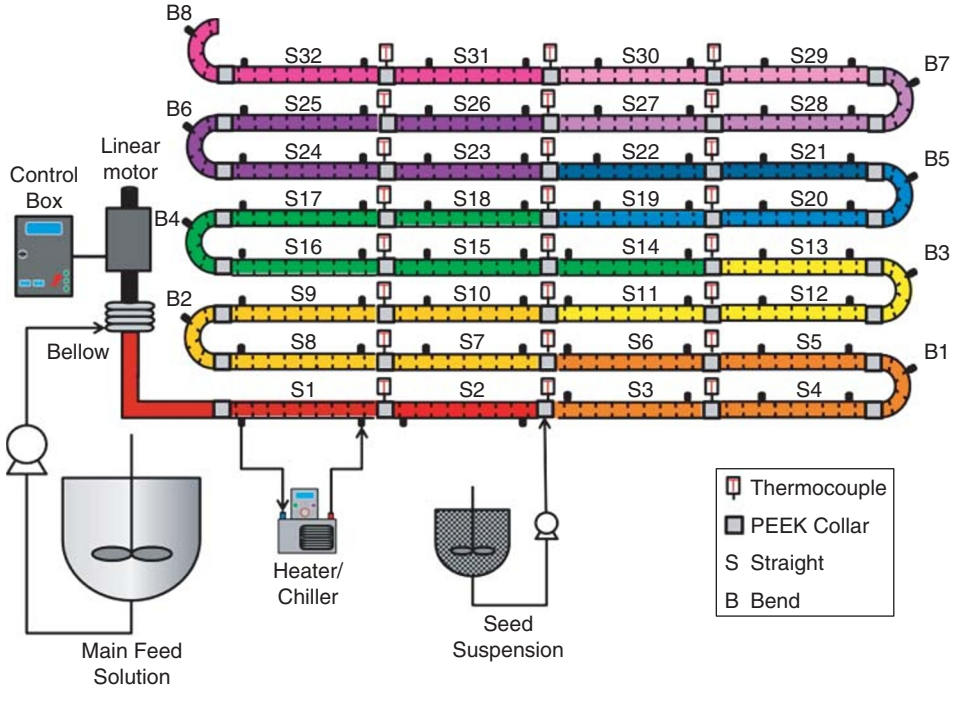

Figure 5.30 *COBC setup for seeded crystallisations. Reprinted with permission from [107]. Copyright 2015 American Chemical Society.*

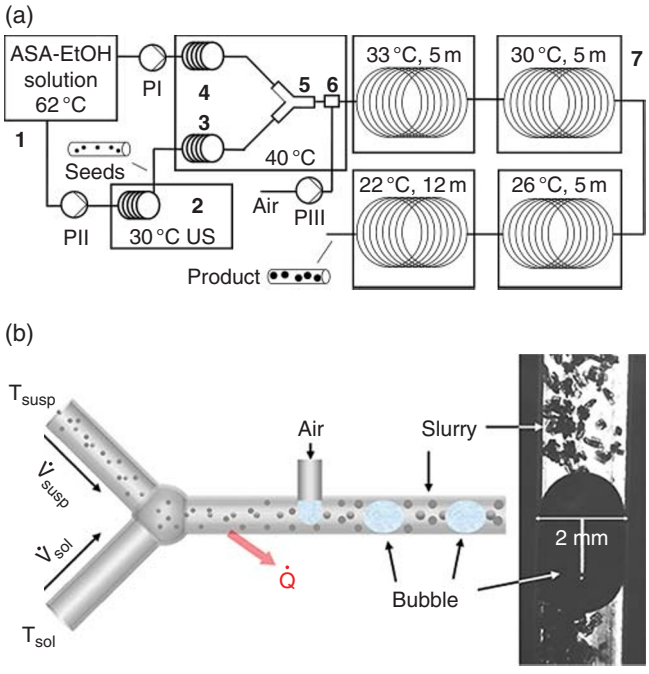

Figure 5.31 *(a) Schematic of the plug flow setup with ultrasound for* in situ *seed generation and (b) y-mixer where solution and air are mixed to generate segmented flow. Reprinted with permission from [28]. Copyright 2012 American Chemical Society.*

condition was reached rapidly, increasing seed loading resulted in decreased difference between the seed and product crystal sizes (as more individual particles were introduced). Decreasing seed size whilst maintaining the same seed mass per slurry volume also resulted in a decreased difference between seed and product crystal sizes. They also highlighted the ability to adjust the temperature profile along the tube to find the optimum between sufficiently fast crystal growth, high purity, length of crystalliser and flow rate. Following on from this Eder and co-workers [28] removed the need for a secondary seed stream by applying ultrasound to a portion of the feed solution in order to induce nucleation and generate seeds in situ (Figure 5.31). In this case an additional inlet of air was produced to act as an immiscible fluid to produce a segmented flow. This combination of ultrasound and segmented flow allowed for supply of seeds of constant quantity and quality as well as minimising the span of the residence time distribution.

5.4.3.6 Lactose

Siddique and co-workers [83] also employed ultrasound in the cooling crystallisation of lactose. In this case sonication was utilised in a multi-orifice oscillatory baffled crystalliser (Figure 5.32) with residence times of up to 4 h. Steady state was achieved after 1.5 residence times with a total operation of four residence times. This study also highlighted the process intensification ability of continuous processing by reducing the cycle time from

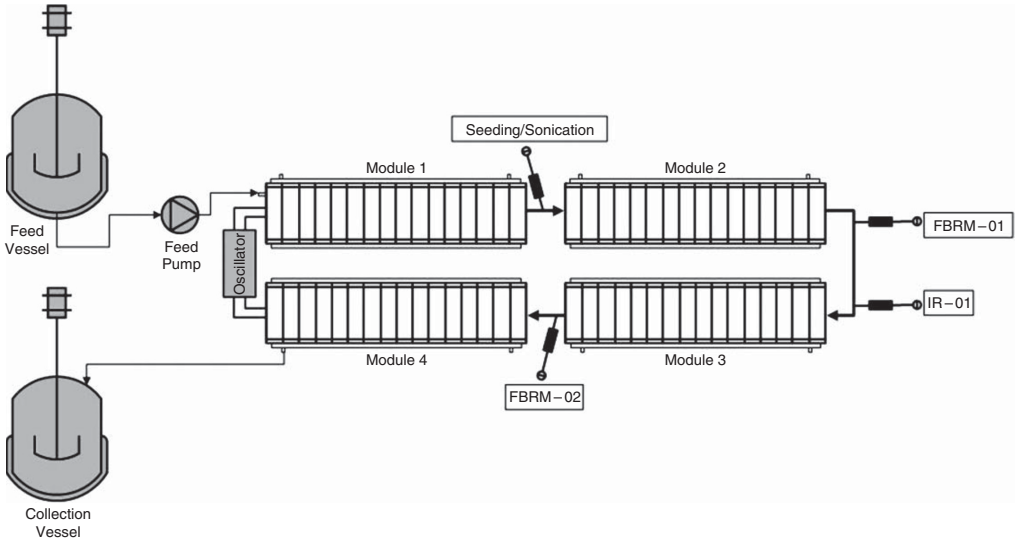

Figure 5.32 *Schematic of multi-orifice oscillatory baffled crystalliser with ultrasound. Reprinted with permission from [83]. Copyright 2015 American Chemical Society.*

13–20 h to 4 h. Narrower particle size distributions were also produced when compared to the equivalent batch process, with the ability to tailor the mean particle size through ultrasound intensity or cooling profile.

5.4.4 Impinging Jet

Similar to the Roughton mixer described previously (Section 5.4.3.3), impinging jet crystallisers are a form of micromixer which can rapidly mix two streams to generate supersaturation. Typically solvent/anti-solvent mixing but can be hot/cold streams for a cooling effect. Jet design can be either open or confined with an open geometry suitable for screening experiments as it is flexible and unlikely to clog but is subject to splashing and solvent evaporation. In comparison a confined geometry avoids evaporation, allows more control over the flow directions, allowing higher jet velocities to be reached, but does have a higher probability of clogging. Downstream of the mixer can either be a tubular section to generate plug flow, as in the Roughton mixer example, or the stream can be discharged directly into a MSMPR. Tari and co-workers [109] compared the performance of an impinging jet to cooling, reverse anti-solvent and anti-solvent combined with ultrasound processes for the crystallisation of glycine. This study demonstrated the ability of impinging jets to generate very fine particle size distributions compared to traditional processes (Figure 5.33). Tari and co-workers [109] also studied the effect of jet velocity,

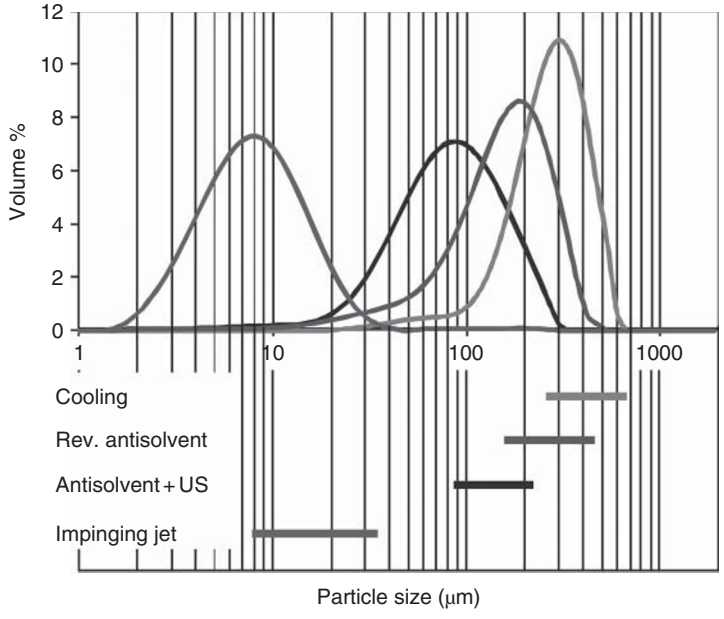

Figure 5.33 *Particle size distribution and average particle size range produced by different crystallisation methods. Top: particle size distribution of the product. Bottom: average particle size ranges, D(v,0.5) attained with the given method. Reprinted with permission from [109]. Copyright 2015 Elsevier.*

a study which was also carried out by Jiang and co-workers [110] on an undisclosed compound. Both these studies highlighted the ability to tune the particle size distribution by varying the jet velocity.

5.4.5 Microfluidics

Although not strictly relevant to industrial scale crystallisation, microfluidic devices have been gaining popularity as a high-throughput screening tool to determine solubility, kinetic or polymorphic data [111, 112]. The most common types of microfluidic devices focus on the creation of nl to μl droplets of solution, usually separated by an immiscible fluid. This allows each droplet to be treated as an individual crystalliser. Combined with the relative ease at which droplets can be produced a wide range of conditions for crystal formation can be screened. For further information the readers are encouraged to look at the comprehensive review by Leng and Salmon [113] or details on construction from Ildefonse and co-workers [114], Goyal and co-workers [112] or Zhang and co-workers [115].

5.5 Process Monitoring, Analysis and Control

5.5.1 Process Monitoring and Analysis

Given the complex range of subprocesses associated with crystallisation (primary and secondary nucleation, crystal growth, agglomeration and attrition), developing process understanding to design and control continuous crystallisations can be challenging and will benefit from exploiting suitable process analysis and monitoring approaches. Process analytical technology (PAT) is defined by the United States Food and Drug Administration (FDA) as a system of technologies for designing, analysing and controlling manufacturing processes through measurements during processing. This has been well established in the bulk chemical industry and is becoming increasingly applied for pharmaceutical and fine chemical processes [116]. PAT has been specifically applied for crystallisation [117–119] where temperature, concentration and supersaturation can be measured in the solution phase and particle size and shape, size distribution, polymorphic composition and the extent of agglomeration or breakage can be measured in the solid phase using a number of different methods. The incorporation of real time (i.e. results produced within seconds) and in-line or non-invasive measurements also brings the opportunity to measure process dynamics without the risk of artefacts or misleading results due to removing and processing samples outside the reactor (Table 5.6). The introduction of a probe can effectively act as a baffle within the process stream, disrupting the fluid or slurry flow potentially creating dead zones, or may also act as a surface for fouling. At-line sampling can also be useful, for example, combined with HPLC or UPLC methods, though care must be taken to manage temperature control, prevent particle classification to ensure representative sampling and to avoid blockage in sampling lines in the presence of particles.

The availability and use of in-line spectroscopy techniques for crystallisation monitoring has seen rapid expansion in the last decade. In particular, attenuated total reflectance (ATR) ultraviolet (ATR-UV) [120–122], ATR-Fourier transform mid-infrared (FTIR) [106, 123, 124] and Raman spectroscopy [125–127] approaches have all been shown to have utility. These techniques have also been implemented for operating crystallisation

Table 5.6 *Summary of types of PAT implementation for continuous crystallisation*

Type of analysis	Description	Common examples related to crystallisation
Off-line	Manual sampling, analysis elsewhere	XRPD, DSC, conventional particle sizing measurements[a]
At-line	Manual sampling, analysis next to process	HPLC, GC, MS[a]
On-line	A sample from process passes through analyser	Spectroscopic or sizing flow cell measurements
In-line	No sampling: probe inserted directly into reactor	Spectroscopic measurements, FBRM, PVM
Non-invasive	No sampling: no direct contact between sample and probe	Raman, optical imaging

[a]see also Section 5.6

processes via supersaturation control (SSC) [128–132] or through direct control approaches such as direct nucleation control (DNC) [42, 133, 134] using focussed beam reflectance measurement (FBRM) and particle vision measurement (PVM). While these calibration free approaches are attractive, particularly from an industry perspective, the inherent properties of the process such as nucleation and growth kinetics are not considered, giving rise to potential vulnerability under extreme conditions (e.g. high nucleation or low growth rates) and from unexpected variations. As a result, robust calibration strategies are essential for PAT incorporation (Table 5.7).

Simple univariate calibration approaches (e.g. peak height models) linking in-line spectroscopic data to supernatant concentration have associated issues, such as poor reproducibility, limited ability for hardware and calibration transfer and poor correction for external variables such as temperature, which can limit the utility of such models in terms of predictive capability. Temperature-corrected calibrations are essential to control crystallisations which are performed over a wide temperature range. Correcting for spectral shifts and broadening of spectral bands as a result of temperature fluctuations [135] allows the application of process monitoring in cooling crystallisation and requires multivariate calibration approaches [136, 137]. A number of multivariate methodologies have been applied for the correction of temperature fluctuations in spectroscopic data, principally for near-infrared (NIR) measurements [138–141], where temperature is included in the calibration experimental design and modelled using piecewise direct standardisation (PDS) [142, 143] and

Table 5.7 *PAT techniques for monitoring continuous crystallisation*

Attribute to measure and control	PAT method
Solution concentration	UV, IR, Raman
Number of particles	FBRM, imaging (PVM)
Crystal form of particles	Raman
Size of particles	FBRM, imaging (PVM)
Shape of particles	FBRM, imaging

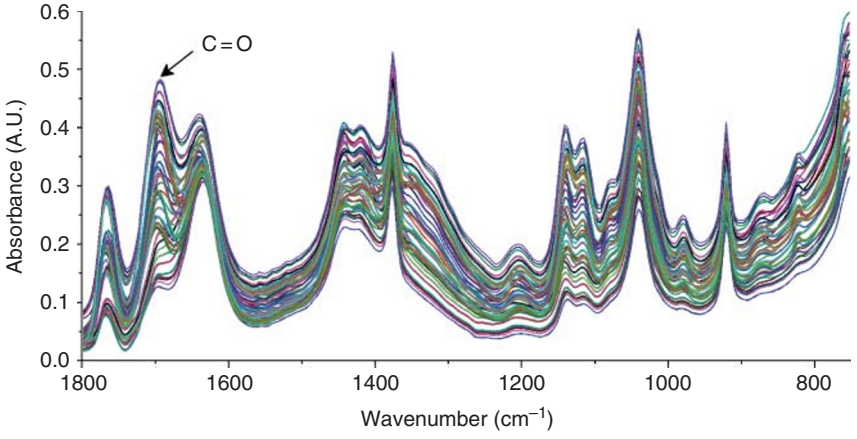

Figure 5.34 *Overlay of a series of mid-ATR-FTIR spectra for a fixed concentration solute-solvent system highlighting the effect of variable temperature across a wide spectral range.*

loading space standardisation (LSS) [135, 144] approaches to correct for complex nonlinear spectral variations. These approaches do have limitations in the range of temperature which can be corrected and can be non-trivial to develop and apply (Figure 5.34). A robust calibration approach requires identifying the concentration and temperature range of the process and gathering a representative series of spectral data to describe known compositions across this range (Figure 5.35). Having established the calibration, the measurement can then be used to quantify process responses to changes in conditions or for direct control of concentration, for example.

Févotte and co-workers reported a calibration procedure for ATR-FTIR measurements applied to solution crystallisation processes [145]. This built on previous studies [146–148] that recognised the need to compensate for temperature sensitivity in the measurement due to inter- and intramolecular interactions. Although the univariate approach only used a correlation between an individual solute peak and solution concentration, the calibration had a maximal relative error of 2.3% which can be of sufficient accuracy for practical application where more precise control is not required. Nagy and co-workers also reported a calibration procedure for ATR-UV monitoring and control [149]. The method used the first derivative of the absorbance spectra at two wavelengths and applied a simple nonlinear calibration function. Mahmud and co-workers reported a multivariate calibration procedure for the cooling crystallisation of L-glutamic acid with ATR-FTIR using partial least squares (PLS) to fit the calibration model [150]. A 5-factor model was developed and applied, with a typical percentage error of 4.79%, highlighting PLS as an efficient approach in correcting for temperature dependent measurements.

There are multiple physical transformations and hence rate parameters that dictate the actual performance of a crystallisation. Although rather sophisticated mathematical models have been published for some specific continuous pharmaceutical crystallisers, the vast majority of models for primary and secondary nucleation processes, size-dependent growth, phase transformations, attrition, agglomeration and morphology rely on semi-empirical kinetic models. Obtaining reliable experimental kinetic data on these processes is a key step to inform robust process design and PAT can play a role in addition to traditional

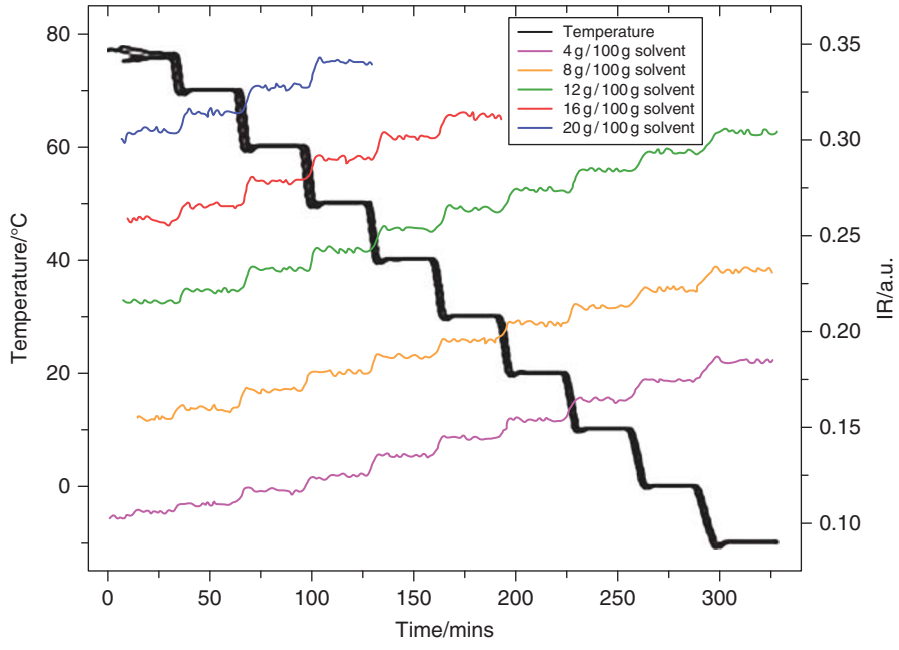

Figure 5.35 *A full calibration data set for a given solute-solvent system. Five variable temperature experiments in the selected spectral range can be observed.*

off-line techniques. Indeed, the ability to collate relevant data in real time that describe the changes in temperature, solution concentration and particle number and size would be a major advance in accelerating process development.

Population balance models, for example, require accurate parameter estimates as well as particle size distributions that can be difficult to accurately measure in-situ using existing PAT sensors. Focused beam reflectance measurement (FBRM) allows chord length measurement but has a non-unique relationship to the three-dimensional particle size information that is actually required for these models. Nonetheless the FBRM probe is a powerful tool for the *in situ* identification of nucleation (i.e. particle formation via increased particle counts) in crystallisation processes [133, 151]. The chord length distribution obtained from FBRM also provides information relating to the size and shape of particles that can be used to monitor and control growth [133], attrition [152] and agglomeration [153] processes. FBRM can also be used to provide information on the surface properties of crystals influencing their processability [154]. Inverse techniques to calculate the actual particle size distribution from the chord length distribution obtained from FBRM have also been developed and provide a basis for direct control of particle size distribution without the need for off line measurement of particle size and shape [155, 156]. Sensors have also been developed for *in situ* monitoring of crystal shape but tend to be challenging to use or are only applicable for certain types of crystals [157]. Low cost web cameras have been demonstrated for non-invasive, *in situ* monitoring of early signs of encrustation [158]. This

approach used image analysis to develop a fouling metric indicator that would allow early identification of the need for corrective actions during continuous crystallisation due to a build-up of crystals on the vessel walls or heat transfer surfaces.

5.5.2 Crystallisation Control Strategies

For the majority of crystallisation systems, a basic feedback control strategy (e.g. PID, cascade) is designed to follow empirical operating policies (e.g. linear temperature profile, anti-solvent addition or evaporation rate) [159]. The advancement of *in situ* sensors and calibration methods has enabled precise real-time measurement of solute concentration (e.g. via ATR-FTIR, ATR-UV/Vis) and the characteristics of the crystal population's mass, size and morphology. This has enabled more advanced control strategies to be developed and applied [49, 160–162]. Generally these can be differentiated into two main categories: model-based and model-free control. However, increasingly hybrid control strategies have also been developed that combine model-based and model-free techniques.

5.5.2.1 Model-based Control

The earliest examples of model-based control strategies demonstrated the benefits of using a programmed cooling profile which was calculated off line [163, 164]. Since then, major advances have allowed for the control of various aspects of product quality [165]. For a model-based optimisation the solution must be constrained by the equipment limitations (e.g. maximum and minimum temperature values, maximum and minimal cooling rates, maximum volume, limits on anti-solvent addition rate etc.) The crystallisation must also satisfy a productivity constraint that ensures the desired yield. Quality constraints can also be included such as those found in [166–168]. The effects of non-ideal mixing via computational fluid dynamics can also be incorporated [169].

Typically a model-based strategy will consist of:

1. *The process model*. This describes the product quality and process performance of the crystallisation. This is used either in real-time or off line to achieve the desired performance or quality. This will typically consist of the population balance equation, material and energy balances and the kinetic models for the crystallisation rate processes. The model should give a robust and accurate description of the crystallisation process in the selected crystalliser. Therefore, there is always the need to carry out parameter estimation and validation steps before it can be applied in the controller design.
2. *A dynamic observer*. Provides an estimate of the state of a real system from appropriate measurements. This is a crucial component of the model-based control strategy to achieve robust offset-free control. Different types of observers have been used in crystallisation control and a comparison between the different types of observers for crystallisation control has been performed [170].
3. *A dynamic optimiser* which is used to determine the optimal trajectory to reach the desired state of the process at the lowest possible cost. The efficiency and robustness of the optimiser therefore plays an important role in the design of the control system.

Model-based control strategies can provide the theoretically optimal operating conditions and generally require fewer experiments to develop, when properly designed, when compared to statistical experimental design. Model-based approaches also have the benefit of increased process understanding although this can be at the cost of development time and material to develop and validate the models. Of course, uncertainty will exist within the kinetic models given the ill-defined physics of some of the processes involved, and this needs to be taken into account to avoid poor performance of the controller when applied.

5.5.2.2 Model-free Control

Model-free control approaches are based on the direct use of sensors or PAT-based measurements in feedback control of crystallisation processes. Whilst these approaches are based on defined models relating the response of the process to changes in process conditions, they are entirely empirical and do not assign any physical or mechanistic significance to the parameters. For example, for supersaturation control the objective is to control the crystallisation process by maintaining supersaturation at specific values at each stage of the process to enable a desired operating trajectory through the phase diagram [171, 172]. The state of the crystallisation process at any location in the process can be determined using actual concentration and temperature measurements and the concentration trajectory adjusted by varying the temperature. This approach provides the advantage that the operating curve can be defined based on prior understanding of the crystallisation process, to avoid triggering unwanted mechanisms, such as nucleation or polymorphic transformations by allowing the process to move out with the MSZW [173]. However, a controlled move to out with the MSZW to initiate crystallisation followed by supersaturation control has been shown to be a valid strategy for particle size control [42, 172]. In the majority of reported applications, constant supersaturation is used for a setpoint although the approach conceptually allows to specify more complex trajectories in the phase diagram. For example in the case of systems with complicated phase behaviour, for example, with multiple forms (polymorphs, hydrates, solvates etc.) superaturation can be manipulated directly as required to maintain the desired form. The schematic representation of supersaturation control approach is shown in Figure 5.36.

Model-free control strategies can often result in close to optimal crystallisation performance though, just as with model-based control approaches, it is important to understand the strengths and limitations of the model, the sensors being used and potential uncertainties that would result in the model operating out with sensible ranges. In the case of supersaturation control, particle attributes are not controlled directly and it may be possible for two separate crystallisation runs controlled at the same supersaturation to produce products with different attributes due to unmeasured disturbances including accidental seeding, attrition, agglomeration, fouling or variations in input materials.

5.5.2.3 Hybrid Strategies

A hybrid control strategy is one which combines features of both model-based and model-free strategies into a single strategy or utilises one to generate data for the other. Although supersaturation control can produce high quality crystals, the setpoint for

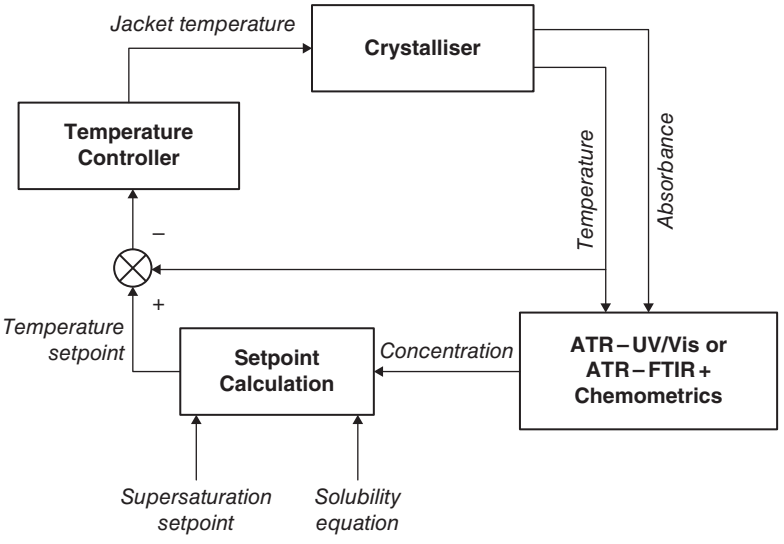

Figure 5.36 *Schematic representation of the model-free control approaches for supersaturation control. Set points can be adjusted to maintain supersaturation at the required value in response to transients or fluctuations in the process. Reprinted with permission from [173]. Copyright 2013 Elsevier.*

supersaturation is either arbitrarily chosen or found by trial and error. To address this issue Nagy and Aamir [174] incorporated an analytical solution of the population balance equation and a nonlinear optimisation (model-based aspect) into the supersaturation control (model-free aspect) to find the optimal setpoint trajectory, in this case amount of seed, to target a specific size distribution shape, Figure 5.37. One key aspect of model-based strategies is the determination of the key process kinetic parameters in order to accurately model a given crystallisation system. These parameters are usually determined through fitting to well designed experiments. Cao and co-workers [175] demonstrated the possibility of using supersaturation control to first generate high supersaturation for determination of nucleation kinetics, followed by low constant supersaturation for estimating growth kinetics. In order to determine a robust temperature/cooling profile which would not be subject to batch to batch variability of the shape of the crystal size distribution, Nagy [176] developed a hierarchical structure with a low level supersaturation control (model-free approach) driving the system through the phase diagram, the set point of which was optimised at a higher level by solution of the population balance equation to counteract the effect of changing operating conditions.

5.6 Particle Characterisation

The development of robust continuous crystallisation processes requires a detailed understanding of how crystal quality is influenced by the process conditions and changes in key rate processes. Standard chemical and physical off line characterisation tools remain essential in this respect allowing samples of material taken at different positions from the continuous process to be analysed for chemical and physical consistency. This can inform

Table 5.8 *Summary of off line chemical and physical analytical techniques of value in the characterisation of pharmaceutical solids produced from crystallisation processes*

Analytical method	Information provided
Optical microscopy	Crystal morphology, colour, size and shape Lattice strain or twinning Identify presence of polymorphs from mixed morphologies
Laser diffraction	Determine particle size distribution for dry or wet dispersed particles Identify particle aggregation or agglomeration
Dynamic vapour sorption	Assess hygroscopicity from mass change as a function of %RH or organic vapour Identify structural transformations from non-solvated to solvated forms Mass loss on drying
Inverse gas phase chromatography	Measurement of particle surface energies Quantification of amorphous content
BET analysis	Specific surface area measurement of particulate materials Porosity of powder beds or formulated systems
Solubility/dissolution	Determine equilibrium saturation solubility and influence of pH, T and impurities Solution mediated phase transformations Dissolution rate (intrinsic dissolution rate)
Scanning electron microscopy	Morphology and surface structure of particles Influence of processing on particles Agglomeration and attrition of particles
Atomic force microscopy	Mechanical properties of crystal faces Surface topology and dynamics Surface roughness
Single crystal diffraction	Unit cell, space group atomic co-ordinates, displacement parameters 3-D molecular conformation and intermolecular packing Absolute configuration Morphology and indexing of crystal faces
X-ray powder diffraction	Phase identification for polycrystalline sample Quantitative analysis of composition of mixtures Unit cell, space group and atomic co-ordinates. Crystallinity in amorphous/crystalline mixed phase samples Size/strain analysis of particle microstructure Variable temperature and %RH studies
Mid FT-IR	Characteristic absorption spectrum for polymorphic forms Identify non-solvated and solvated forms Distinguish amorphous and crystalline forms Quantification of mixtures

(*continued*)

Table 5.8 *(Continued)*

Analytical method	Information provided
Raman	Characteristic scattering spectrum for crystalline and amorphous forms Track lattice changes as a function of temperature and pressure Combine with microscopy for Raman mapping studies
Near IR	Characteristic absorption bands from O-H, C-H, and N-H stretches Detection of polymorphs and solvates Sensitive to water, useful for monitoring drying
Solid-state NMR	Determine number of unique formula units in unit cell Identify disorder Identify polymorphs and solvates
Terahertz spectroscopy	Molecular conformation and intermolecular packing Identify crystalline and amorphous solids Can combine with imaging
Differential scanning calorimetry (DSC)	Thermal transitions (desolvation; crystallisation; T_g; melt) Heat capacity, C_p, and heats of transition, ΔH Relative stabilities of polymorphs
Thermal gravimetric analysis	Measure weight loss on heating associated with solvent loss Enable calculation of solvate stoichiometry
Melting point	Measure characteristic melting points for crystalline forms Assess purity
Hot-stage microscopy	Changes in particles as a function of temperature Structural transformations including desolvation Melting point
Solution NMR	Identification of molecular species from dissolved solid and mother liquor Sample purity Identification of impurities
GC/LC-MS	Chemical analysis of crystals and mother liquor Separate volatile (GC) or non-volatile (LC) components Identify impurities (MS)

on the dynamics of the process during early process development as well as during start-up, operation and shut-down to inform process design and control. There are a large number of analytical methods that may be used to determine the physical properties and structure of pharmaceutical solids and it will often be necessary to combine data from several techniques in order to fully characterise a material [7, 177, 178] (Table 5.8).

5.7 Concluding Remarks

Continuous crystallisation offers the potential for flexible and effective control of particle attributes to achieve improved performance in formulation and final product application.

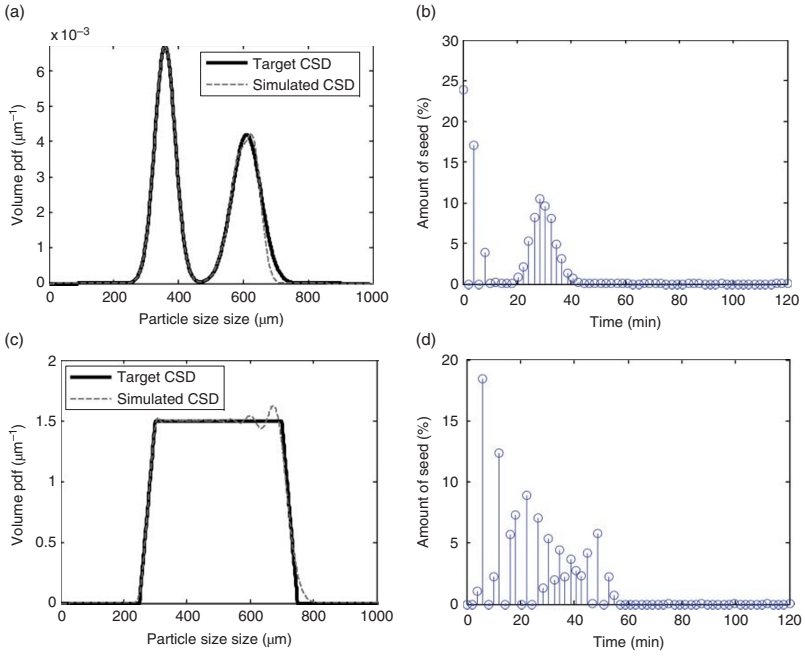

Figure 5.37 *Results for the dynamic seed addition for bimodal and trapezoidal distributions (a) and (c) show the comparisons of target and simulated CSDs at the end of the batch, and (b) and (d) illustrate the dynamic seed addition profiles, with amount of seed in wt%. Reprinted with permission from [174]. Copyright 2012 Elsevier.*

This will require careful design and crystallisation control strategies to be developed and whilst significant progress has been made in these areas, gaps in fundamental understanding of nucleation, growth and in crystal structure–property relationships and on the influence of process conditions on key transformations remain. Further developments in these areas will provide new opportunities to engineer particles with the required attributes to meet product performance needs by first intent and to design robust, scalable continuous processes to deliver them consistently (Figure 5.37).

There is also a need to develop and apply: (1) effective methods for gathering experimental physical data, quickly from limited material and (2) useful modelling tools to support process development and control. Equipment availability is also an important consideration and whilst there is a wide array of process technologies available, challenges also remain around standardisation, managing the presence of particles in flow, scalability, managing fouling and the need for effective, robust PAT for monitoring and controlling suspensions [179]. There is also a well recognised need to develop the right skills for the existing and future workforce to enable the implementation of continuous crystallisation processes to be fully realised including early implementation in development and through to manufacture.

References

[1] Baxendale I.R., Braatz R.D., Hodnett B.K. et al. (2015) Achieving continuous manufacturing: technologies and approaches for synthesis, workup, and isolation of drug substance. *Journal of Pharmaceutical Sciences*, **104**(3), 781–791.

[2] Badman C., Trout B.L. (2015) Achieving continuous manufacturing. *Journal of Pharmaceutical Sciences*, **104**(3), 779–780.

[3] Mascia S., Heider P.L., Zhang H.T. et al. (2013) End-to-end continuous manufacturing of pharmaceuticals: integrated synthesis, purification, and final dosage formation. *Angew Chem-Int Edn*, **52**(47), 12359–12363.

[4] Adamo A., Beingessner R.L., Behnam M. et al. (2016) On-demand continuous-flow production of pharmaceuticals in a compact, reconfigurable system. *Science*, **352**(6281), 61–67.

[5] Variankaval N., Cote A.S., Doherty M.F. (2008) From form to function: crystallization of active pharmaceutical ingredients. *AICHE Journal*, **54**(7), 1682–1688.

[6] Chen J., Sarma B., Evans J.M.B., Myerson A.S. (2011) Pharmaceutical crystallization. *Crystal Growth and Design*, **11**(4), 887–895.

[7] Florence A.J. (2009) The solid state, in *Modern Pharmaceutics*, 5th edn, vol. **1** (eds Florence A., Siepmann J.), Springer, New York, pp. 253–310.

[8] Winn D., Doherty M.F. (2000) Modeling crystal shapes of organic materials grown from solution. *Aiche J*, **46**(7), 1348–1367.

[9] Randolph A.D. (1969) Effect of crystal breakage on crystal size distribution in a mixed suspension crystallizer. *Industrial and Engineering Chemistry Fundamentals*, **8**(1), 58–63.

[10] Reddy C.M., Padmanabhan K.A., Desiraju G.R. (2006) Structure-property correlations in bending and brittle organic crystals. *Crystal Growth and Design*, **6**(12), 2720–2731.

[11] Brunsteiner M., Jones A.G., Pratola F. et al. (2005) Toward a molecular understanding of crystal agglomeration. *Crystal Growth and Design*, **5**(1), 3–16.

[12] Tavare N.S. (1986) Mixing in Continuous Crystallizers. *AICHE Journal*, **32**(5), 705–732.

[13] Castagnoli C., Yahyah M., Cimarosti Z., Peterson J.J. (2010) Application of quality by design principles for the definition of a robust crystallization process for casopitant mesylate. *Org Process Res Dev*, **14**(6), 1415–1427.

[14] Yu L.X. (2008) Pharmaceutical quality by design: Product and process development, understanding, and control. *Pharm Res*, **25**(4), 781–791.
[15] Jiang M., Wong M.H., Zhu Z. et al. (2012) Towards achieving a flattop crystal size distribution by continuous seeding and controlled growth. *Chemical Engineering Science*, **77**, 2–9.
[16] Lawton S., Steele G., Shering P. et al. (2009) Continuous crystallization of pharmaceuticals using a continuous oscillatory baffled crystallizer. *Organic Process Research and Development*, **13**(6), 1357–1363.
[17] Schaber S.D., Gerogiorgis D.I., Ramachandran R. et al. (2011) Economic analysis of integrated continuous and batch pharmaceutical manufacturing: a case study. *Industrial and Engineering Chemistry Research*, **50**(17), 10083–10092.
[18] McGlone T., Briggs N.E.B., Clark C.A. et al. (2015) Oscillatory flow reactors (OFRs) for continuous manufacturing and crystallization. *Organic Process Research and Development*, **19**(9), 1186–1202.
[19] Alvarez A.J., Singh A., Myerson A.S. (2011) Crystallization of cyclosporine in a multistage continuous MSMPR crystallizer. *Crystal Growth Des*, **11**(10), 4392–4400.
[20] Su Q., Nagy Z.K., Rielly C.D. (2015) Pharmaceutical crystallisation processes from batch to continuous operation using MSMPR stages: Modelling, design, and control. *Chemical Engineering and Processing: Process Intensification*, **89**, 41–53.
[21] Lai T.-T.C., Cornevin J., Ferguson S. et al. (2015) Control of polymorphism in continuous crystallization via mixed suspension mixed product removal systems cascade design. *Crystal Growth Des*, **15**(7), 3374–3382.
[22] Zhang H., Quon J., Alvarez A.J. et al. (2012) Development of continuous anti-solvent/cooling crystallization process using cascaded mixed suspension, mixed product removal crystallizers. *Org Process Res Dev*, **16**(5), 915–924.
[23] Ferguson S., Morris G., Hao H. et al. (2013) Characterization of the anti-solvent batch, plug flow and MSMPR crystallization of benzoic acid. *Chemical Engineering Science*, **104**, 44–54.
[24] Ricardo C., Xiongwei N. (2009) Evaluation and establishment of a cleaning protocol for the production of vanisal sodium and aspirin using a continuous oscillatory baffled reactor. *Organic Process Research and Development*, **13**(6), 1080–1087.
[25] Lobry E., Lasuye T., Gourdon C., Xuereb C. (2015) Liquid–liquid dispersion in a continuous oscillatory baffled reactor–application to suspension polymerization. *Chemical Engineering Journal*, **259**, 505–518.
[26] Konig C., Bechtold-Peters K., Baum V. et al. (2012) Development of a pilot-scale manufacturing process for protein-coated microcrystals (PCMC): Mixing and precipitation – Part I. *Eur J Pharm Biopharm*, **80**(3), 490–498.
[27] Alvarez A.J., Myerson A.S. (2010) Continuous plug flow crystallization of pharmaceutical compounds. *Cryst Growth Des*, **10**(5), 2219–2228.
[28] Eder R.J.P., Schrank S., Besenhard M.O. et al. (2012) Continuous sonocrystallization of acetylsalicylic acid (ASA): Control of crystal size. *Crystal Growth and Design*, **12**(10), 4733–4738.
[29] Narducci O., Jones A.G., Kougoulos E. (2011) Continuous crystallization of adipic acid with ultrasound. *Chemical Engineering Science*, **66**(6), 1069–1076.
[30] Eden R.J.P., Radl S., Schmitt E. et al. (2010) Continuously seeded, continuously operated tubular crystallizer for the production of active pharmaceutical ingredients. *Crystal Growth and Design*, **10**(5), 2247–2257.
[31] Wong S.Y., Tatusko A.P., Trout B.L., Myerson A.S. (2012) Development of continuous crystallization processes using a single-stage mixed-suspension, mixed-product removal crystallizer with recycle. *Crystal Growth Des*, **12**(11), 5701–5707.
[32] Wierzbowska B., Hutnik N., Piotrowski K., Matynia A. (2011) Continuous mass crystallization of vitamin C in L(+)-ascorbic acid-ethanol-water system: size-independent growth kinetic model approach. *Crystal Growth and Design*, **11**(5), 1557–1565.

[33] Quon J.L., Zhang H., Alvarez A. et al. (2012) Continuous crystallization of aliskiren hemifumarate. *Crystal Growth and Design*, **12**(6), 3036–3044.
[34] Wong S.Y., Cui Y.Q., Myerson A.S. (2013) Contact secondary nucleation as a means of creating seeds for continuous tubular crystallizers. *Crystal Growth and Design*, **13**(6), 2514–2521.
[35] Mersmann A. (2001) *Crystallization Technology Handbook*, 2nd edn, Marcel Dekker, New York.
[36] Mullin J.W. (2001) *Crystallization*, 4th edn, Butterworth-Heinemann, Oxford.
[37] Davey R.J., Garside J. (2000) *From Molecules to Crystallizers*, Oxford University Press, Oxford.
[38] Myerson A.S. (2002) *Handbook of Industrial Crystallization*, 2nd edn, Butterworth-Heinemann, Woburn.
[39] Gilbert S.W. (1991) Melt crystallization - process analysis and optimization. *AICHE Journal*, **37**(8), 1205–1218.
[40] Rittner S., Steiner R. (1985) Melt crystallization of organic-substances and its large-scale application. *Chem-Ing-Tech*, **57**(2), 91–102.
[41] Beckmann W. (2013) *Crystallization: Basic Concepts and Industrial Applications*, John Wiley & Sons, Ltd, Chichester.
[42] Saleemi A., Rielly C., Nagy Z.K. (2012) Automated direct nucleation control for in situ dynamic fines removal in batch cooling crystallization. *Crystengcomm*, **14**(6), 2196–2203.
[43] Brito A.B.N., Giulietti M. (2007) Study of lactose crystallization in water–acetone solutions. *Crystal Research and Technology*, **42**(6), 583–588.
[44] Muller F.L., Fielding M., Black S. (2009) A practical approach for using solubility to design cooling crystallisations. *Organic Process Research and Development*, **13**(6), 1315–1321.
[45] Lindenberg C., Krattli M., Cornel J. et al. (2009) Design and optimization of a combined cooling/antisolvent crystallization process. *Crystal Growth and Design*, **9**(2), 1124–1136.
[46] Nagy Z.K., Fujiwara M., Braatz R.D. (2008) Modelling and control of combined cooling and antisolvent crystallization processes. *Journal of Process Control*, **18**(9), 856–864.
[47] Jones H.P., Davey R.J., Cox B.G. (2005) Crystallization of a salt of a weak organic acid and base: Solubility relations, supersaturation control and polymorphic behavior. *J Phys Chem B*, **109**(11), 5273–5278.
[48] Kim S.T., Kwon J.H., Lee J.J., Kim C.W. (2003) Microcrystallization of indomethacin using a pH-shift method. *International Journal of Pharmaceutics*, **263**(1/2), 141–150.
[49] Mesbah A., Huesman A.E.M., Kramer H.J.M. et al. (2011) Real-time control of a semi-industrial fed-batch evaporative crystallizer using different direct optimization strategies. *AIChE Journal*, **57**(6), 1557–1569.
[50] Fages J., Lochard H., Letourneau J.J. et al. (2004) Particle generation for pharmaceutical applications using supercritical fluid technology. *Powder Technology*, **141**(3), 219–226.
[51] Söhnel O., Garside J. (1992) *Precipitation: Basic Principles and Industrial Applications*, Butterworth-Heinemann, London.
[52] Garside J., Davey R.J. (1980) Secondary contact nucleation – kinetics, growth and scale-up. *Chemical Engineering Communications*, **4**(4/5), 393–424.
[53] Mersmann A.S., R. ; Kind, M.; Pohlisch, J. (1988) Attrition and secondary nucleation in crystallizers. *Chem Eng Technol*, **11**(1), 80–88.
[54] Nývlt J. (1968) Kinetics of nucleation in solutions. *Journal of Crystal Growth*, **3**/4, 377–383.
[55] Sangwal K. (2011) Some features of metastable zone width of various systems determined by polythermal method. *Crystengcomm*, **13**(2), 489–501.
[56] Kashchiev D., Borissova A., Hammond R.B., Roberts K.J. (2010) Effect of cooling rate on the critical undercooling for crystallization. *Journal of Crystal Growth*, **312**(5), 698–704.

[57] Kobari M., Kubota N., Hirasawa I. (2013) Deducing primary nucleation parameters from metastable zone width and induction time data determined with simulation. *Crystengcomm*, **15**(6), 1199–1209.
[58] Larson M.A. (1981) Secondary nucleation – an analysis. *Chemical Engineering Communications*, **12**(1/3), 161–169.
[59] Chianese A., Diberardino F., Jones A.G. (1993) On the effect of secondary nucleation on the crystal size distribution from a seeded batch crystallizer. *Chemical Engineering Science*, **48**(3), 551–560.
[60] Brandel C., ter Horst J.H. (2015) Measuring induction times and crystal nucleation rates. *Faraday Discuss*, **179**, 199–214.
[61] Jiang S.F., ter Horst J.H. (2011) Crystal nucleation rates from probability distributions of induction times. *Crystal Growth and Design*, **11**(1), 256–261.
[62] Kulkarni S.A., Kadam S.S., Meekes H. et al. (2013) Crystal nucleation kinetics from induction times and metastable zone widths. *Crystal Growth and Design*, **13**(6), 2435–2440.
[63] Davey R.J., Back K.R., Sullivan R.A. (2015) Crystal nucleation from solutions – transition states, rate determining steps and complexity. *Faraday Discuss*, **179**, 9–26.
[64] Dunning W.J.S., A. J. (1954) Nucleation in sucrose solutions. *Proceedings of the Proc Agric Industries 10th International Conference*, pp. 19–24.
[65] Davey R.J.S., S. L. ; ter Horst, J. H. (2013) Nucleation of organic crystals – a molecular perspective. *Angew Chem Int Edn*, **52**(8), 2166–2179.
[66] Erdemir D., Lee A.Y., Myerson A.S. (2009) Nucleation of crystals from solution: classical and two-step models. *Accounts Chem Res*, **42**(5), 621–629.
[67] Briggs N.E.B. (2015) *Polymorph Control of Pharmaceuticals within a Continuous Oscillatory Baffled Crystalliser*. PhD thesis, University of Strathclyde, Glasgow.
[68] Beckman J.R., Randolph A.D. (1977) Crystal size distribution dynamics in a classified crystallizer: Part II. Simulated control of crystal size distribution. *AIChE Journal*, **23**(4), 510–520.
[69] Garside J., Jancic S.J. (1978) Prediction and measurement of crystal size distribution for size-dependent growth. *Chem Eng Sci*, **33**(12), 1623–1630.
[70] Garside J. (1985) Industrial crystallization from solution. *Chemical Engineering Science*, **40**(1), 3–26.
[71] Alander E.M., Rasmuson A.C. (2005) Mechanisms of crystal agglomeration of paracetamol in acetone–water mixtures. *Industrial and Engineering Chemistry Research*, **44**(15), 5788–5794.
[72] Kawashima Y., Imai A., Takeuchi H. et al. (2003) Improved flowability and compactibility of spherically agglomerated crystals of ascorbic acid for direct tableting designed by spherical crystallization process. *Powder Technology*, **130**(1/3), 283–289.
[73] Randolph A.D., Larson M.A. (1988) *Theory of Particulate Processes: Analysis and Techniques of Continuous Crystallization*, 2nd edn, Academic Press, London.
[74] Myerson A.S., Krumme M., Nasr M. et al. (2015) Control systems engineering in continuous pharmaceutical manufacturing. Continuous Manufacturing Symposium. *Journal of Pharmaceutical Sciences*, **104**(3), 832–839.
[75] Yang Y., Nagy Z.K. (2015) Combined cooling and antisolvent crystallization in continuous mixed suspension, mixed product removal cascade crystallizers: Steady-state and startup optimization. *Industrial and Engineering Chemistry Research*, **54**(21), 5673–5682.
[76] Bermingham S.K., Neumann A.M., Kramer H.J.M. et al. (2000) A design procedure and predictive models for solution crystallisation processes. *AICHE Sym S*, **96**(323), 250–264.
[77] Jolliffe H.G., Gerogiorgis D.I. (2015) Process modelling and simulation for continuous pharmaceutical manufacturing of ibuprofen. *Chem Eng Res Des*, **97**, 175–191.
[78] Vetter T., Burcham C.L., Doherty M.F. (2015) Designing robust crystallization processes in the presence of parameter uncertainty using attainable regions. *Industrial and Engineering Chemistry Research*, **54**(42), 10350–10363.

[79] Shaikh L.J., Bari A.H., Ranade V.V., Pandit A.B. (2015) Generic framework for crystallization processes using the population balance model and its applicability. *Industrial and Engineering Chemistry Research*, **54**(42), 1053948.
[80] Teoh S.K., Rathi C., Sharratt P. (2016) Practical Assessment Methodology for Converting Fine Chemicals Processes from Batch to Continuous. *Organic Process Research and Development*, **20**(2), 414-31.
[81] Cheng Y.S., Lam K.W., Ng K.M., Wibowo C. (2010) Workflow for Managing Impurities in an Integrated Crystallization Process. *Aiche Journal*, **56**(3), 633-49.
[82] ICH Guideline Q3C (R5) on Impurities: Guideline for Residual Solvents, (2011).
[83] Siddique H., Brown C.J., Houson I., Florence A.J. (2015) Establishment of a Continuous Sonocrystallization Process for Lactose in an Oscillatory Baffled Crystallizer. *Organic Process Research and Development*, **19**(12), 1871–1881.
[84] Kirwan D.J., Orella C.J. (2002) Crystallization in the pharmaceutical and bioprocessing industries, in *Handbook of Industrial Crystallization*, 2nd edn, (ed. Myerson A.S.), Butterworth-Heinemann, Woburn, pp. 249–266.
[85] Vetter T., Burcham C.L., Doherty M.F. (2014) Regions of attainable particle sizes in continuous and batch crystallization processes. *Chemical Engineering Science*, **106**, 167–180.
[86] Levenspiel O. (1999) *Chemical Reaction Engineering*, John Wiley & Sons, Ltd, Chichester.
[87] Powell K.A., Saleemi A.N., Rielly C.D., Nagy Z.K. (2015) Periodic steady-state flow crystallization of a pharmaceutical drug using MSMPR operation. *Chemical Engineering and Processing: Process Intensification*, **97**, 195–212.
[88] Chemaly Z., Muhr H., Fick M. (1999) Crystallization kinetics of calcium lactate in a mixed-suspension-mixed-product removal crystallizer. *Industrial and Engineering Chemistry Research*, **38**(7), 2803–2808.
[89] Ferguson S., Ortner F., Quon J. et al. (2014) Use of continuous MSMPR crystallization with integrated nanofiltration membrane recycle for enhanced yield and purity in API crystallization. *Crystal Growth and Design*, **14**(2), 617–627.
[90] Gerard A., Muhr H., Plasari E. et al. (2014) Effect of calcium based additives on the sodium bicarbonate crystallization in a MSMPR reactor. *Powder Technology*, **255**, 134–140.
[91] Hou G., Power G., Barrett M. et al. (2014) Development and characterization of a single stage mixed-suspension, mixed-product-removal crystallization process with a novel transfer unit. *Crystal Growth and Design*, **14**(4), 1782–1793.
[92] Yang Y., Song L., Gao T., Nagy Z.K. (2015) Integrated upstream and downstream application of wet milling with continuous mixed suspension mixed product removal crystallization. *Crystal Growth and Design*, **15**(12), 5879–5885.
[93] Kozik A., Hutnik N., Piotrowski K., Matynia A. (2014) Continuous reaction crystallization of struvite from diluted aqueous solution of phosphate(V) ions in the presence of magnesium ions excess. *Chemical Engineering Research and Design*, **92**(3), 481–490.
[94] Hutnik N., Piotrowski K., Wierzbowska B., Matynia A. (2011) Continuous reaction crystallization of struvite from phosphate(V) solutions containing calcium ions. *Crystal Research and Technology*, **46**(5), 443–449.
[95] Lai T.-T.C., Ferguson S., Palmer L. et al. (2014) Continuous crystallization and polymorph dynamics in the L-glutamic acid system. *Organic Process Research and Development*, **18**(11), 1382–1390.
[96] Tai C.Y., Shei W.-L. (1993) Crystallization kinetics and product purity of α-glutamic acid crystal. *Chemical Engineering Communications*, **120**(1), 139152.
[97] Wierzbowska B., Hutnik N., Piotrowski K., Matynia A. (2011) Continuous mass crystallization of vitamin c in l(+)-ascorbic acid−ethanol−water system: size-independent growth kinetic model approach. *Crystal Growth and Design*, **11**(5), 1557–1565.

[98] Wierzbowska B., Koralewska J., Piotrowski K. et al. (2008) Kinetic aspects of a continuous mode of mass crystallization of vitamin C in the L(+)-ascorbic acid-methanol-water system. *Chemical and Process Engineering*, **29**(2), 345–360.

[99] Wierzbowska B., Piotrowski K., Hutnik N., Matynia A. (2008) Continuous crystallization of vitamin C in L(+)-ascorbic acid-methanol-water system. An SDG kinetic model approach. *Chemical and Process Engineering*, **29**(4), 1083–1094.

[100] Wierzbowska B., Piotrowski K., Koralewska J. et al. (2009) Kinetics of nucleation and growth of L-sorbose crystals in a continuous MSMPR crystallizer with draft tube: Size-independent growth model approach. *Korean J Chem Eng*, **26**(1), 175–181.

[101] Power G., Hou G., Kamaraju V.K. et al. (2015) Design and optimization of a multistage continuous cooling mixed suspension, mixed product removal crystallizer. *Chemical Engineering Science*, **133**, 125–139.

[102] Peña R., Nagy Z.K. (2015) Process intensification through continuous spherical crystallization using a two-stage mixed suspension mixed product removal (MSMPR) system. *Crystal Growth and Design*, **15**(9), 4225–4236.

[103] Galan K., Eicke M.J., Elsner M.P. et al. (2015) Continuous preferential crystallization of chiral molecules in single and coupled mixed-suspension mixed-product-removal crystallizers. *Crystal Growth and Design*, **15**(4), 1808–1818.

[104] Zhao L., Raval V., Briggs N.E.B. et al. (2014) From discovery to scale-up: α-lipoic acid : nicotinamide co-crystals in a continuous oscillatory baffled crystalliser. *CrystEngComm*, **16**(26), 5769–5780.

[105] Brown C.J., Adelakun J.A., Ni X.-W. (2015) Characterization and modelling of antisolvent crystallization of salicylic acid in a continuous oscillatory baffled crystallizer. *Chemical Engineering and Processing: Process Intensification*, **97**, 180–186.

[106] Ferguson S., Morris G., Hao H. et al. (2012) In-situ monitoring and characterization of plug flow crystallizers. *Chemical Engineering Science*, **77**, 105–111.

[107] Briggs N.E.B., Schacht U., Raval V. et al. (2015) Seeded crystallization of β-L-glutamic acid in a continuous oscillatory baffled crystallizer. *Organic Process Research and Development*, **19**(12), 1903–1911.

[108] Eder R.J.P., Schmitt E.K., Grill J. et al. (2011) Seed loading effects on the mean crystal size of acetylsalicylic acid in a continuous-flow crystallization device. *Crystal Research and Technology*, **46**(3), 227–237.

[109] Tari T., Fekete Z., Szabó-Révész P., Aigner Z. (2015) Reduction of glycine particle size by impinging jet crystallization. *International Journal of Pharmaceutics*, **478**(1), 96–102.

[110] Jiang M., Li Y.-E.D., Tung H.-H., Braatz R.D. (2015) Effect of jet velocity on crystal size distribution from antisolvent and cooling crystallizations in a dual impinging jet mixer. *Chemical Engineering and Processing: Process Intensification*, **97**, 242–247.

[111] Ildefonso M., Revalor E., Punniam P. et al. (2012) Nucleation and polymorphism explored via an easy-to-use microfluidic tool. *Journal of Crystal Growth*, **342**(1), 9–12.

[112] Goyal S., Economou A.E., Papadopoulos T. et al. (2016) Solvent compatible microfluidic platforms for pharmaceutical solid form screening. *RSC Advances*, **6**(16), 13286–13296.

[113] Leng J., Salmon J.-B. (2009) Microfluidic crystallization. *Lab on a Chip*, **9**(1), 24–34.

[114] Ildefonso M., Candoni N., Veesler S. (2012) A Cheap, Easy Microfluidic Crystallization Device Ensuring Universal Solvent Compatibility. *Organic Process Research and Development*, **16**(4), 556–560.

[115] Zhang S., Ferté N., Candoni N., Veesler S. (2015) Versatile microfluidic approach to crystallization. *Organic Process Research and Development*, **19**(12), 1837–1841.

[116] Simon L.L., Pataki H., Marosi G. et al. (2015) Assessment of recent process analytical technology (pat) trends: a multiauthor review. *Organic Process Research and Development*, **19**(1), 3–62.

[117] Barrett P., Smith B., Worlitschek J. et al. (2005) A review of the use of process analytical technology for the understanding and optimization of production batch crystallization processes. *Organic Process Research and Development*, **9**(3), 348–355.
[118] Nagy Z.K., Fevotte G., Kramer H., Simon L.L. (2013) Recent advances in the monitoring, modelling and control of crystallization systems. *Chem Eng Res Des*, **91**(10), 1903–1922.
[119] Yu L.5., Lionberger R.A., Raw A.S. et al. (2004) Applications of process analytical technology to crystallization processes. *Advanced Drug Delivery Reviews*, **56**(3), 349–369.
[120] Billot P., Couty M., Hosek P. (2010) Application of ATR-UV spectroscopy for monitoring the crystallisation of UV absorbing and nonabsorbing molecules. *Organic Process Research and Development*, **14**(3), 511–523.
[121] Helmdach L., Feth M.P., Ulrich J. (2013) Integration of process analytical technology tools in pilot-plant setups for the real-time monitoring of crystallizations and phase transitions. *Organic Process Research and Development*, **17**(3), 585–598.
[122] Saleemi A.N., Rielly C.D., Nagy Z.K. (2012) Monitoring of the combined cooling and antisolvent crystallisation of mixtures of aminobenzoic acid isomers using ATR-UV/vis spectroscopy and FBRM. *Chemical Engineering Science*, **77**, 122–129.
[123] Henry M., Puel F.E., Perrichon P.D. et al. (2008) SGGP 2007 – Understanding and modelling of crystallization mechanisms by in-situ analytical technologies monitoring. *Int J Chem React Eng*, **6**, 11–14.
[124] Pollanen K., Hakkinen A., Reinikainen S.P. et al. (2005) IR spectroscopy together with multivariate data analysis as a process analytical tool for in-line monitoring of crystallization process and solid-state analysis of crystalline product. *J Pharmaceut Biomed*, **38**(2), 275–284.
[125] Pataki H., Markovits I., Vajna B. et al. (2012) In-line monitoring of carvedilol crystallization using Raman spectroscopy. *Crystal Growth and Design*, **12**(11), 5621–5628.
[126] Qu H.Y., Louhi-Kultanen M., Kallas J. (2007) Additive effects on the solvent-mediated anhydrate/hydrate phase transformation in a mixed solvent. *Crystal Growth and Design*, **7**(4), 724729.
[127] Scholl J., Bonalumi D., Vicum L. et al. (2006) In situ monitoring and modeling of the solvent-mediated polymorphic transformation of L-glutamic acid. *Crystal Growth and Design*, **6**(4), 881–891.
[128] Barrett M., McNamara M., Hao H.5. et al. (2010) Supersaturation tracking for the development, optimization and control of crystallization processes. *Chem Eng Res Des*, **88**(8A), 1108–1119.
[129] Duffy D., Barrett M., Glennon B. (2013) Novel, calibration-free strategies for supersaturation control in antisolvent crystallization processes. *Crystal Growth and Design*, **13**(8), 3321–3332.
[130] Gron H., Borissova A., Roberts K.J. (2003) In-process ATR-FTIR spectroscopy for closed-loop supersaturation control of a batch crystallizer producing monosodium glutamate crystals of defined size. *Industrial and Engineering Chemistry Research*, **42**(1), 198–206.
[131] Liotta V., Sabesan V. (2004) Monitoring and feedback control of supersaturation using ATR-FTIR to produce an active pharmaceutical ingredient of a desired crystal size. *Organic Process Research and Development*, **8**(3), 488–494.
[132] Pataki H., Csontos I., Nagy Z.K. et al. (2013) Implementation of Raman signal feedback to perform controlled crystallization of carvedilol. *Org Process Res Dev*, **17**(3), 493–499.
[133] Abu Bakar M.R., Nagy Z.K., Saleemi A.N., Rielly C.D. (2009) The impact of direct nucleation control on crystal size distribution in pharmaceutical crystallization processes. *Crystal Growth and Design*, **9**(3), 1378–1384.
[134] Saleemi A.N., Steele G., Pedge N.I. et al. (2012) Enhancing crystalline properties of a cardiovascular active pharmaceutical ingredient using a process analytical technology based crystallization feedback control strategy. *International Journal of Pharmaceutics*, **430**(1/2), 56–64.
[135] Chen Z.P., Morris J., Martin E. (2005) Correction of temperature-induced spectral variations by loading space standardization. *Anal Chem*, **77**(5), 1376–1384.

[136] Du W., Chen Z.P., Zhong L.J. et al. (2011) Maintaining the predictive abilities of multivariate calibration models by spectral space transformation. *Anal Chim Acta*, **690**(1), 64–70.
[137] Rajalahti T., Kvalheim O.M. (2011) Multivariate data analysis in pharmaceutics: A tutorial review. *International Journal of Pharmaceutics*, **417**(1/2), 280–290.
[138] Haaland D.M. (2000) Synthetic multivariate models to accommodate unmodeled interfering spectral components during quantitative spectral analyses. *Appl Spectrosc*, **54**(2), 246–254.
[139] Swierenga H., Wulfert F., de Noord O.E. et al. (2000) Development of robust calibration models in near infra-red spectrometric applications. *Anal Chim Acta*, **411**(1/2), 121–135.
[140] Wang Y.D., Kowalski B.R. (1993) Temperature-compensating calibration transfer for near-infrared filter instruments. *Anal Chem*, **65**(9), 1301–1303.
[141] Wulfert F., Kok W.T., Smilde A.K. (1998) Influence of temperature on vibrational spectra and consequences for the predictive ability of multivariate models. *Anal Chem*, **70**(9), 1761–1767.
[142] Barring H.K., Boelens H.F.M., de Noord O.E., Smilde A.K. (2001) Optimizing meta-parameters in continuous piecewise direct standardization. *Appl Spectrosc*, **55**(4), 458–466.
[143] Wulfert F., Kok W.T., de Noord O.E., Smilde A.K. (2000) Correction of temperature-induced spectral variation by continuous piecewise direct standardization. *Anal Chem*, **72**(7), 1639–1344.
[144] Chen Z.P., Morris J. (2008) Improving the linearity of spectroscopic data subjected to fluctuations in external variables by the extended loading space standardization. *Analyst*, **133**(7), 914–922.
[145] Lewiner F., Klein J.P., Puel F., Fevotte G. (2001) On-line ATR FTIR measurement of supersaturation during solution crystallization processes. Calibration and applications on three solute/solvent systems. *Chemical Engineering Science*, **56**(6), 2069–2084.
[146] Dunuwila D.B., K.A. (1996) ATR FTIR spectroscopy for in situ analysis of crystallization. *Proceedings 13th Symposium on Industrial Crystallization*, ATR, Toulouse, pp. 45–54.
[147] Dunuwila D.D., Berglund K.A. (1997) ATR FTIR spectroscopy for in situ measurement of supersaturation. *Journal of Crystal Growth*, **179**(1/2), 185–193.
[148] Groen H.R., K. J. (1999) Application of ATR FTIR spectroscopy for on-line determination of solute concentration and solution supersaturation. *Proceedings 14th International Symposium on Industrial Crystallization*, FTR, Cambridge, pp.65–67.
[149] Simone E., Saleemi A.N., Tonnon N., Nagy Z.K. (2014) active polymorphic feedback control of crystallization processes using a combined raman and ATR-UV/Vis spectroscopy approach. *Crystal Growth and Design*, **14**(4), 1839–1850.
[150] Borissova A., Khan S., Mahmud T. et al. (2009) In situ measurement of solution concentration during the batch cooling crystallization of L-glutamic acid using ATR-FTIR spectroscopy coupled with chemometrics. *Crystal Growth and Design*, **9**(2), 692–706.
[151] Barrett P., Glennon B. (2002) Characterizing the metastable zone width and solubility curve using lasentec FBRM and PVM. *Chem Eng Res Des*, **80**(A7), 799–805.
[152] Kougoulos E., Jones A.G., Wood-Kaczmar M.W. (2005) Modelling particle disruption of an organic fine chemical compound using Lasentec focussed beam reflectance monitoring (FBRM) in agitated suspensions. *Powder Technology*, **155**(2), 153–158.
[153] Yu Z.Q., Tan R.B.H., Chow P.S. (2005) Effects of operating conditions on agglomeration and habit of paracetamol crystals in anti-solvent crystallization. *Journal of Crystal Growth*, **279**(3/4), 477–488.
[154] Abu Bakar M.R., Nagy Z.K., Rielly C.D. (2010) Investigation of the effect of temperature cycling on surface features of sulfathiazole crystals during seeded batch cooling crystallization. *Crystal Growth and Design*, **10**(9), 3892–3900.
[155] Worlitschek J., Mazzotti M. (2004) Model-based optimization of particle size distribution in batch-cooling crystallization of paracetamol. *Cryst Growth Des*, **4**(5), 891–903.

[156] Agimelen O.S., Hamilton P., Haley I. et al. (2015) Estimation of particle size distribution and aspect ratio of non-spherical particles from chord length distribution. *Chemical Engineering Science*, **123**, 629–640.
[157] Nagy Z.K., Braatz R.D. (2012) Advances and new directions in crystallization control. *Annu Rev Chem Biomol Eng*, **3**, 55–75).
[158] Tachtatzis C., Sheridan R., Michie C. et al. (2015) Image-based monitoring for early detection of fouling in crystallisation processes. *Chemical Engineering Science*, **133**, 82–90.
[159] Myerson A. (2002) *Handbook of Industrial Crystallization*, Elsevier Science, London.
[160] Braatz R.D. (2002) Advanced control of crystallization processes. *Annual Reviews in Control*, **26** I, 87–99.
[161] Fujiwara M., Nagy Z.K., Chew J.W., Braatz R.D. (2005) First principles and direct design approaches for the control of pharmaceutical crystallization. *Journal of Process Control*, **15**(5), 493–504.
[162] Nagy Z.K. (2009) Model based robust control approach for batch crystallization product design. *Computers and Chemical Engineering*, **33**(10), 1685–1691.
[163] Jones A.G., Mullin J.W. (1974) Programmed cooling crystallization of potassium sulphate solutions. *Chemical Engineering Science*, **29**(1), 105–118.
[164] Mullin J.W., Nývlt J. (1971) Programmed cooling of batch crystallizers. *Chemical Engineering Science*, **26**(3), 369–377.
[165] Nagy Z.K., Braatz R.D. (2012) Advances and new directions in crystallization control. *Annual Review of Chemical and Biomolecular Engineering*, **3**, 55–75.
[166] Corriou J.P., Rohani S. (2008) A new look at optimal control of a batch crystallizer. *AIChE Journal*, **54**(12), 3188–3206.
[167] Sarkar D., Rohani S., Jutan A. (2006) Multi-objective optimization of seeded batch crystallization processes. *Chemical Engineering Science*, **61**(16), 5282–5295.
[168] Worlitschek J., Mazzotti M. (2004) Model-based optimization of particle size distribution in batch-cooling crystallization of paracetamol. *Crystal Growth and Design*, **4**(5), 891–903.
[169] Woo 5.Y., Tan R.B.H., Chow P.S., Braatz R.D. (2006) Simulation of mixing effects in antisolvent crystallization using a coupled CFD-PDF-PBE approach. *Crystal Growth and Design*, **6**(6), 1291–1303.
[170] Mesbah A., Huesman A.E.M., Kramer H.J.M., Van Den Hof P.M.J. (2011) A comparison of nonlinear observers for output feedback model-based control of seeded batch crystallization processes. *Journal of Process Control*, **21**(4), 652–666.
[171] Nagy Z.K., Chew J.W., Fujiwara M., Braatz R.D. (2008) Comparative performance of concentration and temperature controlled batch crystallizations. *Journal of Process Control*, **18**(3/4), 399–407.
[172] Saleemi A.N., Rielly C.D., Nagy Z.K. (2012) Comparative investigation of supersaturation and automated direct nucleation control of crystal size distributions using ATR-UV/vis spectroscopy and FBRM. *Crystal Growth andand Design*, **12**(4), 1792–1807.
[173] Nagy Z.K., Fevotte G., Kramer H., Simon L.L. (2013) Recent advances in the monitoring, modelling and control of crystallization systems. *Chemical Engineering Research and Design*, **91**(10), 1903–1922.
[174] Nagy Z.K., Aamir E. (2012) Systematic design of supersaturation controlled crystallization processes for shaping the crystal size distribution using an analytical estimator. *Chemical Engineering Science*, **84**, 656–670.
[175] Cao Y., Kariwala V., Nagy Z.K. (2012) Parameter estimation for crystallization processes using Taylor method. *Proceedings of the Advanced Control of Chemical Processes*, **2012**, 18–27.
[176] Nagy Z.K. (2009) Model based robust control approach for batch crystallization product design. *Computers andand Chemical Engineering*, **33**(10), 1685–1691.
[177] Threlfall T.L. (1995) Analysis of organic polymorphs – a review. *Analyst*, **120**(10), 2435–2460.

[178] Yu L., Reutzel S.M., Stephenson G.A. (1998) Physical characterization of polymorphic drugs: an integrated characterization strategy. *Pharmaceutical Science and Technology Today*, **1**(3), 118–127.

[179] Page T., Dubina H., Fillipi G. et al. (2015) Equipment and analytical companies meeting continuous challenges. Continuous Manufacturing Symposium. *Journal of Pharmaceutical Sciences*, **104**(3), 821–831.

6

Continuous Fermentation for Biopharmaceuticals?

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6.1 Introduction

6.1.1 Definition of Fermentation

A fermentation process can be described as the chemical breakdown of a substrate through the metabolism of a microorganism [1]. The substrate is converted to biomass and product through the aerobic or anaerobic metabolism of the microorganism, all depending on the composition of substrate and product, and the fermentation conditions that are applied. Fermentations are carried out in either batch, fed-batch, or continuous mode, depending on the required volumetric productivity, and the host system.

Fermentation processes are utilized for the production of bulk chemicals, fine chemicals, and pharmaceuticals [2, 3]. Some of the noteworthy bulk chemicals produced by fermentation are ethanol from sugar or lignocellulosic material, and 1,3-propanediol from glucose. The production of α-amylase with *Sacharomyces cerevisiae* is an example of how microorganisms can produce fine chemicals such as enzymes from glucose as feedstock [4]. In terms of value, pharmaceuticals and biopharmaceuticals present the largest market of products produced by fermentation, among which monoclonal antibodies, Erythropoietin (EPO) and human insulin should be mentioned as well-established example processes.

Continuous Manufacturing of Pharmaceuticals, First Edition.
Edited by Peter Kleinebudde, Johannes Khinast, and Jukka Rantanen.
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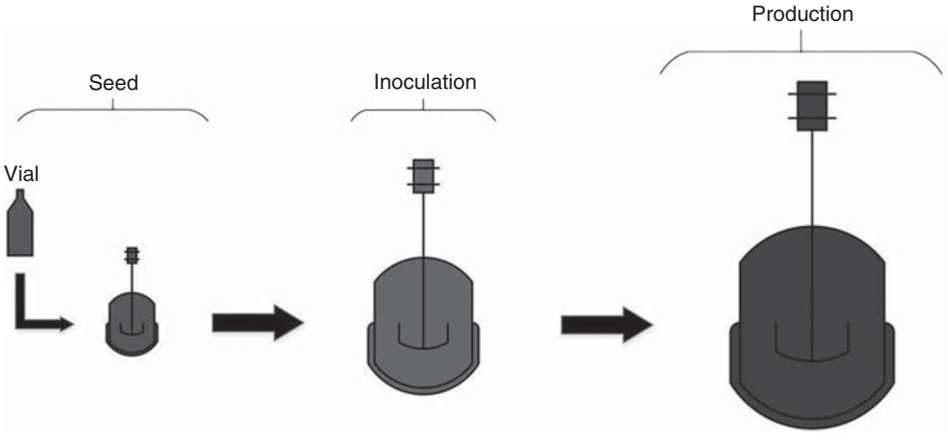

Figure 6.1 *Typical fermentation train of biopharmaceuticals from seed to industrial production.*

6.1.2 Production of Biopharmaceuticals

The market size for fermentation products differs tremendously between technologies, as does the product value. For instance 80 000 kt of ethanol is produced every year, giving a market of € 40 billion, whereas 1 kt of biopharmaceuticals are produced every year with a market size of € 55 billion [5]. The contrast in the required annual volumetric production exemplifies the special requirements for the production of biopharmaceuticals. Due to the magnitude of the desired volumetric production rate, biopharmaceuticals are usually produced in considerably smaller bioreactors compared to bulk chemicals [6]. A typical production of a biopharmaceutical is depicted in Figure 6.1.

A large portion of the efforts invested in process development is in fact focused on strain development. The production strain, which has undergone extensive metabolic engineering, is preserved in a uniform cell bank of vials which are frozen and ready to be used to seed each production train. The seed fermentation stage provides optimal conditions for the initial growth of this inoculum, which is slow to grow as it adapts to the growth environment after freezing. Once a certain cell density is reached, a second batch process follows in order to produce sufficient cell mass to inoculate the production scale vessel. The key performance indicators change during this production scheme from growth rate and cell viability in the seed and inoculum tanks, to product titer and quality in the production vessel [6].

6.1.3 Structure of Chapter

The focus of this chapter is on the potential for the production of biopharmaceuticals utilizing continuous fermentations with microbial systems. However, the use of mammalian cell culture is excluded from this review in order to reduce and focus the scope of the chapter.

The chapter covers operational aspects specific to fermentation processes and compares the process types to show the benefits and challenges of implementing a continuous system. This also includes a discussion of process monitoring and control considerations. Continuous operation is then the focus for the rest of the chapter, where a review is made of

continuous fermentation processes applied at an industrial scale. As there are only limited applications of continuous operations for the production of biopharmaceutical products, the comparison is made to other fermentation products, which are operated in continuous processes on an industrial scale.

In fact, the only well-known example of continuous production of biopharmaceuticals on an industrial scale is the production of human insulin with baker's yeast; a production process operated by Novo Nordisk. Since there are so few examples of the production of biopharmaceuticals using continuous fermentation processes with microbial systems, the final section of this chapter focuses on trying to find an explanation for this situation.

The production of biopharmaceuticals from mammalians cells will not be reviewed in detail in this chapter, as it differs greatly from continuous fermentation. However, a small review of products produced from perfusion systems is included as inspiration for further study of the topic.

6.2 Operation of Fermentation Systems

6.2.1 Comparison of Different Cultivation Systems

This section compares the typical modes of operation: batch, fed-batch, and continuous. An overview of the advantages and disadvantages can be found in Section 6.2.1.5.

6.2.1.1 Batch Fermentation

In a batch fermentation, all substrates and nutrients required in the process are available at the time of inoculation. There is no inflow of new medium to the reactor, nor is there an outflow from the reactor (Figure 6.2). It is often assumed that batch reactors maintain a constant volume, but practically this is not the case due to acid/base addition for pH control and evaporation due to aeration. Reactor conditions are dynamic, as the substrate concentration decreases over time and the product and biomass concentrations increase.

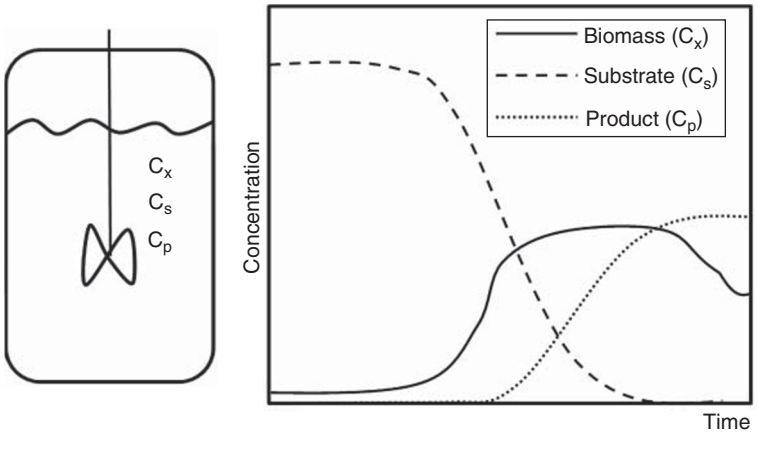

Figure 6.2 *Schematic overview of a batch fermentation, where there are no medium flows entering or leaving the reactor.*

Substrate and product inhibition can be major issues, as at the start of the fermentation substrate concentrations are high, and at the end of the fermentation product concentrations are high. Another disadvantage is significant downtime, since the operation is relatively short, and cleaning is required between each batch.

The major advantages of a batch fermentation are the easy set-up and operation, and the process robustness [7]. There is also a low risk of contamination as the fermentation is operated as a closed system.

Mass balance for batch fermentations for component *i*:

$$\frac{\mathrm{d}V_L\, C_i}{\mathrm{d}t} = \pm q_i C_x V_L \tag{6.1}$$

6.2.1.2 Fed-batch Fermentation

A fed-batch fermentation usually starts with a short phase of batch operation. Once this initial load of substrate is depleted, a feed is started in which fresh substrate is fed to the reactor, as shown in Figure 6.3. The feeding regime allows for control of production and consumption rates in the reactor, as the substrate concentration fed to the reactor is usually a limiting factor in the bioprocess. This also means that substrate inhibition can be controlled. There may be a controller implemented to regulate the rate of feed addition, or a predefined feed trajectory is applied. As there is no flow out of the reactor, product inhibition could still be an issue. In fact, it has a larger influence in fed-batch fermentations than in batch fermentations, as the end concentration of the product is typically significantly higher in fed-batch operation. Higher cell densities can also be reached than in batch fermentations [7].

Due to constant inflow and no outflow, the reactor volume increases over time, and fill level should be managed. Due to the flexibility of substrate addition and reactor filling in the fed-batch vessel, this production mode is highly adaptable to different processes. It may therefore be suitable in cases where multiple products are produced in the same facility. As

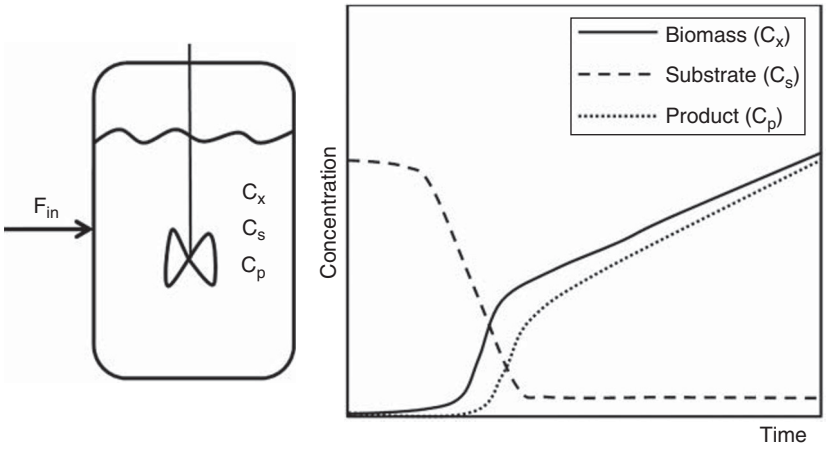

Figure 6.3 *Schematic overview of a fed-batch fermentation, where there is a feed entering the reactor, but no flow leaving the reactor.*

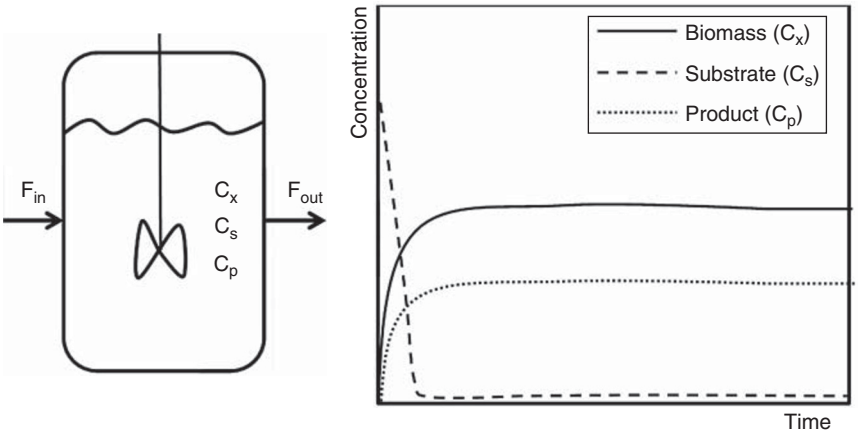

Figure 6.4 *Schematic overview of a continuous fermentation, where there is a feed entering the reactor, and a flow leaving the reactor.*

with batch operation, there is significant reactor down time, since the operation is relatively short, and cleaning is required between each batch.

Mass balance for fed-batch fermentations for component *i*:

$$\frac{\mathrm{d}V_L\, C_i}{\mathrm{d}t} = \pm F_{in} C_{i,in} \pm q_i C_x V_L \tag{6.2}$$

6.2.1.3 Continuous Fermentation

In a continuous fermentation there is a constant inflow of medium into the bioreactor and a constant outflow of fermentation broth containing biomass and product from the bioreactor [8], as shown in Figure 6.4. The process is often operated such that the volume of the reactor remains constant, with a fixed flow rate in and out of the reactor, meaning that production and consumption rates remain constant over time, assuming a steady state. This operation is referred to as a chemostat [9]. If the substrate is the rate-limiting factor, then the growth rate of the organism is determined by the rate of feed addition, relative to the volume. In this case, F_{in}/V_L is referred to as the dilution rate. Other alternative operation strategies include a turbidostat, whereby the dilution rate is fixed in order to achieve a fixed biomass concentration at the outlet, or an auxostat, whereby the dilution rate is fixed in order to control a process condition to a fixed value, for example, pH [9].

Both substrate and product inhibition can be overcome by continuous operation, since the substrate is fed continuously over time and therefore the concentration can be kept low, while the product is continuously removed from the reactor. Since the product is continuously removed, there is also the benefit of a short residence time for the product, which is favorable when the product has limited stability [10]. This may be especially relevant to biopharmaceutical products.

Other major advantages of continuous fermentations compared to (fed-)batch fermentations are the high volumetric efficiency and conversion rates [11]. This in turn reduces the capital costs and maintenance costs [12]. It is possible to run the continuous process for a

much longer time, and therefore reduce the downtime. There is also a practical advantage of operating continuously in order to combine with a continuously operated downstream process for continuous product purification.

Another practical benefit to consider for fermentation processes is the ease of scale up. Due to the productivity increase, smaller vessels can be used for continuous processes. This then means that it is in principle possible to have the same vessels for pilot and commercial scale, meaning faster process development [13]. Scale up is a common challenge surrounding fermentation technologies.

The major disadvantages of continuous operation comprise operational costs and robustness. There are increased operational costs due to greater medium requirements. Due to feed addition, there is also an increased risk of contamination for a continuous fermentation. Another major issue can be the higher probability of mutation due to the longer operational time, which also decreases the robustness of the process [7]. There are also challenges in order to operate and control a continuously operated system, as discussed in more detail in the following section.

Mass balance for continuous fermentations for component *i*:

$$\frac{\mathrm{d}V_L\, C_i}{\mathrm{d}t} = \pm F_{in} C_{i,in} - F_{out} C_{i,out} \pm q_i C_x V_L \tag{6.3}$$

6.2.1.4 Continuous Biopharmaceutical Fermentations

When considering continuous fermentation processes for the production of pharmaceutical products, the major advantage is the short residence time in the fermenter. Due to the constant outflow from the reactor, the product residence time is low. This is advantageous for biopharmaceutical production, as there may be low protein stability under the conditions in the reactor, and the product may be degraded over time [10].

6.2.1.5 Summary

Table 6.1 provides a summary of the operational considerations for the three reactor configurations discussed.

6.2.2 Monitoring of Continuous Fermentation Processes

The previous section introduces some operational considerations for the continuous process. This is now extended to focus on monitoring, which is of importance in order to control

Table 6.1 *Comparison of the three cultivation modes*

	Batch	Fed-batch	Continuous
Substrate inhibition	High	Low	Low
Product inhibition	High	High	Low
Cell density	Low	High	High
Capital costs	High	High	Low
Operational costs	Low	Low	High
Robustness	High	High	Low

and optimize the process. Key parameters of interest are usually the substrate, product, and biomass concentrations, as these parameters will give a direct insight into the performance of the bioreactor.

6.2.2.1 Sampling

The monitoring of bioreactors can be either off-line, on-line, or at-line [14]. Off-line monitoring involves the extraction of samples from the reactor and relocation to analytical devices, which are usually located in a separate laboratory. There can be a considerable gap between the time when the sample is taken and the time the sample is analyzed. With at-line monitoring, on the other hand, samples extracted from the reactor are analyzed immediately afterwards. The last monitoring option is on-line, where probes are inserted into the reactor, and measure a signal in real-time. Examples of widely used on-line probes are the pH probe and the temperature probe. A specific fermentation process related challenge is that on-line probes need to be sufficiently robust in order to withstand a sterilization of the bioreactor content.

6.2.2.2 Real-Time Monitoring

Real-time monitoring is preferable in comparison to off-line monitoring, due to the manual labour requirements and the slow response time associated with off-line monitoring. Real-time monitoring can give direct information on the operating conditions inside the bioreactor, which is beneficial for control, optimization, and validation of the bioprocess [15]. This is in agreement with the process analytical technology (PAT) regulations issued by the United States Food and Drug Administration (FDA) [16]. However, real-time monitoring of biopharmaceutical fermentations is also under strict regulations, as all changes to a bioreactor set-up involve risks. The most commonly used monitoring devices measure the pH, the temperature (both with on-line probes), the dissolved oxygen (DO) concentration, and the off-gas composition. In addition, the carbon evolution rate (CER), and the oxygen uptake rate (OUR), can be calculated based on off-gas analysis, to gain insight into the process characteristics. This can give an insight into the metabolic state of the system, although it is not a direct measure of the system state. For this, direct monitoring of specific components in the broth is needed, a topic which has gained increasing attention over the last years, as there is a high variety of on-line probes which can measure various substrates, products and biomass concentrations. Real-time monitoring can be performed either on-line, with probes inside the reactor (*in situ*), or at-line, where sampling is automated, and the samples are directly led to a measuring device.

6.2.2.3 On-line Probes

Many reviews have been written on the application of different probes for the monitoring of bioprocesses. Cervera *et al.* [17] have written an extensive review on near-infrared spectroscopy, which is able to detect a wide variety of compounds in the near-infrared (NIR) region. One of the major disadvantages of this technique is the interference caused by solid particles, such as biomass, but also gas bubbles. Another interfering substance is water, which dominates the spectrum when NIR is used on a fermentation broth.

Furthermore, extensive calibration is required to overcome these interferences. Other spectroscopy probes available are mid-infrared spectroscopy (MIR) [18], Raman spectroscopy [19], fluorescence spectroscopy [20], and dielectric spectroscopy [21]. MIR and Raman spectroscopy are also able to detect substrates and products dissolved in the liquid phase. While MIR has similar disadvantages as NIR, Raman spectroscopy experiences less interference but is also significantly more expensive than the former two techniques. Fluorescence spectroscopy can monitor biological compounds, such as NADH, on-line, which can result in the biomass, substrate, and product concentrations through chemometric modeling. Dielectric spectroscopy can monitor the biomass concentration by sending out an electric field and measuring the cell capacitance. The most often published biomass monitoring methods have been compared to each other by Kiviharju *et al*. [22], showing that it depends on the type of process which method would be the most suitable.

The above-mentioned methods are promising to increase the knowledge of what is happening inside a reactor, and thus gain a significant amount of control of the process. However, so far only dielectric spectroscopy is widely used at the industrial scale [23], mainly in the beer industry [21].

6.2.2.4 Applications in Continuous Fermentations

Besides the "standard" measurements of the pH, the temperature, DO, CER, and OUR, it is also necessary to monitor the weight of the bioreactor during continuous fermentation. This is of importance in order to control the flow rates in and out of the reactor [24]. Another aspect of biopharmaceutical fermentations is that it is desired to measure the protein concentration. Product purity can be analyzed by measuring the host cell protein populations through enzyme-linked immunosorbent assays with polyclonal antibodies [23]. The main advantage of this method is that low concentrations can be detected. However, a disadvantage is that non-immunoreactive proteins cannot be detected by this method. A second method, usually SDS-PAGE or another method involving polyacrylic gels, is needed to detect these proteins.

6.2.3 Control of Continuous Fermentation Processes

The previous section highlights the issue of measurement availability in a typical fermentation process. This, therefore, causes challenges for process modeling and control. This section discusses the application of modeling tools to bioprocesses and continues to discuss the considerations for control of continuous fermentation processes.

6.2.3.1 Modeling for Control Applications

Advanced control strategies require a process model which then forms the basis for calculating the control action. For industrial fermentation, only a certain level of model complexity is realistic based on the available measured parameters to base the model on, and the level of understanding of the dynamics of the process. Typical model states and model inputs are shown in Table 6.2, which relates to the previous discussion of available measurement technologies. As previously discussed, there is a lack of on-line sensors for key parameters,

Table 6.2 *Model inputs, disturbances and states for a typical fermentation process*

Input/disturbances	States
Feed rate	Biomass concentration
Feed concentration	Product concentration
DO	Substrate concentration
pH	Volume
Temperature	
CER	
OUR	

such that important process states such as the biomass and the product concentration are not measured in real-time.

Fermentation modeling may be based on both empirical methods and mechanistic principles. [25]. Empirical methods can be useful when there is a lack of understanding of the underlying mechanisms, and are often used in an initial phase to modeling, and which can be incorporated into a mechanistic relation when further understanding exists. Mechanistic models are more generic representations in comparison to empirical relations, which are often only applicable to certain operating conditions [25]. Due to a lack of measurements, soft sensor approaches can be used in order to estimate some of the important state variables [26]. With the aid of such modeling techniques, it is possible to implement more complex monitoring and control methods which aid the development of continuous fermentation processes.

Modeling and control of biological processes is challenging due to the highly non-linear dynamics, such that model parameters are not constant, but are instead dependent on the state of the process [27]. This is especially applicable when discussing the feed rate, as small changes in input can drive the system to a different operating point [28]. An example of this is overfeeding with substrate, which may cause the organism to produce unwanted by-products due to an excess of it [29]. This is very hard to model, due to the complex nature of metabolic pathway structures, and a lack of understanding of the system dynamics. In addition it is not possible to measure the state variables with the standard probes used. This is the challenge to overcome in order to maintain a steady operating condition in a continuous system.

6.2.3.2 Typical Control Variables

The control problem for a fermentation process typically involves regulation of pH, dissolved oxygen tension, temperature, and feed rate. These parameters are highly interdependent, due to the dynamics of cell growth.

Figure 6.5 shows the highly interdependent nature of the fermentation system. This suggests a multivariate control system is highly desirable in order to regulate these variables, while taking into account the effect on the system as a whole. In order to properly model the system dynamics, it must also be possible to characterize the input feed, in terms of feed concentration as well as flow rate. If a model-based control system is to be implemented, then there must be characterization of the effect of input disturbances on the system.

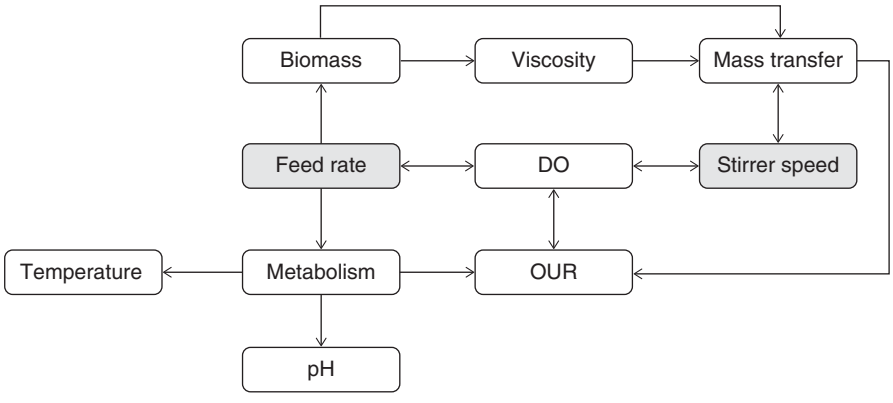

Figure 6.5 *Interdependency between fermentation parameters, highlighting the challenge of fermentation modeling and control. DO in the center is a typical control variable; gray shading indicates typical manipulated variables.*

This control problem can be approached with multiple methods, and there are examples in the literature of continuous fermentation control applications, although predominantly at laboratory scale [30]. In addition, a key consideration for any control system applied to continuous operation is also the start-up and shut-down procedures, in order to reach the desired operating point, and then to end the operation in a stable manner [31].

6.2.3.3 Control Structure for a Continuous Process

Continuous operation is not achievable without sufficient process control to ensure a stable operating condition where the process parameters are all within the constraints of the process, despite system disturbances. The nature of industrial processes, with disturbances and measurement noise, means that steady-state operation is an ideal description; however, the operation point should be stable with respect to the input disturbances. This requires a more complex control approach which considers wider system boundaries than the single unit operation, referred to as plant-wide control [32] (Figure 6.6).

The regulation of the desired control variables by use of in-line measurements is considered the "regulatory control layer" for the process. This typically involves proportional integral derivative (PID) control systems to regulate manipulated variables based on a set point. This control layer operates on a time-scale of seconds and is the primary control layer, ensuring the product quality and reproducibility of the process.

Due to the highly interdependent nature of bioprocess variables, it may not be possible to independently control multiple states in the system. The implementation of a supervisory control layer is therefore required. This updates the set points to the regulatory layer, in order to adapt to system disturbances and achieve the optimal condition across the multiple states.

An optimization control layer then considers the plant-wide operation. This is in order to schedule the unit operations and avoid bottlenecks in the processing, and also to operate each unit operation taking into account any available knowledge of the operation state from

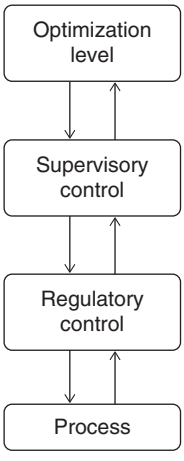

Figure 6.6 *Plant-wide control structure.*

the upstream process [13]. In addition to this, there are demands on throughput in order to achieve the product demand. This layer then sends desired set points for the regulatory control layer, with a time-scale in the order of hours [32].

The final level of control considers the overall profitability and scheduling of the plant, since the continuous operation of the fermentation process means there are requirements to integrate the upstream and downstream processes.

In order to achieve these control objectives, it is first necessary to have sufficient knowledge of the system, in the form of measurements and models in order to predict the current states in the process and the process response to changes in input. This is an area where the biopharmaceutical industry lags behind other industries [33]. The development of models for biological systems is challenging due to highly non-linear dynamics and a lack of mechanistic understanding of process phenomena. Modeling is the primary stage in control strategy development.

6.2.3.4 Control for Continuous Biopharmaceutical Production Processes

One of the challenges of implementing a continuous process is the need for more complex control systems. Although this is a challenge for process development, the application of advanced control strategies can be a powerful tool since their use is in line with the Quality by Design (QbD) requirements as defined by the FDA [34, 35]. The regulatory demands on process monitoring and control in the pharmaceutical industry are highly stringent, so there is great interest in bioprocess monitoring and control in order to meet these demands. This may be considered as an additional driver for the pharmaceutical industry specifically.

The QbD regulations require that critical quality attributes (CQAs) are defined for the process and product [34]. The allowable variation range of these CQAs is defined to create a product design space, where the quality of the product can be assured if the CQAs are controlled within these allowable limits. This shows that the use of advanced control strategies can be a complementary tool in a QbD approach to manufacturing.

6.3 Continuous Fermentation Examples

This section discusses the application of continuous fermentation in three different industries; ethanol fermentation, lactic acid fermentation, and single cell protein production. As previously discussed, there are few examples of the production of biopharmaceuticals using continuous fermentation processes with microbial systems at an industrial scale. This section instead investigates which products are produced industrially by continuous fermentation systems. The process characteristics can then be compared to the requirements for a pharmaceutical process, to determine the feasibility of this operation mode.

6.3.1 Continuous Ethanol Fermentation

Bioethanol is certainly the most valuable renewable fuel regarding its current and future application in the transportation sector. In 2014 about 97 billion liters of fuel alcohol were produced worldwide [36]. Ethanol is biologically synthesized through fermentation from sugars, starch, and lignocellulosic biomass by employing several types of yeast and some bacteria. *S. cerevisiae* is, by far, the most commonly used strain [37], mostly due to characteristics such as high ethanol tolerance and anaerobic metabolism.

Fed-batch and continuous fermentation processes are widely used within the industrial ethanol industry. In Brazil, 30% of ethanol manufacturing plants utilize continuous fermentation processes. This operation mode is preferred for economic reasons [38]. In a typical continuous ethanol manufacturing process, raw materials such as sugar cane, beet juice, molasses, and saccharified corn, are continuously fed to a fermentation tank. At the same time, part of the medium contained in the cultivation vessel is withdrawn. A cascade of stirred bioreactors is employed and, to reach higher cell concentration, yeasts are usually recovered using a storage tank downstream of the bioreactor cascade and partially recycled (Figure 6.7). Both fermentation and distillation are carried out simultaneously to maintain low sugar and ethanol concentration inside the fermenter. In this way, the inhibitory effect of high sugar levels on ethanol production is considerably reduced.

Nevertheless, a suitable alternative to suspended cells is proper cell immobilization. This approach gives a further increase in the yeast cell concentration within the fermenters. The immobilization of yeast cells on a supporting material involves both technical and economic disadvantages during an ethanol fermentation process [39]. Taking advantage of the spontaneous flocculation of yeast cells, Hsiao *et al*. proposed the concept of self-immobilized cells

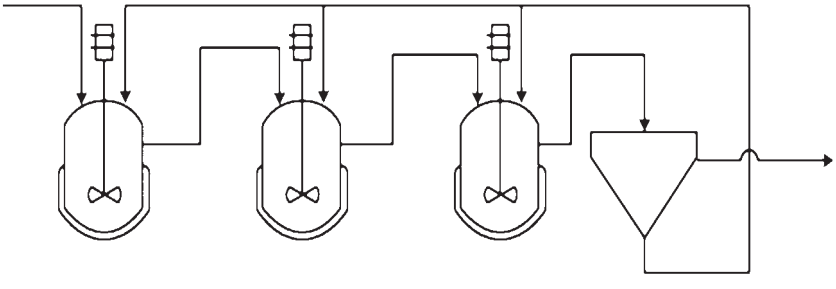

Figure 6.7 *Schematic representation of a continuous ethanol fermentation process with yeast recirculation.*

[40]. Self-immobilization of yeast cells has been proven to be an effective way to solve the drawbacks arising from the immobilization on supporting materials. The self-flocculating yeast cells can be retained in each fermenter due to gravity while the broth can flow out of the upstream fermenters to the next downstream vessel at a controllable rate. Compared with ethanol fermentation with free yeast cells, where recovery must be made by centrifugation or filtration, yeast flocks can be recovered by sedimentation from the fermentation broth. In this way, both the capital investment of more complex separation devices and the energy consumption related to the operation of the more costly equipment is saved [41].

The design and operation of bioreactors suitable for continuous ethanol fermentation with self-immobilized yeast cells can be challenging. Two main prerequisites should be met for a proper bioreactor design; homogeneous suspension and the effective immobilization of yeast flocs within the fermenter. To fulfill these technical requirements Bai *et al.* [41] validated a cultivation system called a suspended-bed bioreactor (SBR). This type of cultivation system was developed in analogy to the tower fermenters already employed in the continuous brewing manufacturing process [42]. In 2005, an SBR system was successfully scaled-up and a commercial fuel ethanol plant with a total cultivation volume of 1000 m^3 and an overall production capacity of 200 Mt/year was established. The operation of this fuel ethanol plant has been an important platform for demonstrating the advantages of a cultivation system with self-immobilized yeast cells. In fact, its efficiency was validated with respect to both immobilized yeast cells on supporting materials and free yeast cells [39].

6.3.2 Continuous Lactic Acid Fermentation

Lactic acid can be produced by microbial fermentation or by chemical synthesis. Due to the benefits of optically pure product, gentle processing conditions, and cheap renewable feedstock, a vast majority of lactic acid is produced by fermentation [43]. Microbial lactic acid can be produced by several microorganisms such as bacteria, yeast, fungi, cyanobacteria, and algae. Among them, *Lactobacillus delbrueckii* is considered the most efficient producer strain [44]. Due to the increasing popularity of polylactic acid (PLA) as biodegradable plastic, it is highly desired to reduce the cost of lactic acid production as an intermediate in the manufacturing of biobased polymers. This will lead to a lower cost of obtaining PLA that will help in expanding the market share and range of applications for this interesting biomaterial. In 2003 the Cargill (Dow) fermentation process for lactic acid manufacturing, the NatureWorks™ process, was ready for large-scale production. With a capacity of about 190 Mt/year of lactic acid obtained from the fermentation of dextrose, this process permits the relatively low-cost continuous production of lactic acid-based PLA [45].

The lactic acid fermentation industry is a mature, developed sector. Nevertheless, continuous production of lactic acid has not yet shown a significant advantage with respect to batch or fed-batch cultivation systems. Indeed, the potential of continuous lactic acid production needs to be further explored. One promising direction is in the development of a new generation of integrated membrane bioreactors that could be employed in multi-stage high cell density continuous cultivation systems [46]. Such a system would allow the production of lactic acid with a titer equivalent to the fed-batch, but with much higher productivity than in the semi-continuous mode. Therefore, a drastic reduction of the high production costs involved in the actual process could be obtained [41].

6.3.3 Single Cell Protein Production

Proteins and amino acids are essential food ingredients for humans and animals. Soya beans and fish have been important sources of protein for animal feed. In turn, the animals have served as protein sources in human nutrition. The rapidly increasing world population generates the challenge of providing necessary food sources. In particular protein supply poses a problem since essential amino acids cannot be replaced. One possible solution to this problem is single cell protein (SCP) production.

The protein content in *Methylococcus capsulatus* is high and often referred to as SCP. The microorganism *M. capsulatus* can grow on cheap carbon sources such as methane and methanol. The SCP is produced by fermentation and hydrolysis of *M. capsulatus* using methanol, oxygen, nitric acid, and minerals as the feedstock. The dried biomass contains up to 70% protein, having a good amino acid profile. The protein can be used as animal food.

Unlike many other biochemicals, SCP is a commodity product. Therefore, it is essential that the production of SCP is energy and nutrient efficient and can be produced at a high yield. The cultivation normally involves several basic process engineering operations, such as stirring and mixing of a multi-phase system (gas–liquid–solid), transport of oxygen from the gas bubbles through the liquid phase to the microorganisms, and heat transfer from the liquid phase to the surroundings. One of the main problems in the production of SCP is the mass transfer of oxygen from the supplied gas to the liquid media, as well as the efficient recovery of the biomass. An attractive future alternative to classical fermentation systems is the cultivation of the organism in a continuous U-loop reactor, as shown in Figure 6.8.

The principle of the U-loop reactor is to continuously circulate a part of the fermentation medium in the U-loop. When the medium is sent through the loop, it is saturated with oxygen and substrate. Oxygen is added by a jet into the system, and in addition static mixers

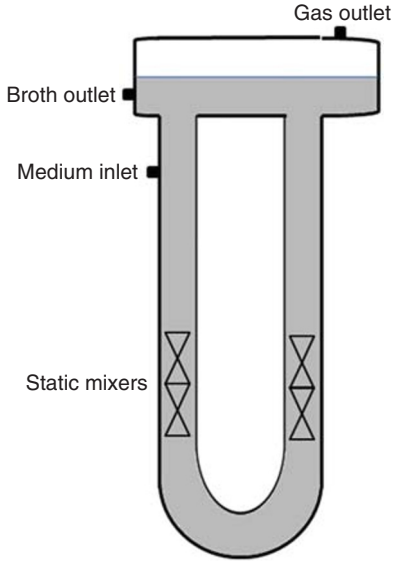

Figure 6.8 *Schematic diagram of a U loop reactor.*

are placed not far from the injection point to break up the bubbles of oxygen and possibly also methane. This increases the mass transfer of oxygen from the gas to the liquid phase. The top tank functions as a separator where the gas is released from the outlet [47]. A cooling jacket is installed around the loop to remove the metabolic heat from the system. *M. capsulatus* is sensitive to the temperature, pH, and substrate concentration. Thus there is a risk of process instability and further washout as a consequence of disturbances during process operation. Therefore, good control is needed to maximize the biomass produced, by employing the methodology discussed in Section 2. Industrial scale production of SCP was established by the company Norferm A/S.

6.4 Discussion

The prospects and challenges of utilizing continuous fermentation to produce biopharmaceuticals is discussed in this final section of this chapter, with emphasis on the required process knowledge compared with batch or fed-batch fermentation. Further, the area of applicability of continuous fermentations is assessed in this section.

An important observation is indeed that continuous cultivation is the exception, not the rule, for the production of biopharmaceuticals using microbial systems. One could, of course, wonder about a potential explanation for this important observation, which stands in contrast to the fact that continuous fermentation can have a number of important process advantages (Table 6.1). One possible explanation is the fact that the pharmaceutical industry in general, and that, of course, includes the production of biopharmaceuticals, is extremely focused on having a short time to market strategy [48]. This means that once a drug candidate is approved, it has to be made available to the customers as soon as possible, in order to maximally exploit the remaining patent lifetime of a drug candidate. As a result of the short time to market thinking, there is usually extensive focus on host strain development, in order to gain the highest possible expression levels for the drug candidate. An increased expression level has advantages from a production process point of view since it potentially leads to a substantial reduction in the downstream processing cost. Process development, especially for the fermentation, is usually done relatively fast, in order to have – as soon as possible – sufficient product available for marketing of the drug candidate. As a result, the process development of fermentation processes usually ends up with rather traditional solutions relying on either batch or fed-batch fermentation (Figure 6.9).

Another important factor is the capital cost investment required as well. Table 6.1 shows that continuous production has an advantage in this aspect compared to batch and fed-batch production. However, that comparison is valid when an entirely new process has to be installed. In many cases, existing equipment is used for starting up a new batch or fed-batch production process, and if that is the case, batch and fed-batch operation have a clear advantage, of course, since only limited capital investment will be needed to start up a new production in already existing batch or fed-batch bioreactor equipment compared to building a completely new continuous fermentation plant [13, 51].

Production volume is also an important element that can explain the limited implementation of continuous process technology for the fermentation of biopharmaceuticals [51]. The examples given above illustrate that it was relatively easy to find examples of continuous fermentation processes for production of several bulk chemicals, that is, altogether

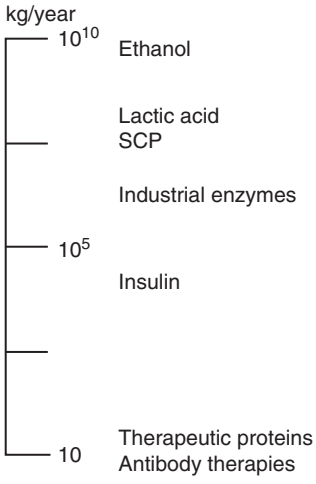

Figure 6.9 *Annual global production of fermentation products referenced in this work. [49, 50].*

production processes with a large production volume. The same can be said for the production of human insulin using fermentation, which is produced in continuous mode: human insulin is a blockbuster product, and that might be one of the factors explaining why continuous production was chosen. It is sometimes difficult to predict, due to the fact that there often are competing products treating the same disease, whether a drug candidate will become a blockbuster drug. This uncertainty about the required future production capacity can also contribute to the fact that process development usually results in more traditional batch or fed-batch process solutions [13].

An important observation is that continuous cultivation is much more established for production systems based on mammalian cells [52]. Although this topic is beyond the scope of this chapter, a summary is provided in Table 6.3.

Continuous fermentation processes have the advantage that they can be controlled rather tightly, which is certainly an advantage in terms of delivering a constant product quality [31]. However, also here, the time required to develop a suitable control strategy, including potentially the time required to introduce novel on-line measurement equipment on a production process is, in our opinion, often perceived as a major hurdle that stands in the

Table 6.3 *A short review of commercial continuous perfusion cultures for biopharmaceuticals produced from mammalian cell culture*

Name	Product	Type	Reference
Myozyme®	Alglucosidase alpha	Enzyme	[52]
Kogenate®	Antihemophilic factor VIII	Protein	[53]
STELARA®	Ustekinumab	Antibody	[54]
Cerezyme®	Beta-glucocerebrosidase	Enzyme	[55]
Remicade®	Infliximab	Antibody	[56]
Simulect®	Basiliximab	Antibody	[52]

way for potential development of a continuous fermentation process. Batch processes are usually recipe-driven, that is, only limited on-line measurement is required. Fed-batch processes are usually operated using rather simple control strategies, where the main focus is on controlling the feed rate.

6.5 Conclusions

This chapter provides an overview of continuous fermentation processes with the aim of discussing their application to biopharmaceutical products. This covers both technical process characteristics and cost considerations. An overview of continuous fermentation processes shows that there are few examples of continuous biopharmaceutical production, with insulin production being one known exception. In the discussion, we also consider the risk of implementing a change of paradigm, away from traditional batch or fed-batch processing, and towards a fully integrated continuous production process. Due to these business challenges, and the nature of the pharmaceutical industry, we highlight a number of reasons why, we believe, continuous operation is not adopted more widely in the pharmaceutical industry for production of biopharmaceuticals. These areas of consideration are summarized in Figure 6.10.

It is very unlikely that the current situation will be changed. That is: will we see a development of considerably more continuous fermentation processes using microbial systems for the production of biopharmaceuticals? The answer to this question is: most probably not.

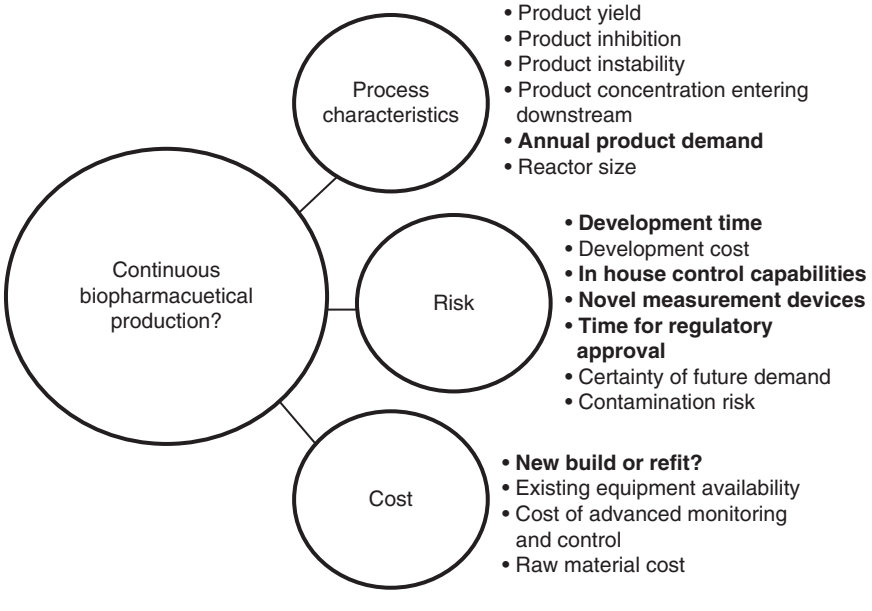

Figure 6.10 *Considerations for development of a continuous process for biopharmaceutical production. In bold are the key terms we believe limit the application of continuous processes for production of biopharmaceuticals.*

References

[1] von Stockar U, Maskow T, Liu J, Marison IW, Patiño R (2006) Thermodynamics of microbial growth and metabolism: an analysis of the current situation. *J Biotechnol* **121**:517–533.

[2] Brethauer S, Wyman CE (2010) Review: Continuous hydrolysis and fermentation for cellulosic ethanol production. *Bioresour Technol* **101**:4862–4874.

[3] Will HHC (2011) A brief history of perfusion. *Bioprocess Int* **9**:24–30.

[4] Headon DR, Walsh G (1994) The industrial production of enzymes. *Biotechnol Adv* **12**:635–646.

[5] Jiménez-González C, Poechlauer P, Broxterman QB, et al (2011) Key green engineering research areas for sustainable manufacturing: A perspective from pharmaceutical and fine chemicals manufacturers. *Org Process Res Dev* **15**:900–911.

[6] Li F, Vijayasankaran N, Shen A, Kiss R, Amanullah A (2010) Cell culture processes for monoclonal antibody production. *MABS* **2**:466–479.

[7] Thiry M, Cingolani D, Thiry M (2002) Optimizing scale-up fermentation processes. *Biotechnol Lett* **20**:103–105.

[8] Heijnen JJ, Terwisscha van Scheltinga A H, Straathof A J (1992) Fundamental bottlenecks in the application of continuous bioprocesses. *J Biotechnol* **22**:3–20.

[9] Villadsen J, Nielsen J, Lidén G (2011) *Bioreaction Engineering Principles*. Springer, Heidelberg.

[10] Vogel JH, Nguyen H, Giovannini R, Ignowski J, Garger S, Salgotra A, Tom J (2012) A new large-scale manufacturing platform for complex biopharmaceuticals. *Biotechnol Bioeng* **109**:3049–3058.

[11] Verbelen PJ, De Schutter DP, Delvaux F, Verstrepen KJ, Delvaux FR (2006) Immobilized yeast cell systems for continuous fermentation applications. *Biotechnol Lett* **28**:1515–1525.

[12] Cheryan M, Mehaia MA (1983) A high-performance membrane bioreactor for continuous fermentation of lactose to ethanol. *Biotechnol Lett* **5**:519–524.

[13] Cooney CL, Konstantinov KB (2014) White paper 4 – continuous bioprocessing. *Int Symp Contin Manuf Pharm* **2014**: 1–13.

[14] Carloni A, Turner APF (2010) *Bioprocess Monitoring*. In: Flickinger MC (ed.) Encycl. Ind. Biotechnol. Bioprocess, Biosep. Cell Technol. John Wiley & Sons, Inc., New York, pp. 1–18.

[15] Schügerl K (2001) Progress in monitoring, modeling and control of bioprocesses during the last 20 years. *J Biotechnol* **85**:149–173.

[16] Rathore a. S, Bhambure R, Ghare V (2010) Process analytical technology (PAT) for biopharmaceutical products. *Anal Bioanal Chem* **398**:137–154.

[17] Cervera AE, Petersen N, Lantz AE, Larsen A, Gernaey K V. (2009) Application of near-infrared spectroscopy for monitoring and control of cell culture and fermentation. *Biotechnol Prog* **25**:1561–1581.

[18] Roychoudhury P, Harvey LM, McNeil B (2006) The potential of mid infrared spectroscopy (MIRS) for real time bioprocess monitoring. *Anal Chim Acta* **571**:159–166.

[19] Iversen J a, Berg RW, Ahring BK (2014) Quantitative monitoring of yeast fermentation using Raman spectroscopy. *Anal Bioanal Chem* **406**:4911–4919.

[20] Marose S, Lindemann C, Ulber R, Scheper T (1999) Optical sensor systems for bioprocess monitoring. *Trends in Biotech* **17**:30–34.

[21] Asami K (2002) Characterization of biological cells by dielectric spectroscopy. *J Non Cryst Solids* **305**:268–277.

[22] Kiviharju K, Salonen K, Moilanen U, Eerikäinen T (2008) Biomass measurement online: The performance of in situ measurements and software sensors. *J Ind Microbiol Biotechnol* **35**:657–665.

[23] Champion K, Madden H, Dougherty J, Shacter E (2005) Defining Your product profile and maintaining control over it, part 2. *Bioprocess Int* **2005**:52–57.

[24] Kim DY, Yim SC, Lee PC, Lee WG, Lee SY, Chang HN (2004) Batch and continuous fermentation of succinic acid from wood hydrolysate by Mannheimia succiniciproducens MBEL55E. *Enzyme Microb Technol* **35**:648–653.
[25] Gernaey K V, Lantz AE, Tufvesson P, Woodley JM, Sin G (2010) Application of mechanistic models to fermentation and biocatalysis for next-generation processes. *Trends Biotechnol* **28**:346–354.
[26] Sagmeister P, Wechselberger P, Jazini M, Meitz A, Langemann T, Herwig C (2013) Soft sensor assisted dynamic bioprocess control: Efficient tools for bioprocess development. *Chem Eng Sci* **96**:190–198.
[27] Lübbert A, Simutis R (1994) Using measurement data in bioprocess modelling and control. *Trends Biotechnol* **12**:304–311.
[28] Montague G., Morris AJ, Bush JR (1987) Fermentation process control: considerations in control scheme development. *1987 American Control Conference*, pp. 44–48.
[29] Alford JS (2006) Bioprocess control: Advances and challenges. *Comput Chem Eng* **30**:1464–1475.
[30] Maher M, Dahhou B, Zeng FY (1995) Experimental results in model reference adaptive estimation and control of a fermentation process. *Control Eng Pract* **3**:313–320.
[31] Myerson AS, Krumme M, Nasr M, Thomas H, Braatz RD (2014) White Paper 6 -- control systems engineering in continuous pharmaceutical manufacturing. *Int Symp Contin Manuf Pharm* **2014**:1–10.
[32] Larsson T, Skogestad S (2000) Plantwide control – A review and a new design procedure. *Bioresour Technol* **91**:209–240.
[33] Sonnleitner B (2013) Automated measurement and monitoring of bioprocesses: key elements of the M3C strategy. *Adv Biochem Eng Biotechnol* **132**:1–33.
[34] FDA (2004) *PAT – A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance*. FDA, Rockville.
[35] Rathore AS, Winkle H (2009) Quality by design for biopharmaceuticals. *Nat Biotechnol* **27**:26–34.
[36] Renewable fuels Association (2014) *World Fuel Ethanol Production*. Available at: http://ethanolrfa.org/pages/World-Fuel-Ethanol-Pro (accessed 2 February 2017).
[37] Walker GM (2010) Bioethanol: science and technology of fuel alcohol. *Bioresour Technol* **101**:3272–3287.
[38] Sánchez ÓJ, Cardona C a. (2008) Trends in biotechnological production of fuel ethanol from different feedstocks. *Bioresour Technol* **99**:5270–5295.
[39] Zhao XQ, Bai FW (2009) Yeast flocculation: New story in fuel ethanol production. *Biotechnol Adv* **27**:849–856.
[40] Hsiao HY, Chiang LC, Yang CM, Chen LF, Tsao GT (1983) Preparation and performance of immobilized yeast cells in columns containing no inert carrier. *Biotechnol Bioeng* **25**:363–375.
[41] Bai FW, Anderson W a., Moo-Young M (2008) Ethanol fermentation technologies from sugar and starch feedstocks. *Biotechnol Adv* **26**:89–105.
[42] Seddon, A. W (1975) Continuous tower fermentation – experiences in establishing large scale commercial production. *Tech Quarterly, Master Brew Assoc Am* **12**:130–137.
[43] Abdel-Rahman MA, Tashiro Y, Sonomoto K (2013) Recent advances in lactic acid production by microbial fermentation processes. *Biotechnol Adv* **31**:877–902.
[44] Li T, Chen X, Chen J-C, Wu Q, Chen G-Q (2014) Open and continuous fermentation: Products, conditions and bioprocess economy. *Biotechnol J* **9**:1503–1511.
[45] Villadsen J (2007) Innovative technology to meet the demands of the white biotechnology revolution of chemical production. *Chem Eng Sci* **62**:6957–6968.
[46] Chang HN, Jung K, Choi J-D-R, Lee JC, Woo H-C (2014) Multi-stage continuous high cell density culture systems: a review. *Biotechnol Adv* **32**:514–525.

[47] Prado-Rubio O a., Jørgensen JB, Jørgensen SB (2010) Systematic model analysis for single cell protein (SCP) production in a U-loop reactor. *Comput Aided Chem Eng* **28**:319–324.
[48] Hansen KRN, Grunow M (2015) Planning operations before market launch for balancing time-to-market and risks in pharmaceutical supply chains. *Int J Prod Econ* **161**:129–139.
[49] Doran PM (2013) Bioprocess Engineering Principles. *Bioprocess Eng Princ*. Available at: doi: 10.1016/B978-0-12-220851-5.00016-2 (accessed 2 February 2016).
[50] Heinzle E, Biwer AP, Cooney CL (2007) *Development of Sustainable Bioprocesses: Modeling and Assessment*. John Wiley & Sons, Ltd, London.
[51] Croughan MS, Konstantinov KB, Cooney C (2015) The future of industrial bioprocessing: Batch or continuous? *Biotechnol Bioeng* **112**: 301–319.
[52] Pollock J, Ho S V, Farid SS (2013) Fed-batch and perfusion culture processes: economic, environmental, and operational feasibility under uncertainty. *Biotechnol Bioeng* **110**:206–219.
[53] Shapiro AD (2007) Anti-hemophilic factor (recombinant), plasma/albumin-free method (octocog-alpha; ADVATE) in the management of hemophilia A. *Vasc Health Risk Manag* **3**:555–565.
[54] European Medicines Agency (2009) *Assessment Report for Stelara*. European Medicines Agency, Paris.
[55] Whitford WG (2013) Supporting continuous processing with advanced single-use technologies. *BioProcess International* **28**:17–25.
[56] Abhinav AS, Etzel MR, Gadam S (2006) *Process Scale Bioseparations for the Biopharmaceutical Industry*. CRC Press, London.

7

Integrated Continuous Manufacturing of Biopharmaceuticals

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7.1 Background

7.1.1 Current Status of Manufacturing of Biopharmaceuticals

Currently, the manufacturing of biopharmaceuticals is mainly performed in a batch-wise operation for reasons for that are manifold. Manufacturing processes have evolved from the biochemist's/molecular biologist's laboratory during the drug discovery phase. Traditionally in such laboratories, the cultivation of cells and purification is performed in very small scale in a batch-wise manner. At this stage of development, process optimization is not a priority. The ultimate goal is speed and short time to market. Development time is indeed the critical factor in the biopharmaceutical industry. At more advanced stages of development of a biopharmaceutical, for example, early clinical phase, there is still no incentive to switch to continuous manufacturing. In the past only a few products have been manufactured continuously. In particular, we refer to the continuous production of labile blood coagulation factors, which is based on a perfusion process. Apart from the instability of the product there was no need for a continuous process. Indeed companies did not see any necessity to produce in a continuous manner. In addition to a lack of economic incentive, four other obstacles prevented continuous production of proteins in the past. These are instability of the cell line, batch definition, high cost of media, and not fully functional

Continuous Manufacturing of Pharmaceuticals, First Edition.
Edited by Peter Kleinebudde, Johannes Khinast, and Jukka Rantanen.
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cell retention devices. Media supplements were a major reason for malfunctioning in these devices. Early cell culture products were produced with media supplemented with fetal calf serum and progressive fouling was observed. In a conventional process the production starts from the working cell bank, ideally every time from a single cell. These cells are expanded in the laboratory and then transferred to seed bioreactors and from there to the production reactor. Such reactors have a volume up to 25 m^3 for mammalian cells and up to 40 m^3 for microbial cells. The broth is typically harvested by centrifugation. For secreted cell culture systems the product is further purified and concentrated by a sequence of chromatography and membrane filtration steps. In cases where mammalian cells are used for production, two orthogonal, dedicated virus inactivation steps must be implemented. Other unit operations are rarely used for this class of products. For intra-cellular products mainly produced by microbial cells, cell disruption is performed by high pressure homogenization, and in the case of products deposited as inclusion bodies also a refolding and oxidation step is included. PEGylation of proteins is also a common step [55]. Often PEG is conjugated to a protein in order to either increase half-life or shield antigenic domains in a protein. Flocculation, precipitation, and crystallization are also used for downstream processing, but to a lesser extent than chromatography and membrane filtration [62]. A cationic surface is always included in downstream processing of recombinant proteins. Anion-exchange chromatography material or membranes efficiently bind host cell DNA and endotoxins, because of their negative charge.

A full-scale continuous process for a biological product has been in operation for many years for a non-recombinant product. The Scottish Blood Transfusion Center and the Cutter Laboratories in Berkeley, California, had a licensed factory for the continuous manufacturing of blood plasma proteins using cold ethanol precipitation, also known as Cohn fractionation [13, 50]. The continuous manufacturing plant was in operation for many years. The basic technology was continuous precipitation using a CSTR. Even a continuous thawing process for FVIII-containing cryoprecipitate has been implemented [26]. The plant in Scotland was closed because the health authorities requested a narrow residence time distribution due to potential harm by TSE-contaminated plasma. This request could not be fulfilled in a short time because the CSTR had inherently a very wide residence time distribution. Reconfiguration was too time-consuming, and therefore the production was converted into batch mode.

However, continuous biomanufacturing gained momentum in the past few years on a general basis. The discussion was initiated in part by the FDA [40], but also the continuous manufacturing initiative at MIT swapped to biomanufacturing. The company Genzyme pioneered the field by establishing a fully continuous manufacturing train from the production bioreactor to the final purified product [83]. Also the supply industry has realized that continuous manufacturing will be the next generation process for biopharmaceuticals and therefore they have started to provide equipment to run unit operations (semi-)continuously.

Several companies have already started to gradually change their mode of operation. First of all by the parallelization of product trains. When production is performed with multiple trains in a staggered mode, a pseudo-continuous process is realized. In large-scale production of recombinant antibodies this way of production is very common. Although the individual unit operations are performed in batch, the product is harvested in a cyclic pseudo-continuous manner. Typically, up to six bioreactors operate in a staggered manner feed one downstream train. A lot of economic benefit achievable through continuous

manufacturing is already gained by this mode of operation. Establishing this kind of hybrid process is the beginning of a gradual transfer from batch mode towards continuous manufacturing.

Another step towards continuous manufacturing is the so-called straight-through or seamless processing. As shown in Figure 7.1 especially downstream processing is achieved by the interconnection of a lot of unit operations, which consist mainly of chromatographic steps. Often the eluate of a chromatographic separation cannot be loaded to the next one without prior conditioning. When the different product streams of the individual unit operations are directly interconnected, seamless or straight-through processing is achieved. This is also a prerequisite for an efficient continuous process, although it is possible to convert the conditioning steps also to a continuous mode.

7.1.2 Challenges to Developing Continuous Processes

A very basic definition of the adjective "continuous" describes something that occurs over space or time without interruption. In the case of manufacturing, continuous means the production of a biopharmaceutical with the same quality attributes over a certain period of time without interruption. At the end of the production process the product must be divided into small portions, because the pharmaceutical is administered in discrete units in clearly defined doses. Each dose must be related to a certain batch. This was considered to be an obstacle for the implementation of continuous manufacturing by the industry in the beginning, but there is a clear regulatory framework available today. A batch/lot is laid down in the code of the United States Federal Regulations (21 CFR 210.3) as follows:

> "A batch is a specific quantity of a drug or other material that is intended to have uniform character and quality within specified limits, and is produced according to a single manufacturing order during the same cycle of manufacture. A batch refers to the quantity of material and does not specify the mode of manufacture."

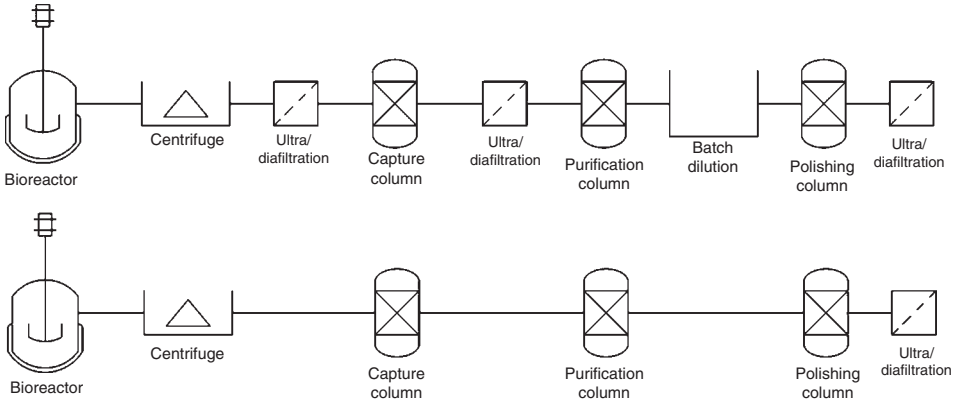

Figure 7.1 *Comparison of a hypothetical process for manufacturing of a biopharmaceutical with a conventional process (top) and a seamless process (bottom). The seed bioreactors are not shown.*

This legal framework is backing all efforts to manufacture in a continuous manner. It is the manufacturer who determines a batch/lot at the product collection step. It can simply be defined by either the production time period or a certain amount of product. In batch mode the process is by definition in a transient state. In continuous manufacturing steady state is not a prerequisite, but leads to very robust processes. It is sufficient that the system is not disturbed.

The biggest challenge in continuous biomanufacturing is the stability of the cell line. A cell changes its genetic and epigenetic imprint after each division [38, 76]. At the end of the production phase we do not have the same distribution of cell types as at the beginning. This happens in batch production as well as in continuous production. Numerous attempts have been made to improve the stability of expression cell lines [4, 47]. As a consequence, nowadays processes can be established which run stably for 60 days.

A major challenge when several unit operations are coupled is the propagation of disturbances from one unit operation to the next. This problem can only be dealt with by small buffer (surge) tanks/bags. This adds extra costs for tanks/bags or needs advanced process controls in the system.

For a continuous process in-line and on-line sensors are required, which are preferably non-destructive. Such sensors are not readily available. The continuous process offers the advantage of feedback and feed-forward control and therefore very robust systems can be established.

Another challenge for continuous manufacturing is process development. Currently scale-down equipment is often not commercially available. In case of tubular reactors it is not possible to work in the same flow regime as in large reactors. It is almost impossible to generate a turbulent flow in a capillary. With modern computational tools such as computational fluid dynamics, however, we can avoid a lot of experimental work and the optimal theoretical solution found in silico only needs to be verified in the laboratory or pilot plant.

7.1.3 Rationale for Continuous Biomanufacturing

Several reasons have been brought up as incentives for continuous biomanufacturing. First of all, there is the cost advantage of reducing the footprint of the plant with all its consequences [58, 59]. Additionally, continuous manufacturing gives leverage for automation and a reduction of labor costs, but at the expense of more complexity. Second, it has been mentioned that continuous manufacturing may lead to more homogeneous products and a reduction of product failure. Continuous processes are perfectly suited for fast processes requiring an exactly defined reaction time or residence time. Very simple operations are, for instance, the adjustment of pH. Such a process is much easier to control in a continuous operation. Dissolution of protein or aggregates can be achieved with extreme conditions in a fraction of a minute. Such reactions cannot be performed in batch, for example, by a stirred tank reactor, because the mixing time in a large reactor is in the order of several minutes. All fast mixing processes and heat transfer processes are fully scalable to large scale when operated in continuous mode.

Furthermore continuous manufacturing minimizes unproductive equipment time by omitting delays during repeated startup and shutdown phases. This is an inherent advantage

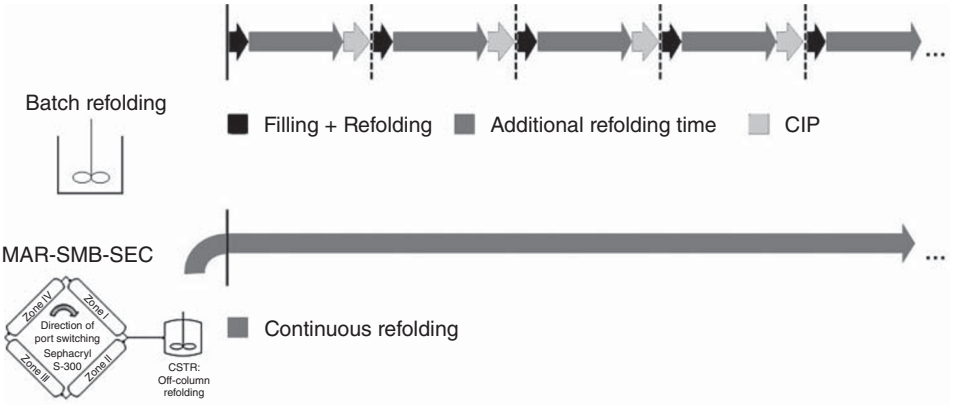

Figure 7.2 *Comparison of a batch and a continuous refolding process using matrix assisted refolding. In the continuous operation the system is started and then run continuously, while in the batch system the reactor must be filled, operated and cleaned in a cyclic manner. During filling and CIP the reactor is "idle" because it does not generate product. Details are described by Wellhoefer* et al. *[85].*

of continuous manufacturing in general. This aspect gets more prominent the longer the process is performed without interruption (Figure 7.2).

Nevertheless, there are still open questions concerning continuous manufacturing processes: Do we need steady state for continuous operation? What is the best definition of a batch complying with the legal framework? Can we vary the time point of collection or amount of material collected? What is the best way for separating multi-component systems in counter-current mode?

7.2 Continuous Upstream Processing

7.2.1 Cell Lines and Cell Line Stability

Conventional microbial expression constructs are not suited for continuous manufacturing. The cells have a very short generation time and expression plasmids are lost during each cell division. Recently, genome integrated expression constructs have been developed which are much more stable [72]. Using this approach, protein expression is stable over a time period of 300 h. This is definitely not possible with a plasmid encoded expressions system [48]. With this development also microbial system have a potential for continuous manufacturing, although the state of the art is batch and fed batch culture. Currently licensed products are made with Chinese hamster ovarian cells (CHO), baby hamster kidney cells (BHK), murine melanoma cells (NS0), and mouse myeloma (SP2/0) [15]. Insect cells are also very interesting but still in the process of development. Only influenza vaccine Flublok is licensed as a product manufactured with insect cells [49]. Plant cell culture with carrot cells is used to produce a therapeutic enzyme [54].

CHO cells with the variants DXB11 and DG44 are the most promising candidates for the further improvement of stability but many glycol-engineered variants are also

available [89]. They are already used for continuous cultivation in bioreactors. The genome of the production cell and also of the parent animal has been sequenced [8]. The cells grow in serum-free media as non-anchorage dependent cells and exert a high specific productivity of up to 30 pg protein/(cell · day). This is about 30% of the total protein content of the cell. Thus it is clear that high titers are more easily achieved by increasing the cell concentration in the bioreactor rather than by boosting the cell specific productivity. This is the incentive for industry to switch to perfusion culture.

7.2.2 Perfusion Reactor

The majority of continuous upstream processes for the production of recombinant proteins are performed in so-called perfusion reactors. Essentially, the cells are maintained in the reactor and perfused with medium. The retention is achieved either by devices keeping the cells in the reactor, such as filters, hydrocyclones or centrifuges, or by growing the cells on a porous material (packed bed reactor) inside the reactor [86, 90]. In principle the system is fed by a seed reactor which is needed to inoculate the production reactor. In the production reactor the cells are expanded to a certain density and then perfusion is started. Product can be collected when the system is in steady state. The major problem is to keep the cells in a growth-arrested state while the product is still synthesized. This is not fully possible, thus dead cells are washed out at the same rate as new cells are generated. The growth arrest has also been achieved by lowering the cultivation temperature [10, 16]. It is still a matter of debate whether this industrial practice, called hypothermia, affects the product quality attributes such as glycosylation or other post-translational modification [71]. In modern perfusion reactors one or two volume changes per day are achieved. This is also the basis for designing the entire process. Reactors are run for up to 60 days. The advantage of the perfusion reactor is the high cell density which can be achieved and as a consequence high titers. This has been made possible by feeding very rich media, which is only economical when cheap ingredients are used. Another advantage of the perfusion rector is that toxic compounds are also removed and cannot accumulate in the reactor.

The perfusion reactor and the ability to produce proteins in high concentration is the key technology to drive biomanufacturing towards continuous operations [14].

7.2.3 Cell Retention Devices

Numerous cell retention devices have been used in the past. These are spin-filters [25], ultrasonic devices [20, 87], hydrocyclones [21, 57] and centrifuges such as centritech [11]. A breakthrough technology is attenuated tangential flow (ATF) filtration (Figure 7.3). With this device, fouling of membranes is avoided or at least substantially reduced. In an intermittent way cell culture broth is pumped through a membrane by a diaphragm pump. The cells are retained and a relatively clear supernatant is harvested. Then the flow is reversed and the cells are flushed back into the bioreactor. The entire process is operated at a relatively low shear with a frequency of 12 cycles/min.

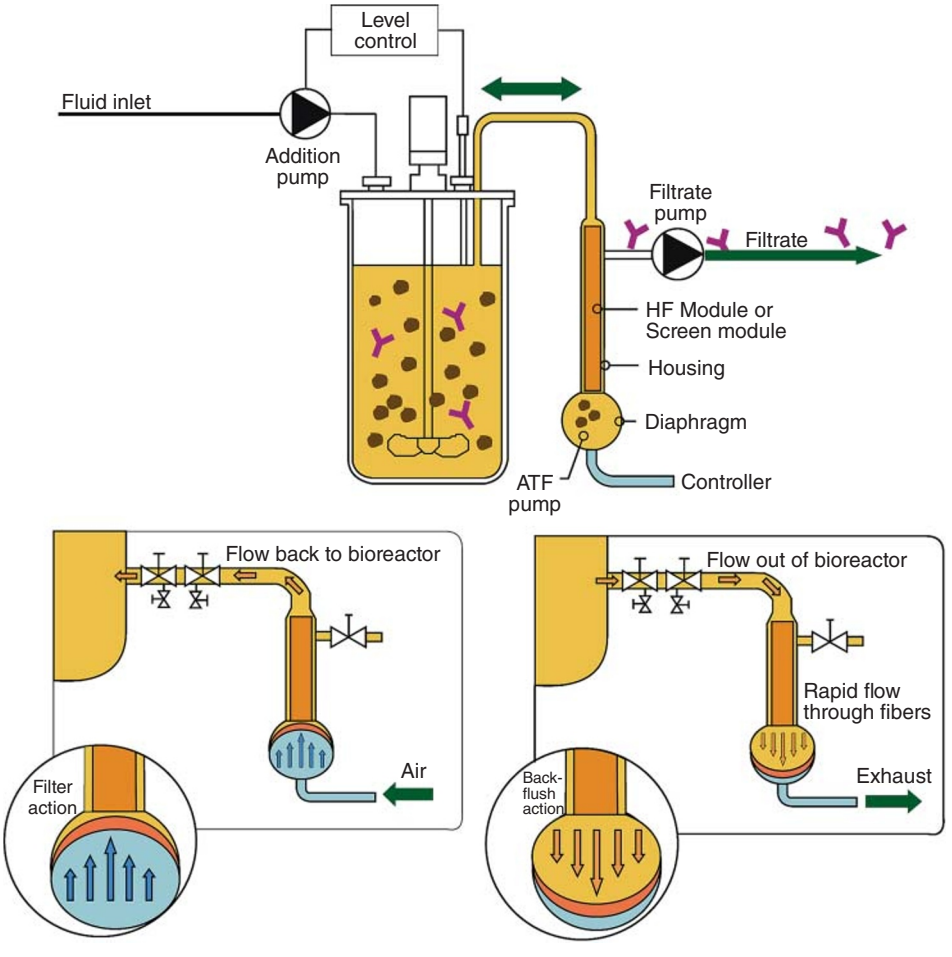

Figure 7.3 *The ATF system of Repligen integrates a diaphragm pump, a stainless steel housing and a single-use hollow fiber filter cartridge. The operation is as follows: (1) Pressurized air flows into the bottom of the ATF pump. (2) The air pressure forces the diaphragm gently up, displacing liquid and creating a fast flow of cell culture media across the surface of the hollow fiber filter. (3) Media flows rapidly through the filter fibers, with a cell-free filtrate being generated. (4) The cell culture fluid remaining on the upstream side of the hollow fiber filter is returned back into the bioreactor. (5) The system then reverses: air is exhausted through the pump bottom. (6) The diaphragm moves down creating a rapid flow of cell culture media from the bioreactor back into the ATF system. The system is now ready for the next cycle. Reproduced with kind permission of Repligen.*

Cells can also be cultivated on a porous matrix, which serves as an anchor for the cells. These reactors are also called packed bed reactors. They have been used for several decades, but never reached large-scale manufacturing. An inherent disadvantage of such reactors

is the nutrient, metabolite, oxygen and pH gradient formed in these systems. As a consequence, a spatial distribution of supply of nutrient and environmental conditions is observed in such reactors. These gradients increase with scale. The Celligen packed bed bioreactor was used already in the 1990s for the production of hybridoma cells [80]. An annular porous bed containing the cells was perfused. High cell densities could be achieved. Meanwhile similar concepts have developed where cells are retained by nanofibers or other porous materials [78, 90]. These types of reactors are preferably used for anchorage-dependent cells and virus production. Scale up is complicated due to the nutrient gradients, but recent developments (iCellis®) are very promising, at least for a scale which is sufficient for vaccine and virus vector production. Cells have also been cultivated in hollow fibers [84]. However, this system is not widely used for production of proteins, but rather for tissue culture.

7.2.4 Chemostat and Turbidostat

Continuous stirred tank reactors (CSTRs) can be also used for the cultivation of cells. The cells are grown in an aerated stirred tank reactor. Nutrient is continuously fed and product is removed at the same volumetric flow rate as the feed enters the reactor. The flow rate of nutrient divided by the reactor volume is called the dilution rate. Biochemical engineers distinguish between chemostat and turbidostat. In the chemostat the kinetics of the process are controlled by the influx of nutrients, whereas in the turbidostat the kinetics of the process are controlled by constant biomass. In contrast, the perfusion reactor fully retains the biomass in the reactor. The CSTR is not really suited for large-scale animal cell production as a high cell density cannot be achieved. This is the prerequisite for a high titer in the production of proteins and the titer in turn is the most important parameter for process economics. The cost of goods is strongly related to the titer. Needless to say, the costs of downstream processing are also rapidly declining with increasing titer. On the other hand, the CSTR can be used to study the effect of steady state [2]. Steady state is a stationary state in which compounds are continuously fed and reaction products withdrawn from the vessel.

The characteristic of a steady state is an open system and the reaction kinetics in the system and mass transfer properties determine the equilibrium concentrations of, for example, living cells, and other reactor compartments. We must distinguish chemical/thermodynamic equilibrium and homeostasis from steady state. After a disturbance there is a tendency to return to the status quo for homeostatic systems or systems which reach a thermodynamic equilibrium, but not for a system with steady state. It is not necessary to have a steady state in a production system. In an unsteady state or transient process, system properties vary with time. Batch and fed batch processes are inherently transient. Continuous processes are unsteady during startup and shutdown. Changing from one set of process conditions to another also creates an unsteady state. Fluctuations in the input or control variables create an unsteady state as well. The cells are never in steady state whereas the macroscopic system must be for continuous manufacturing. For the large-scale production of biopharmaceuticals chemostat and turbidostat are currently not used.

7.2.5 Overview of Products Produced by Continuous Upstream Processing

The products made by perfusion culture are summarized in Table 7.1. Some of the products have vanished from the market. Recently a fully continuous production process was

Table 7.1 *Cell culture products and reactor types for manufacturing of biopharmaceuticals by perfusion and continuous culture (data from Pollok and Farid [60] and Desai [17])*

Product	Protein or mAb	Indication	Company	First approved	Perfusion mode/CSTR	Reactor size (L)	Reactor number
ReoPro®	mAb-abciximab	PCTA	Janssen Biotech	1994	Spin-filter (internal)	500	5-20 (Leiden)
Cerezyme®	Beta-glucocere-brosidase r.FSH	Gaucher disease	Genzyme	1994	Gravity settler	2000	4 (Allston)
Gonal-f	r.FSH	Anovulation	Merck-Serono	1997	Spin-filter	ND	ND
Refacto®	r.Factor VIII	Haemophilia A	Pfizer	1997	Centrifuge	12000	unknown
Remicade®	mAb-infliximab	RA + other Al diseases	Janssen Biotech	1998	Spin-filter (internal)	500	5-20 (Leiden)
					Spin-filter (external)	1000	8 (Malvern)
Simulect®	mAb-basiliximab	Transplant rejection	Novartis	1998	Rotational Sieve filtration	250	ND
Rebif®	Interferon beta-1a	Multiple sclerosis	Merck-Serono	1998	Fixed bed	75	22 (Corsier-sur-Vevey)
Kogenate-FS®	r.Factor VIII	Haemophilia A	Bayer	2000	Gravity settler	200	8 (Berkeley)
Benefix®	r.Factor IX	Haemophilia B	Pfizer	2000	Semi-continuous re-feed	12000	unknown

(*continued*)

Table 7.1 *(*Continued*)*

Product	Protein or mAb	Indication	Company	First approved	Perfusion mode/CSTR	Reactor size (L)	Reactor number
Xigris®	r.activated protein C	Sepsis	Eli Lilly	2001	Gravity settler	1500	2 (CMO)
Advate®	r.Factor VIII	Haemophilia A	Baxalta	2003	CSTR	2500	unknown
Fabrazyme®	Agalsidase beta	Fabry disease	Genzyme	2003	Gravity settler	2000	2 (Allston)
							2 (Framingham)
Myozyme®	Alglucosidase alfa	Pompe disease	Genzyme	2006	Gravity settler	4000	3 (Geel)
Simponi®	mAb-golimumab	RA + other Al diseases	Janssen Biotech	2009	ATF	1000	3 (Cork)
						500	5-20 (Leiden)
Stelara®	mAb-ustekinumab	Psoriasis	Janssen Biotech	2009	ATF	500	5-20 (Leiden)
Rixubis®	r.Factor IX	Hemophilia B	Baxalta	2013	CSTR	2500	unknown

developed at Sanofi for antibody production. It was clearly demonstrated that a homogenous product was obtained. The process consists of a perfusion reactor, capture by protein A, a cation exchange chromatography and final purification. This is the first fully end to end continuous biomanufacturing process. The process was run over 31 days [29].

7.3 Continuous Downstream Processing

7.3.1 Overview of Unit Operations

In downstream processing of biopharmaceutical manufacturing the most important unit operations are chromatography, membrane filtration in the form of micro and/or ultrafiltration, dead-end sterile filtration, depth filtration and centrifugation. Aqueous two-phase extraction, conventional extraction, precipitation and crystallization are used to a lesser extent. For intracellular products homogenization is required. Dissolution of inclusion bodies and subsequent refolding is usually performed in a stirred tank. In traditional processes these unit operations are performed in batch-wise operation. In principle all these unit operations can be performed in a continuous manner. Figure 7.4 shows how such batch operations are converted into continuous operation.

Although there are several options to perform continuous operations, the continuous counter-current operation is perfectly suited for binary mixtures. In biotechnology usually we deal with multi-component mixtures, which can be reduced to a three-component mixture; impurities with a lower affinity to the stationary phase elute before the product can thus be lumped to one component, as can impurities with a higher affinity than the product elute after the product (second component). The product is the third component. For the separation of such a mixture, two systems can be interconnected in series to separate the ternary mixture. Productivity is not decreased when the operation time is sufficiently long. The startup phase and shutdown will be extended in such a case. Usually, in continuous manufacturing the time running in steady state is $\gg 100\times$ the startup and shutdown time. The loss during startup and shutdown is negligible.

7.3.2 Continuous Centrifuges

Disk stack centrifuges allow a truly continuous operation for the separation of two immiscible liquids and are used for extraction or clarification. For harvesting a solid, the operation is quasi continuous with an intermittent ejection of solids. For the clarification of cell culture broth and harvesting of bacteria this method is the method of choice. Centrifugation can be improved by flocculation, but increased product loss is associated with loose flocs. The design has been improved to reduce shear forces to avoid cell disruptions at the centrifuge inlet [61].

Decanters and extraction decanters are used in the production of antibiotics and in food technology for suspensions with a high solid content. They are truly continuous centrifuges with a throughput of up to 400 m^3/h [66]. Currently such equipment is not readily available for biomanufacturing in aseptic design, but this unit operation would be very appealing for integration into a continuous process.

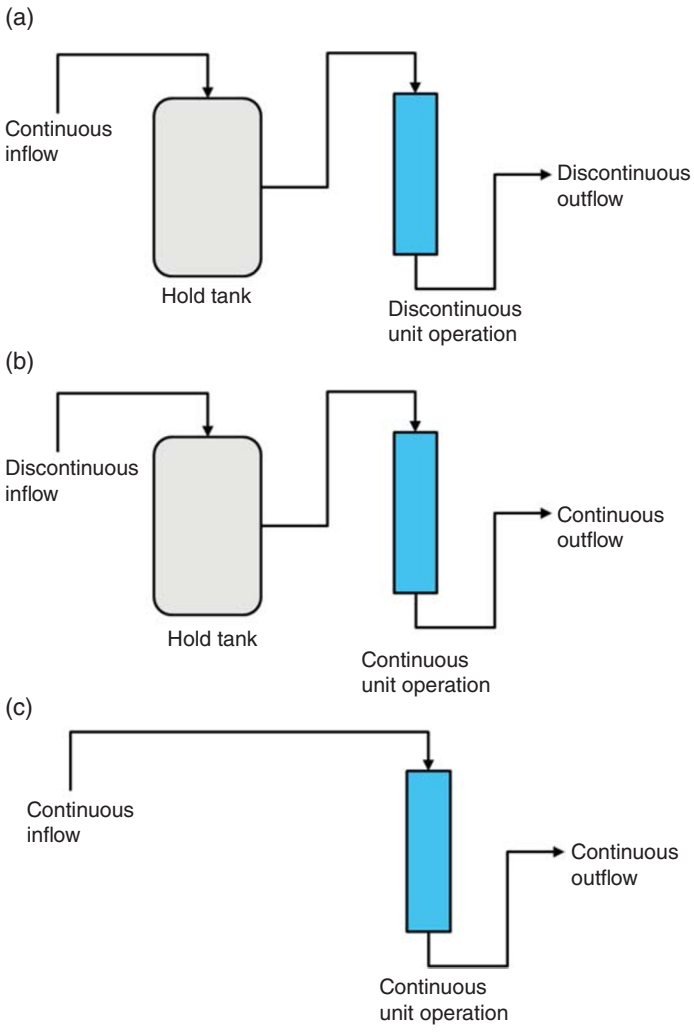

Figure 7.4 *Process integration: classification of continuous unit operations in terms of in- and outflow. Every batch operation can be rendered continuous using a surge tank (a, b) with a volume ≥ the inflow volume of one batch cycle. (c) A fully continuous unit operation accepting a continuous inflow and producing a continuous outflow.*

7.3.3 Continuous Filtration

Two types of filtration are applied in biomanufacturing, namely depth filtration and membrane filtration. Depth filters are often used for removal of solids from dilute suspensions. Typical examples include the harvest from a perfusion reactor or particles formed during downstream processing. Depth filters are also used to clarify a suspension after flocculation. Cationic flocculants (e.g. pDADMAC) have been used to clarify CHO cell culture supernatant [73]. In depth filtration either the solid of the suspension itself or the filter aid

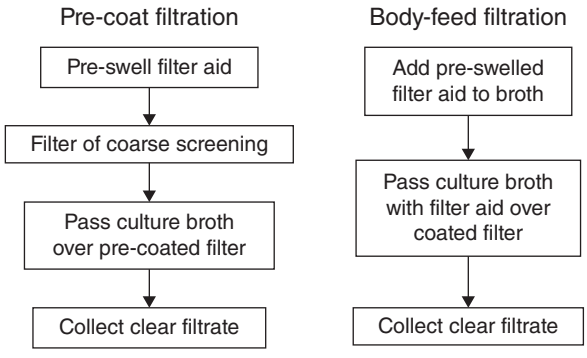

Figure 7.5 *Principle of pre-coat filtration and body field filtration.*

builds up a layer on a screen and retains also small particles. It is distinguished between pre-coat filtration and body–field filtration (Figure 7.5). In pre-coat filtration a screen is coated with the filter aid and then the broth is passed through the filter. In body–field filtration the filter aid is added to the suspension and then passed through the filter. These unit operations are typical for the food industry, for the clarification of juices, vinegar and wine, and have recently also been adapted to the biomanufacturing of antibodies. Meanwhile all major suppliers offer pre-coated membranes for depth filtration in batch mode from very small scale to large scale [69].

Depth filtration is typically operated in batch mode in biomanufacturing, although a fully continuous operation has been developed for the chemical and food industry: the vacuum drum filter. It works best as body–field filtration when the filter aid is added to the suspension. A vacuum drum filter is a rotating drum with a filter. Inside the drum an under-pressure is generated. The suspension is continuously applied to the rotating drum on the outside, clear liquid is sucked through, and the separated solid is continuously removed by a scrapper or knife. Currently equipment is not available for a "functionally closed" process, thus the technology is not yet applied in biomanufacturing.

Operation in parallel with three membranes allows a pseudo continuous operation. The filtration can be easily monitored by back pressure measurements. The filter is regenerated by back flushing. Thus it is possible to harvest either a clear liquid or the solid. Figure 7.6 shows an example for the removal of solid after calcium phosphate flocculation in a pseudo continuous way. Only one out of the three trains is shown. Critical to a successful operation over multiple cycles is the ability to fully regenerate the filter after each loading cycle.

Depth filtration will simplify the downstream processing of biopharmaceuticals, because flocculation is such a powerful operation to remove DNA and large aggregates [67, 70].

Membrane filtration is the second most important unit operation in the manufacturing of biopharmaceuticals. Microfiltration is used to clarify culture broth and ultra-filtration for concentration and buffer exchange in the form of diafiltration. Membrane filtration is also used for virus removal. Every process using mammalian cells must have a size-based virus removal step (nanofiltration). The membrane is designed in a way to allow retention of the virus and permeation of the product. It is the most expensive process step in the downstream processing of biopharmaceuticals.

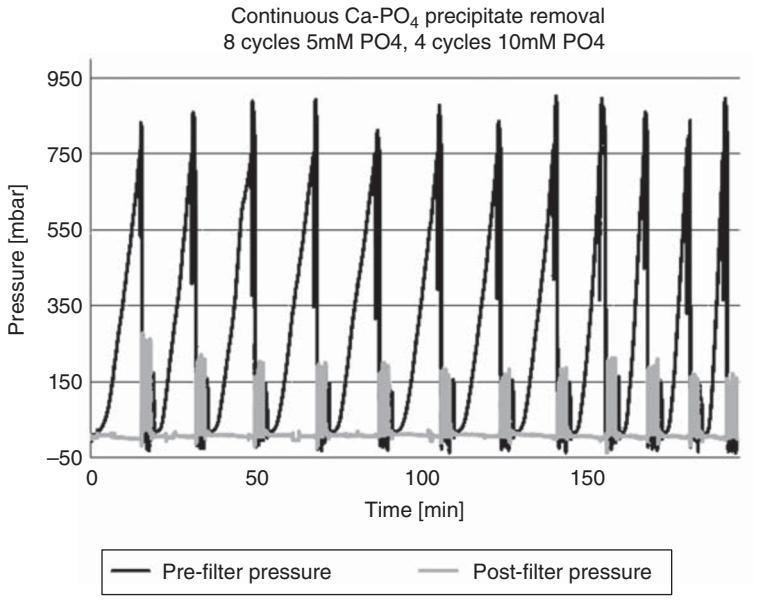

Figure 7.6 *Pseudo continuous removal of flocs after calcium phosphate flocculation of pre-clarified culture supernatant with a laboratory-scale depth filter.*

A truly continuous operation can be achieved by so-called single pass-tangential flow filtration [19]. The removal of solids or the ultrafiltration process is completed when the retentate leaves the filter. The method needs careful control, because fouling or changes in the feedstock may lead to incomplete filtration or concentration. Another continuous membrane filtration method is continuous multi-stage membrane filtration with sequentially arranged filtration units. Such a system is more complex than single pass tangential flow filtration, but less sensitive to changes in the feed stock and fouling because at each stage the process can be adapted according to the outcome of the previous step. The system is frequently used in food technology, but is not yet popular in biomanufacturing. Several hybrids between single pass-tangential flow filtration and continuous multi-stage membrane filtration with sequentially arranged filtration units exist, which are not fully continuous, but offer a possibility to gradually change to continuous operation (Figure 7.7).

7.3.4 Continuous Chromatography

Chromatography is the most important unit operation for downstream processing in biomanufacturing. In annular chromatography the chromatography medium is packed into an annulus which rotates [75]. Feed and buffers are continuously applied at the top and eluate is collected at the bottom. The method is truly continuous, but sterility problems due to sealing difficulties of rotary parts have been observed. As long as these problems are not solved the technology will not be accepted by industry. Annular chromatography is the only real continuous chromatography method. All other methods are pseudo continuous (Table 7.2).

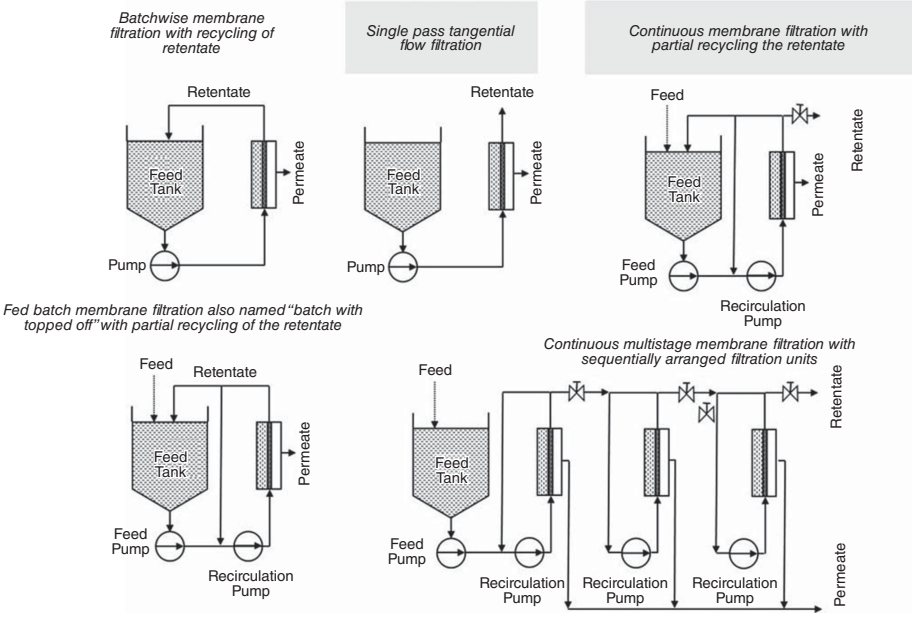

Figure 7.7 *Categories of membrane filtration processes from batch-wise operation to fully continuous. Reproduced from Jungbauer 2013 [36], with kind permission of Elsevier.*

Table 7.2 *Categories of continuous chromatography methods for downstream processing of biopharmaceuticals*

Method	Modifications	Continuous	State	Components
Annular chromatography		True	Steady	Multi
Simulated moving bed (SMB)			Steady	Binary
	4 zone SMB	Pseudo	Steady	Binary
	5-zone SMB	Pseudo	Steady	Ternary
Multi column solvent gradient purification (MCSGP)			Transient	Ternary
Counter current loading				
	3 column counter current loading	Pseudo	Steady	Multi
	2 column counter current loading	Pseudo	Steady	Multi

Counter-current loading was proposed many years ago [35]. Recently it was accepted by industry since practical solutions were offered by the supply industry: chromatography skids and the related software to run the pseudo continuous methods automatically. The method is suited for harvesting, for example, the supernatant of a perfusion culture. Frequently it has been argued that the method has a much higher productivity than a batch column. For chromatography with materials exerting a very steep adsorption isotherm (e.g. protein A affinity chromatography) a maximal 30% higher productivity can be obtained [12]. Counter-current loading is often performed as a two-column process, which is the simplest form of a pseudo continuous chromatographic operation. Often it is also referred to as capture SMB. Starting with a regenerated column, the column is loaded to full saturation. The flow through and the wash for flushing unbound material is loaded onto the second column. When this step is completed the first column is eluted and regenerated. During this operation the second column is loaded and the first column is regenerated before breakthrough of the second column starts. This configuration is only possible when the loading and washing time is longer than the time for elution and column regeneration [1, 3]. This is commonly the case for capture and intermediate purification, but not for high resolution separation.

Counter-current loading has been used for the first real integration of perfusion culture [28, 83] and capture or for fully integrated systems [29]. Counter-current loading will become the workhorse for continuous biomanufacturing, because it combines the high resolution of chromatography and quasi continuous operation. Intermediate purification and polishing steps are often operated in negative mode in which the product is in the flow through and the impurities are bound. In this case the counter-current loading is also possible, because the flow through is collected. The constraint for this mode of operation is that the loading phase is equal to or longer than the elution of impurities and regeneration.

7.3.5 Continuous Precipitation

Precipitation research has gained momentum in recent years, both for impurity removal as well as product precipitation [27, 30, 41, 51, 67, 69, 70, 74, 77, 81]. The high cell densities achieved in upstream processing have boosted antibody titers to 10 g/L [42, 46]. The resulting high solid content and the high amount of cell debris challenge established clarification strategies such as centrifugation and depth filtration. High product titers have rendered the downstream part of an antibody manufacturing process the bottleneck in production. Precipitation is capable and widely used for the flocculation/precipitation of impurities and cell debris in the clarification step as well as an alternative capture step. Precipitation has been used for more than five decades for industrial production in human blood plasma fractionation at full industrial scale [9]. More than 100 t of antibodies are produced by ethanol precipitation worldwide every year. In the past also full-scale continuous immunoglobulin precipitation has been performed from human plasma [13, 26, 50].

Precipitation as a unit operation is composed of two to three sub-unit operations, depending on what is precipitated. In case of impurity precipitation, the actual precipitation is followed by a precipitate removal step. In the case of a more complicated product precipitation, the precipitation is followed by a precipitate capture step and a final re-solubilization step.

In a continuous setup, all three of these sub-unit operations have to be performed in parallel and continuously. A broad range of precipitation techniques are known, but a detailed description of the individual techniques is beyond the scope of this chapter. A summary of precipitants and their industrial application is given in Table 7.3. To make a precipitation reaction amenable to continuous operation, several requirements have to be fulfilled. The final precipitation conditions have to be reached, such as a certain temperature, pH, and final precipitant concentration. In batch operation it is easy to approach the final precipitation condition slowly, for example, by dosing a precipitant at low rates until the desired final concentration is reached. At the same time fast changes are restricted in batch mode, because of mixing limitations and heat transfer in large batch vessels.

In continuous mode, the final precipitant concentration and depletion of undesired concentration gradients can be reached extremely fast, in a matter of seconds, using a single point of addition in a tubular reactor, even at laminar flow, using static mixers (Figure 7.8). Slower dosing can be achieved incrementally by increasing the number of precipitant addition points. Heat transfer is also much improved, due to the beneficial surface to volume ratio of continuous tubular reactors allowing for very fast temperature changes. Once the precipitation conditions have been set, the precipitation kinetics and linear velocity determine the required length of a continuous reactor. The faster the precipitation kinetics, the shorter the required residence time to reach the thermodynamic precipitation equilibrium. Hold times/aging of the precipitate can be required to strengthen the precipitate. Precipitation can be also performed in a CSTR in cases when aging of the precipitant is required. A CSTR has more freedom with regard to power input. However, the effect of power input on precipitation and floc formation is often overestimated (Figure 7.9). For a wide range of volumetric power input into the reactor the floc characteristics do not change.

It has to be stated that the length/size of the continuous reactor is irrelevant at steady-state operation. The reactor length at a given flow rate however determines the lengths of startup

Table 7.3 *Most common precipitants for the precipitation of proteins and their industrial application*

Type	Example of precipitant	Industrial application
Isoelectric precipitation	Acid or base	
Salting out	Cosmotropic salts: ammonium sulfate, potassium sulfate, sodium chloride	
Precipitation by organic solvents	Ethanol, acetone	Blood plasma fractionation, full scale
Precipitation by organic acid	Octanoic acid	Blood plasma fractionation, horse immunoglobulin
Precipitation by non-ionic polymers	Polyethylene gylcol (MR 400–20 000	Blood plasma fractionation, diagnostic antibodies
Precipitation by polyelectrolytes	Polyethyleneimine, polylmethacrylic acid	
Affinity precipitation	Poly(*N*-ethyl-4-vinyl-pridinium bromide), poly(methacryl acid)	
Intelligent (smart) polymers	Poly(*N*-isopropylacrylamide), poly(vinylcaprolactam), poly (vinyl methyl ether)	

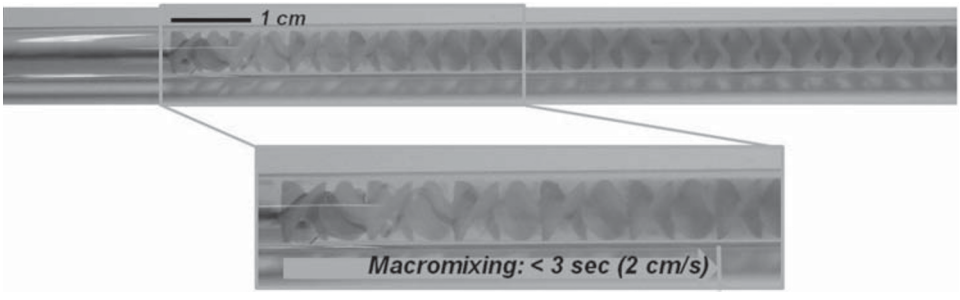

Figure 7.8 *Visualization of rapid mixing of 45 w/v% PEG 6000 with aqueous buffer in a tubular reactor equipped with helical type static mixers. The viscosity was 12 mPa at room temperature.*

and shutdown as well as the residence time distribution. Assuming, for example, a moderate linear velocity in the reactor (2 cm/s), a residence time of 30 min (assuming ideal plug flow) translates into a required reactor length of 36 m. While it has been shown that the precipitation reaction itself can be rendered continuous relatively easily, the picture changes with regard to precipitate removal/recovery and precipitate resolubilization. Precipitated impurities are somewhat easier to separate than precipitated product, because in

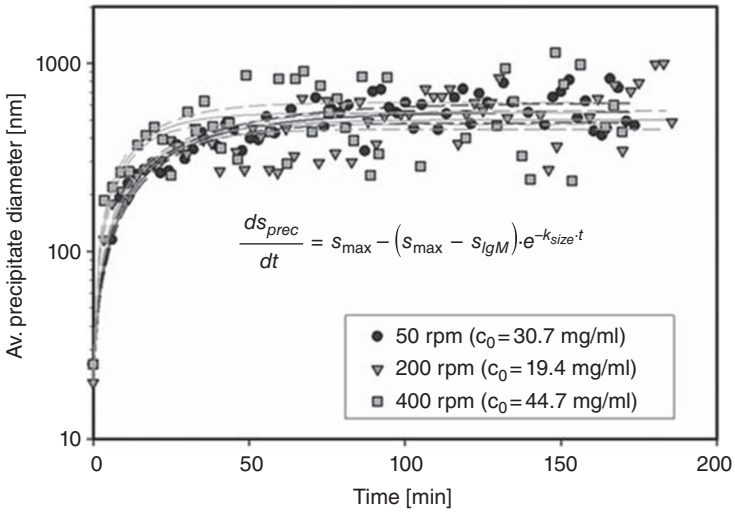

Figure 7.9 *Precipitation of IgM in a stirred tank reactor with PEG, where the size of the precipitate was monitored with a Malvern Zeta Sizer [82].*

the solid–liquid separation step, no attention has to be paid to precipitate characteristics as long as the formation of difficult to remove fines is avoided. Product precipitate on the other hand has to be treated more carefully.

The removal/recovery step is essentially a solid–liquid separation. Centrifugation is the method of choice for batch experiments at laboratory scale. In centrifugation the density difference of the precipitate and the surrounding mother liquor is exploited. Centrifugation however has some inherent disadvantages. The individual precipitate flocs are for example compacted to a paste-like layer at the bottom of the centrifuge bowl. This compaction results in very slow dissolution rates in the order of hours for, for example, PEG precipitated antibodies [30] and is thus undesired in batch operation and a difficult to solve problem in continuous setups.

Continuous or semi-continuous centrifuges exist (see Section 7.3.2), but washing of the precipitate is difficult in the compacted state as well as the re-solubilization of the resulting paste. Apart from centrifugation, dead-end filtration can in principle be employed as capture step (see Section 7.3.3). The precipitate is again compacted on the filter surface and subsequent re-solubilization is a problem. This approach is therefore only applicable for impurity removal.

Literature is very scarce for precipitation in general and especially for continuous precipitation, as in many other areas concerning continuous processing. Only a few publications have dealt with precipitate recovery. Micro- and diafiltration for product precipitate recovery using hollow fiber cross-flow filtration have been tested by two groups and found to be a viable option [30, 41]. The precipitate is concentrated and subsequently washed. The individual precipitate flocs are preserved, resulting in highly accelerated dissolution (Figure 7.10). Both filtration approaches outlined above have to be realized as at least two discontinuously working parallel units that are run intermittently in order to be able to handle continuous inflow.

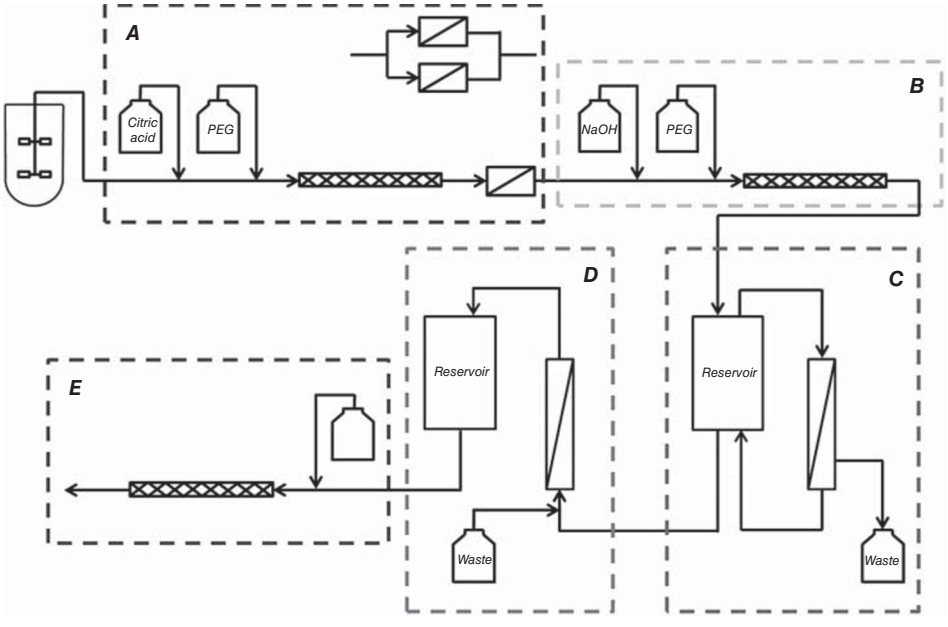

Figure 7.10 *Flow diagram of a fully continuous precipitation using PEG. Step A: precipitation of impurities at low pH by addition of citric acid and low concentrations of PEG. Step B: pH adjustment and further addition of precipitant. Step C: Harvesting of precipitate and concentration thereof. Step D: Washing of precipitate by addition of PEG containing wash buffer. Step E: Resolubilization. Adapted from Hammerschmidt* et al. *[30].*

7.3.6 Continuous Formulation

The majority of biopharmaceuticals and in particular antibodies are formulated as liquid. Other formulations are lyophilized powder or suspensions of crystals. Often high concentrations above 100 mg/mL are required to keep the injection volume within manageable limits. For liquid formulation, ultra- or diafiltration is the state of the art for concentration and buffer exchange into formulation buffer. So-called continuous diafiltration is a batch process. Buffer is added at the same rate to the retentate as the permeate leaves the system. The term continuous only refers to the continuous addition of buffer (Figure 7.11).

A fully continuous process is achieved either by concurrent or counter-current diafiltration. The counter-current diafiltration mode saves buffer. In its simplest form three ultrafiltration units are required. In the last step fresh buffer is added as diafiltration buffer. In the second step permeate from the third step and in the first step permeate from the second step are used as diafiltration buffer, respectively. The method is complex but is a truly continuous operation. The three steps provide a lot of options for process control.

7.4 Process Integration and Single Use Technology

The terms “disposable” and “single use” components are often used interchangeably for equipment that is non-reusable, but is disposed of after usage and replaced by a new unit.

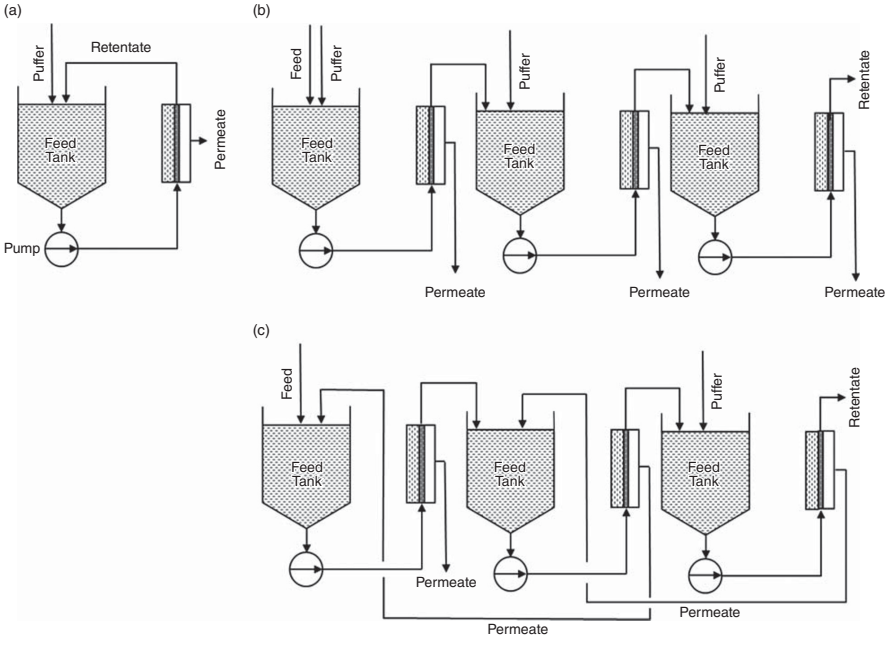

Figure 7.11 *Different modes for diafiltration: (a) continuous diafiltration, (b) continuous concurrent diafiltration, (c) continuous counter-current diafiltration. Reproduced from Jungbauer 2013 [36], with kind permission of Elsevier.*

Unlike their stainless steel counterparts, disposables are usually not subjected to cleaning or sanitization procedures and are offered typically pre-sterilized by gamma radiation and can therefore be quickly put into operation. Often named advantages are the reduction of validation and cleaning costs as well as savings in operational time and a general increase in flexibility. The current upper size limit of about 2000 L hampers their usage in large-scale batch production. During continuous production, much lower volumes have to be handled at any one point in time, and therefore here, the usage of disposables is very appealing.

7.4.1 Disposable Bioreactors

Numerous suppliers offer single use bioreactors up to a volume of 2000 L (Table 7.4). They are not specifically designed for continuous manufacturing. In combination with cell retention devices such as alternating tangential flow (ATF) filtration they are fit for continuous manufacturing in the form of perfusion culture. In continuous manufacturing 2000 L is already considered large scale. Thus full-scale manufacturing can be performed with disposable reactors.

Disposable reactors are suited for the cultivation of mammalian and insect cells. For microbial cells the oxygen transfer is too low. For these production hosts we still rely on stainless steel reactors.

7.4.2 Disposable Unit Operations in Downstream Processing

Disposables are already being used by companies for various tasks. Disposable bags for buffer and media preparation or intermediate hold and transfer tanks are probably the most advanced and widely used disposable technology at the moment, apart from single use filter capsules and bioreactors. However, several vendors are offering entire product lines for disposable manufacturing, encompassing multiple unit operations and also technologies and equipment for sterile connecting and sealing of thermoplastic tubings as well as valves and sensors. Now, entire unit operations can be operated in a fully disposable fashion. An exhaustive list of single use processing solutions for unit operations common to the biopharmaceutical industry has been gathered by Shukla and Gottschalk [68]. Disposable units are available for chromatography up to 60 L, for membrane and depth filtration up to full-scale manufacturing and for mixing up to 2000 L. The advantage of continuous manufacturing is the reduction of footprint. Thus it is possible with currently existing equipment to assemble a full-scale manufacturing. At the current stage columns larger than 60 L are not required for full-scale manufacturing in continuous mode.

One issue of disposable equipment concerns extractables and leachables which might have detrimental effects on cell growth or can contaminate the product. These substances are an often cited reason for not taking up disposable technologies. Extractables are defined as chemical compounds that migrate from any product-contact material (including elastomeric, plastic, glass, stainless steel, or coating components) when exposed to an appropriate solvent under exaggerated conditions of time and temperature. Leachables on the other hand are chemical compounds, typically a subset of extractables, that migrate into a drug formulation from any product contact material as a result of direct contact under normal process conditions or accelerated storage conditions A first leachable, namely

Table 7.4 *Summary of single use bioreactors for production of biopharmaceuticals*

Manufacturer	Control unit	Single-use Reactor	Mode [Stirrer/ Wave]	Working Volume [L]
Eppendorf	BioFlo 320	Bio Blu 0.3c	S	0.1–0.25
	BioFlo 320	Bio Blu 1c	S	0.32–1.25
	BioFlo 320	Bio Blu 3c	S	1.25–3.75
	BioFlo 320	Bio Blu 5p	Packed bed	3.75
	BioFlo 320	Bio Blu 14c	S	3.5–10.5
	BioFlo 320	Bio Blu 50c	S	18–40
	DASGIP	Bio Blu 0.3c	S	0.1–0.25
	DASGIP	Bio Blu 0.3c	S	0.1–0.25
	DASGIP	Bio Blu 1c	s	0.32–1.25
	DASGIP	Bio Blu 1f	s	0.32–1.25
Pall	XRS20		W	2.0–20
	Allegro STR200	Allegro STR200	S	60–200
MerckMillipore		Mobius	S	3
	Mobius 2000		S	400–2000
	Mobius 200		S	40–200
	Mobius 50		S	10–50
GE	WAVE 25		W	0.3–25
	WAVE 200		W	10–100
	WAVE 500/1000		W	50–500
	Xcellerex XDR-10		S	4.5–10
	Xcellerex XDR-50 to 2000		S	50, 200, 500, 1000, 2000
Satorius	BioStart RM	Flexsafe RM	W	0.1–100
	BioStat B	UniVessel SU	S	0.6–2
		CultiBag ORB	Orbital	10–2500
	Biostat STR	CultiBag STR	S	12.5–1000
ThermoFisher	HyPerforma		S	30, 300
	HyPerforma		S	50–500
	HyPerforma		S	2000
Finesse	Bioreactor		S	50–2000
	Rocker		W	5, 10, 25

bis(2,4-di-tert-butylphenyl)phosphate (bDtBPP), a breakdown product of an antioxidant used in many formulations of polyethylene, has been shown to detrimentally affect cell growth [32, 33]. The issue of leachables is becoming increasingly relevant with the increased use of disposables across multiple unit operations.

A detailed life cycle analysis for a batch disposable system has been performed by GE-Healthcare and Biopharm Sevices [56]. They assessed the impact on environment, resources and health by Monte Carlo simulation and came to the conclusion that, in approximately 80% of all simulated cases, traditional (stainless steel) manufacturing had a higher impact. It is very plausible that a smart combination of disposable unit operations and standard stainless steel equipment may have the lowest impact on resources, health, and environment and therefore also contribute to savings.

7.4.3 Full Process Train

The first fully integrated process train was reported by Sanofi [29]. A perfusion system was connected to three periodic counter-current systems to enable production and purification of a biopharmaceutical in a fully continuous manner. Two virus inactivation steps were also included in the continuous process train. An important task was the development of protocols to prevent microbial contamination in the system. The authors called their approach "functionally closed." That means that the system was not sterile in the sense of absence of vegetative microorganisms and spores. It simply means that the germ count was too low for the propagation of microorganism to occur during the production campaign. It is not possible and also not feasible to run a process under fully sterile conditions. The functionally closed system has enormous consequences on process economics. The entire manufacturing process can be performed in rooms with lower air quality. So far a system has been established at a biopharmaceutical company, but no licensed product has been produced in it yet.

Another concept has been proposed by Merck Millipore, but it is still in a conceptual phase and has not been realized although the individual components are commercially available [88].

The functionally closed system also allows the design of the so-called ball room concept [39]. The different unit operations are performed in one big hall (Figure 7.12) rather than in separate compartments. This leads to more flexibility and to substantially reduced production costs.

7.5 Process Monitoring and Control

Continuous processing puts sensors to their limits and makes high demands on sensors with regard to robustness and speed of operation. Traditional off-line analyses are typically not sufficiently fast to provide data for control purposes.

There are different sensor types that allow the acquisition of data in real time or sufficiently fast that the information can be used for control purposes. The FDA categorizes theses sensors in three groups [24]:

- At-line: measurement where the sample is removed, isolated from, and analysed in close proximity to the process stream.
- On-line: measurement where the sample is diverted from the manufacturing process, and may be returned to the process stream.
- In-line: measurement where the sample is not removed from the process stream and can be invasive or non-invasive.

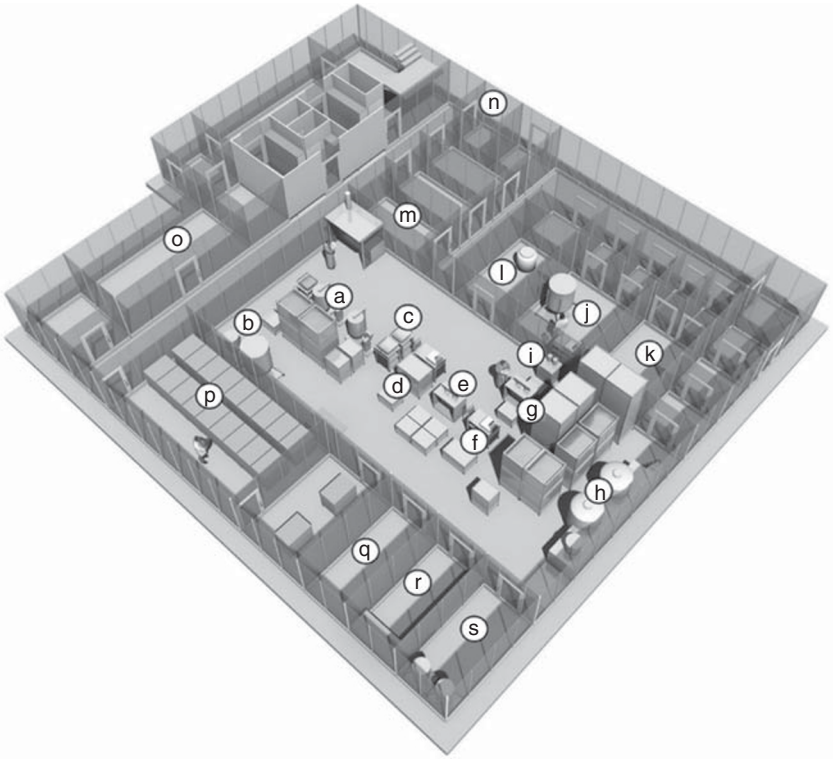

Figure 7.12 *3D-view of the ball room concept for a manufacturing plant of the future. From Klutz* et al.*, 2015 [39], reproduced with kind permission of Elsevier.*

The high degree of automation required for smooth continuous processing of biopharmaceuticals makes the use of a battery of these sensors necessary. Information has to be gathered in or almost in real-time, depending on the process, while in batch approaches, post-run off-line analytics are sufficient. For fully automated continuous processes, model based control algorithms have to be implemented that need process data as model inputs. In depth knowledge of the process is a prerequisite for modeling.

Regulatory agencies support continuous processing and have issued several guidelines that, although not specifically relating to continuous processing, relate directly to on-line monitoring and control – both of which are prerequisites for continuous processing. The quality by design (QbD) initiative promotes biopharmaceutical companies to design processes that yield consistent and reproducible product quality (“quality by design”) rather than testing the quality of the final product only (“quality by testing”) [53]. An in depth understanding of the process, the product and the parameters affecting one or the other is necessary. A high amount of experiments and analytical work is required to gain the necessary knowledge. Companies have embraced design of experiments (DoE) approaches in order to reduce the experimental efforts. DoE is currently the preferred tool in the biopharmaceutical industry to detect process variables affecting the process as

well as interactions between these process variables. In combination with defined critical quality attributes (CQAs) of the product, ranges of critical process parameters (CPPs) can be defined and thus a so called "design space". As long as the process is run within the specified limits, the CQA profile of the product is within the set limits. Consequently, the CPPs have to be monitored and controlled during the process to ensure operation within the established design space. The process analytical technology (PAT) initiative promotes the use of analytical tools and technologies capable of monitoring and finally controlling CPPs [24]. The reliable control of process parameters requires measurements as close to real time as possible at multiple points of the process. Companies profit from the implementation of QbD and PAT approaches by having to file fewer post-approval submissions and experiencing regulatory flexibility. In addition, implementation of a PAT control scheme can broaden the process design space compared to a traditional pooling decision by A280 measurement in, for example, chromatography without leading to lot rejection [64].

Little has been published so far on process monitoring and control of continuous processes in the biopharmaceutical industry. In upstream processing, monitoring of fermentation conditions is accomplished by a set of standard sensors (pH, pO_2, temperature). Advanced monitoring concepts, for example, proton transfer reaction–mass spectroscopy (PTR-MS) for off-gas analysis and black box spectral analysis of the cell suspension and multi-variate data analysis approaches have enabled researchers to predict product titer and biomass concentrations online in *Escherichia coli* fed-batch cultivations [44, 45]. This information can be incorporated, for example, in the control of the feed strategy. Herwig *et al*. developed an on-line sampling device capable of measuring six compounds in *Pseudomonas pastoris* batch cultivations. The obtained data were used for incremental rate and yield calculations [18].

In downstream processing, filtration unit operations are easiest to control using pressure and weight data obtained by a set of conventional pressure sensors and scales. Mass and volumetric flows can be deduced easily and, for example, concentration factors and control actions can be calculated. In centrifugal operations, turbidity measurements of the centrate are used in continuous disk-stack centrifuges to determine the point at which discharge is required.

The most advanced models for continuous operation and commercially available systems can be found for chromatography. UV absorbance at a fixed wavelength (usually 280 nm for proteins) is routinely measured in chromatographic processes and, for example, pooling decisions are based on it. Using spectral data instead of fixed wavelengths, the amount of information can be increased. Based on this, Hubbuch *et al*. [5, 6, 34] developed a tool for automated pooling decisions. It relies on the measurement of mid-UV absorption spectra and PLS regression and allows inline quantification of co-eluting proteins. The drawback is, that calibration using known protein mixtures is required. The first examples of real life samples have been published [7]. So far, the method has been developed for batch chromatography, but there is no reason not to use it for continuous chromatographic setups.

Several groups have demonstrated the capability of HPLC and UPLC for on-line peak pooling decisions in preparative chromatography. Rathore *et al*. utilized RP-UPLC and achieved assay times of 7 min [63, 65]. Kaltenbrunner *et al*. have tested an on-line HPLC

at full production scale. Data intervals of about 30 s were obtained by operating two analytical monolithic columns offset and in parallel. The delay of the process stream and the purity data obtained by HPLC was 96 s. This approach was also used for pooling decisions in batch mode [37].

Warikoo *et al*. [83] were the first who presented an integrated high-density perfusion cell culture and a directly coupled continuous capture step. The continuous capture step consisted of a four-column periodic counter-current chromatography (PCC) setup (Figure 7.13). In such a system, the feed is directed onto one column. When breakthrough is detected, the effluent is directed onto a second column to capture the product and to increase the resin utilization of the first column. When the first column is almost fully loaded, the flow is directly loaded onto the second column. They used a ΔUV-based approach for dynamic control of the column/valve switching.

Ideal sensors should be operating stable, robust with regard to physical conditions such as CIP/SIP cycles, be non-invasive, and have a low frequency of re-calibration.

In continuous operation, working at steady state is desired. By definition, steady state is a state in which all state variables are constant despite ongoing processes, and is thus distinct from chemical equilibrium. Some unit operations such as precipitation can be performed continuous, reaching a state satisfying the above given definition, for example, in a tubular reactor. Steady state is used frequently in this context for unit operations such as continuous chromatography. What is meant by steady state here is the arrival at a state in which consecutive chromatograms of individual cycles are identical or very similar. Currently it is debated if steady state is required for continuous processing. It seems that this is not necessary, but it is important that the system is not disturbed. This in turn means that process control becomes very important.

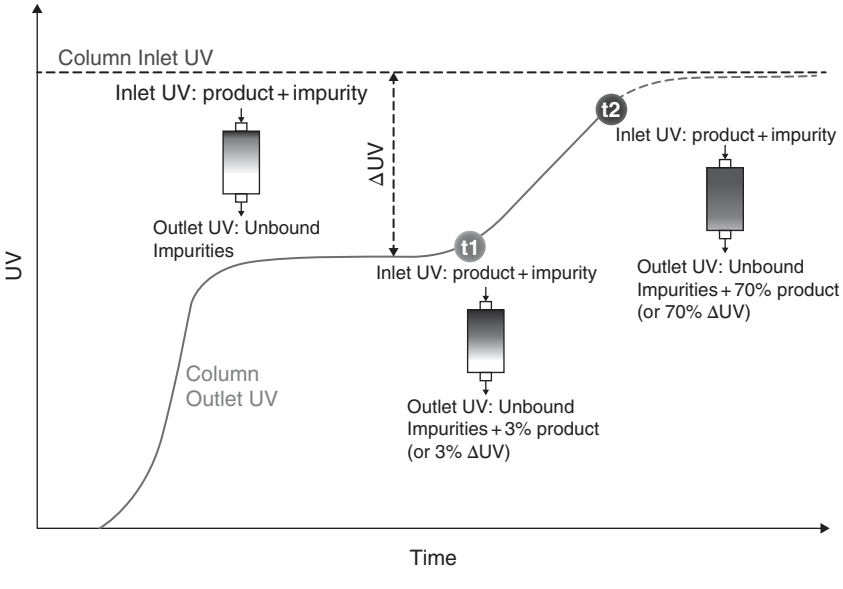

Figure 7.13 *Dynamic control for switch of columns in periodic counter-current control from Warikoo* et al. *[83] Reproduced with kind permission of John Wiley & Son, Inc.*

7.6 Process Economics of Continuous Manufacturing

Continuous processing has been so far primarily used for the production of labile molecules whose inherent lability necessitates short residence times and thus rules out batch production [79]. In recent years the benefits of continuous operation has fueled the interest in this operational mode also for the production of stabile molecules, such as recombinant antibodies [28, 83]. In this instance, manufacturers are faced with two or even more process options with the ultimate goal of delivering a product with specified quality, in high enough amounts at the lowest possible manufacturing costs.

The decision of choosing the best process option is complicated by difficult to quantify factors, such as process robustness and often the legacy of existing large-scale stainless steel facilities available for retrofitting. Since continuous operation in general requires smaller equipment than batch operation of the same unit operation or process, the usage of disposables is in many cases a viable option.

Many case studies came to the same conclusion with regard to the employment of disposables. Namely, that the employment of disposable equipment changes the overall cost structure of a process. Typically, capital costs (investment costs) are significantly reduced by eliminating stainless steel equipment. Costs are shifted towards the consumables costs since disposables such as single-use bags and bioreactors belong to this cost category [31, 52, 88]. The modeling of the introduction of new technologies to existing facilities, rather than building "green field" facilities is another factor with generally high impact on the outcome of economic analyses. Operation of an otherwise more expensive process in a fully depreciated, existing facility substantially decreases cost savings gained by switching to a new process [88].

We [31] used the Biosolve software package (Biopharm Services, UK) to compare the economics of a novel, mainly precipitation-based antibody purification process operated in continuous mode with a state of the art chromatography-based purification process operated in batch. Cost reductions in clinical phase production were mainly attributed to omission of the costly protein A affinity chromatographic resin, that is typically cycled far below its theoretical lifetime in clinical phase production. At very large-scale manufacturing, the production cost contributions of labor are significant. Consequently, cost reductions at this scale were seen due to lower labor requirements of the continuously operated process. This example shows that, apart from the technical aspects of processes, major cost contributions come from non-process related activities and the cost structure of a process can change significantly between small developmental production and large production scale. When comparing different processes or operational modes of the same process the factor of risk and uncertainty associated with each production process or operational mode is another variable in process economics studies. A sophisticated research tool for the economic analysis of biopharmaceutical processes was developed at University College London [22, 23]. The tool can incorporate uncertainty in the economic simulations by stochastic Monte Carlo algorithms using desired failure probabilities of individual steps. These uncertainties include, for example, culture contamination in upstream, titer variability, equipment failure, and filter fouling. The tool has been used for comparing continuous and batch processes, both in up- and downstream processing [60]. The economic analysis of fed-batch and perfusion production, using either spin-filter or alternating tangential flow (ATF) for cell retention, demonstrated the competitiveness of an ATF perfusion strategy, despite a lower

robustness compared to a fed-batch manufacturing process [43]. ATF perfusion strategy outperformed a fed-batch manufacturing process by up to 20% from an economic point of view. Fed-batch strategy on the other hand proved to be more environmentally sustainable with lower consumption of water and consumables. Spin-filter perfusion strategy could not compete across a range of titers and production scales with either of the two other investigated production strategies.

Pollock *et al*. [60] used the tool for the comparison of semi-continuous (periodic counter-current) affinity chromatography and batch chromatograph in a semi-continuous antibody production process. The tool predicted that PCC capture chromatography would offer more significant cost savings (30%) in early-stage clinical phase manufacturing than in late-stage clinical phase (10–15%) and commercial manufacturing (5%). The savings are attributed mainly to savings in direct costs, namely the better utilization of protein A affinity chromatographic resin in the semi-continuous PCC approach.

Most recently, Xenopoulos [88] presented a thorough analysis of a new, integrated platform purification process for recombinant antibodies operated in batch and continuous mode and compared it to the industry standard batch process for recombinant antibody purification. Disposables were used extensively in the new template process. The new platform consisted of a flocculation plus depth filtration for harvest and clarification, followed by protein A affinity chromatography operated in continuous mode and three flow-through chromatographic steps (activated carbon, anion, and cation exchange). His findings were in line with previously published literature. The proposed new, integrated platform process outperformed the industry standard process in both batch and continuous mode. In batch operation, CoGs reductions can be primarily traced back to reductions in facility and labor requirements. In addition, water usage is significantly lowered because of reduced cleaning and sanitization in place requirements. In contrast, costs for consumables are increased due to the extensive usage of disposables in several process steps. Cost savings are higher for clinical phase production (35%) than for small- (24%) or large- (16%) scale commercial production. Operated in continuous mode, additional cost savings are realized by the new template. Again, higher cost benefits are seen for commercial production than for clinical manufacturing. Key contributors in this case are the elimination of intermediate pool tanks as well as shorter process time and small process skids.

7.7 Conclusions

Fully continuous manufacturing of biopharmaceuticals is still in its infancy. There is not a single product on the market that is produced by a fully integrated continuous process. The concept of fully integrated biomanufacturing is being pioneered by Sanofi in Framingham. There, a fully integrated system for antibody manufacturing system has been developed. They have converted batch downstream processing methods into continuous ones, with interconnected individual unit operations directly with each other. The driver for continuous manufacturing is upstream processing, not downstream processing. With perfusion cell culture an increase in productivity can be achieved. An almost enabling technology for long-term perfusion culture is attenuated tangential flow filtration. This technology allows robust cell retention in perfusion culture. Cell culture media becomes inexpensive and thus rich media can be afforded to be fed, leading to higher cell culture titers.

It is obvious to render at least the first purification step, the capture, continuous and to connect it directly to continuous perfusion. The full integration of an entire continuous purification train encompassing all required unit operations up to formulation is only a matter of time. New continuous processes will appear either together with biosimilars or when the economic pressure will further increase. Fully continuous unit operations such as precipitation, flocculation, refolding and virus inactivation have been tested at laboratory and pilot scale and are awaiting implementation into fully integrated processes. Continuous manufacturing is also attractive for manufacturing of biopharmaceuticals in non-privileged countries. The concept of a functionally closed system reduced the need for high end installations to achieve the high air quality required in typical processes. Continuous biomanufacturing will also contribute to improve product quality and is encouraged by the health authorities. The numerous advantages of continuous manufacturing will override the risks associated with its implementation.

Acknowledgments

This work was supported by the Federal Ministry of Science, Research and Economy (BMWFW), the Federal Ministry of Traffic, Innovation and Technology (bmvit), the Styrian Business Promotion Agency SFG, the Standortagentur Tirol, the Government of Lower Austria, and the ZIT-Technology Agency of the City of Vienna through the COMET-Funding Program managed by the Austrian Research Promotion Agency FFG. We thank F. Strobl for helping with the tables.

References

[1] Angarita, M., Müller-Späth, T., Baur, D., *et al.* (2015) Twin-column CaptureSMB: A novel cyclic process for protein A affinity chromatography. *Journal of Chromatography A* **1389**, 85–95.

[2] Bakker, W.A.M., Schäfer, T., Beeftink, H.H., *et al.* (1996) Hybridomas in a bioreactor cascade: Modeling and determination of growth and death kinetics. *Cytotechnology* **21**, 263–277.

[3] Baur, D., Angarita, M., Müller-Späth, T., *et al.* (2016) Optimal model-based design of the twin-column CaptureSMB process improves capacity utilization and productivity in protein A affinity capture. *Biotechnology Journal* **11**, 135–145.

[4] Böhm, E., Voglauer, R., Steinfellner, W., *et al.* (2004) Screening for improved cell performance: Selection of subclones with altered production kinetics or improved stability by cell sorting. *Biotechnology and Bioengineering* **88**, 699–706.

[5] Brestrich, N., Briskot, T., Osberghaus, A., *et al.* (2014) A tool for selective inline quantification of co-eluting proteins in chromatography using spectral analysis and partial least squares regression. *Biotechnology and Bioengineering*, **100**, 807–814.

[6] Brestrich, N., Sanden, A., Kraft, A., *et al.* (2015) Advances in inline quantification of co-eluting proteins in chromatography: Process-data-based model calibration and application towards real-life separation issues. *Biotechnology and Bioengineering* **112**, 1406–1416.

[7] Brestrich, N., Sanden, A., Kraft, A., *et al.* (2015) Advances in inline quantification of co-eluting proteins in chromatography: Process-data-based model calibration and application towards real-life separation issues. *Biotechnology Bioengineering* **112**, 1406–1416.

[8] Brinkrolf, K., Rupp, O., Laux, H., *et al.* (2013) Chinese hamster genome sequenced from sorted chromosomes. *Nature Biotechnology* **31**, 694–695.

[9] Buchacher, A., Iberer, G., (2006) Purification of intravenous immunoglobulin G from human plasma – Aspects of yield and virus safety. *Biotechnology Journal* **1**, 148–163.
[10] Byoung, J.K., Duk, J.O., Ho, N.C., (2008) Limited use of Centritech Lab II centrifuge in perfusion culture of rCHO cells for the production of recombinant antibody. *Biotechnology progress* **24**, 166–174.
[11] Byoung, J.K., Ho, N.C., Duk, J.O., (2007) Application of a cell-once-through perfusion strategy for production of recombinant antibody from rCHO cells in a Centritech Lab II centrifuge system. *Biotechnology Progress* **23**, 1186–1197.
[12] Carta, G., Perez-Almodovar, E.7., (2010) Productivity considerations and design charts for biomolecule capture with periodic countercurrent adsorption systems. *Separation Science Technology* **45**, 149–154.
[13] Cash, J.D., (1981) Clinical use of a human albuminoid preparation (SPPS) produced by the continuous small volume mixing (CSVM) fractionation technique. *Developments in Biological Standardization* **48**, 43–48.
[14] Castilho, L.R., (2015) *Continuous Animal Cell Perfusion Processes: The First Step Toward Integrated Continuous Biomanufacturing*. *Continuous Processing in Pharmaceutical Manufacturing*, Springer, Heidelberg, pp. 115–154.
[15] Chu, L., Robinson, D.K., (2001) Industrial choices for protein production by large-scale cell culture. *Current Opinion in Biotechnology* **12**, 180–187.
[16] Chuppa, S., Tsai, Y.S., Yoon, S., *et al.* (1997) Fermentor temperature as a tool for control of high-density perfusion cultures of mammalian cells. *Biotechnology and Bioengineering* **55**, 328–338.
[17] Desai, S.G., (2015) Continuous and semi-continuous cell culture for production of blood clotting factors. *Journal of Biotechnology* **213**, 20–27.
[18] Dietzsch, C., Spadiut, O., Herwig, C., (2013) On-line multiple component analysis for efficient quantitative bioprocess development. *Journal of Biotechnology* **163**, 362–370.
[19] Dizon-Maspat, J., Bourret, J., D′Agostini, A., *et al.* (2012) Single pass tangential flow filtration to debottleneck downstream processing for therapeutic antibody production. *Biotechnology and Bioengineering* **109**, 962–970.
[20] Doblhoff-Dier, O., Gaida, T., Katinger, H., *et al.* (1994) A novel ultrasonic resonance field device for the retention of animal cells. *Biotechnology Progress* **10**, 428–432.
[21] Elsayed, E.A., Medronho, R.A., Wagner, R., *et al.* (2006) Use of hydrocyclones for mammalian cell retention: Separation efficiency and cell viability (Part 1). *Engineering in Life Sciences* **6**, 347–354.
[22] Farid, S.S., (2007) Process economics of industrial monoclonal antibody manufacture. *Journal of Chromatography B Analytical Technology Biomedicine Life Sciences* **848**, 8–18.
[23] Farid, S.S., Washbrook, J., Titchener-Hooker, N.J., (2007) Modelling biopharmaceutical manufacture: Design and implementation of SimBiopharma. *Computational Chemical Engineering* **31**, 1141–1158.
[24] FDA, (2004) *Guidance for Industry: PAT – A Framework for Innovative Pharmaceutical Development, Manufacturing and Quality Assurance*. FDA, Rockville.
[25] Figueredo-Cardero, A., Chico, E., Castilho, L.R., *et al.* (2009) CFD simulation of an internal spin-filter: Evidence of lateral migration and exchange flow through the mesh. *Cytotechnology* **61**, 55–64.
[26] Foster, P.R., Dickson, A.J., McQuillan, T.A., *et al.* (1982) Control of large-scale plasma thawing for recovery of cryoprecipitate factor VIII. *Vox Sanguinis* **42**, 180–189.
[27] Gefroh, E., Lutz, H., (2014) An alternate diafiltration strategy to mitigate protein precipitation for low solubility proteins. *Biotechnology Progress* **30**, 646–655.

[28] Godawat, R., Brower, K., Jain, S., *et al.* (2012) Periodic counter-current chromatography – design and operational considerations for integrated and continuous purification of proteins. *Biotechnology Journal* **7**, 1496–1508.
[29] Godawat, R., Konstantinov, K., Rohani, M., *et al.* (2015) End-to-end integrated fully continuous production of recombinant monoclonal antibodies. *Journal of Biotechnology* **213**, 13–19.
[30] Hammerschmidt, N., Hintersteiner, B., Lingg, N., *et al.* (2015) Continuous precipitation of IgG from CHO cell culture supernatant in a tubular reactor. *Biotechnology Journal* **10**, 1196–1205.
[31] Hammerschmidt, N., Tscheliessnig, A., Sommer, R., *et al.* (2014) Economics of recombinant antibody production processes at various scales: Industry-standard compared to continuous precipitation. *Biotechnology Journal* **9**, 766–775.
[32] Hammond, M., Marghitoiu, L., Lee, H., *et al.* (2014) A cytotoxic leachable compound from single-use bioprocess equipment that causes poor cell growth performance. *Biotechnology Progress* **30**, 332–337.
[33] Hammond, M., Nunn, H., Rogers, G., *et al.* (2013) Identification of a leachable compound detrimental to cell growth in single-use bioprocess containers. *PDA Journal of Pharmaceutical Science and Technology* **67**, 123–134.
[34] Hansen, S.K., Skibsted, E., Staby, A., *et al.* (2011) A label-free methodology for selective protein quantification by means of absorption measurements. *Biotechnology and Bioengineering* **108**, 2661–2669.
[35] Heeter, G.A., Liapis, A.I., (1995) Perfusion chromatography: performance of periodic countercurrent column operation and its comparison with fixed-bed operation. *Journal of Chromatography A* **711**, 3–21.
[36] Jungbauer, A., (2013) Continuous downstream processing of biopharmaceuticals. *Trends in Biotechnology* **31**, 479–492.
[37] Kaltenbrunner, O., Lu, Y., Sharma, A., *et al.* (2012) Risk–benefit evaluation of on-line high-performance liquid chromatography analysis for pooling decisions in large-scale chromatography. *Journal of Chromatography. A* **1241**, 37–45.
[38] Kim, M., O'Callaghan, P.M., Droms, K.A., *et al.* (2011) A mechanistic understanding of production instability in CHO cell lines expressing recombinant monoclonal antibodies. *Biotechnology and Bioengineering* **108**, 2434–2446.
[39] Klutz, S., Magnus, J., Lobedann, M., *et al.* (2015) Developing the biofacility of the future based on continuous processing and single-use technology. *Journal of Biotechnology* **213**, 120–130.
[40] Konstantinov, K.B., Cooney, C.L., (2015) White paper on continuous bioprocessing. *Journal of Pharmaceutical Sciences* **104**, 813–820.
[41] Kuczewski, M., Schirmer, E., Lain, B., *et al.* (2011) A single-use purification process for the production of a monoclonal antibody produced in a PER.C6 human cell line. *Biotechnology Journal* **6**, 56–65.
[42] Li, F., Vijayasankaran, N., Shen, A., *et al.* (2010) Cell culture processes for monoclonal antibody production. *mAbs* **2**, 466–479.
[43] Lim, A.C., Zhou, Y., Washbrook, J., *et al.* (2005) Application of a decision-support tool to assess pooling strategies in perfusion culture processes under uncertainty. *Biotechnology Progress* **21**, 1231–1242.
[44] Luchner, M., Gutmann, R., Bayer, K., *et al.* (2012) Implementation of proton transfer reaction-mass spectrometry (PTR-MS) for advanced bioprocess monitoring. *Biotechnology Bioengineering* **109**, 3059–3069.
[45] Luchner, M., Striedner, G., Cserjan-Puschmann, M., *et al.* (2015) Online prediction of product titer and solubility of recombinant proteins in Escherichia coli fed-batch cultivations. *Journal of Chemical Technology and Biotechnology* **90**, 283–290.

[46] Malphettes, L., Freyvert, Y., Chang, J., *et al.* (2010) Highly efficient deletion of FUT8 in CHO cell lines using zinc-finger nucleases yields cells that produce completely nonfucosylated antibodies. *Biotechnology and Bioengineering* **106**, 774–783.

[47] Mariati, Yeo, J.H.M., Koh, E.Y.C., *et al.* (2014) Insertion of core CpG island element into human CMV promoter for enhancing recombinant protein expression stability in CHO cells. *Biotechnology Progress* **30**, 523–534.

[48] Marisch, K., Bayer, K., Cserjan-Puschmann, M., *et al.* (2013) Evaluation of three industrial Escherichia coli strains in fed-batch cultivations during high-level SOD protein production. *Microbial Cell Facts* **12**.

[49] Milián, E., Kamen, A.A., (2015) Current and emerging cell culture manufacturing technologies for influenza vaccines. *BioMed Research International* 2015.

[50] Mitra, G., Lundblad, J., (1978) Continuous fractionation of human plasma. *Biotechnology and Bioengineering* **20**, 1037–1044.

[51] Nesta, D.P., Elliott, J.S., Warr, J.P., (2000) Supercritical fluid precipitation of recombinant human immunoglobulin from aqueous solutions. *Biotechnology and Bioengineering* **67**, 457–464.

[52] Novais, J.L., Titchener-Hooker, N.J., Hoare, M., (2001) Economic comparison between conventional and disposables-based technology for the production of biopharmaceuticals. *Biotechnology and Bioengineering* **75**, 143–153.

[53] Pais, D.A., Carrondo, M.J., Alves, P.M., *et al.* (2014) Towards real-time monitoring of therapeutic protein quality in mammalian cell processes. *Current Opinion in Biotechnology* **30**, 161–167.

[54] Paul, M.J., Teh, A.Y.H., Twyman, R.M., *et al.* (2013) Target product selection – where can molecular Pharming make the difference? *Current Pharmaceutical Design* **19**, 5478–5485.

[55] Pfister, D., Morbidelli, M., (2014) Process for protein PEGylation. *Journal of Controlled Release* **180**, 134–149.

[56] Pietrzykowski, M., Flanagan, W., Pizzi, V., *et al.* (2013) An environmental life cycle assessment comparison of single-use and conventional process technology for the production of monoclonal antibodies. *Journal of Cleaner Production* **41**, 150–162.

[57] Pinto, R.C.V., Medronho, R.A., Castilho, L.R., (2008) Separation of CHO cells using hydrocyclones. *Cytotechnology* **56**, 57–67.

[58] Pollock, J., Ho, S.V., Farid, S.S., (2012) Computer-aided design and evaluation of batch and continuous multi-mode biopharmaceutical manufacturing processes. *Computer Aided Chemical Engineering*, **2012**, 487–491.

[59] Pollock, J., Ho, S.V., Farid, S.S., (2013) Fed-batch and perfusion culture processes: Economic, environmental, and operational feasibility under uncertainty. *Biotechnology and Bioengineering* **110**, 206–219.

[60] Pollock, J., Ho, S.V., Farid, S.S., (2013) Fed-batch and perfusion culture processes: economic, environmental, and operational feasibility under uncertainty. *Biotechnology and Bioengineering* **110**, 206–219.

[61] Presentation, P., Leung, W.W.F., (2008) Centrifugal separation in biotechnology. in: *21st American Filtration and Separations Society Annual Conference*, AFSC, Valley Forge, pp. 1053–1062.

[62] Przybycien, T.M., Pujar, N.S., Steele, L.M., (2004) Alternative bioseparation operations: Life beyond packed-bed chromatography. *Current Opinion in Biotechnology* **15**, 469–478.

[63] Rathore, A.S., Parr, L., Dermawan, S., *et al.* (2010) Large scale demonstration of a process analytical technology application in bioprocessing: use of on-line high performance liquid chromatography for making real time pooling decisions for process chromatography. *Biotechnology Progress* **26**, 448–457.

[64] Rathore, A.S., Winkle, H., (2009) Quality by design for biopharmaceuticals. *Nature Biotechnology* **27**, 26–34.

[65] Rathore, A.S., Wood, R., Sharma, A., *et al.* (2008) Case study and application of process analytical technology (PAT) towards bioprocessing: II. Use of ultra-performance liquid chromatography (UPLC) for making real-time pooling decisions for process chromatography. *Biotechnology and Bioengineering* **101**, 1366–1374.

[66] Records, A., Sutherland, K., (2001) *Decanter Centrifuge Handbook*. Elsevier, Amsterdam, pp. 1–14.

[67] Satzer, P., Tscheließnigg, A., Sommer, R., *et al.* (2014) Separation of recombinant antibodies from DNA using divalent cations. *Engineering in Life Sciences* **14**, 477–484.

[68] Shukla, A.A., Gottschalk, U., (2013) Single-use disposable technologies for biopharmaceutical manufacturing. *Trends in Biotechnology* **31**, 147–154.

[69] Singh, N., Arunkumar, A., Chollangi, S., *et al.* (2015) Clarification technologies for monoclonal antibody manufacturing processes: Current state and future perspectives. *Biotechnology and Bioengineering* **33**, 48–53.

[70] Sommer, R., Satzer, P., Tscheliessnig, A., *et al.* (2014) Combined polyethylene glycol and CaCl2 precipitation for the capture and purification of recombinant antibodies. *Processes in Biochemistry* **49**, 2001–2009.

[71] Sou, S.N., Sellick, C., Lee, K., *et al.* (2015) How does mild hypothermia affect monoclonal antibody glycosylation? *Biotechnology and Bioengineering* **112**, 1165–1176.

[72] Striedner, G., Pfaffenzeller, I., Markus, L., *et al.* (2010) Plasmid-free T7-based Escherichia coli expression systems. *Biotechnology and Bioengineering* **105**, 786–794.

[73] Tomic, S., Besnard, L., Fürst, B., *et al.* (2015) Complete clarification solution for processing high density cell culture harvests. *Separation Purification Technology* **141**, 269–275.

[74] Tscheliessnig, A., Satzer, P., Hammerschmidt, N., *et al.* (2014) Ethanol precipitation for purification of recombinant antibodies. *Journal of Biotechnology* **188**, 17–28.

[75] Uretschläger, A., Jungbauer, A., (2002) Preparative continuous annular chromatography (P-CAC), a review. *Bioprocesses Biosystematic Engineering* **25**, 129–140.

[76] Veith, N., Ziehr, H., MacLeod, R.A.F., *et al.* (2016) Mechanisms underlying epigenetic and transcriptional heterogeneity in Chinese hamster ovary (CHO) cell lines. *BMC Biotechnology* **16**.

[77] Velayudhan, A., (2014) Continuous antibody purification using precipitation: An important step forward. *Biotechnology Journal* **9**, 717–718.

[78] Ventini-Monteiro, D., Dubois, S., Astray, R.M., *et al.* (2015) Insect cell entrapment, growth and recovering using a single-use fixed-bed bioreactor. *Scaling up and recombinant protein production. Journal of Biotechnology* **216**, 110–115.

[79] Vogel, J.H., Nguyen, H., Giovannini, R., *et al.* (2012) A new large-scale manufacturing platform for complex biopharmaceuticals. *Biotechnology and Bioengineering* **109**, 3049–3058.

[80] Wang, G., Zhang, W., Jacklin, C., *et al.* (1992) Modified CelliGen-packed bed bioreactors for hybridoma cell cultures. *Cytotechnology* **9**, 41–49.

[81] Warikoo, V., Godawat, R., (2015) A new use for existing technology – continuous precipitation for purification of recombination proteins. *Biotechnology Journal* **10**, 1101–1102.

[82] Tscheliessnig, A., Jungbauer, A. (2008) Precipitation of IgM in a stirred tank reactor with PEG. *ISPPP* **2008**, 52–53.

[83] Warikoo, V., Godawat, R., Brower, K., *et al.* (2012) Integrated continuous production of recombinant therapeutic proteins. *Biotechnology and Bioengineering* **109**, 3018–3029.

[84] Warnock, J.N., Al-Rubeai, M., (2006) Bioreactor systems for the production of biopharmaceuticals from animal cells. *Biotechnology and Applied Biochemistry* **45**, 1–12.

[85] Wellhoefer, M., Sprinzl, W., Hahn, R., *et al.* (2014) Continuous processing of recombinant proteins: Integration of refolding and purification using simulated moving bed size-exclusion chromatography with buffer recycling. *Journal of Chromatography A* **1337**, 48–56.

[86] Woodside, S.M., Bowen, B.D., Piret, J.M., (1998) Mammalian cell retention devices for stirred perfusion bioreactors. *Cytotechnology* **28**, 163–175.
[87] Woodside, S.M., Piret, J.M., Gröschl, M., *et al.* (1998) Acoustic force distribution in resonators for ultrasonic particle separation. *AIChE Journal* **44**, 1976–1984.
[88] Xenopoulos, A., (2015) A new, integrated, continuous purification process template for monoclonal antibodies: Process modeling and cost of goods studies. *Journal of Biotechnology* **213**, 42–53.
[89] Yang, Z., Wang, S., Halim, A., *et al.* (2015) Engineered CHO cells for production of diverse, homogeneous glycoproteins. *Nature Biotechnology* **33**, 842–844.
[90] Zhang, Y., Stobbe, P., Silvander, C.O., *et al.* (2015) Very high cell density perfusion of CHO cells anchored in a non-woven matrix-based bioreactor. *Journal of Biotechnology* **213**, 28–41.

8

Twin-screw Granulation Process Development: Present Approaches, Understanding and Needs

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8.1 Introduction

The opportunity to change the manufacturing paradigm in the pharmaceutical industry from predominantly batch processing to a fully integrated continuous processing became accomplishable in the last decade. Beside the recently perceived increased regulatory freedom, a major credit also goes to the equipment manufacturers for their contributions towards the development of a continuous "from powder to tablet" manufacturing line and in-line measurement systems. However, extensive research is still needed to support this transition, both in terms of developing the detailed understanding of the unit operations and in propagating this to process design and control. Wet granulation is one such key unit operation in solid dosage manufacturing.

Twin-screw granulation is an emerging continuous wet granulation technique which allows great flexibility in equipment design and choosing process variables. Based on

Continuous Manufacturing of Pharmaceuticals, First Edition.
Edited by Peter Kleinebudde, Johannes Khinast, and Jukka Rantanen.
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the published literature, twin-screw granulation studies can be broadly classified into data-driven studies and (semi-)mechanistic studies. The experimental data-driven studies mostly investigate the link between process settings and granulation performance using multivariate data analysis [1–4]. However, despite these efforts, the effect of process settings on the evolution and kinetics of granule formation to obtain a certain resulting granule structure is not as well established as the batch granulation processes. Moreover, the pharmaceutical sector is traditionally trained with empirical models which do not allow for transferring knowledge between systems. Thus, in the past years (semi-)mechanistic studies towards understanding the transport, mixing and the constitutive mechanisms of wet granulation in a twin-screw granulator (TSG) were also performed using both experimental 5–9] and theoretical [10–13] approaches. These studies attempt to acquire a more fundamental understanding of the continuous granulation processes which can be used for reducing experimental data collection, allowing for transferring knowledge between systems (which cannot be done with empirical models) and improving process and equipment design, process control, and process efficiency.

In this book chapter, we mainly discuss research which has been performed to develop a mechanistic description of continuous twin-screw wet granulation process by combining experimental and theoretical modelling-based approaches. This is mainly intended to demonstrate that experimental results, when linked to a theoretical model, can provide a fundamental basis and detailed description for the underlying parameters, such as granulation time, mixing and constitutive mechanisms in the case of twin-screw wet granulation. However, before getting into mechanistic details and discussion, we first introduce the key components of a twin-screw granulation module and the basics of its application as a high-shear wet granulation tool.

8.2 Continuous Wet-granulation using a TSG

The continuous twin-screw granulation system is operated as part of a continuous manufacturing line. Here, the specific example of the ConsiGma™ manufacturing line by GEA Pharma Systems (Collette™, Wommelgem, Belgium; Figure 8.1) has been used as example to describe the twin-screw granulation operation. The twin-screw granulation module consists of a powder feeder, a granulation liquid addition system and a TSG. The powder feeder to the TSG [(a) in Figure 8.1] operates based on the loss in weight control principle and feeds the powder continuously into the granulator [(c) in Figure 8.1]. The weight loss during the feeder operation is used to calculate the feed factor which is used by the powder dosing motor to determine the necessary speed to obtain a preset powder feed rate. A pre-blended mixture consisting of excipients and active pharmaceutical ingredients (APIs) is fed and passed through a rotational bridge breaker into the feed segment of the granulator. A bridge breaker prevents bridging and ensures the mixing of feed before entering the granulation unit.

To achieve wet granulation, liquid is pumped into the granulator through two injection nozzles mounted in the work segment of the granulator [(b) in Figure 8.1]. The preset liquid addition rate is controlled based on the loss in weight principle which is used to determine the rotation speed of the peristaltic pump. As these peristaltic pumps consist of a head with three rollers producing three liquid pulses per revolution, the two pumps related to the liquid injection nozzles are kept out-of-phase. The granulation unit [(c) in Figure 8.1] consists of a barrel enclosing two co-rotating self-wiping screws (Figure 8.2).

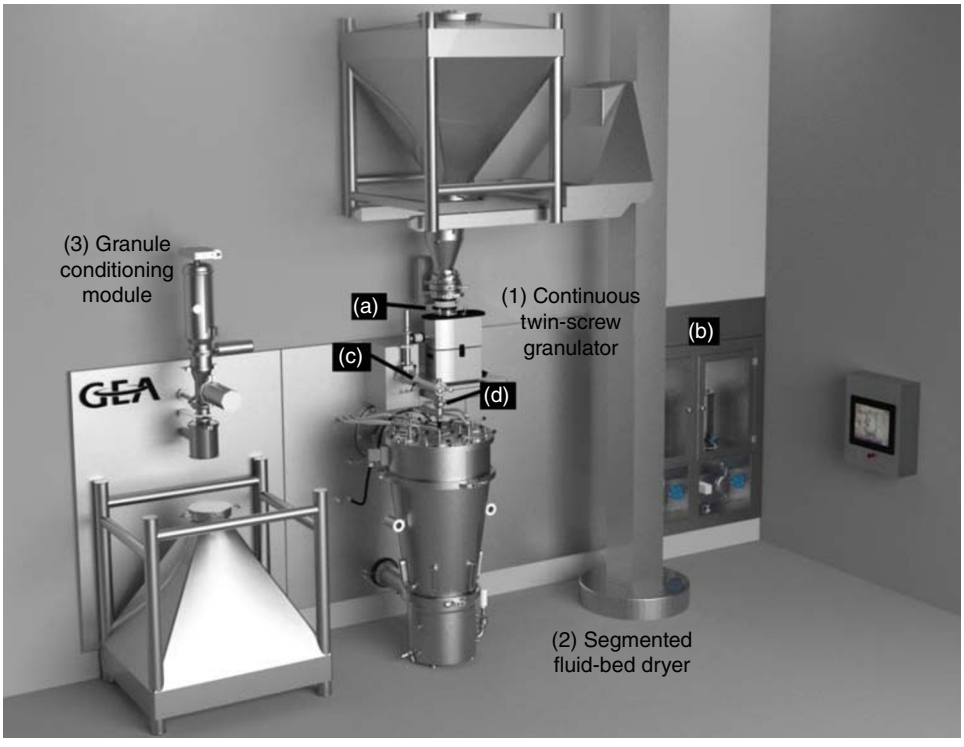


Figure 8.1 *Three main units of the continuous manufacturing line, ConsiGma™ by GEA Pharma Systems (Collette™, Wommelgem, Belgium). The continuous twin-screw granulation system contains (a) powder feeder, (b) liquid addition system, (c) twin-screw granulator and (d) wet granules transfer line (Courtesy of GEA Pharma Systems).*

Based on the function of a specific segment, the granulator can be divided into three segments, that is a feed segment, a work segment and a discharge segment (a, b and c in Figure 8.3). In the feed segment, the dry powder is fed into the barrel containing screws with transport elements. The powder in this segment is dry blended while being transported to the work segment. In the work segment, the powder is mixed, wetted and granulated. The granulation liquid is added via two nozzles, one for each screw, after which the material reaches the mixing zone which consists of kneading discs (Figure 8.2).

Further down, since granulation occurs by a combination of capillary and viscous forces binding particles in the wet state, the wetted material is distributed, compacted and elongated by the kneading discs of the mixing zones, changing the particle morphology from small (micro-structure) to large (macro-structure). A number of wet granulation sub-processes such as aggregation and breakage take place during this processing (Figure 8.2). The modular structure of the screws allows changing the number of kneading discs, hence the length of the mixing zone. The material is mixed, compacted and chopped to form irregular and porous granules by the succeeding transport elements and kneading blocks. The rotation of the screws conveys the material in the axial direction through the different zones of the TSG by drag and flow-induced displacement forces and thus causing mixing and granulation. The wet granules produced by the granulator leave the unit through the discharge zone of the barrel [(d) in Figure 8.1] and are pneumatically

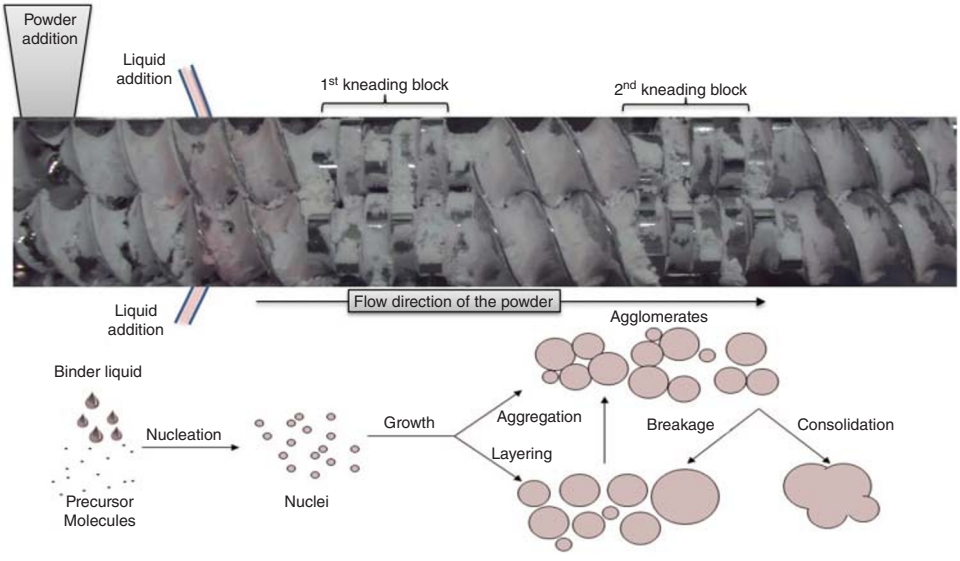


Figure 8.2 *Screw configuration with 12 kneading discs (two mixing blocks, each containing six kneading discs) indicating the geometry of the screws used in a TSG [11].*

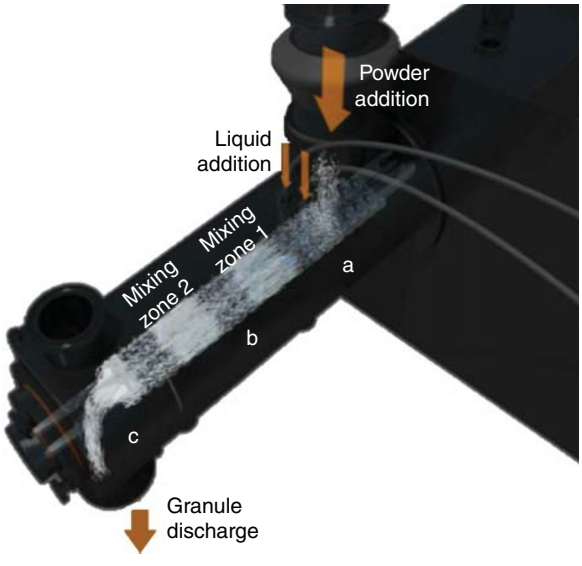


Figure 8.3 *The feed segment (a), work segment (b) and discharge segment (c) of a TSG during operation.*

transported to the six-segmented fluidised bed dryer [(2) in Figure 8.1]. For new generation systems, the TSG is placed on top of the dryer and the transport of wet granules to the dryer is gravimetric. The dried granules are thereafter pneumatically transported to the granule-conditioning module [(3) in Figure 8.1] which includes a screen and a process

analytical technology (PAT) toolbox to measure critical quality attributes such as granule size distribution (GSD), humidity and content uniformity.

8.3 Components of High Shear Wet Granulation in a TSG

To improve the process understanding regarding the TSG, the first step is the identification of the most critical aspects of the twin-screw wet granulation unit, which dictate the final granule quality during continuous high shear wet granulation (HSWG).

Being a continuous operation, the TSG operates at a steady state and therefore it is critical to quantify how much time is actually spent by the material inside the TSG barrel. In other words, how much time is available for the material to granulate because, once the material leaves the granulator, the field conditions responsible for wet granulation are no longer available. Hence, characterisation of the material flow and mixing in the TSG is required, based on the characteristic residence time distribution (RTD) of material inside the granulator.

As the screw geometry and process conditions affect the field conditions inside the TSG barrel, thus changing the mixing and local residence time, it is critical to examine the particle size and shape evolution along the length of the granulator. It is also important to understand the role of different screw elements in the screw geometry and how their role in shaping the GSD changes for different process conditions.

Beside the decomposition of different mechanisms taking place during twin-screw wet granulation, the potential link between the residence time, mixing (both axial and solid–liquid mixing) and the resulting GSD inside the granulator barrel should be confirmed at varying process and equipment settings, hence accounting for the inherent flexibility of the TSG. Since residence time and its distribution, as well as solid–liquid mixing all dictate the final granulation yield, the measurement of the resulting GSD is necessary to understand the overall influence of different flow and mixing conditions during twin-screw granulation. This knowledge is required to find an optimal way to execute the process, bearing in mind the required CQAs.

As discussed in the introduction, the knowledge can be ideally derived and improved from the combined effort of experimental and modelling studies. Thus, the hypothesis based on the results from experimental studies should be tested through mathematical models which describe and analyse the overall granulation process as it progresses along the length of the granulator. Additionally, in order to consolidate the results for multi-scale applications, a scale-independent approach is desired. The regime maps theory and particle-scale modelling based on fundamental principles of physics can in this respect be applied to describe the twin-screw granulation process.

Henceforth, various aspects of wet-granulation in a TSG, such as granulation time, mixing and particle size evolution, are discussed along with the benefits in terms of knowledge growth by combination of experimental and mathematical methods.

8.4 Material Transport and Mixing in a TSG

The solid–liquid mixing in a TSG must be achieved in a short period by appropriate arrangement of transport and kneading elements in the granulator barrel allowing the production

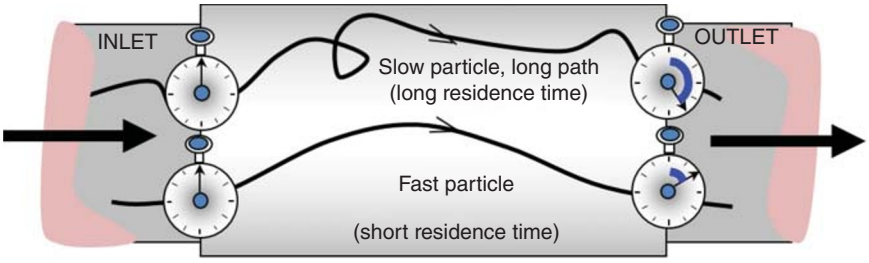


Figure 8.4 *Due to non-ideal plug flow transport in the twin-screw granulator, the material spends different times, leading to a residence time distribution.*

of granules with a GSD suitable for tableting. This is because the TSG displays a very short residence time (2–20 s) compared to that of batch high-shear granulators operating for minutes to hours. Therefore, it is interesting to investigate how different process and equipment settings lead to changes in the residence time. However, since transport inside the granulator is not an ideal plug flow, some material spends more time than other material leading to a RTD at the granulator outlet (Figure 8.4). This difference in axial velocity of the material leads to axial mixing of the material inside the TSG barrel. Thus, a dedicated RTD study provides details both on the mean granulation time and on the axial mixing inside the granulator. Beside the axial mixing, the mixing of wetted material also depends on the role of kneading elements which mainly contribute to material homogenisation by distributive mixing [14]. Thus, in order to understand the mixing which consequently leads to a certain granulation yield, both axial and solid–liquid mixing of the bulk material should be accounted for. This is also very important as a residence time change may also result in an alteration in flow regime inside the TSG. If this transition is from a mixed flow to the plug flow regime, it is not desirable for mixing which is ultimately required for proper granulation [8]. Thus, the material flow dictating granulation time and mixing inside the granulator should be investigated both for different process parameters (material throughput and screw speed) and for equipment parameters (number of kneading discs and the stagger angle).

8.4.1 Granulation Time in a TSG

The most promising feature about twin-screw wet granulation is the ability to process a high material throughput with a short residence time (typically a few seconds). Although from a productivity point of view, this time gain with respect to batch granulation (which takes much more time) is preferred, its implications on the extent of the granulation rate processes and consequently the granulation yield can be unfavourable [15]. This is because, within this limited time frame, both homogeneous distribution of granulation material (especially solid–liquid mixing) and different rate processes of granulation such as aggregation and breakage have to occur to produce a final GSD. Thus, the main aim of process design for achieving a high granulation yield in continuous twin-screw granulation should be to keep the residence time sufficiently longer than the mixing time of the material transported across the granulator barrel.

Due to this immense importance, experimental investigation of RTD in a TSG and its impact on granulation performance has attracted the attention of several research groups.

Dhenge *et al*. [16] measured the RTD using the sampling cup method under different processing conditions and showed that process parameters such as screw speed and liquid to solid (L/S) ratio have vital influence on the residence time. El Hagrasy *et al*. [15] applied the same approach for RTD measurement to estimate the effect of changes in composition of raw material as well as changes in the viscosity of the granulation liquid on the granule properties. However, measurement of RTD using the sampling cup method for a very fast process like twin-screw granulation is very difficult and can lead to a significantly high measurement error, making this method unsuitable [17]. Recently, Li *et al*. [17] used a visual technique based on digital video recording to measure RTD as a function of feed rate during twin-screw granulation. Results from that study indicated a significant increase in $\bar{t}$ and a narrowing of RTD at higher feed rate. In a remarkable attempt, Lee *et al*. [18] obtained the RTD for TSG using positron emission particle tracking (PEPT) to study the axial mixing of the processed material inside the TSG barrel, which is essential information for the optimisation of the obtained granule properties. Although this technique is very powerful for investigating the local residence time in the material, the single-particle tracking method also suffers from major challenges due to requirement of change in granulator design itself and experimental error due to inability to track the total flow behaviour, which is not desirable as some material paths are so rare that they will not be followed by a finite number of tracer paths through the equipment [8]. Kumar *et al.* [8] addressed this challenge by applying an image data collection method based on near infrared (NIR) chemical imaging (CI) to measure a tracer (theophylline anhydrate) which was injected into the granulator and monitored to investigate the RTD of the tracer inside the barrel as a function of process settings.

All these methods rely on the impulse response principle, Thus, an RTD obtained by injecting a pulse of tracer into the system inlet is used to calculate the residence time function, $e(t)$, calculated as:

$$e(t) = \frac{c(t)}{\int_0^\infty c(t)\mathrm{d}t} \tag{8.1}$$

where $c(t)\mathrm{d}t$ is the concentration of the tracer at the outlet between t and $t + \Delta t$. The exit age distribution of the tracer molecule is derived from the tracer concentration c_i between t and $t + \delta t$ in the temporal profile of the discrete measurement calculated as:

$$e(t) = \frac{c_i}{\sum_{i=1}^{t} c_i \Delta t} \tag{8.2}$$

This tracer map is transformed into the exit age distribution curve, that is the RTD based on the mean tracer concentration, $e(t)$ between t and $t + \mathrm{d}t$, which is then used to calculate the mean residence time $\bar{t}$ as the ratio of the first and the zero-th moment using the following equation:

$$\bar{t} = \frac{\int_0^\infty t.e(t)\mathrm{d}t}{\int_0^\infty e(t)\mathrm{d}t} \tag{8.3}$$

Experimental studies to investigate RTD in TSG have showed that the screw speed most significantly changes the residence time of material during operation [8, 16, 18]. This is mainly related to a high conveying rate of the rapidly moving twin-screw which reduces the mean residence time $\bar{t}$ [16, 18]. Moreover, the sequential change in the process parameters

(material throughput, screw speed, L/S, etc.) and the screw configuration (number of kneading elements and their stagger angle) in the experimental studies demonstrated that not only the parameters independently affect the residence time, but their interaction strongly changes depending on the flow regime inside the granulator, which drives the residence time of the material (Figure 8.5). The flow restriction caused by an increasing number of kneading discs increases $\bar{t}$ by increasing the plug flow component in the TSG [11]. Thus, if the distributive mixing is insufficient, the changes in the flow regime inside the granulator also lead to a reduced efficiency. Moreover, increasing the stagger angle or reducing the screw speed for a screw configuration with a high number of kneading discs quickly changes the flow regime into a critical plug flow level, leading to granulator jamming. Similarly, material throughput is reported as a parameter leading to reduction in the $\bar{t}$ at a high throughput [3], which was also confirmed by other studies [6, 8]. This is mainly attributed to the increased throughput force of the material leading to a low $\bar{t}$. However, the limits of this hypothesis was also demonstrated in terms of effect reversal, that is an increase in $\bar{t}$ with increasing material throughput at high fill degree conditions [8]. It was shown that the extra conveying rate is limited by the conveying capacity of the screws which cannot be increased inexhaustibly by an increasing material throughput. Interestingly, an increasing L/S results in an increase in $\bar{t}$, as was obtained by Dhenge *et al*. [4] and Vercruysse *et al*. [5], but the torque level of the granulator is reduced. This suggests that an increase in the amount of liquid made the material more cohesive and resistant to flow, which increased the

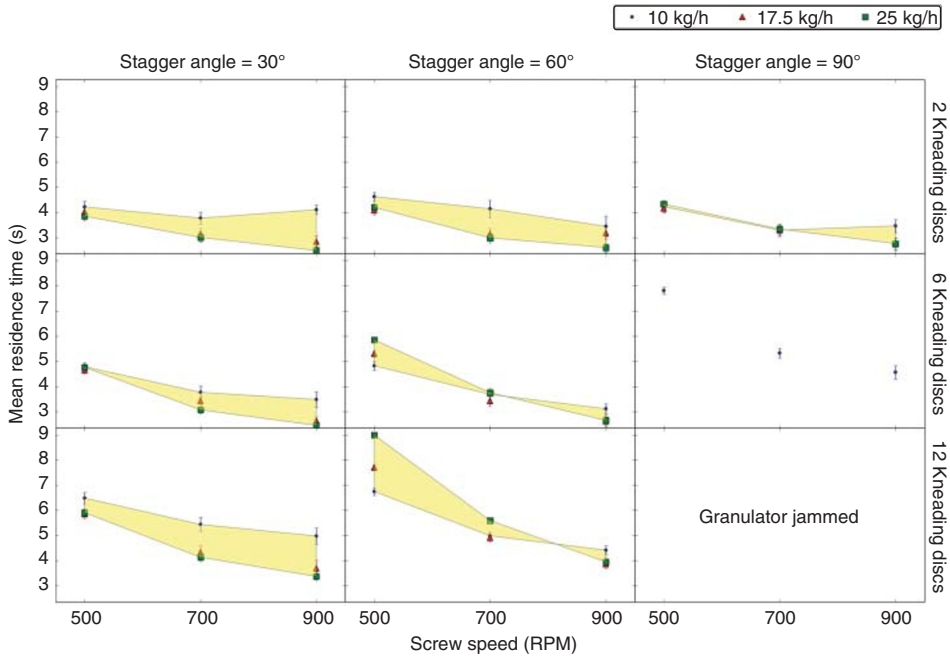


Figure 8.5 *Mean residence time* $\bar{t}$ *and standard deviation based on the experimental RTD profile at various material throughputs (10–25 kg/h), number of kneading discs (2, 6, 12), stagger angle (30–90°) and different screw speeds (500–900 rpm) [8].*

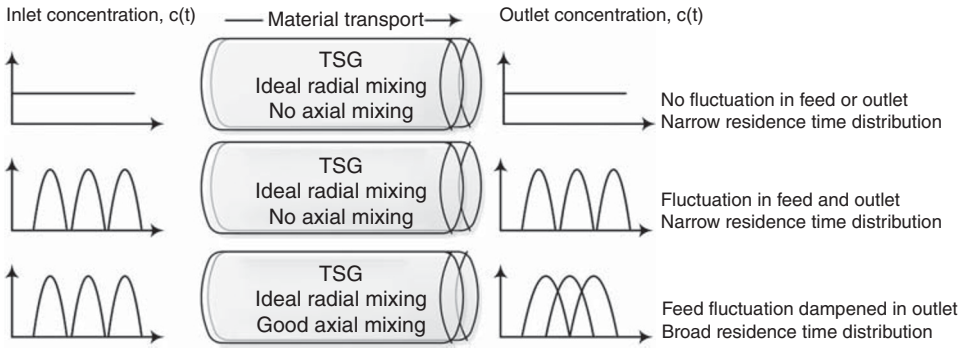


Figure 8.6 *Radial and axial mixing as a function of the material feeding characteristics and the RTD in a TSG.*

granulation time [19]. However, lowering of torque despite longer time spent by material confirms that the granulation liquid at a high fill ratio had a lubricating effect on the screw rotation without increasing the conveying rate.

8.4.2 Mixing in a TSG

The mixing inside a TSG is related to the functional role of the screw configuration as well as the induced shear by the rotating screws based on the process settings. The bulk mixing is classified as axial or radial based on the direction of spread in the granulator barrel. In the high-shear environment of a TSG, a good radial mixing is required to ensure a homogeneous distribution with a constant material throughput (top scheme in Figure 8.6). However, in the case of variations in the material and process inputs, which is inevitable in a pharmaceutical manufacturing environment [20], lack of axial mixing will lead to the same amount of variability in the outlet (middle scheme in Figure 8.6). A good axial mixing in addition to the radial mixing during granulation in TSG is thus required to avoid the effect of any inhomogeneities at the inlet on the produced granules (bottom scheme in Figure 8.6). The feeding rate of the granulation material, the screw speed and the screw configuration can be independently chosen to achieve the desired mixing level of the material, both in terms of axial mixing and in terms of bulk mixing of solid and liquid. As discussed earlier, the RTD exhibited by the system yields distinctive evidence regarding the degree of axial mixing occurring within the system. On the other hand, a knowledge of solid–liquid mixing requires detailed investigation of wet granules produced from the TSG [5].

8.4.2.1 Axial Mixing

Broadening of the RTD indicates the significant appearance of axial mixing, which in its turn varies based on process conditions and screw configuration in the TSG (Figure 8.7). The $\sigma_{\bar{t}}^2$ mvar, which expresses the width of the RTD, is calculated as:

$$\sigma_{\bar{t}}^2 = \frac{\int_0^\infty (t-\bar{t})^2 \cdot e(t)\mathrm{d}t}{\int_0^\infty e(t)\mathrm{d}t} \tag{8.4}$$

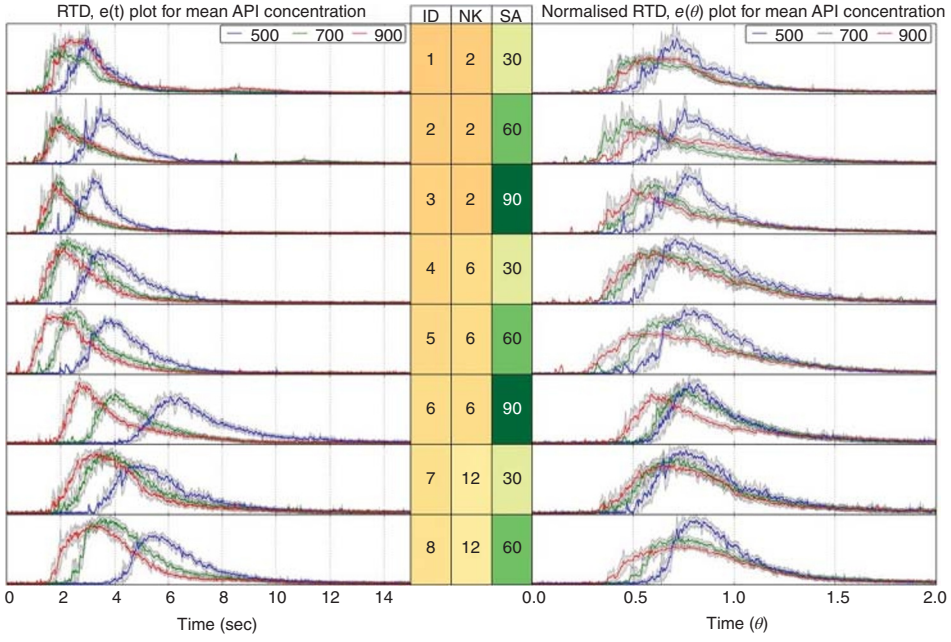


Figure 8.7 *The residence time distribution (left) and normalised residence time distribution (right) profiles with a shaded region denoting the standard deviation at different screw speed (500, 700 and 900 rpm) at material throughput of 10 kg/h during various experiments (ID) using twin-screw granulation [SA: stagger angle (°), NK: number of kneading discs (–)].*

The normalisation of this variance $\sigma_{\bar{t}}^2$ mvar yields the normalised variance σ_{θ}^2:

$$\sigma_{\theta}^2 = \frac{\sigma_{\bar{t}}^2}{\bar{t}^2} \tag{8.5}$$

Furthermore, the ratio of RTD variance and the delay in onset of RTD gives the Péclet number Pe. The dimensionless Pe represents the ratio of the rate of axial transport by convection and the rate of axial transport by diffusion or dispersion. By treating the boundary condition of the granulator as a closed system with no dispersion or radial variation in concentration either upstream or downstream, the following equation can be derived [21]:

$$\sigma_{\theta}^2 \approx \frac{2\mathrm{Pe} - 2 + 2 \cdot e^{-\mathrm{Pe}}}{\mathrm{Pe}^2} \tag{8.6}$$

When σ_{θ}^2 var approaches zero, Pe tends to infinity indicating that the extent of axial mixing is low and the material transport characteristics in the granulator approach those of a plug-flow reactor (PFR). This regime is not favourable in continuous processing, as shown by Kumar *et al*. [8] where the conditions leading to a greater extent of plug flow ultimately resulted in very low axial mixing and a complete disruption due to jamming of the TSG.

The screw geometry, scale and process parameters play a major role in imposing the degree of axial mixing. Kumar *et al*. [8] showed that, at a higher screw speed, the axial

mixing increased, which was quantified by the rise in σ_θ^2 and the lowering of Pe. Similarly, at a low filling condition with reduced material feed rate and few kneading discs, axial mixing increased. However, at a high fill condition increasing screw speed only reduced $\bar{t}$ without increasing the axial dispersion as flow becomes plug flow-like, which was also indicated by a high Pe. At a low screw speed the Pe increased sharply with feed rate, number of kneading elements and stagger angle, indicating a transition to plug flow when the throughput exceeded the conveying capacity. These results were contradictory to the earlier presented results by Dhenge *et al*. [16] and Lee *et al*. [18], who investigated RTD at a lower screw speed and material throughput with a granulator containing a smaller diameter screw and suggested that the extent of axial mixing is similar regardless of the screw speed, feed rate and screw configuration. In a recent review by Seem *et al*. [19], these differences have been discussed and more in-depth investigations of axial mixing using granulators of different scales and design are suggested.

8.4.2.2 Solid–liquid Mixing

Mixing powders together with a liquid is a challenging task in a TSG as the mixing time domain is limited and cannot be extended beyond a certain limit, for the reasons discussed in Section 8.4.1. The formation of liquid bridges between the powder particles results in aggregation to produce larger granules. Thus, a homogeneous liquid distribution within the powder is desired both to initialise the wet granulation and to obtain granules exhibiting a narrow GSD. An uneven liquid distribution was suggested as the cause of a broad GSD and lump formation using a TSG by El Hagrasy *et al*. [15]. Despite this critical importance, the mixing of solid and liquid in a TSG is the least studied aspect of twin-screw granulation due to the difficulties in obtaining samples and performing real time analysis of wet granule product for moisture content homogeneity. Dhenge *et al*. [22] performed experiments using a co-rotating twin screw granulator with the metal barrel top replaced by a transparent acrylic glass for powder flow visualisation. This study was useful to understand the local field condition such as surface velocity of dry and wet materials or granules in the granulator. However, the modified barrel property forced the researchers to alter the screw configuration which consisted only of conveying screws and the granulation conditions such as operation at a low screw speed in order to make it a relatively low-shear system. Sayin *et al*. [9] recently used the same approach to visualise the flow in newly proposed distributive mixing elements used for twin-screw granulation. Beside the challenge of local flow visualisation, understanding the overall liquid distribution and its dynamics is no less challenging. In a landmark study by Vercruysse *et al*. [5], solid–liquid mixing was quantified using NIR-CI of the granules produced from a granulator operating at steady state. The study highlighted the fact that equipment design settings like the liquid addition location and the periodicity of the applied pump can lead to a significant variation in the moisture content distribution and are thus critical to the granulator design. In another detailed study by Kumar *et al*. [23] the mixing of solid and liquid was quantified as a mixing index (MI) of the produced granules and the mixing dynamics were quantified as frequency and amplitude of variations in the mean moisture profile of each run. The study suggested that an increasing number of kneading discs improves the liquid distribution in the material after the TSG, which was also observed earlier by Vercruysse *et al*. [5]

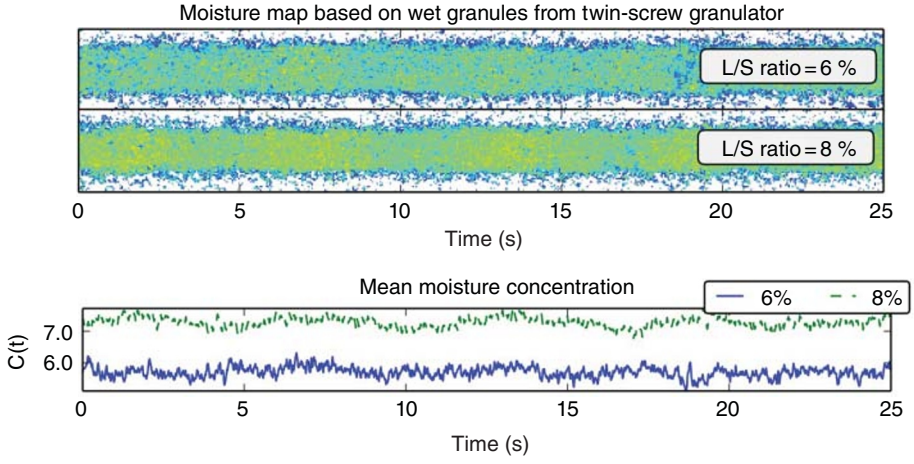


Figure 8.8 *A moisture map was used to calculate the mixing index; and the frequency and amplitude of the corresponding mean temporal profile was used to track dynamics of moisture content at different process conditions.*

(Figure 8.8). However, the present study also demonstrated that despite improvement in bulk solid–liquid mixing by the increasing number of kneading discs, the required quality of mixing inside the TSG barrel was still not achieved, which led to a broad GSD. Further increase in the number of kneading discs may indeterminately improve the bulk mixing, but will limit the feasible operating ranges of the process settings by increasing the plug-flow fraction in the transport profile, leading to an undesirable high torque level. Therefore, along with the efforts to modify the TSG screw configuration using conventional screw elements (conveying and kneading elements), efforts should also be directed into exploring non-conventional screw elements with modified geometries. Some efforts in this direction such as application of distributive mixing elements by [9], screw mixing elements by [24] and distributive flow elements by [25] have already shown positive results in terms of a narrower GSD. The study by Kumar *et al*. [23] also showed that, although a high material throughput and a high screw speed are desired for process efficiency, their exclusive increase causes inefficient solid–liquid mixing which is not desirable.

8.5 Granule Size Evolution During Twin-screw Granulation

Along with the granulation time and mixing degree of the material, the local field conditions (such as shear, free liquid and fill ratio) inside the transport and mixing zones of the granulator lead to the dominance of one constitutive granulation mechanism over others, resulting in a certain quality of granules at the TSG outlet. At the same time, the process (material throughput and screw speed) and equipment parameters (number of kneading discs and stagger angle) not only affect the transport and mixing discussed in Section 8.4, but also the field conditions and their interrelationship. Therefore, it is important to diagnose both the spatial evolution of particle size in the TSG as well as the link between residence

time, solid–liquid mixing and the consequently produced GSD for suitable tuning from the granulator configuration and the process conditions.

8.5.1 Granule Size and Shape Dynamics in a TSG

Knowledge regarding the primary shaping mechanisms behind particle size and shape distribution during wet granulation in a TSG is more limited, compared to high shear mixers, due to the opacity of the granulator [4, 6]. The flow visualisation studies performed by Dhenge *et al*. [22] and Sayin *et al*. [9] and discussed in Section 8.4.2 tried to characterise the change in flow structures in dense flow of particles, but the granular growth dynamics could not be investigated. Kumar *et al*. [7] applied another strategy in a TSG in which the barrel could be opened to collect samples from several locations inside the TSG. Although this technique could not visualise the granular flow dynamics, it allowed a detailed experimental investigation of the granule size and shape dynamics in the granulator at actual process conditions (Figure 8.9). One of the key observations of this study was that an increasing number of kneading discs in the screw configuration not only increased the fraction of larger granules for the downstream sample locations (such as 3 and 5 in Figure 8.9) which were located after the kneading blocks, but also increased it at the sample location which was located upstream of the kneading block (location 1 in Figure 8.9). This suggested that, along with the distributive mixing by the kneading block of the screw and dispersive mixing by the slippage of material at a high screw speed, a third mixing mechanism also exists in the TSG in which the built-up material before the "flow restricted" kneading zone is force-mixed with the incoming materials due to the throughput force. The results also suggested that the increasing throughput is beneficial and can lead to an increased amount of larger granules in the successive mixing zone only when sufficient granulation liquid is present to make strong agglomerates. However, a further granule size enlargement was observed which also corresponded with broadening of the distribution after the second kneading block [7]. This suggested a mixed granulation regime, that is, along with aggregation, size reduction mechanisms such as attrition and breakage also take place in the second kneading block. Moreover, spherification of granules was observed along the granulator length and for an increasing number of kneading discs (Figure 8.9). El Hagrasy *et al*. [6] also reported a greater consolidation due to chopping off the edges of the brittle and elongated granules in the second kneading block of the TSG.

8.5.2 Link Between RTD, Liquid Distribution and GSD in a TSG

Depending on the dominance of different size changing mechanisms based on the residence time, axial as well as solid–liquid mixing, and field conditions in transport and mixing zones of the TSG, the amount of certain size fractions in the produced granules dominates. Therefore, these interrelations were investigated recently by Kumar *et al*. [23] to discover the residence time and mixing settings which resulted in a certain granulation performance. Furthermore, the influence of process settings which lead to a variation in the residence time and mixing and can be applied to efficaciously steer the GSD profile were investigated. An increase in the number of kneading discs and L/S are generally suggested parameters to increase the granulation yield in TSG studies [6, 26, 27]. However,

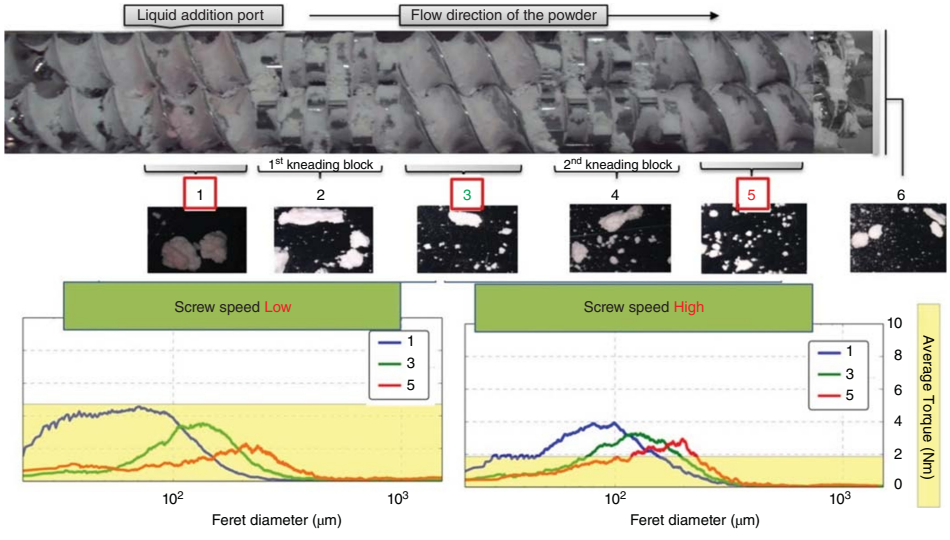
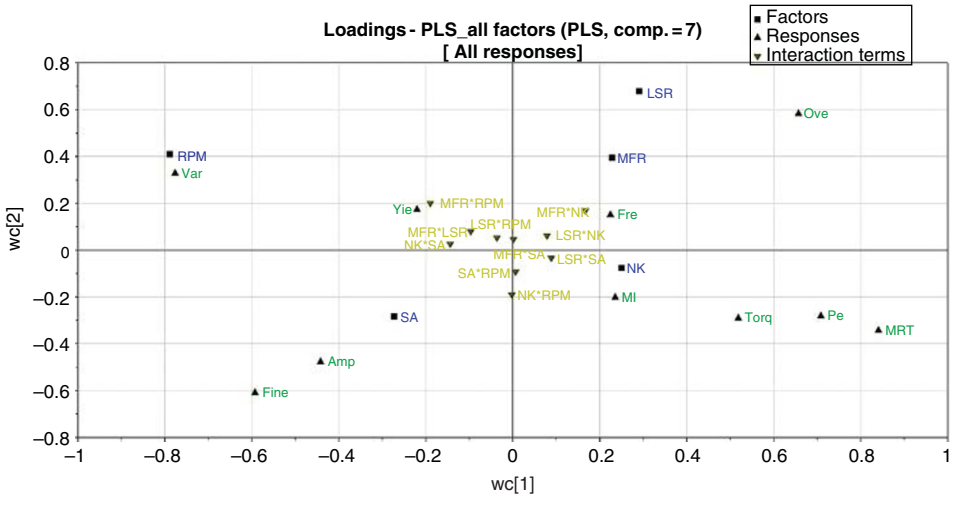


Figure 8.9 *Changes in the GSD based on the Feret diameter of the granules (see [27]) at different sampling locations along the screw length: 1, before first kneading block; 2, on the first kneading block; 3, between first and second kneading block; 4, on the second kneading block; 5, after the second kneading block; 6, outlet of the granulator. A screw configuration with 12 kneading discs (two blocks) was used in the twin screw granulator and resulted in three different GSD for sample locations 1, 3 and 5.*

increasing these parameters results in a broad GSD, which is not desirable [7, 15]. The study presented by Kumar *et al*. [23] showed that an increasing number of kneading discs did not significantly contribute to increasing the yield fraction, despite an improvement in bulk solid–liquid mixing and an increase in the residence time. This was reflected by the partial least squares (PLS) loading plots for this study where the number of kneading discs (NK) and yield fraction (Yie) are negatively correlated (Figure 8.10). Moreover, the yield fraction did not change significantly by increasing the L/S, since most of the additional liquid resulted in the formation of oversized granules, as indicated by the positive correlation between L/S (LSR) and oversized fraction (Ove) in Figure 8.10. Instead, the yield fraction reduced significantly by an increasing material throughput which is ultimately linked to the reduced residence time due to a higher throughput force as well as an inferior solid–liquid mixing, which is mostly driven by distributive mixing by the kneading discs. The measured torque of the granulator drive indicating power input to the system, Pe quantifying the axial mixing, MI quantifying the solid–liquid mixing and $\bar{t}$ quantifying the average time spent by the material inside the granulator are positively correlated, as can be seen in the loadings plot. On the other hand, all three size fractions (fine, yield and oversized granules) are located in different regions, suggesting that they have different important contributing factors. Moreover, the desired condition for the responses such as a high residence time, a good axial mixing, a good solid–liquid mixing and a resulting high yield fraction are favoured by different factors. This evidently suggests that the yield fraction of granules in the GSD obtained by the TSG is low due to inferior performance of the kneading discs in the solid–liquid mixing. Thus, other mixing element configurations should be explored as discussed in Section 8.4.2.



Torque (N = 51; DF = 35; R2 = 0.85), Mean residence time (N = 51 ; DF = 35; R2 = 0.89),
Normalised variance (N = 51; DF = 35; R2 = 0.77), Peclet number (N = 51; DF = 35; R2 = 0.65),
Fine (N = 51; DF = 35; R2 = 0.87), Yield (N = 51; DF = 35; R2 = 0.50), Oversized (N = 51; DF = 35; R2 = 0.83),
Mixing index (N = 51; DF = 35; R2 = 0.39), Frequency N = 49; DF = 33; R2 = 0.51),
Amplitude N = 49; DF = 33· R2 = 0.81)

Figure 8.10 *Scatter plot with PLS loadings of the two first model dimensions [23].*

8.6 Model-based Analysis of Twin-screw Granulation

A mechanistic understanding of the transport of materials and the kinetics of granulation in a TSG can be developed and improved by using theoretical models which are closely coupled with experimental data, as discussed in the introduction. Such a model can provide detailed information about several crucial responses which cannot be easily measured and thus far correlated with in-line dynamic torque which is a zero-dimensional measurement, leading to very limited process knowledge. Thus, the data from an experimental study on RTD was used to identify the most suitable conceptual model and apply it in order to improve the knowledge regarding material transport in a TSG [11, 28]. Similarly, the data from the experimental investigation of RTD was used along with experimental data regarding the GSD evolution in a TSG to propose and calibrate a modelling framework based on a population balance model (PBM) for the mixing zones of the TSG [10, 13].

8.6.1 Modelling RTD in a TSG

Efforts toward the predictive modelling of RTD in a TSG are sparse compared to other fields employing extrusion-based systems, such as the food and polymer industries [29]. This is mainly due to difficulties in defining the intrinsic physico-chemical properties of the formulation mixture in the opaque and high-shear process environment of the TSG [30]. Thus, drastically simplified hypotheses are required to solve local mass balances, which are very complex to be solved. Kumar *et al*. [31] presented a one-dimensional transport model based on screw geometry and material characteristics. The extensive numerical simulation of flow and transport in the TSG using the discrete element method (DEM) can be another approach for RTD prediction. However, DEM requires enormous numerical and computational effort due to the large number of equations, the strong coupling between various physical processes and the difficulties in resolving boundaries of the flow domain in the intermeshing twin screw involved. Thus such an approach is more complex and less efficient, giving acceptable results only for specific zones of the screw. However, conceptual flow modelling is another approach, in which the transport process is modelled as a combination of ideal reactors, the PFR having no axial mixing and the *n* having perfect axial mixing. Originally derived for chemical reactors, different types of single and multi-stage models and their applications have been widely discussed in the literature [21, 32–34]. For a non-ideal flow system like the TSG, the conceptual model used for RTD modelling generally consists of combinations of a plug-flow fraction (p) and a finite number of continuously stirred tank reactors (n) with stagnant pockets or dead fractions (d) to closely represent the flow pattern. This approach was also adopted by Lee [28] to explain the experimental RTDs obtained from PEPT measurements in a continuous TSG.

The conceptual modelling based on a tanks in series (TIS) approach allows identification of different flow components based on ideal flow reactors. In the plug-flow component the convective transport is larger than the dispersive transport and in the well-mixed component, indicated by a continuously stirred tank reactor (CSTR), the dispersive transport dominates and dead zones occur where the material transport was either excessively back-mixed or spent a much longer time than the $\bar{t}$ in the stagnant pockets that exist in the TSG [33]. In order to have a physical significance, the model structure should be able to characterise the real process through its parameters. Among different possible conceptual RTD models

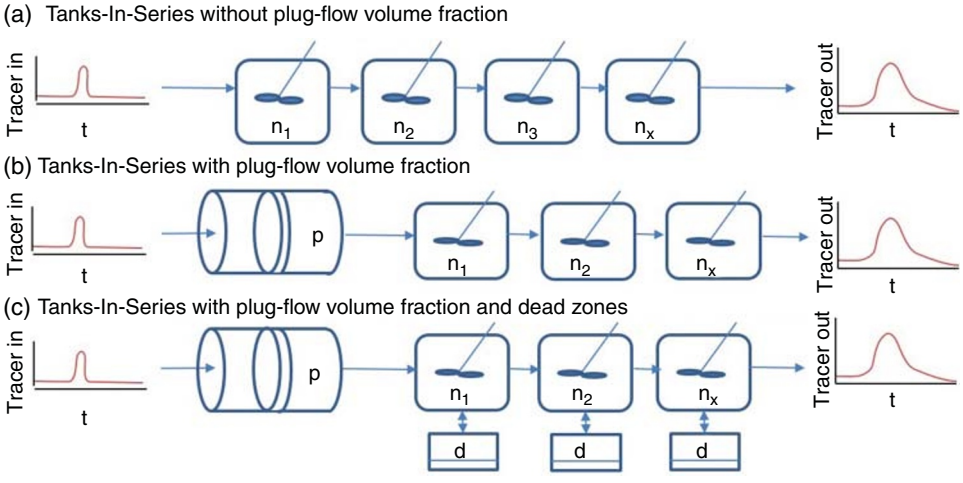


Figure 8.11 *Schematic diagram of three conceptual models based on non-ideal flow for the RTD in a TSG with a series of continuously stirred tank reactors: (a) without a plug-flow volume fraction, (b) with a plug-flow volume fraction and (c) with plug-flow volume fraction and dead zones [11].*

that have been discussed by Levenspiel [32], both Lee [28] and Kumar *et al.* [11] used two common model candidates to simulate the RTD of the twin-screw granulator: the TIS model without a plug-flow volume fraction and the TIS with a plug-flow volume fraction (Figure 8.11). The TIS model without a plug-flow volume fraction is a one-parameter flow model expressed as:

$$e(\theta) = \frac{n(n\theta)^{n-1}}{(n-1)!}\exp(-n\theta) \tag{8.7}$$

where n is the number of continuously stirred tank reactors. The closer the n value to unity, the higher the degree of mixing and vice versa. The TIS model containing a p as well is a three-parameter flow model given by:

$$e(\theta) = \frac{b[b(\theta-p)]^{n-1}}{(n-1)!}\exp[-b(\theta-p)]$$
$$\text{where } p = \frac{t_{\min}}{\bar{t}} \text{ and } b = \frac{n}{1-p} \tag{8.8}$$

where $t_{\min}$ is the minimum residence time and p is the fraction of the volume of the TSG that is assumed to correspond to the plug-flow volume fraction. Kumar *et al.* [11] also tested the TIS including a plug-flow volume fraction and dead zones at different process conditions (Figure 8.11).

For the TIS model with both p and d, which is a four-parameter flow model, the calculation of $e(\theta)$ and p in Equation (8.8) remains the same, whereas b is modified as [34]:

$$b = \frac{n}{(1-p)(1-d)} \tag{8.9}$$

where d is the dead zone of a CSTR, indicating the fraction of material which is either excessively back-mixed or has spent much longer time than $\bar{t}$ in the stagnant pockets that

exist in the TSG. Normally, this material spends more than twice the $\bar{t}$, and the average velocity is much smaller compared to the well mixed region, leading to a long tail in the RTD. Hence, the four parameters that are present in these models are $\bar{t}$, n, p and d. Major considerations for the selection of a flow model are the physical significance of the model and the number of adjustable parameters. Lee [28] applied RTD measured using PEPT and found that the TIS model containing a p suitability defines the RTD of a TSG. However, as the RTD measurement results by Lee *et al*. [18] differed significantly from measurements by Kumar *et al*. [8] for the reasons discussed in Section 8.4.1, it is also reflected in the selection of RTD model. Kumar *et al*. [11] found that the TIS model assuming a plug-flow fraction (p) in series with a finite number of well-mixed tanks (n) with dead zones (d) was the most suitable conceptual model for describing the experimentally measured residence time distribution in a twin-screw granulator.

The study by Kumar *et al*. [11] suggested that the mixing zones containing the kneading elements support plug-flow transport in the TSG. The excess of material in this region also prevents back-mixing inside the granulator, hence decreasing the size of the dead zone. The thickness of the slip layer of material which forms against the barrel wall at a low shear condition supports an increase in the plug-flow component and an increase in the dead fraction. Thus, either a high throughput force by increasing throughput or increasing the shear level by a high screw speed reduces the plug-flow component, leading to more axial mixing in the TSG. This finding was of significant importance since earlier studies always assumed TSG as a plug-flow device such that increasing throughput leads to an increased plug-flow fraction [16]. As the TSG was assumed as a plug-flow system, it was also believed that the level of back-mixing in the TSG is low. The results about the increasing amount of axial mixing and its excess leading to the dead fraction confirms that a significant back-mixing occurs in the TSG. The axial mixing reflected by a broadening of the RTD is necessary to compensate for process variations, as discussed in Section 8.4.2. However, excessive broadening leading to a long tail region of the RTD, as reflected by a dead zone, should be avoided to control the traceability of the material as it moves on to the next unit operation.

Beside the modelling and system identification, this also established that the combination of modelling and dedicated experimental data collection is very effective for gaining an improved insight into the transport and mixing characteristics of material in the TSG. Although such a modelling approach study is not "generic" to all formulations due to the likely difference in the granulation behaviour of different formulations (such as microcrystalline cellulose and dibasic calcium phosphate), the conceptual modelling approach which was found to be suitable is generic and can be repeated for other excipients. Once this knowledge is further built for different excipients, the observations from these studies can be compared for (dis-)similarities between specific excipients and the knowledge can be applied in a generic model that will be able to predict all test formulations, thereby reducing dependence on experimental study.

8.6.2 Tracking GSD in a TSG using PBM

Experimental studies provide local information regarding material flow, mixing and GSD. However, the fundamental basis, that is a mechanistic understanding of the shift in the GSD within different locations in the barrel and at different process conditions cannot be

measured experimentally; this requires theoretical investigation using a suitable modelling framework and its calibration and verification experimentally [30]. The PBM framework is frequently used for this purpose as it can mathematically describe the discrete events such as aggregation and breakage which can occur and lead to discrete changes in particle size and thus produce or remove particles of a certain size termed birth and death, respectively. The general form of a population balance equation (PBE) for a well-mixed system is given as:

$$\frac{\partial n}{\partial t}(x,t)\frac{\partial n}{\partial x}\left[n\frac{\mathrm{d}x}{\mathrm{d}t}\right](x,t) = \cup_{\text{birth}}(x,t) - \cup_{\text{death}}(x,t) \tag{8.10}$$

where x is a scalar-state variable that represents particle size, $n(x,t)$ represents the number distribution of particles, $\frac{\partial}{\partial x}\left[n\frac{\mathrm{d}x}{\mathrm{d}t}\right](x,t)$ represents the continuous growth or attrition loss along the internal coordinate of the particle diameter, $\cup_{\text{birth}}$ and $\cup_{\text{death}}$ represent the net formation and depletion rate of particles resulting from all discrete granulation mechanisms such as aggregation and breakage. Including the effects of aggregation and breakage explicitly, the PBM becomes [35]:

$$\begin{aligned}\frac{\partial n}{\partial t}(x,t) + \frac{\partial}{\partial x}\left[n\frac{\mathrm{d}x}{\mathrm{d}t}\right](x,t) = {} & \frac{1}{2}\int_0^x \beta(x-y,y)n(x-y,t)n(y,t)\mathrm{d}y \\ & - n(x,t)\int_0^\infty \beta(x,y)n(y,t)\mathrm{d}y \\ & + \int_0^\infty S(y)b(x,y)n(y,x-y)n(y,t)\mathrm{d}y \\ & - S(x)n(x,t)\end{aligned} \tag{8.11}$$

where β is the aggregation kernel, $b(x,y)$ is the breakage kernel and S is the selection function. Equation (8.11) is an integro-partial differential equation, and an analytical solution can only be found for simple $\beta(x,y)$ and $b(x,y)$ functions. However, these generally correspond to non-physical cases. Thus, numerical approaches are required for more complex functions describing real-life systems [30].

The PBM framework developed and calibrated by Barrasso *et al*. [13] and Kumar *et al*. [10] linked experimental measurements with the constitutive mechanisms of granulation. Barrasso *et al*. [12] used a multi-component PBM for tracking the liquid content and porosity of each particle size class during twin-screw granulation. The experimental data from El Hagrasy *et al*. [15] was used in this study for estimating parameters of two liquid-dependent aggregation kernels by comparing the model prediction with the experimental trends. This exercise applied data for the samples collected from the granulator outlet and therefore a lumped-parameter approach was adopted for the development of the model. Kumar *et al*. [10] developed and calibrated a PBM framework which linked the experimental measurements with the constitutive mechanisms of the granulation, namely aggregation and breakage, which are expected to dominate in the mixing zones of the TSG. The modular structure of the TSG is always targeted during experimental studies and the screw configuration is modified to render a regime-separated state of granulation [6]. However, in the presented study by Kumar *et al*. [10], it was shown that, along with the screw configuration, the regime separation also required suitable process conditions. It was observed in this study that at a high material throughput and for a screw configuration with two mixing zones, the low screw speed resulted in a mixed granulation regime, that is aggregation and breakage

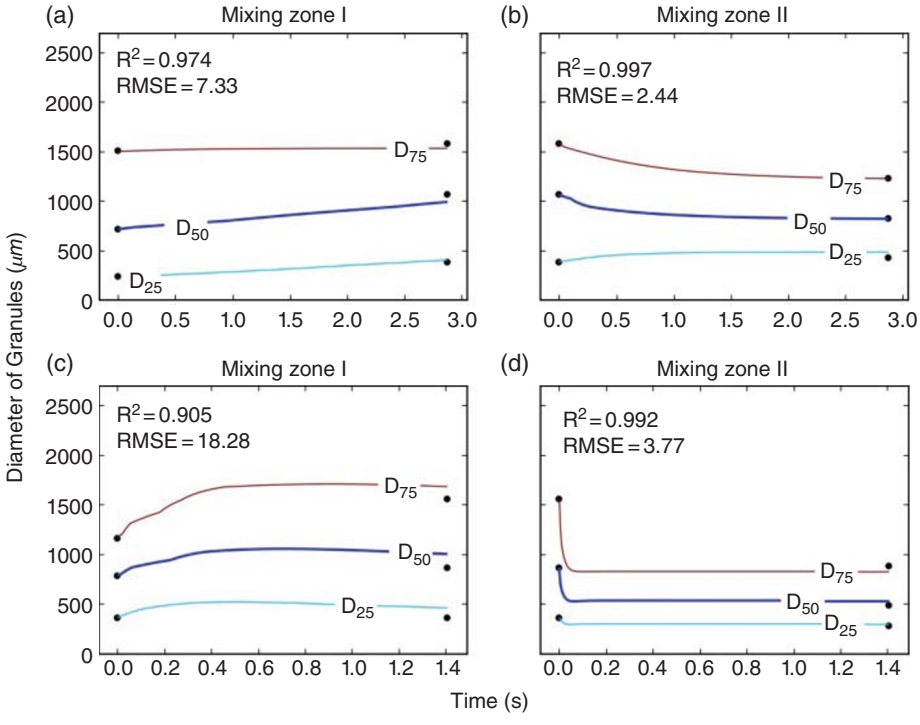


Figure 8.12 *Experimental (•) and simulated (—) trends for dynamic change in quartiles of the GSD (D_{25},D_{50} and D_{75}) at low [(a) and (b)] and high [(c) and (d)] screw speeds for the first [(a) and (c)] and second [(b) and (d)] mixing zones [10].*

occurred simultaneously in the second mixing zone. However, increasing the screw speed for the same configuration and condition resulted in separation of the aggregation and breakage between the two mixing zones of the granulator (Figure 8.12). Such a diagnosis of the process to achieve a "regime-separated" state is important as that would allow improved control granule properties compared to the conventional batch granulation equipment like high shear mixers in which all granulation sub-processes occur simultaneously.

8.7 Towards Generic Twin-screw Granulation Knowledge

By performing a number of separate experiments on a TSG, one can render the behaviour or regime of the twin-screw wet granulation process for a certain granulator setting. With the aid of this regime map, more insight into the granulation processes may be gained and the expected behaviour of the process can be predicted [36, 37]. This should eventually lead to an improved design and control of the twin-screw granulation processes. Additionally, as the understanding regarding the TSG process improves with experimental and model-based studies, there is also a need to reduce the dependence of the model on the experimental data by adopting more mechanistic models. This is especially required when the aim is to optimise either the process, or the design of the equipment in terms of change in granulation

material or a change in screw geometry. Therefore, efforts were done to simulate the mixing of solid and liquid at particle scale in the mixing zone of the TSG using a DEM approach.

8.7.1 Regime Map Approach

The flexibility of the TSG in choosing process and equipment parameters to achieve the desired size and properties of the granules makes twin-screw granulation a potentially appealing technology. This led to a wide range of studies with focus on adjusting parameters such as binder addition method, number and stagger angle of kneading elements in the screw configuration, granulation barrel temperature, liquid addition rate, powder feed rate and screw speed [3, 15, 38, 39] and different scales [2]. However, to comprehend the applicability and limits of the process variables in a scale-independent manner for improved understanding about the granulation processes, the regime theory is applied as presented by Iveson *et al*. [36] and Hapgood *et al*. [40] in early work. To extend this understanding to the twin-screw granulation process, Dhenge *et al*. developed two regime maps, one for the TSG with conveying zone only [22] and the other where both conveying and mixing zones were present [4]. Both regime maps mapped the granulation characteristics as under-wetted, nuclei, crumb, granules and over-wetted or paste based on the relation between the modified deformation value and the pore saturation which was assumed as a function of L/S and viscosity of the granulation liquid, that is L/S × viscosity. The modified deformation value was calculated as $\beta = \frac{T}{V} \times \frac{1}{\tau}$, where T, V, τ are torque (Nm), volume of material in the barrel (m^3) and strength of the granules (MPa), respectively. The pore saturation was assumed to be a function of L/S and the viscosity of the granulation liquid, that is L/S × viscosity. Dhenge *et al*. [22] observed that, without the mixing zone, the wet, big, loose and weak agglomerates termed as nuclei were produced in different amounts based on the deformation values (β). It was suggested in the other regime map by Dhenge *et al*. [4] that a transition of regimes can be achieved by applying change in the screw configuration and process conditions (Figure 8.13).

Following this study, also a regime map for a co-rotating TSG was proposed by Tu *et al*. [41]. The studied parameters were L/S ratio, screw speed and screw configuration. This showed that a reduction in screw speed led to an increased fill level of the TSG barrel, which showed a direct correlation with an increase of friction force and torque. Similarly, an increase in the L/S ratio correlated with a high fill level and torque. Depending on the screw configuration, three regimes were suggested: granulation, extrudate and blocked regime. Granules with a large size and narrow GSD were obtained for increased binder addition and screw speed and using a screw configuration that provided sufficient mixing [41]. However, scale-dependent parameters, such as screw speed and torque, were used for the development of this regime map. This limited the applicability of the study towards a TSG with a different screw diameter [42]. Also, a bi-modal GSD was obtained for several runs of this study. Thus, using only the mean granule size is not valid for granule size characterisation in many of these conditions.

As all these regime maps provide guidance towards mapping of the wet granulation by a TSG based on one formulation and equipment design, the results should be examined with a range of materials and equipments. Identifying limited applications of current TSG regime maps Kumar *et al*. [43] presented maps described as “process maps” which were

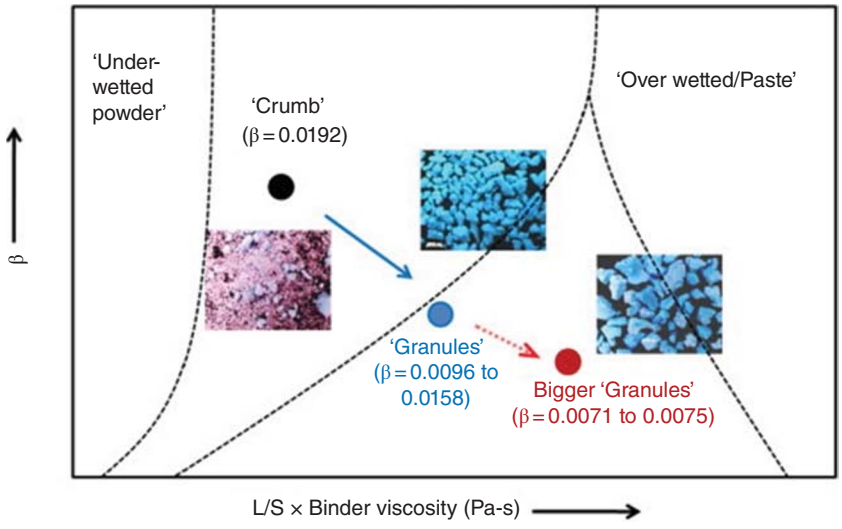


Figure 8.13 *Granule growth regime map for twin screw granulation by Dhenge et al. [4].*

in line with the efforts for developing a generalised regime map. In this study, to comprehend the applicability and limits of the process variables in a scale-independent manner, the specific mechanical energy (SME) which involves the combination of screw speed, material throughput and torque required to rotate the screws was correlated with the applied liquid to solid ratio to propose process maps. The study suggested that, although increasing L/S strongly drives the GSD towards a large mean granule size, increasing the energy input to the system can be effectively used to lower the mean granule size and also narrow the width of the size distribution. This observation also corresponds with the observation regarding solid–liquid mixing in Section 8.4.2 where an increased shear by the high screw speed and increasing number of kneading discs resulted in an improved mixing and a higher yield fraction. However, due to the inherent flexibility in design and operation of the TSG which allowed more than one process setting to produce the same effect, different process maps for two different screw configurations (1 × 6 and 2 × 6 kneading discs) were made to reduce such possibility. Moreover, the formulation properties and operating variables that control wet granulation behaviour in a TSG are strongly coupled, as evidenced by different results obtained from various studies performed at different process conditions. Despite the scale-independence of the parameters (SME, L/S ratio), more process maps for formulations with significantly different raw material properties are necessary due to their likely differences in granulation behaviour. Therefore, for a reliable and more generalised regime map, the most relevant dimensionally homogeneous terms, that is dimensionless groups should be identified (Figure 8.14). This is done by preparation of a "relevance list" which contains parameters originating from formulation, equipment and granulation process settings of the TSG. For details regarding such an approach the reader is referred to [44].

Additionally, in order to improve the understanding of the wet granulation process using TSG, process knowledge should be further developed both under steady state and

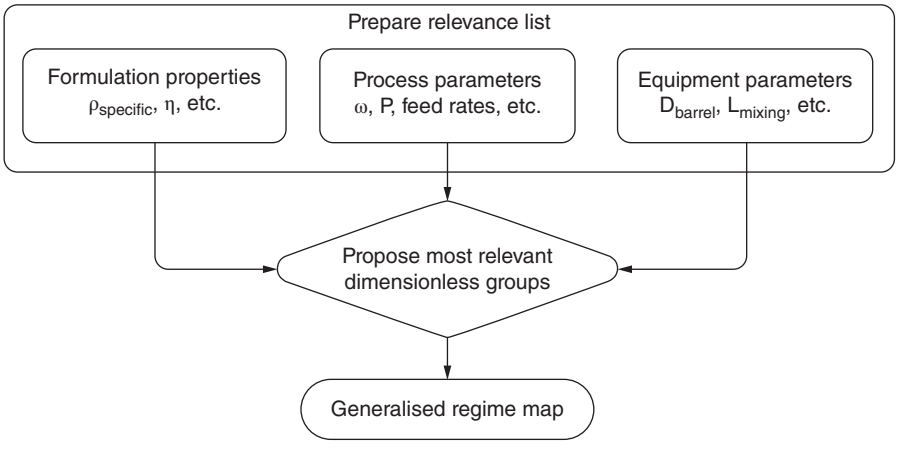


Figure 8.14 *Steps required to develop a generalised granulation regime map for twin-screw granulation [45].*

dynamic conditions. For this purpose, the application of mechanistic models incorporating the underlying mechanisms in the model framework is suggested [36]. A validated model thus obtained can potentially be used to define the design space of the process for future optimization of the twin-screw granulation process.

8.7.2 Particle-scale Simulation using DEM

As twin-screw granulation technology is fairly new, not only is the mechanism of granulation relatively unknown, but also changes in design need to be explored to obtain efficiency, as discussed in Sections 8.4.2 and 8.5.2. This calls for a modelling approach which can inherently consider the effects caused by both the geometry of the TSG and the field conditions.

DEM-based simulations that track individual granules (i.e., ensembles of particles) are frequently used [13, 46, 47]. This type of simulations are referred to as "granule scale", since phenomena on the scale of the granules, typically with a size of 100–1000 μm, can be predicted. The advantage of these simulations is that a comparably small number of entities (i.e., granules) has to be tracked and granules are allowed to break or aggregate. This opens the door for investigating the effect of the actual geometry of a TSG.

Variations in granule properties, such as porosity and liquid content, are often accounted for in this type of DEM simulation using empirical correlations for, for example, the coefficient of restitution or Young's modulus [48]. Therefore for closures of mechanisms such as aggregation, breakage and consolidation, which cause changes in particle size and other properties, a multi-scale approach is suggested where DEM data is collected and used within a PBM by either one-directional or bidirectional coupling. Typically, a granule-scale DEM simulation with particle size of 100–1000 μm is preferred for either one-directional or bidirectional coupling of DEM with PBM as these simulations have to track a comparably smaller number of entities (i.e., granules) and can be performed with better balance between the computation time of PBM and DEM. Recently, Barrasso *et al*. [47] applied

bi-directional coupling between particle-scale DEM and PBM in the case of a twin-screw wet granulation process. The model showed sensitivities to the screw configuration, process parameters such as screw speed, liquid to solid ratio and material properties such as binder viscosity and pore saturation. However, this bi-directional coupling of a PBM-DEM model for wet granulation depends on the assumption that liquid is distributed evenly with respect to particle volume, which is not the case as shown experimentally by Vercruysse *et al*. [5]. In fact, achieving a homogeneous distribution of liquid which largely controls the constitutive mechanisms of the twin-screw granulation is the primary requirement for driving the granulation process towards the required state. Therefore, investigating the drivers for particle and liquid mixing in TSG is key to the understanding of the twin-screw wet granulation process.

The other more rigorous approach is to perform particle-scale DEM simulation for understanding the solid–liquid mixing by tracking each particle as well as the liquid exchange network, that is the liquid distribution inside the system was also tracked [49]. However, as these simulations are computationally very expensive, simulation of the dense particle system in the complete TSG is impossible within a reasonable time frame. Therefore, a more tractable and equally powerful approach was adopted by simulating the particle system in the mixing element section of the TSG to unravel the fundamentals of solid–liquid mixing (Figure 8.15). This led to a novel finding that solid–liquid mixing starts with a quick transfer of liquid from the particle surface to bridges and these thick bridges later redistribute the liquid to form more bridges. As this reallocation of liquid bridges is a delayed event,

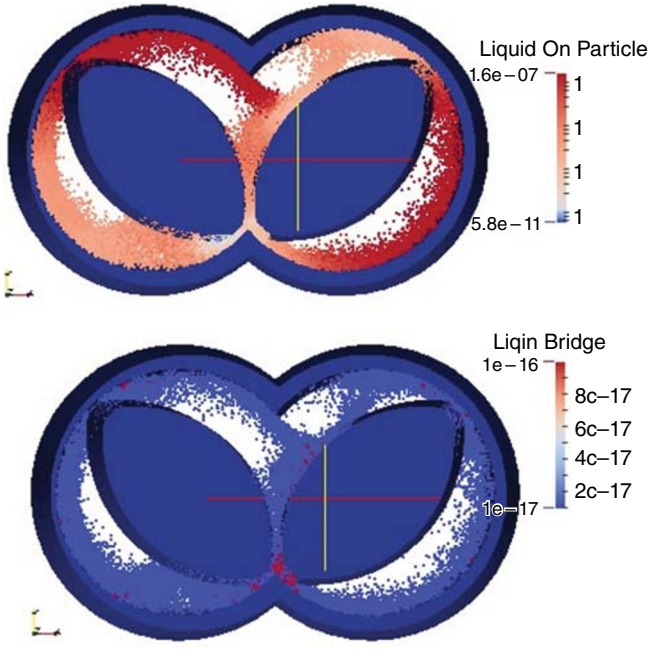


Figure 8.15 *Visualisation of granulation mixing of liquid and powder during wet granulation using particle scale simulation of the mixing zone of the TSG [49].*

it can safely be deduced that the agglomeration cannot be achieved earlier without quicker wetting of the particles. The visualisation of DEM data also suggested that the liquid bridge formation is most dominant in the inter-meshing region of the kneading elements. Providing access to complete detail of the particle dynamics, this approach can be very useful for extensive analysis of the twin-screw granulation system.

8.8 Strengths and Limitations of the Current Approaches in TSG Studies

In the field of pharmaceutical twin-screw wet granulation, a wide range of different experiments has been performed in previous years. However, in the absence of a satisfactory link between the experimental results and the mechanistic principles or theory, the results from these studies find only limited practical application. Integration of process engineering (modelling) and pharmaceutical sciences (measurements) disciplines will allow the development of knowledge regarding rate processes, their interaction and quantification by advanced measurement tools and the development of models to improve the prediction of the process state in a continuous system. Moreover, the rheo-kinetics of material in the TSG cannot be visualised easily by experimental studies. On the other hand, rigorous modelling of material transport and kinetics in a TSG requires the closure of particle velocity profiles, a multi-particle multiphase interaction model, a mechanistic definition of granulation sub-processes and all the complex moving geometry of the screw channels. Since such an approach is more complex and less efficient, and if applied can give acceptable results only for specific zones of the TSG, the adopted integrated approach can be believed to be the best possible approach to understand the twin-screw granulation process at this moment. Filling the knowledge gaps will be helpful in achieving process design and control for efficiency and accuracy and can also be used for scale-up predictions, which is crucial for the transition towards continuous processing in industrial solid dosage manufacturing.

Process development studies are rapidly adopting more efficient tools, like the application of design of experiments (DoE), statistical modelling and data characterisation approaches. However, a more integrated approach adopting the strengths of both methodologies, experimental and theoretical, for an in depth investigation of twin-screw granulation by conceptualisation and calibration of models on the basis of the experimental data can yield a robust model which can later be used for further diagnosis of transport and kinetics in a TSG. In this respect, the application of an optimal experimental design (OED) approach is suggested for devising the most necessary dynamic experiments based on model candidates in such a way that the resulting experimental data, when used for parameter estimation, provide the best possible statistical quality for system identification [50]. The modelling approaches presented in Section 8.6 outlined the success of models in presenting a more realistic and in depth description of the twin-screw granulation process.

The present twin-screw granulation studies are also facing an additional challenge due to the strong influence of formulation properties which can lead to completely different granulation behaviours, for reasons not properly identified during process development. The studies performed to date mostly rely on a simple formulation or a placebo formulation based on α-lactose monohydrate and microcrystalline cellulose and so on to verify each hypothesis. However, it can easily be expected that water-insoluble fillers, such as microcrystalline cellulose and dibasic calcium phosphate, will have a different granulation

behaviour from α-lactose monohydrate. Thus, the methods used in studies in the literature (both data collection and modelling) should be repeated for a broad spectrum of excipients with a significantly different behaviour. A more generic process map should be developed based on these findings so that process development for the change in formulation mixture can be more quickly based on existing process knowledge.

Beside, the practical application of theoretical models linking experimental data to mechanistic principles requires an investigation of the mechanistic link between transport, mixing and wet granulation in the TSG and the critical quality attributes (CQAs) such as granule density and friability, which is still missing. The main remaining challenge in the area of continuous processing and twin-screw granulation lies in the development of new measurement techniques, which are able to measure the fundamental granule properties, preferably *in situ*. Following extensive research conducted on software sensor technology in the last few years, also in other related fields facing the challenge of opaque multiphase system, it becomes more and more attractive for the industry to use software sensors in real applications. As the concept of a software sensor is to replace the more complex direct measurement by a suitable algorithm to calculate the desired quantity from other easily measurable data with pre-existing hardware sensors, the development of mechanistic models which describe the relationships between different parameters in a system, and conceptual models representing the system behaviour in terms of the relationship between input and output can promote further development in this area.

As the gaps and potential research needs of building fundamental knowledge on pharmaceutical twin-screw wet granulation are well identified and the regulators have opened up to increasingly rely on the science- and risk-based holistic development of pharmaceutical processes and products for commercialisation, the opportunity as well as responsibility lies with academic and industrial partners to develop a systematic framework and scientific approach to fill the gaps and utilise this opportunity efficiently to transit towards continuous manufacturing.

8.9 Glossary

API	active pharmaceutical ingredient.
β	Aggregation kernel [m^3s^{-1}].
$b(x, y)$	Breakage function [m^3].
CQA	critical quality attribute.
CSTR	continuously stirred tank reactor.
d	ead volume fraction [−].
DEM	discrete element method.
$e(t)$	Residence time distribution function, [s^{-1}].
GSD	granule size distribution.
HSWG	high shear wet granulation.
L/S	liquid-to-solid ratio.
MI	mixing index.
n	Number of continuously stirred tank reactors [−].
NIR	near infrared.
NIR-CI	near infrared chemical imaging.

$n(x, t)$ Number distribution of particles [−].
PBE population balance equation.
PBM population balance model.
Pe Péclet number, [−].
PEPT positron emission particle tracking.
p Plug-flow volume fraction, [−].
PFR plug-flow reactor.
PLS partial least squares.
$\mathfrak{R}_{birth}$ Net formation rates of particles by discrete event aggregation and breakage [s^{-1}].
$\mathfrak{R}_{death}$ Net depletion rates of particles by discrete event aggregation and breakage [s^{-1}].
RTD residence time distribution.
S Selection function [s^{-1}].
SME specific mechanical energy.
σ_θ^2 Normalised variance, [−].
σ_t^2 Mean centered variance, [s].
TIS tanks-in-series.
$\bar{t}$ Mean residence time, [s].
t_{min} Minimum residence time [s].
TSG twin-screw granulator.
x Scalar-state variable such as particle size [m, m^3].

References

[1] Van Melkebeke B, Vervaet C, Remon JP (2008) Validation of a continuous granulation process using a twin-screw extruder. *Int J Pharm.* **356**(1/2):224–230.

[2] Djuric D, Van Melkebeke B, Kleinebudde P, Remon JP, Vervaet C (2009) Comparison of two twin-screw extruders for continuous granulation. *Eur J Pharm Biopharm.* **71**(1): 155–160.

[3] Dhenge RM, Cartwright JJ, Doughty DG, Hounslow MJ, Salman AD (2011) Twin screw wet granulation: Effect of powder feed rate. *Adv Powder Technol.* **22**(2):162–166.

[4] Dhenge RM, Cartwright JJ, Hounslow MJ, Salman AD (2012) Twin screw wet granulation: Effects of properties of granulation liquid. *Powder Technol.* **229**:126–136.

[5] Vercruysse J, Toiviainen M, Fonteyne M, Helkimo N, Ketolainen J, Juuti M, *et al*. (2013) Visualization and understanding of the granulation liquid mixing and distribution during continuous twin screw granulation using NIR chemical imaging. *Eur J Pharm Biopharm.* **86**(3):383–392.

[6] El Hagrasy AS, Litster JD (2013) Granulation rate processes in the kneading elements of a twin screw granulator. *AIChE J.* **59**(11):4100–4115.

[7] Kumar A, Vercruysse J, Bellandi G, Gernaey KV, Vervaet C, Remon JP, *et al*. (2014) Experimental investigation of granule size and shape dynamics in twin-screw granulation. *Int J Pharm.* **475**(1/2):485–495.

[8] Kumar A, Vercruysse J, Toiviainen M, Panouillot PE, Juuti M, Vanhoorne V, *et al*. (2014) Mixing and transport during pharmaceutical twin-screw wet granulation: Experimental analysis via chemical imaging. *Eur J Pharm Biopharm.***87**(2):279–289.

[9] Sayin R, Hagrasy ASE, Litster JD (2015) Distributive mixing elements: Towards improved granule attributes from a twin screw granulation process. *Chemical Engineering Science.* **125**:165–175.

[10] Kumar A, Gernaey KV, De Beer T, Nopens I (2015) Model-based characterisation of twin-screw granulation system for continuous solid dosage manufacturing. *Comput Aided Chem Eng.* **37**:2165–2170.
[11] Kumar A, Vercruysse J, Vanhoorne V, Toiviainen M, Panouillot PE, Juuti M, *et al*. (2015) Conceptual framework for model-based analysis of residence time distribution in twin-screw granulation. *Eur J Pharm Sci.* **71**:25–34.
[12] Barrasso D, Walia S, Ramachandran R (2013) Multi-component population balance modeling of continuous granulation processes: A parametric study and comparison with experimental trends. *Powder Technol.* **241**:85–97.
[13] Barrasso D, Hagrasy AE, Litster JD, Ramachandran R (2015) Multi-dimensional population balance model development and validation for a twin screw granulation process. *Powder Technol*. **270**(part B):612–621.
[14] Kohlgrüber K, Bierdel M (2008) *Co-rotating Twin-screw Extruders: Fundamentals, Technology, and Applications*. Hanser Verlag, Berlin.
[15] El Hagrasy AS, Hennenkamp JR, Burke MD, Cartwright JJ, Litster JD (2013) Twin screw wet granulation: Inuence of formulation parameters on granule properties and growth behavior. *Powder Technol.* **238**:108–115.
[16] Dhenge RM, Fyles RS, Cartwright JJ, Doughty DG, Hounslow MJ, Salman AD (2010) Twin screw wet granulation: Granule properties. *Chem Eng J.* **164**(2/3):322–329.
[17] Li H, Thompson MR, O'Donnell KP (2014) Understanding wet granulation in the kneading block of twin screw extruders. *Chem Eng Sci.* **113**:11–21.
[18] Lee KT, Ingram A, Rowson NA (2012) Twin screw wet granulation: the study of a continuous twin screw granulator using positron emission particle tracking (PEPT) technique. *Eur J Pharm Biopharm.* **81**(3):666–673.
[19] Seem TC, Rowson NA, Ingram A, Huang Z, Yu S, de Matas M, *et al*. (2015) Twin screw granulation – A literature review. *Powder Technol.* **276**:89–102.
[20] Sochon RPJ, Zomer S, Cartwright JJ, Hounslow MJ, Salman AD (2010) The variability of pharmaceutical granulation. *Chem Eng J.* **164**(2/3):285–291.
[21] Fogler HS (2006) *Elements Of Chemical Reaction Engineering*. Pearson international edition. Prentice Hall Professional, New York.
[22] Dhenge RM, Washino K, Cartwright JJ, Hounslow MJ, Salman AD (2013) Twin screw granulation using conveying screws: Effects of viscosity of granulation liquids and flow of powders. *Powder Technol.* **238**:77–90.
[23] Kumar A, Alakarjula M, Vanhoorne V, Toiviainen M, Juuti M, Vervaet C, *et al*. (2015) Linking granulation performance with residence time and granulation liquid distributions in twin-screw granulation: An experimental investigation. *Eur J Pharm Sci.* **37**:1–16.
[24] Vercruysse J, Burggraeve A, Fonteyne M, Cappuyns P, Delaet U, Assche IV, *et al*. (2015) Impact of screw configuration on the particle size distribution of granules produced by twin screw granulation. *Int J Pharm.* **479**(1):171–180.
[25] Meier R, Thommes M, Rasenack N, Krumme M, Moll KP, Kleinebudde P (2015) Simplified formulations with high drug loads for continuous twin-screw granulation. *Int J Pharm.* **496**(1):12–23.
[26] Dhenge RM, Cartwright JJ, Hounslow MJ, Salman AD (2012) Twin screw granulation: Steps in granule growth. *Int J Pharm.* **438**(1/2):20–32.
[27] Thompson MR (2015) Twin screw granulation – review of current progress. *Drug Dev Ind Pharm.* **2015**:1–9.
[28] Lee KT (2013) *Continuous Granulation of Pharmaceutical Powder using a Twin Screw Granulator*. University of Birmingham, Birmingham.
[29] Gao Y, Muzzio FJ, Ierapetritou MG (2012) A review of the residence time distribution (RTD) applications in solid unit operations. *Powder Technol.* **228**:416–423.

[30] Kumar A, Gernaey KV, De Beer T, Nopens I (2013) Model-based analysis of high shear wet granulation from batch to continuous processes in pharmaceutical production – A critical review. *Eur J Pharm Biopharm.* **85**(3, part B):814–832.
[31] Kumar A, Gernaey KV, De Beer T, Nopens I (2013) One dimensional model of the prediction of residence time distribution granulation in a twin-screw granulator. In: *6th International Granulation Workshop*, pp. 117–125.
[32] Levenspiel O (1999) *Chemical Reaction Engineering*, 3rd edn. John Wiley & Sons, Ltd, London.
[33] Puaux JP, Bozga G, Ainser A (2000) Residence time distribution in a corotating twin-screw extruder. *Chemical Engineering Science.* **55**(9):1641–1651.
[34] Kumar A, Ganjyal GM, Jones DD, Hanna MA (2008) Modeling residence time distribution in a twin-screw extruder as a series of ideal steady-state flow reactors. *Journal of Food Engineering.* **84**(3):441–448.
[35] Pinto MA, Immanuel CD, Doyle FJ (2007) A feasible solution technique for higher-dimensional population balance models. *Comput Chem Eng.* **31**(10):1242–1256.
[36] Iveson SM, Litster JD, Hapgood K, Ennis BJ (2001) Nucleation, growth and breakage phenomena in agitated wet granulation processes: a review. *Powder Technol.* **117**(1):3–39.
[37] Litster J, Ennis B (2004) *The Science and Engineering of Granulation Processes*, vol. **15**. Springer, Heidelberg.
[38] Vercruysse J, Córdoba Díaz D, Peeters E, Fonteyne M, Delaet U, Van Assche I, *et al*. (2002) Continuous twin screw granulation: Inuence of process variables on granule and tablet quality. *Eur J Pharm Biopharm.* **82**(1):205–211.
[39] Djuric D (2008) *Continuous Granulation with a Twin-screw Extruder*. Cuvillier Verlag, Berlin.
[40] Hapgood KP, Litster JD, Smith R (2003) Nucleation regime map for liquid bound granules. *AIChE J.* **49**(2):350–361.
[41] Tu WD, Ingram A, Seville J (2013) Regime map development for continuous twin screw granulation. *Chem Eng Sci.* **87**:315–326.
[42] Muteki K, Yamamoto K, Reid G, Krishnan M (2011) De-risking scale-up of a high shear wet granulation process using latent variable modeling and near-infrared spectroscopy. *Journal of Pharmaceutical Innovation.* **6**(3):142–156.
[43] Kumar A, Dhondt J, De Leersnyder F, Vercruysse J, Vanhoorne V, Vervaet C, *et al*. (2015) Development of regime map for steady-state high shear wet twin-screw granulation. In: *7th International Granulation Workshop*, pp. 236–245.
[44] Zlokarnik M. 1 (2011) *Dimensional Analysis and Scale-up in Theory and Industrial Application*. Informa Healthcare, London, pp. 1–57.
[45] Kumar A, Dhondt J, Vercruysse J, Leersnyder FD, Vanhoorne V, Vervaet C, *et al*. (2015) Development of a process map: A step towards a regime map for steady-state high shear wet twin screw granulation. *Powder Technol.* **276**:103–109.
[46] Sen M, Singh R, Vanarase A, John J, Ramachandran R (2012) Multi-dimensional population balance modeling and experimental validation of continuous powder mixing processes. *Chem Eng Sci.* **80**:349–360.
[47] Barrasso D, Eppinger T, Pereira FE, Aglave R, Debus K, Bermingham SK, *et al*. (2015) A multi-scale, mechanistic model of a wet granulation process using a novel bi-directional PBM-DEM coupling algorithm. *Chem Eng Sci.* **123**:500–513.
[48] Sarkar A, Wassgren CR (2009) Simulation of a continuous granular mixer: Effect of operating conditions on flow and mixing. *Chem Eng Sci.* **64**(11):2672–2682.
[49] Kumar A, Radl S, Khinast J, Gernaey KV, De Beer T, Nopens I (2015) Detailed simulation of particle and liquid distribution in the mixing zone of a twin-screw granulator. *AIChE Annual Meeting*, pp. 105–113.
[50] Fedorov V (2010) Optimal experimental design. *Wiley Interdisciplinary Reviews: Computational Statistics.* **2**(5):581–589.

9

Continuous Line Roller Compaction

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9.1 Roller Compaction

Roller compaction is a dry granulation method which transforms powder into a solid via powder densification between rotating rolls. It is widely used in many industries: pharmaceutical, food, mineral and metal. Roller compaction works inherently continuously thus it is very promising unit operation in the continuous manufacturing lines of solid dosage forms such as tablets and capsules. Granulation is often required in the manufacturing of tablets and capsules due to issues of poor flowability, segregation, content uniformity, and dust formation. The advantages of dry granulation over wet granulation are fairly simple operation, no requirement of an energy intensive drying step, and suitability for temperature-sensitive and easily hydrolyzed compounds. In principle, roller compaction is a simple operation. Powder is fed by gravity or feeder between two counter-rotating rolls which form it into a ribbon which is subsequently crushed to granules with a mill (Figure 9.1).

9.2 Main Components of a Roller Compactor

The main components of a roller compactor are hopper, feeding system (gravity, vibration, and/or screw), de-aeration systems (vacuum), rolls, cheek plates, and mill. Also, there may be some additional accessories such as temperature control and recirculation units. There are only a few roller compactor manufacturers for pharmaceutical applications and roll configurations vary between them: (i) horizontal (Bepex, Freund/Vector, Fitzpatrick),

Continuous Manufacturing of Pharmaceuticals, First Edition.
Edited by Peter Kleinebudde, Johannes Khinast, and Jukka Rantanen.
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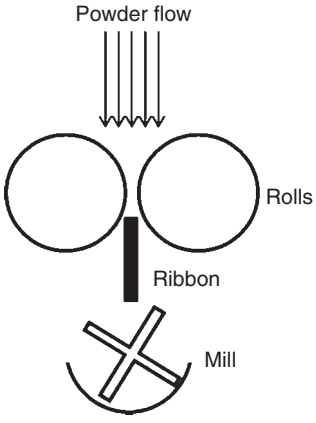

Figure 9.1 *Principles of roller compaction.*

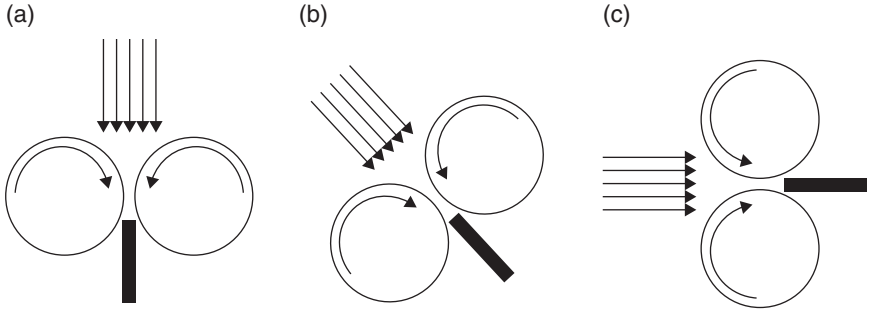

Figure 9.2 *Horizontal (a), inclined (b), and vertical (c) roll configurations.*

(ii) inclined (Gerteis), (iii) vertical (Alexanderwerk; Figure 9.2). Each of the roll configurations has their own advantages and disadvantages.

The most crucial components of roller compactor are the hopper and feeding systems, since they mostly affect the variation of the quality of ribbon and consequent granules [1, 2]. The key task of feeding systems is to feed powder to the rolls as smoothly as possible. Screw feeding is one of the most common feeding systems. Screws are either straight or slightly tapered. The number of screws varies typically from one (horizontal and inclined roll configuration) to two (inclined and vertical roll configuration). In order to minimize the effect of wall friction between hopper wall and powder, screws and hopper are designed with minimal clearances. Feeding powder to rolls presents a few challenges. First, a geometrical challenge, since feeding systems are typically round but the compaction zone between rolls is rectangular. This tends to cause a variation in feed along the width of a roll that results in variability of ribbon density along the ribbon width and powder leakage between rolls and cheek plates. Second, the screw flight exerts oscillating pressure distribution along the width of the rolls that results in variability in ribbon density. This can be reduced by using multiple flight screws, increasing the distance between screw tip and rolls, and rounding off

the end of screw flight. Third, feeding systems cause densification of powder, thus air has to escape from the feeding system. To help de-aeration, vacuum systems can be implemented for the feeding systems.

Roll surface design can be smooth, fluted, knurled, or it can contain pockets which will form briquettes. The main purpose of different roll surfaces is to provide good friction between the deforming powder and roll. Also, surface design may help ribbon breakage during milling. Other important roll features are roll width diameter and roll gap. An integral part of the rolls is the sealing system which seals the rotating rolls and the fixed parts of the roller compactor, preventing powder leakage.

To mill the ribbon to granules, mills are typically integrated with the roller compactor. Most often the mills are conventional impact mills where an oscillating or rotating milling bar forces the ribbon through the desired screen. After, the mill granules may be fractionated or used as is.

It becomes evident from the above description of the main components of a roller compactor that there is only a very limited number of adjustable parameters in a roller compactor. Typically they are: feed screw rpm, roll rpm, and milling bar oscillation rate or rotating rpm. In some roller compactors the gap width between the rolls is fixed, thus the roll force/pressure is not directly adjustable but depends on feed screw rpm and roll rpm. In other roller compactors the gap width is not fixed which makes it possible to also adjust roll force/pressure.

9.3 Theory of Powder Densification in Roller Compaction

Even though roller compaction seems a fairly simple process at first glance it has proven to be very complex to understand fundamentally. This is mostly because densification involves a great a number of shearing forces introduced by the feed screw and the rotating rolls. The main phases of powder densification under pressure are: particle rearrangement, particle deformation, particle bonding, and elastic recovery after pressure release. Particle deformation can be divided into: elastic deformation, plastic deformation, fragmentation, and viscoelastic deformation, which is a combination of elastic and plastic deformation. In the pure form of deformation, elastic, plastic, and fragmentation are time-independent; thus deformation is only dependent on pressure. Viscoelastic deformation is both time- and pressure-dependent. The time-dependent deformation properties of powders are not as critical in roller compaction as it is in tableting since the rate of shear is much lower in roller compaction than in tableting. In reality, pharmaceutical powders do not behave as ideal particles but instead often have a combination of deformation properties.

In roller compaction powder densification can be divided into the three regions: slip/entry, nip, and release/extrusion [1–4]. The boundaries between each region are defined by four angular positions: the entry angle, the nip angle, the neutral angle, and the release angle (Figure 9.3). The slip region starts at the angle (slip/entry angle) where finite pressure is detected towards rolls, or due to the geometry of roller compactor, where powder becomes to contact with rolls. Powder is fed to the slip/entry region by screw feeder or gravity, which induces a positive feed pressure to the region. This positive feed pressure can be part of a control system. In the slip region powder densifies mostly by particle rearrangement and de-aeration as only a minor pressure is applied to powder.

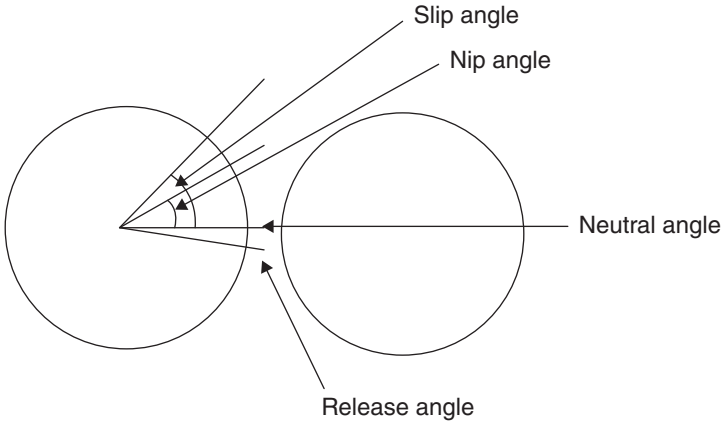

Figure 9.3 *Slip, nip, and release regions.*

The entry/slip region is mostly governed by friction between wall and particles and interparticulate friction which drives the powder towards the next region (nip region). In the slip region particles slip on the surface of a rotating roll and there is a velocity gradient between the roll and the particles adjacent to the roll surface.

At the nip angle point the velocity gradient has vanished and the velocity of the roll surface and particles adjacent to the roll surface becomes equal. Now, powder is "nipped" to the roll and pressure starts to increase exponentially as the roll gap decreases during the course of roll rotation. In this region particle deformation and bonding occur. The nip region ends at the point of the closest roll gap (neutral angle) and the release/extrusion region begins. As the roll reaches the neutral angle, frictional force changes direction. Before, neutral angle frictional forces push the powder towards the gap, and after, the neutral angle frictional forces are directed away from the gap. After, the neutral angle pressure decreases rapidly. The size of the release region depends on how much elastic deformation has been stored in the ribbon and thus is very material-dependent.

As can been seen from the above, powder densification in roller compaction includes a lot of shear (particle rearrangement) and frictional forces that are properties which are difficult to measure directly. Thus, the fundamental understanding of roller compaction and quantitative models to describe roller compaction have been pointed out to be challenging. The reasons for difficulties in modeling are the nonlinear behavior of contact and frictional conditions, the constitutive behavior of the deforming powder which faces significant evolution of its mechanical properties when it desifies, the lack of material-related parameters (e.g., frictional coefficients), and experimental difficulties to verify the validity of models (e.g., densities in different regions, feed stress, and frictional conditions [4]).

Johanson (1965) [5] developed the first analytical model for roller compaction that was capable of predicting the roll surface pressure, force, and torque from achievable material parameters and the geometry of rolls. However, it took roughly 40 years before Johanson's model was pointed out to be reasonably well validated by experiments that required the development of instrumentation for roller compactors. Also many other models have been proposed, such as slab analysis methods, but they have gained only a little attention in

pharmaceutical applications [6]. The most promising and realistic modeling methods are advanced computational methods like finite element modeling (FEM) and discrete element modeling (DEM) [4]. However, from those experiments it was concluded that more accurate material models are required for the satisfactory implementation of those models.

9.4 Johanson Model

The Johanson model based on the powder mechanics theory of Jenike and Shield (1959) [7] to describe pressure distribution on rolls [3]. The model assumes that material behaves like an isotropic, frictional, cohesive, compressible and obeys the effective yield function proposed by Jenike and Shield [7]. The equation of the effective yield locus is combined with the equations of equilibrium, resulting in a hyperbolic system of partial differential equations. These equations can be solved using the appropriate boundary conditions. The most crucial quantity is the nip angle (α), defined as the angle at which a system switches from a slip condition to a no-slip condition. The pressure gradient ($d\sigma/dx$) for a slip condition is given by:

$$\left(\frac{d\sigma}{dx}\right)_{\text{Slip}} = \frac{4\sigma\left(\frac{\pi}{2} - \theta - \nu\right)\tan\delta_E}{\left(\frac{D}{2}\right)\left(1 + \frac{S}{D} - \cos\theta\right)[\cot(A-\mu) - \cot(A+\mu)]} \tag{9.1}$$

Where θ is the roll angle, S is the roll gap, D is the roll diameter, μ is the friction coefficient between the roll and the powder, δ_E is the effective angle of internal friction. Parameter A is given by:

$$A = \frac{\theta + \nu + \frac{\pi}{2}}{2} \tag{9.2}$$

and ν is given by:

$$2\nu = \pi - arcsin\left(\frac{sin\phi_W}{sin\delta_E}\right) - \phi_W \tag{9.3}$$

Where ϕ_w is the angle of wall friction. The effective angle of internal friction (δ_E) and angle of wall friction (ϕ_w) are determined by experiment using, for example, a ring shear tester. In the no-slip region, the Johanson model assumes the continuity transport theorem is valid [8]. This means that the powder flow between the rolls is laminar and there is no velocity gradient through the ribbon thickness direction.

$$\frac{\rho_\alpha}{\rho_\theta} = \frac{V_\theta}{V_\alpha}, \tag{9.4}$$

where ρ_α and ρ_θ are the densities at nip angle α and roll angle θ, respectively, and V_α and V_θ are the corresponding volumes, satisfying the continuity assumption. Next, Johanson related the density with stress trough compressibility factor (K) which is obtained from the slope of logarithmic plot of the density as a function of pressure in uniaxial compaction with a punch and die system.

$$\frac{\sigma_\alpha}{\sigma_\theta} = \left(\frac{\rho_\alpha}{\rho_\theta}\right)^K = \left(\frac{V_\theta}{V_\alpha}\right)^K \tag{9.5}$$

where σ_α and σ_θ are the pressures at nip angle α and roll angle θ. By adding a geometric relationship, it can be derived that:

$$\left(\frac{V_\theta}{V_\alpha}\right)^K = \left[\frac{\left(1+\frac{S}{D}-cos\alpha\right)\cos\alpha}{\left(1+\frac{S}{D}-\cos\theta\right)\cos\theta}\right]^K \tag{9.6}$$

Combining Equations (9.5) and (9.6):

$$\sigma_\theta = \sigma_\alpha\left[\frac{\left(1+\frac{S}{D}-\cos\alpha\right)\cos\alpha}{\left(1+\frac{S}{D}-\cos\theta\right)\cos\theta}\right]^K \tag{9.7}$$

The pressure gradient $(\mathrm{d}\sigma/\mathrm{d}x)$ for no-slip condition (nip condition) is derived by differentiating Equation (9.7) with respect to x, where $x = D/2\ \sin\theta$:

$$\left(\frac{\mathrm{d}\sigma}{\mathrm{d}x}\right)_{\text{No-slip}} = \frac{K\sigma_\theta\left(2\cos\theta-1-\frac{S}{D}\right)\tan\theta}{\frac{D}{2}\left(1+\frac{S}{D}-\cos\theta\right)\cos\theta} \tag{9.8}$$

For nip angle α the pressure gradients in the slip and no-slip regions are equal at the nip angle, thus:

$$\left(\frac{\mathrm{d}\sigma}{\mathrm{d}x}\right)_{\text{Slip}} = \left(\frac{\mathrm{d}\sigma}{\mathrm{d}x}\right)_{\text{No-slip}} \tag{9.9}$$

Hence, α can be deduced by solving Equations (9.1) and (9.8):

$$\frac{4\left[\left(\frac{\pi}{2}\right)-\alpha-\nu\right]\tan\delta_E}{\cot(A-\mu)-\cot(A+\mu)} = \frac{K\left[2\cos\alpha-1-\left(\frac{S}{D}\right)\right]\tan\alpha}{\cos\alpha} \tag{9.10}$$

Equation (9.7) can also presented graphically plotting pressure gradients in the slip and nip regions as a function of the angle. The nip angle is determined from the point where the slip and nip pressure gradients cross each other (Figure 9.4).

The value of the model is the link between process parameters and material properties. Since the pressure is typically applied to the rolls as an overall hydraulic pressure of press force (R_f), the relationship for pressure distribution between rolls can be used to relate R_f to the peak pressure ($P_{\max}$) applied at minimum gap separation:

$$R_f = \frac{P_{\max}WDF}{2} \tag{9.11}$$

Where W is the width of roll, D is the diameter of roll, and F is as follows:

$$F = \int_{\theta=0}^{\theta=\alpha(\delta_E,\phi_W,K)}\left[\frac{\frac{S}{D}}{\left(1+\frac{S}{D}-\cos\theta\right)\cos\theta}\right]^K\cos\theta\,\mathrm{d}\theta \tag{9.12}$$

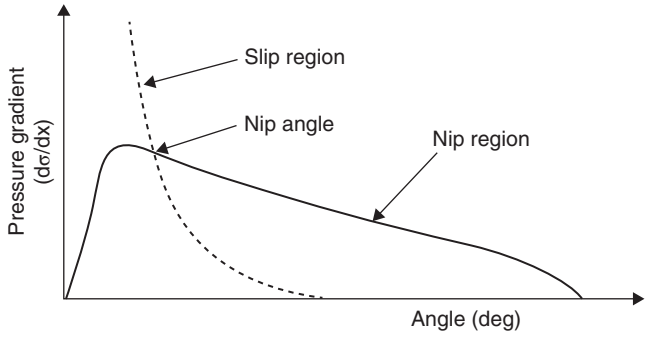

Figure 9.4 *Schematic illustration to the determination of nip angle.*

The key quality attribute for roller compaction is the relative ribbon density (γ_R). Relative ribbon density can be estimated from the peak pressure using a simple power low analogy (relationship between material density and pressure) as in Equation 9.5:

$$\gamma_R = \gamma_0 P_{max}^{1/K} \tag{9.13}$$

Where γ_0 is the preconsolidation relative density. By combining process parameters, equipment geometry and material properties (Equations 9.11–9.13) the relative ribbon density can be obtained as follows:

$$\gamma_R = \gamma_0 \left(\frac{2R_f}{\int_{\theta=0}^{\theta=\alpha(\delta_E,\phi_W,K)} \left[\frac{\frac{S}{D}}{\left(1+\frac{S}{D}-\cos\theta\right)\cos\theta} \right]^K \cos\theta \, d\theta} \right)^{1/K} \tag{9.14}$$

9.5 Modified Johanson Model

A criticism of Johanson's model is that it does not explicitly take into account roll speed and especially that it is very sensitive for nip pressure which dictates the entire pressure profile. Reynolds *et al*. [9] used a modified version of the Johanson model where they predicted the relative ribbon density as a function of screw speed to roll speed ratio (N_S/N_R), roll force (R_f), and preconsolidation relative density (γ_0). The modified Johanson model starts with the idea that the roll gap is not controlled in all instances but the speed of feed screw is the key process attribute. From the mass balance the mass flow rate of ribbon is:

$$\dot{m}_r = \rho_{\text{true}} \gamma_R \bar{v} W S \tag{9.15}$$

Where ρ_{true} the material true density, v is the average speed of material between rolls (assuming no-slip at the roll surface), W is the width of rolls, and S is the gap between rolls.

$$\bar{v} = \pi D N_R \tag{9.16}$$

where N_R is the rotation of the rolls. For a screw feeder the mass flow rate is typically proportional to the screw rotation rate:

$$\dot{m}_S = c_S N_S \tag{9.17}$$

Where c_S is the screw constant and N_S is the rotation rate of the feed screw. At the steady state, assuming no-slip and no-leakage of the powder Equations (9.15) to (9.17) can be combined to:

$$\frac{N_S}{N_R} = \frac{\pi}{c_S}\rho_{\text{true}}\gamma_R D W S \tag{9.18}$$

Now this equation provides a direct relationship to the relative ribbon density without the knowledge of roll gap:

$$\gamma_R = \gamma_0 (2R_f)^{\frac{1}{K}} \left(WD \int_{\theta=0}^{\theta=\alpha(\delta_E,\phi_W,K)} \left[\frac{c_S N_S}{\pi \rho_{\text{true}} \gamma_R W D^2 N_r \left(1 + \frac{c_S N_S}{\pi \rho_{\text{true}} \gamma_R W D^2 N_R} - \cos\theta\right) \cos\theta} \right]^K \cos\theta \, \mathrm{d}\theta \right)^{-\left(1/K\right)} \tag{9.19}$$

However this equation requires a number of parameters which have to be obtained through experiments, calibration, and/or fitting. Roll force (R_f) can be in some cases obtained directly from equipment, or in the case of a hydraulic pressure-controlled roll, through calibration. The screw constant (c_S) can be obtained from experiments. It can be determined simply by weighing the material output as a function of time, assuming that all fed material passes through the rolls. Alternatively, Equation (9.18) can be used if all other parameters are known. Other parameters are: effective angle of friction (δ_E), angle of wall friction (ϕ_W), and compressibility (K), which can be obtained as described earlier. For material true density (ρ_{true}) a standard pycnometric measurement can be used. The ribbon relative density has to be measured using appropriate methods such as true and envelope density measurements. Then the preconsolidation relative density can be obtained from:

$$\log(\gamma_R) = \frac{1}{K}\log(\mathrm{P}_{\max}(\mathrm{K})) + \log(\gamma_0) \tag{9.20}$$

Reynolds (2010) [9] and later Souihi (2015) [10] observed that compressibility factor (K) varied depending on the determination of approach. A compressibility factor determined from Equations (9.19) and (9.20) gave lower values than the uniaxial test with a conventional punch and die system. This led to over-prediction of the relative ribbon density. The explanation for this phenomenon is that the uniaxial test is a so-called "in die" method whereas the measurement of ribbon density after roller compaction presents an "out of die" method. An out of die method allows elastic recovery of the ribbon before measurement of its density and thus a lower relative ribbon density is observed.

It should be noted that a modified Johanson model assumes a constant nip angle similarly to the original Johanson model. Also it does not take into account pressure variation along the width of the roll, but assumes uniform pressure distribution, which is not a realistic description of pressure distribution in roller compaction. It is well-known from the literature that the center of a roll is subjected to a higher pressure than the roll edges. In addition, the Johanson and modified Johanson models include many material parameters which must be obtained from experiments and data fitting which are sometimes difficult to acquire and always contain measurement errors. So, a good understanding of the Johanson models and

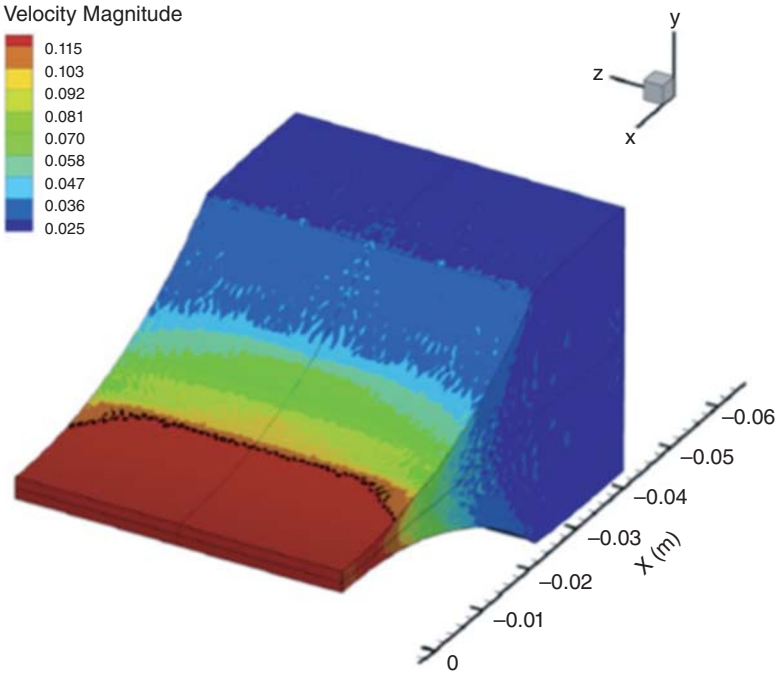

Figure 9.5 *Three-dimensional velocity distribution during ribbon formation [12].*

caution are needed when these models are implemented to describe the roller compaction process.

Bi *et al*. (2014) [8] observed that the Johanson model strongly over-predicted the maximum roll pressure. Authors claimed that the assumptions of the Johanson model for laminar flow in the nip region, mass continuity theory, or no velocity gradient through the ribbon thickness as the powder moves to the minimum gap between are not valid. They referred to FEM studies by Muladi *et al*. (2012, 2013) [11, 12] which clearly support their claims (Figure 9.5). It becomes apparent that there is a velocity gradient through the ribbon thickness and thus the mass continuity theorem needs to be adjusted in order to get the correct maximum roll pressure and subsequently the ribbon relative density.

Bi *et al*. (2014) [8] proposed a correction factor f_θ (actual fraction of powder delivered from nip angle α to the angle θ). Now Equation (9.5) becomes:

$$\frac{\sigma_\alpha}{{\sigma_\theta}^{\mathrm{AMC}}} = \left(\frac{f_\theta \rho_\alpha}{{\rho_\theta}^{\mathrm{AMC}}}\right)^K = \left(\frac{V_\theta}{f_\theta V_\alpha}\right)^K \tag{9.21}$$

AMC stands for "after mass correction". By combining Equations (9.21) and (9.6), Equation (9.22) is derived.

$${\sigma_\theta}^{\mathrm{AMC}} = \sigma_\alpha \left[\frac{f_\theta\left(1+\frac{S}{D}-\cos\alpha\right)\cos\alpha}{\left(1+\frac{S}{D}-\cos\theta\right)\cos\theta}\right]^K \tag{9.22}$$

Also Equation (9.12) gets a new form:

$$F_{\text{new}} = {f_0}^K \int_{\theta=0}^{\theta=\alpha(\delta_E, \phi_W, K)} \left[\frac{\frac{S}{D}}{\left(1 + \frac{S}{D} - \cos\theta\right)\cos\theta} \right]^K \cos\theta \, \mathrm{d}\theta \tag{9.23}$$

And thus the maximum roll surface pressure from Equation (9.11) can be rewritten as:

$$P_{\max} = \frac{2R_f}{f_\theta^K DWF} \tag{9.24}$$

Rearranging Equation (9.24), the maximum roll surface pressure after mass correction is:

$$P_{\max}^{\text{AMC}} = f_0^K P_{\max} \tag{9.25}$$

where:

$$P_{\max}^{\text{AMC}} = \frac{2R_F}{DWF} \tag{9.26}$$

$P_{\max}^{\text{AMC}}$ is set equal to the axial stress derived from the in-die compression. $P_{\max}$ is predicted using the standard Johanson's model and K is the standard compressibility constant. The challenge of Equation (9.25) is that f_0 has to be determined and it is related to many parameters, including wall friction angle, effective angle of internal friction, compressibility constant, nip angle, roll width, roll diameter, roll gap, and roll force. Thus the accuracy of those parameters is critical in order to get the correct f_0 value. Bi *et al*. (2014) [8] were able to get very accurate predictions of roll pressures after modification of the Johanson model with mass correction.

9.6 Experimental Observations of Pressure Distribution from Instrumented Roller Compactors

In general there are two types of roller compactors to control roll pressure: (i) both rolls fixed, and (ii) one roll fixed and another roll "floating" (typically controlled by hydraulic pressure). In the case of both rolls fixed, roll pressure is a function of feed screw speed and roll speed. As roll speed increases and/or feed screw speed decreases the roll pressure decreases. This kind of roller compactor is actually very sensitive to the mass flow rate variation introduced by a helical feed screw configuration. In the case of a floating roll configuration, the roll pressure stays constant with the aid of hydraulic pressure. As feed rate or roll speed change, the gap between the rolls changes accordingly.

Instrumented roller compactors are valuable tools in the development of roller compaction processes and formulations. Instrumentation is typically performed by installing miniature piezoelectric transducers or load cells into the roll surface (Figure 9.6). Several authors have conducted roller compaction studies with instrumented roller compactors [3, 4, 10] and quite consistent results can be drawn from these studies regarding to the main features of pressure distribution (Figure 9.7). It is possible to determine the nip angle from the pressure versus roll angle plot by placing tangents to upward and downward parts of a plot. The nip angle is the angle between tangents. It can be seen that peak pressure typically locates a few degrees before the neutral angle (0°). Also, there is a

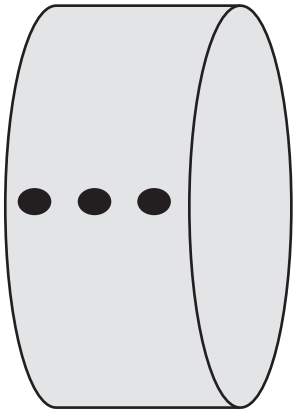

Figure 9.6 *Force/pressure sensors installed at the surface of roll.*

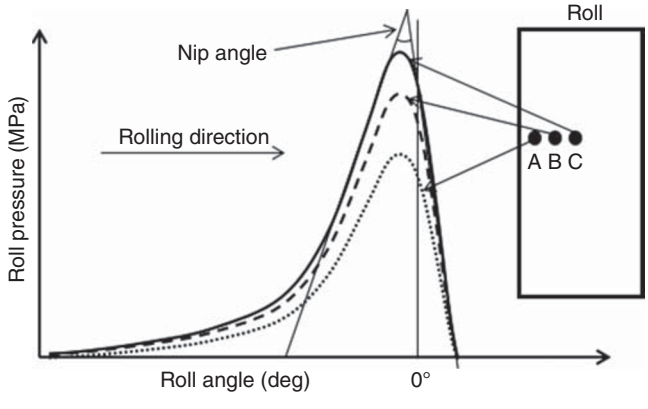

Figure 9.7 *Schematic illustration of roll pressure as a function of roll angle. Sensor location A represents pressure sensor at the edge of the roll, location B sensor between edge and center and location C sensor at the centerline of the roll.*

strong variation of pressure depending on the location of sensor (along the roll width). Pressure at the centerline sensor can be even two times higher than at the edge sensor. This is explained by the feed screw pushing the powder directly towards the centerline and thus there is more powder in the center of the roll than at the edges.

However, after several rotations of the roll, it was observed that the maximum pressure point varied along the sensor location. It was found that the variation was related to the flight of the feed screw. Thus it can be concluded that pressure distribution varies along the roll width and with time. This cannot be modeled with fairly simple one-dimensional Johanson models, but more complex models are required to capture these findings.

Some instrumented roller compactors are capable of measuring shear stresses introduced to the roll (Figure 9.8). At the beginning (roll angle >> 0°) there exists only a minor shear stress. As the roll angle approaches 0°, shear stress inverts its direction, and a few degrees

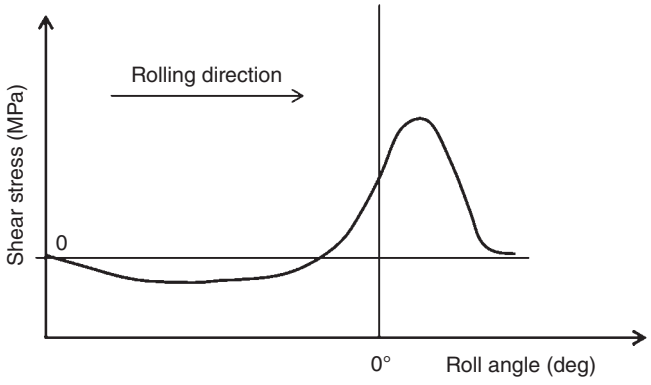

Figure 9.8 *Schematic illustration of shear stress as a function of roll angle.*

after, the neutral angle reaches its maximum. It should be noted that shear stress is much stronger after the neutral angle than before.

9.7 Off-line Characterization of Ribbon Quality

The most important quality attribute of roller compaction is the ribbon relative density (i.e., solid fraction or porosity). The ribbon relative density directly affects the granule size and size distribution and subsequently the tablet strength and weight variability. As the ribbon relative density increases as a function of roll pressure, the granule size increases. As granule size increases, tablet strength tends to decrease due to the lower specific surface area (i.e., less surface area for bonding) and work hardening, especially with plastically deforming materials. Thus there is a delicate balance between the particle size of granules and the compactability of granules that has to be determined for each roller compaction formulation. Increased particle size enhances the flowability and content uniformity, diminishing the dusting and segregation with the cost of compactability. If there is variability in the ribbon relative density, it increases the particle size distribution which decreases the flowability. On the other hand, this increases the compactability of the granules.

There are several off-line methods available for ribbon relative density measurements. Mercury intrusion porosimetry and pycnometric methods (true and envelope methods) are the reference methods for ribbon relative density. However, these methods are quite slow and difficult techniques to be applied routinely. Moreover, they do not describe the spatial heterogeneity of ribbon relative density, but are like bulk measurement techniques which describe the total or bulk ribbon relative densities.

Miguélez-Morán (2009) [13] compared three techniques to measure the spatial heterogeneity of the ribbon relative density. They were sectioning, micro-indentation, and X-ray micro-computed tomography. Their advantage is that they all provide good spatial resolution of the ribbon relative density, and X-ray micro-computed tomography proved to be outstanding, with micron-level resolution. A disadvantage is that they all require careful calibration (except sectioning). Sectioning is by far the simplest method for measuring the ribbon relative density. The ribbon is sectioned into blocks of a certain size and the

dimensions of these blocks are measured using a slide caliper and a micrometer. Weight is measured with a high precision balance and density is calculated as a ratio of the mass to the volume of the blocks. Comparing this density to the true density, the ribbon relative density (i.e., porosity or solid fraction) can be calculated. In micro-indentation measurements, a certain type (round or pyramid) of tip is pressed with a predetermined force/pressure onto the surface of studied material. The area of indentation is measured using image analysis and that area is correlated with a known relative density or porosity. Typically, calibration is performed with known porosities of tablets. X-ray micro-computed tomography (X-ray CT) can provide by far the most detailed picture of spatial heterogeneity of ribbon relative density. Modern X-ray CT equipment can achieve well below 10 μm spatial resolution of density. The disadvantage of X-ray CT is that, with high resolution, measurement times are long (object size 10 × 10 mm) and even longer if the object is large. X-ray CT also requires calibration against samples of known density/porosity. Since the origin of signal in the X-ray CT is based on density, in multicomponent samples (each component has its own density) careful data analysis is required in order to get correct interpretation of the variability in the real ribbon density variation.

Miguélez-Morán (2009) [13] used a laboratory roller compactor (by gravity feed) to produce ribbons from a microcrystalline cellulose and magnesium stearate blend. Figure 9.9 illustrates the average relative density of ribbon as a function of ribbon width measured with three different techniques. Generally, all techniques produced very equal results. Also this nicely illustrates that the ribbon relative density is indeed higher at the center of ribbon, as discussed earlier. Fairly low relative densities at the edges of the ribbon can be mainly explained by gravity feeding. Also practically no length-wise density variation was observed due to gravity feeding.

Guigon and Simon (2003) [14] studied the influence of a force feeding system on roller compaction. They used sodium chloride as a model material and its light-transmitting property to detect density variation along the ribbon (length-wise). They found a sinusoidal

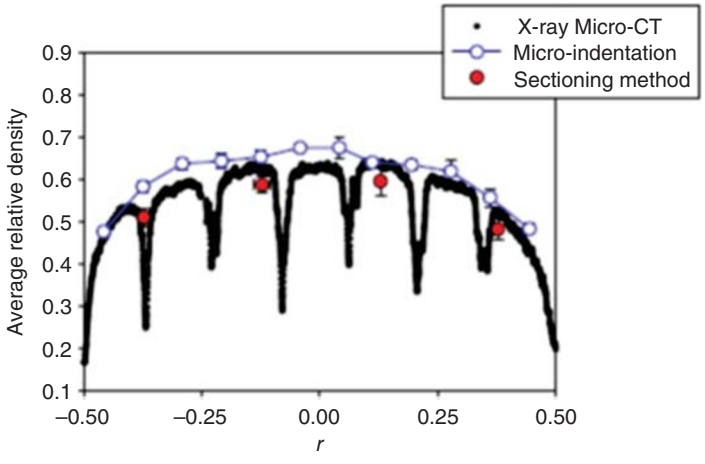

Figure 9.9 *Average relative density of ribbon as a function of ribbon width measured by sectioning, micro-indentation, and X-ray micro-computed tomography [13].*

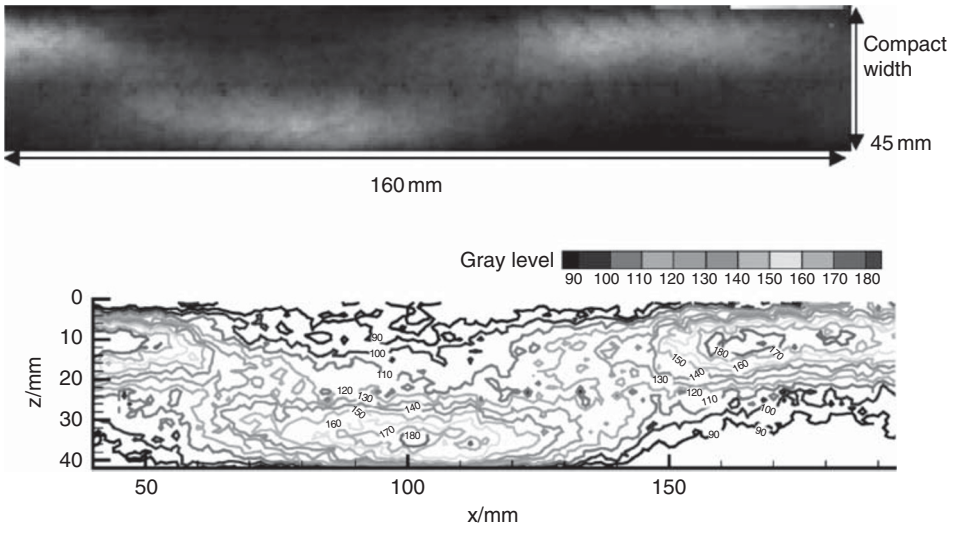

Figure 9.10 *Sinusoidal density variation in sodium chloride ribbon [14].*

density variation along the ribbon that strongly correlated with the feed screw rotation rate (Figure 9.10). Similar observations can be found from the three-dimensional FEM model (Figure 9.11) [12].

9.8 In-line Monitoring of Roller Compaction Process

The aim of in-line process monitoring is to get a better process understanding according to a quality by design (QbD) and process analytical technology (PAT) framework. The methods described above are off-line techniques and they can be used as reference and calibration methods for the in-line measurements. At the time there exists only one real in-line technique for ribbon density monitoring (and some other mechanical characteristics of ribbon) which is near infra-red (NIR) spectroscopy (NIRS). The challenge with NIR is that it probes both chemical and physical information from the sample. Thus a good understanding of the NIR method and multivariate data analysis is required to extract those quantities from NIR spectra. Most often peaks in NIR spectra are related to chemical information in the sample whereas baseline shifts and slope variations are related to the physical and mechanical properties of sample. For example, sample density and NIR absorbance have a strong positive correlation. A higher density gives a rise in the baseline as there is more material interacting with the incident NIR illumination. Standard NIR measurements are often point measurements which do not provide spatial information from the sample. A powerful NIR technique to probe the spatial information of the sample is NIR chemical imagining (NIR-CI). In many publications NIR-CI has performed so well off-line that it can be implemented to roller compactors as an in-line tool with appropriate interfacing.

Lim *et al*. (2011) [15] used the NIR-CI method to monitor the ribbon porosity of microcrystalline cellulose after roller compaction (Alexanderwerk Inc.). As a reference method

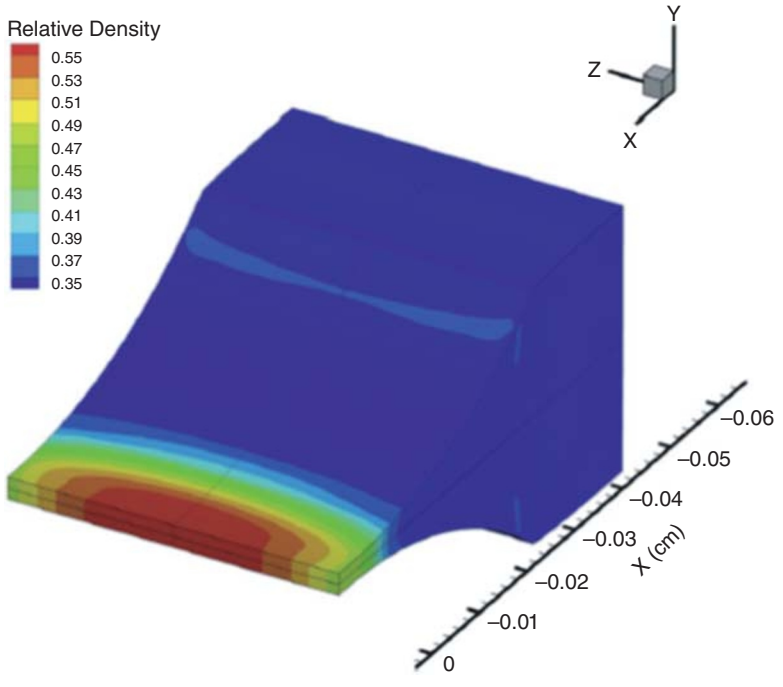

Figure 9.11 *Relative density distribution during ribbon formation, three-dimensional FEM model [12].*

they used pycnometers to measure the true and envelope densities for the calculation of porosity as follows:

$$P\% = \left(\frac{1 - \rho_{\text{envelope}}}{\sigma_{\text{true}}} \right) * 100\% \tag{9.27}$$

They correlated the measured porosity with the mean absorbance from NIR-CI in order to get the calibration curve for porosity. The plot (Figure 9.12) illustrates the performance of NIR-CI as a monitor of ribbon porosity. The intensity plot reveals the same information as discussed earlier: the center of ribbon is denser that the edges of ribbon. It might be noted that density difference between center and edges is somewhat smaller in Figure 9.12 than in Figure 9.9. Thus, the force feeder smooths the density variation along the width of ribbon slightly better compared to gravity feed.

Khorasani *et al.* (2015) [16] demonstrated the applicability of NIR-CI to monitor both chemical (drug content) and physical (porosity) information from a ribbon. They used microcrystalline cellulose (MCC; 60% w/w) and acetylsalicylic acid (ASA; 40% w/w) as a model formulation. In order to differentiate the chemical and physical information from NIR spectra they utilized principal component analysis (PCA) and partial least squares (PLS; Figure 9.13). According to the loading analysis of the PCA model (three principal components; PC), the first PC explained 95.1% of the variation and was highly correlated to the average spectrum of MCC and ASA. Variation in PC1 loading was mainly due to baseline shifts caused by physical variation (porosity). The loading plot of the second PC

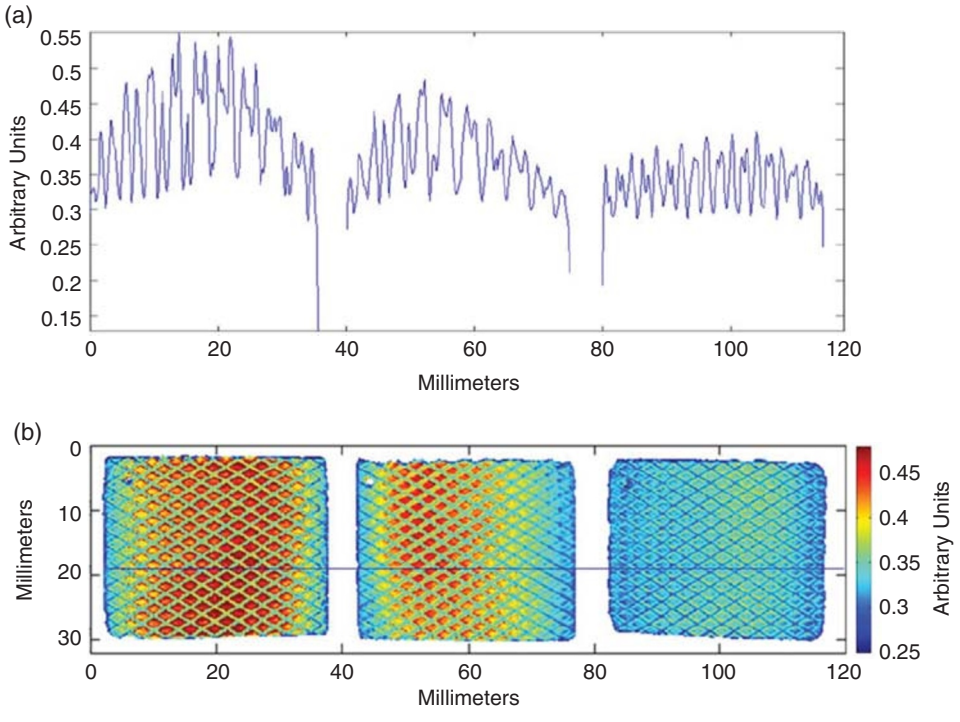

Figure 9.12 *(a) Line projection of porosity variation across sample width [horizontal solid line in plot (b)]. (b) Intensity images of porosity. Measured bulk porosities were 26.35, 36.56, and 50.27%, from left to right [15].*

was very similar to the pure ASA spectrum. So the second PC can be used to monitor ASA content. The final PC included features from the pure MCC spectrum, so respectively, it can be used to monitor MCC content.

Other physical information such as particle size, tensile strength, Young's modulus and moisture content can be also obtained from NIR measurements after careful data analysis and calibration [17, 18].

9.9 Formulative Aspects of Roller Compaction

The main aspect of roller compaction formulation design is the tabletability of roller-compacted granules. Tabletability or compactability of roller-compacted granules strongly depends on the deformation mechanism of the excipients and drug. Plastically deforming materials tend to lose their compactability due to work hardening. Plastically deforming materials are also sensitive to granule size and lubrication. The effect of work hardening, granule size and lubrication on tablet strength with plastically deforming materials is a complex phenomenon and the root cause for reduced tablet strength is often difficult to identify [19]. In work hardening, material loses its compactability in each compression (roller compaction) and its resistance to permanent deformation increases in

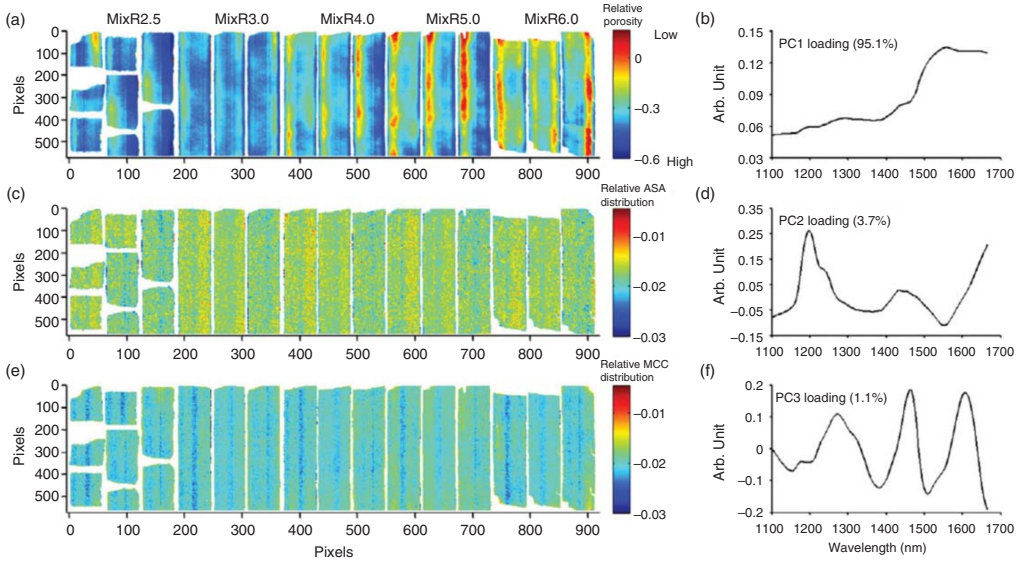

Figure 9.13 *NIR-CI images to monitor chemical and physical information from the ribbon. First principal component contains porosity information (a) and (b). Second principal component: ASA content (c) and (d). Third principal component: MCC content (e) and (f) [16].*

subsequent compressions (tableting), causing reduced tensile strength of tablets. Plastic materials are also sensitive to granule size. As particle size increases the specific surface area for bonding decreases, resulting in reduced tensile strength of tablets. In addition lubricants (e.g., magnesium stearate) cover the particle surface and thus prevent bond formation and again cause reduced tensile strength of tablets. Brittle materials are much less prone to difficulties due to work hardening, granule size, and lubrication since they break under pressure and new pure surfaces become available for bond formation.

Formulation design starts with the characterization of the drug compound properties, especially the deformation mechanism of drug and drug loading [1]. If the drug loading is low then the formulator has a larger availability of different excipients and formulation design is not an issue. The rule of thumb in formulation design is to balance between the plastic and brittle behavior of formulation. Typical plastic fillers are microcrystalline cellulose and its modification, starch, and starch derivatives. Example of a brittle filler is calsiumphosphate and its different forms (anhydrous and hydrous). Sugars (lactose, mannitol) are mostly brittle and partially plastic. Especially lactose is a very good candidate for roller compaction formulations since it is practically insensitive to issues of work hardening, granule size, and lubrication. Also there are many different grades of lactose available. Binders are typically added to increase the strength of ribbon and granules. Microcrystalline cellulose can act as a filler and binder. Other typical binders are polyvinylpyrrolidone, cellulose derivatives like HPMC and HPC, polyethylene glycol, and Carbopol. Binders are typically plastic materials and they are used with high-dose, brittle drug compounds. Usually small particle size (i.e., large surface area) binders are preferred in order to achieve full coverage of binder into the surface of large brittle particles. In some cases a disintegrant is needed to achieve proper disintegration time and/or dissolution rate. Croscarmellose sodium, crospovidone, sodium starch glycolate, alginate, starch, and pregelatinized starch are common disintegrants. Lubricant also has an important role in roller compaction formulations. On the other hand, it reduces the friction between powder and equipment surfaces but it also changes the effective angle of internal friction (δ_E), angle of wall friction (ϕ_w), tensile strength of tablets (depending on deformation mechanism), disintegration time, and dissolution rate. Thus, a good process and formulation understanding is required when deciding the optimal lubricant level in roller compaction formulation. Stearic acid and its derivatives, stearic acid salts (e.g., magnesium stearate), talc, polyethylene glycols, surfactants, and glycerol behenate are common lubricants. Also glidants (silicon dioxide, talc, and corn starch) might be used to improve the flowability of the powder.

Extra dimension can be added to the formulation design of roller compaction when it is decided what components belong to the so-called intra-granular composition and which components can be added to the external composition. That is, after roller compaction, some excipients are mixed to the roller-compacted granules to achieve the satisfactory tableting properties or preferred disintegration time and/or dissolution rate of tablet.

9.10 Roller Compaction as a Unit Operation in Continuous Manufacturing

Considering roller compaction as a unit operation in the continuous manufacturing of tablets or capsules, there are a few issues which need to be highlighted. The first point in continuous manufacturing consisting of several unit operations in series is mass flow rate

Figure 9.14 *Continuous production line in the University of Eastern Finland, School of Pharmacy [20].*

synchronization which applies to every continuous process. Commonly there are at least two unit operations before roller compaction: continuous powder feeding and continuous blending (Figure 9.14).

After the roller compaction granules can directly go to tableting or there can be another feeding and blending unit operation between roller compaction and tableting. Input and output mass flow rates have to match between each of these unit operations. Preferably mass flow rates are monitored and controlled in each unit operation, which is not always a simple task with powder and granular materials. The most convenient way is simply to use balances. However, the implementation of a weighing system might not be as straightforward as it seems, since the pieces of equipment are connected to each other, creating the possibility of a disturbance to the weighing system. Key parameters to monitor and control material flow in continuous processes are mass hold and residence time distribution (RTD). Mass hold tells how much material is in the unit operation at the time. RTD describes how the step change or pulse in the input parameters is spread out in the unit operation. In plug flow systems the step change or pulse remains unchanged when material moves through each unit operation. In pharmaceutical continuous manufacturing of solids each unit operation involves a considerable amount of back-mixing which causes the spreading of step change or pulse in the input parameters as material moves through the unit operation. This causes longer and broader residence time distributions. Another point in the mass flow rate synchronization is the out of specification situation. If one unit operation runs out of

specification, the product from that unit operation must be directed to the waste. Meanwhile the previous and following unit operations must have buffer capacity, otherwise they must slow down or even shut down which is not desirable. Another point is the recovery of mass flow disturbances after the out of specification. It might be possible to run a continuous process at a higher production rate up to the point of the out of specification unit operation in order to catch up to the production rate of the following unit operations without compromising intermediate product quality. Or vice versa, unit operations following the out of specification unit operation are slowed down so that previous unit operations can achieve the desired production rate.

9.11 Process Control of Continuous Roller Compaction

Recent advances in process control design and optimization of pharmaceutical continuous manufacturing mostly utilize gPROMS (Process Systems Enterprise Limited, UK) and MathLab (The MathWorks, Inc., UK). These software packages provide multiple tools for process control design, optimization, and simulation. In a series of papers, Hsu *et al* (2010a, 2010b) [21, 22] built, from first principles, a dynamic model for the roller compaction process based on Johanson's rolling theory and material balance equations. With the aid of a dynamic model they were able to simulate the effect of three input variables (feed speed, roll speed, and roll pressure) on two main output parameters (ribbon density and thickness, and from these the production rate). It is notable that with this dynamic model they were able not only to simulate the effect of individual input variables on output parameters, but also to simulate the interaction effects of input variables on output parameters. This makes it possible to evaluate whether interactions are linear or nonlinear, which will have a great importance in the selection of control strategies. In the second part of their study, they evaluated different control strategies (multi-loop proportional integral derivative; PID; linear and nonlinear model predictive control; MPC) for the on-line process control of roller compaction process, together with the dynamic roller compaction model which they developed in the first part of their study [22]. PID control structure is very common control scheme and it has been used for over 70 years in many industries. The disadvantage of PID control structure is that it consists of multiple tuning parameters, especially if the process dynamics is complex (many input and output parameters with interactions). Even today, there is no common approach or algorithm to optimize the parameters of multi-loop PID controllers. MPC instead is based on an existing process model and it provides a systematic approach to design a multivariable control system. On the other hand, MPC is a very computation-intensive, especially in fast and nonlinear dynamic processes. Hsu *et al.* (2010b) [22] summarized that a nonlinear MPC controller gave the best performance but was impractical due to the high computational cost. A comparison between linear MPC and multi-loop PID controllers pointed out that the linear MPC was better and they suggested it as a high-performance control strategy for roller compaction.

One of the most advanced demonstrations of the implementation of a control strategy for the continuous manufacturing of tablets via roller compaction is maybe the publication from Singh *et al.* (2012) [23]. They modeled a continuous manufacturing line consists of feeders, blender, roller compactor, mill, and tablet press by utilizing a first principles, model-based

flowsheet simulation with gPROMS to simulate the continuous manufacturing line. They designed a control system based on PID controllers (altogether 42 controller tuning parameters). Roller compactor ribbon density (CQA) and throughput (CPP) were critical process variables which were controlled by roll hydraulic pressure and roll speed. The main interest of their study was to compare open-loop and closed-loop controller performance to detect disturbance rejection and to set point tracking. They found that a closed-loop approach worked better than an open-loop approach and that controller system performance was satisfactory. They concluded that the automated control system could be improved by using MPC, as Hsu *et al.* (2010b) have already demonstrated.

Unfortunately, these two examples of designing, optimizing, and simulating the development of a control system for roller compaction and continuous manufacturing have only been conducted *in silico*. They should be implemented using a real continuous manufacturing line in order to demonstrate their real potential and applicability.

9.12 Conclusions

The major advantage of roller compaction is that it is inherently a continuous operation. The key product quality attribute is the relative ribbon density since it directly affects the granule bulk density and subsequently the tablet mass variation, particle size, and size distribution of milled ribbon, affecting flowability, dusting, segregation and tablet tensile strength (especially in plastic materials). The critical process quality attribute is the granule production rate which directly depends on the ribbon relative density. Much research is yet needed in order to create an appropriate monitor and control environment for roller compaction. Proposed models for roller compaction are still too simple to capture all features of roller compaction. It seems that advanced computational models like FEM and DEM can significantly contribute to increase our understanding of roller compaction. However for in-line process monitoring and control purposes they are too time-consuming at the moment. For ribbon relative density measurements NIR-CI seems to be the only potential technique. It has been demonstrated to be capable of capturing both chemical and physical information from ribbon in-line after proper calibration and multivariate data analysis. It is evident that modern simulation tools are needed in the design, optimization, and simulation of on-line control systems for roller compaction and continuous manufacturing of pharmaceutical product in general.

Unfortunately, in spite of the great number of publications about the theory of roller compaction, various PAT tools for the in-line monitoring of CQA for roller-compacted inter-mediate product, and the control strategies of roller compaction in the sense of continuous manufacturing, demonstrations of actual implementation of roller compaction as an unit operation in continuous manufacturing lines is missing from pharmaceutical literature. Obvious reasons for this could be the lack of full continuous manufacturing lines, especially in academic research groups, and the pharmaceutical industry may not be willing to publish their advances in continuous manufacturing. Another reality is that the ideology of continuous manufacturing of pharmaceuticals is still a very young research area. Thus the real advantages, potential, and applicability of roller compaction as a unit operation in continuous manufacturing lines remain an open question.

As a conclusion, roller compaction as a unit operation in the continuous manufacturing of tablets and capsules is a very potential choice for granulation. It is inherently a

continuous operation, it does not require an energy-intensive and time-consuming drying step like continuous wet granulation methods. However there is still lot of room for research in the implementation of roller compaction into continuous manufacturing lines which will be an obvious next step in continuous manufacturing research.

References

[1] Teng, Y., Qiu, Z.,Wen, H. (2009) Systematic approach of formulation and process development using roller compaction. *European Journal of Pharmaceutics and Biopharmaceutics*, **73**, 219–229.

[2] Kleinebudde, P. (2004) Roll Compaction/dry granulation: pharmaceutical applications. *European Journal of Pharmaceutics and Biopharmaceutics*, **58**, 317–326.

[3] Bindhumadhava, G., Seville, J.P.K., Adams, M.J., *et al*. (2005) Roll compaction of a pharmaceutical excipients: experimental validation of rolling theory for granular solid. *Chemical Engineering Science*, **60**, 3891–3697.

[4] Cunningham, J.C., Winstead, D., Zavaliangos, A. (2010) Understanding variation in roller compaction through finite element-based process modeling. *Computer and Chemical Engineering*, **34**, 1058–1071.

[5] Johanson, J.R. (1965) A rolling theory for granular solids. *Journal of Applied Mechanics*, **32**, 842–848.

[6] Katashinskii, V.P. (1986) Analytical determination of specific pressure during the rolling of metal powders (in Russian). *Soviet powder metal ceramic*, **10**(6), 765–772.

[7] Jenike, A.W., Shield, R.T. (1959) On the plastic flow of coulombic solids beyond original failure. *Journal of Applied Mechanics Transactions, Series E*, **26**, 599–602.

[8] Bi, M., Alavare-Nunez, F., Alvarez, F. (2014) Evaluating and modifying Johanson's model to improve its predictability. *Journal of Pharmaceutical Sciences*, **103**, 2062–2071.

[9] Reynolds, G., Ingale, R., Roberts, R., *et al*. (2010) Practical application of reller compaction process modeling. *Computers and Chemical Engineering*, **34**, 1049–1057.

[10] Souihi, N., Reynolds, G., Tajarobi, P., *et al*. (2015) Roll compaction process modeling: tranfer between equipment and impact of process parameters. *International Journal of Pharmaceutics*, **484**, 192–206.

[11] Muladi, A.R., Litster, J.D., Wassgren, C.R. (2012) Modeling the powder roll compaction process: comparison of 2-D finite element method and the rolling theory for granular solids (Johanson's model). *Powder Technology*, **221**, 90–100.

[12] Muladi, A.R., Litster, J.D., Wassgren, C.R. (2013) Validation of 3-D finite element analysis for predicting the density distribution of roll compacted pharmaceutical powder. *Powder Technology*, **237**, 386–399.

[13] Miguélez-Morán, A.M., Wu, C-Y., Dong. H., *et al*. (2009) Characterization of density distribution in roller-compacted ribbons using micro-indentation and X-ray micro-computed tomography. *European Journal of Pharmaceutics and Biopharmaceutics*, **72**, 173–182.

[14] Guigon, P., Simon, O. (2003) Roll press design – influence of force feed systems on compaction. *Powder Techonology*, **130**, 41–48.

[15] Lim, H., Dave, V.S., Kidder, L. (2011) Assessment of the critical factors affecting the porosity of roller compacted ribbons and the feasibility of using NIR chemical imagining to evaluate the porosity distribution. *International Journal of Pharmaceutics*, **410**, 1–8.

[16] Khorasani, M., Amigo, J.M., Sonnergaard, J. (2015) Visualization and prediction of porosity in roller compacted ribbons with near-infrared chemical imagining (NIR-CI). *Journal of Pharmaceutical and Biomechanical Analysis*, **109**, 11–17.

[17] Gupta, A., Peck, G.E., Miller, R.W., *et al*. (2004) Nondestructive measurements of the compact strength and the particle-size distribution after milling of roller compacted powders by near-infrared spectroscopy. *Journal of Pharmaceutical Sciences*, **93**, 1047–1053.

[18] Gupta, A., Peck, G.E., Miller, R.W., *et al*. (2005) Teal-time near-infrared monitoring of content uniformity, moisture content, compact density, tensile strength, and Young's modulus of rolled compacted blends. *Journal of Pharmaceutical Sciences*, **94**, 1589–1597.

[19] Mosig, J., Kleinebudde, P. (2015) Critical evaluation of root cause of the reduced compactability after roll compaction/dry granulation. *Journal of Pharmaceutical Sciences*, **104**, 1108–1118.

[20] Simonaho, S-P., Ketolainen, J., Ervasti, T., Toiviainen, M., Korhonen, O. (2016) Continuous manufacturing of tablets with PROMIS-line – Introduction and case studies from continuous feeding, blending and tableting. *European Journal of Pharmaceutical Sciences*, Available at: doi:10.1016/j.ejps.2016.02.006 (accessed 2 February 2016).

[21] Hsu, S-H., Reklaitis, G.V., Venkatasubramanian, V. (2010a) Modeling and control of roller compaction for pharmaceutical manufacturing. Part I: Process dynamics and control framework. *Journal of Pharmaceutical Innovations*, **5**, 14–23.

[22] Hsu, S-H., Reklaitis, G.V., Venkatasubramanian, V. (2010b) Modeling and control of roller compaction for pharmaceutical manufacturing. Part II: Control system design. *Journal of Pharmaceutical Innovations*, **5**, 24–36.

[23] Singh, R., Ierapetritou, M., Ramachandran, R. (2012) An engineering study on the enhanced control of continuous manufacturing of pharmaceutical tablets via roller compaction. *International Journal of Pharmaceutics*, **438**, 307–326.

10

Continuous Melt Extrusion and Direct Pelletization

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10.1 Introduction

In general, hot melt extrusion (HME) is a continuous process, widely used in polymer processing for providing a homogeneous material stream in terms of distribution, temperature and flow rate, as input for granulation or to make semi-finished parts, such as films. Concerning pharmaceutical processing, interest in continuous manufacturing has increased significantly in the last years, leading to an increased interest in the use of HME as a platform for advanced manufacturing concepts in the pharmaceutical industry. Furthermore, HME is used as a processing platform for amorphous solid dispersions, stabilized nano-suspensions to enhance the dissolution rates of poorly soluble and low-dose feeding of highly active active pharmaceutical ingredients (APIs).

Similar to traditional HME, the formulation consists of a thermoplastic polymer matrix "filled" with the API, as well as processing and application excipients, such as plasticizers, anti-tacking agents, colorants, stabilizers, pore formers and others. Thereby, release of the API is controlled by the matrix and the structure of the dosage form.

The processing window of HME processes is limited by the softening temperature of the matrix (lower limit) and by the degradation temperature of the API or matrix (upper limit).

Continuous Manufacturing of Pharmaceuticals, First Edition.
Edited by Peter Kleinebudde, Johannes Khinast, and Jukka Rantanen.
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Accordingly, the formulation affects the processability and robustness of the process and impacts:

- The process temperature and pressure
- Screw configuration and speed
- Residence time
- Cooling and pelletizing

The extrusion process itself provides a homogeneous material to a downstream process. Such a continuous downstream process forms the final product (strands, pellets, sheets, powders, etc.) of the extrusion line, which then can be converted into the final dosage form (e.g., strands being cut and milled or pellets filled into capsules). An appropriate downstream process is selected based on the targeted dosage form, the material properties, such as rheology, and the product's purity and production costs.

Due to the nature of the formulations, the processing window is narrow, requiring a sound understanding of the material behavior (e.g., rheology) and a consistent and robust process analytical technology (PAT) and control approach. Especially nonsteady-state processes, such as start-up, concentration changes or any form of process disturbances demand a PAT setup and a control strategy to ensure product quality.

Although the process settings and control procedures may be based on long existing manufacturing science from polymer processing, the unique pharmaceutical demands require significant efforts in the design of formulations and processes. For example, the mass throughputs are generally smaller, regulatory aspects have to be taken into account and the process design shows a stronger focus on start-up and shut-down sequences. Therefore, the adaption and application of HME has to be done carefully considering the requirements of pharmaceutical processing.

10.2 The Extruder

The extrusion of melted and flowable material is a continuous process. Thereby, the raw materials are conditioned (e.g., melted mixed, devolatilized) in the barrel by conveying with a high-shear screw. This process can be divided into [1]:

- Feeding of the raw material
- Compacting of the polymer
- Melting
- Homogenization
- Devolatilization
- Forcing the melt through the die

An extrusion line generally consists of [1]:

– Feeder(s)
– Twin or single-screw extruder
– Dies for intermediates (e.g., pellets) or semi-finished parts (e.g., films)
– Online analysis systems (e.g., concentration, throughput, homogeneity)
– Strand cooling or direct pelletization

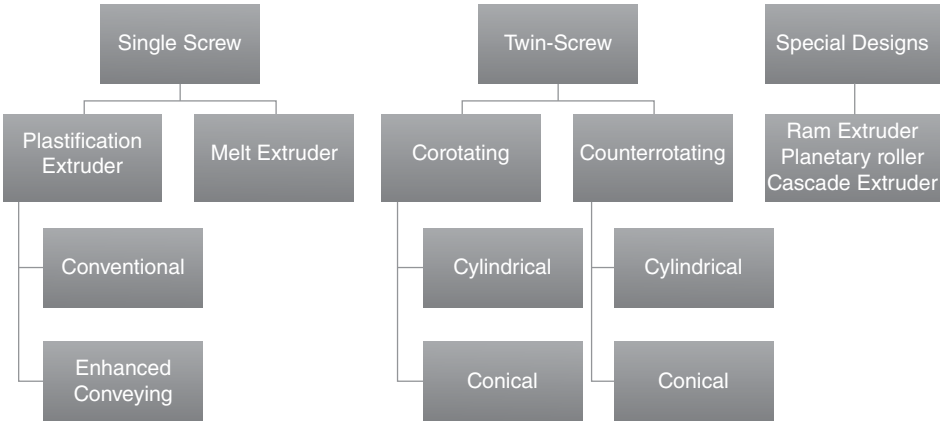

Figure 10.1 *Classification of screw extruders (according to [2]).*

The main function of the extruder is the supply of homogeneous (temperature, composition) melt to the die in sufficient and constant quantity. Thereby, various techniques, respectively models, are applied. Figure 10.1 displays an overview of different extruder types.

Generally, the extruder consists of:

- A machine bed
- A drive unit (motor, gear, thrust bearing)
- A plastification unit (screw, barrel, heating and cooling)
- Measurement and control technology

Figure 10.2 shows the different components of the plastification unit and their function.

Extruders are normally characterized by the screw diameter in mm and the screw length as multiples of the diameter (e.g., 18–40·D). The conveying of the solid raw material (e.g., powders or granules) is caused by the friction of the mass on the surface of the cylinder and the screw. The melting of the polymer is induced by heat conduction from the heated barrel wall and – mostly – by dissipation of shear energy introduced by friction and shear (see Figure 10.3). While the conductive heat arises from the heated barrel, the dissipated heat is due to the internal (polymer–polymer) and external (polymer–cylinder resp. screw) friction. Due to the shear heat in the very thin melt film, the melting is accelerated. The melt is scraped by the active edge, by which a melt vortex is formed in front of the active edge. This collected melt together with a leakage flow circulate around the solid. Furthermore, the heat flow from the screw into the solid leads to a melt film between the screw and the solid. Finally, the whole solid bed is surrounded by melt, which penetrates into the solid fraction depending on the packing density and porosity of the solid bed [2, 3].

The molten polymer is transported by coupled motion with the surface of the screw. The melt transport consists of a transverse flow and a flow in channel direction, which is divided into a drag flow and the particular pressure flow induced by a pressure gradient. These two types of material flow are superimposed. Accordingly, the material flow through the extruder is determined by the pressure flow/drag flow ratio. Low-pitch conveying elements can in general build up more pressure than high-pitch ones. Depending on the

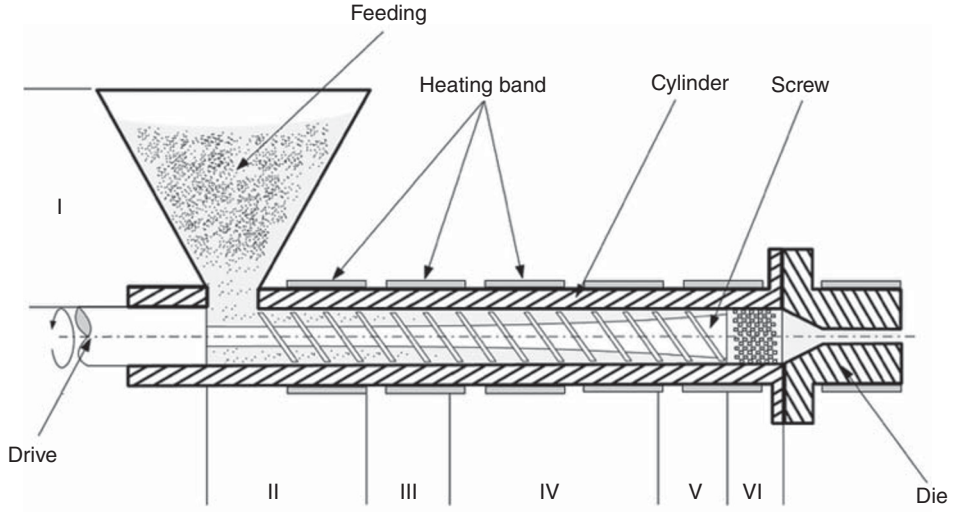

Figure 10.2 *Plastification unit: I – feeding; II – solid conveying; III – start of melting; IV – melting; V – metering; VI – mixing.*

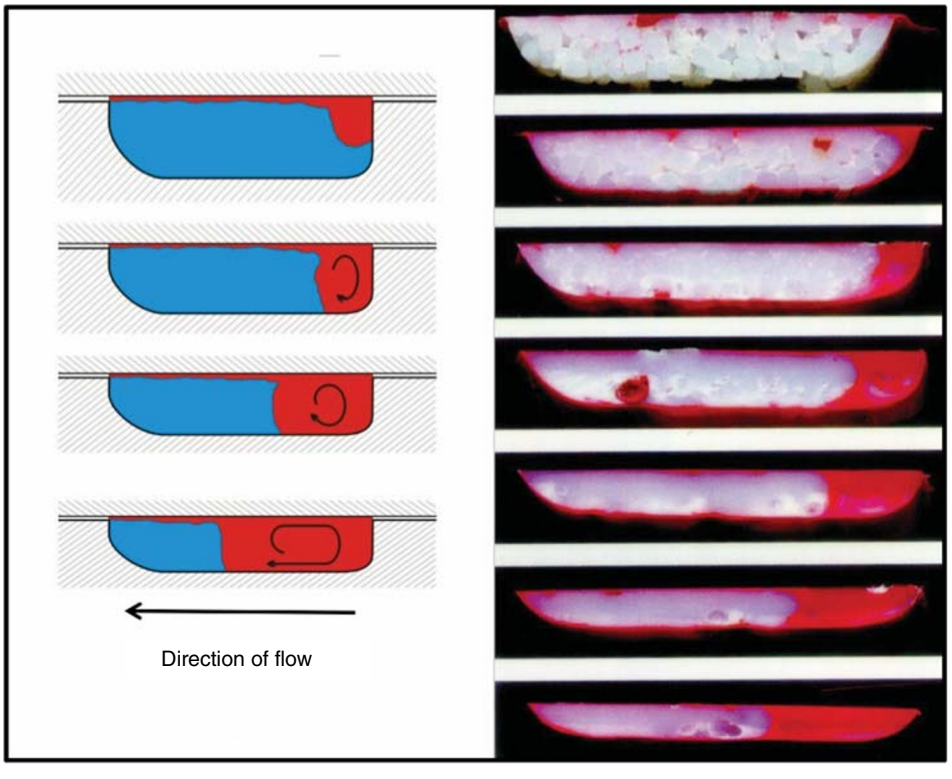

Figure 10.3 *Plastification with wall adhering melt. Picture courtesy of Montanuniversitaet Leoben, Polymer Processing.*

raw materials and the demanded thermal and mechanical homogeneity of the melt, special screw geometries such as barrier screws, shear or mixing elements are applied [3].

10.3 Feeding

The mixing capability of the extruder allows dampening of short-term or high-frequency fluctuations. Long-term or low-frequency deviations, on the contrary, are passed through the extruder undampened [4]. The frequency range for fluctuations that can be dampened depends on the screw design and process conditions, such as throughput and screw speed. The residence time distribution of a setup at certain operating points contains all the information about the axial mixing performance along the extruder. In pharmaceutical applications, the average residence time of the extruder typically is within a few minutes. Usually, a narrow residence distribution is desired in order to limit the thermal and mechanical stress on the material. However, this results in a limited back-mixing in the extruder and dampening of input fluctuations. Thus, accurate feeding is crucial for pharmaceutical extrusion. Since many solid materials used in pharmaceutical applications are available as powders only and often display poor flowability, accurate dosing is not trivial. Moreover, relatively low throughputs occur compared to other industries, such as food and plastics. Especially, in process development it is also a challenge to operate feeders at low fill levels, due to limited material availability.

10.3.1 Solid Feeding

For pharmaceutical solids, the most frequently used system is the twin-screw, loss in weight (LIW) feeder. Advantages are the closed containment of the material up to the point where the material leaves the feeder and their capability of handling materials with poor flowability. The twin screw is preferred to the single-screw setup because of its self-wiping geometry, which is especially important when handling materials that tend to adhere to metal surfaces. There are also other feeder types available, such as rotating disc feeders, vibratory feeders or belt feeders, but they are less frequently used. All types of feeders have multiple tasks to fulfill:

- Storage of powder in a hopper
- Providing mass flow of the material in the hopper to the dosing element (e.g. screw, disc, vibration chute or belt)
- Dosing the material at the desired gravimetric feed rate (i.e., in g/h)

For non-compressible material volumetric feeding can be sufficient. Volumetric feeding means, that the feeder conveys constantly a certain volume of material. This is done by setting a certain screw speed, disc rotation speed, vibration frequency or belt speed. Unfortunately, incompressible materials are the exception in pharmaceutical powders. Thus, the feeder needs to adapt the movement of the dosing element based on the current bulk density. For that gravimetric feeding is applied, where the feeder is put on a balance (load cell) measuring the feed rate from the weight change over time (LIW is detected). Based on the calculated feed rate, the screw speed, disc rotation speed, vibration frequency or

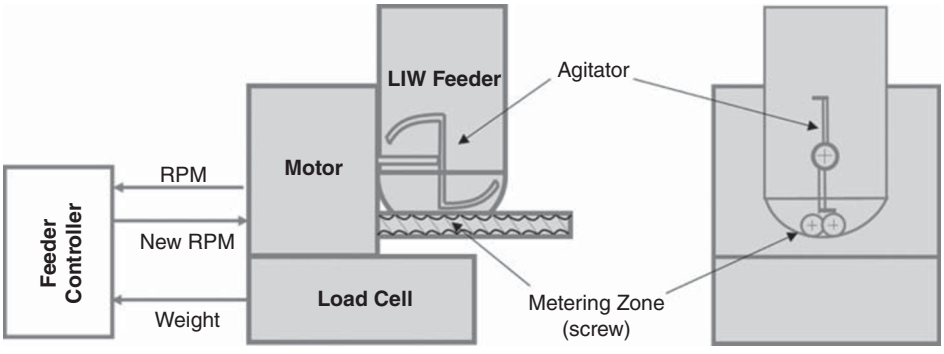

Figure 10.4 *LIW feeder with feed rate control based on weight detection.*

belt speed are adapted. An example for a LIW twin-screw feeder with feed rate control is shown in Figure 10.4.

The vast majority of certified good manufacturing practice (cGMP) feeders used in continuous manufacturing are screw feeders. Thus, these feeders are discussed in more detail here.

10.3.2 LIW Screw Feeders

The LIW screw feeder consists of a hopper with an agitator, one or two screws, a balance and a motor with a controller.

There are several sizes and modifications of LIW screw feeders available. They range from low-throughput, twin-screw microfeeders (15 g/h) up to single screw feeders with up to 1500 kg/h.

Depending on the particle size and target feed rate several screw geometries can be selected. For agglomerating powders it is also possible to mount discharge screens on the feeder outlet to make the powder flow more uniform.

For selecting the right feeder setup several aspects need to be considered. First, one has to take into account the flow rate that should be achieved. The hopper should be able to store a sufficient amount of material in order to allow a reasonlable refilling frequency. As a rule of thumb, refilling should be done at 60% of the maximum fill by filling up the hopper to 80% fill level for compressible powders. Thus, for a flow rate of 4 kg/h (assuming an average bulk density of 0.3 g/cm^3) 2200 cm^3 of material are fed from the hopper within 10 min. Assuming the hopper is refilled every 10 min, the hopper should have a volume of at least 12 L. Thus, the bigger the hopper volume, the less often is refilling necessary and problems during refilling system are less serious (i.e., loss of weight information). Since the whole hopper is placed on the balance, the resolution of the scale is determined by the maximum gross weight of the hopper and material. Thus, a very big and heavy hopper cannot be weighed as accurately as small one. In production, refilling is usually done by an automated system, with a fixed refilling interval. During the refilling, many feeders offer different strategies to adapt the screw speed, while the weight signal cannot be used for control of the screw speed. The simplest way is to keep the screw speed constant, until

a reliable value is available for the hopper weight. Then the screw speed is adapted to the speed that was used at that fill level before. A more sophisticated control method is to decrease the screw speed in a linear fashion or in steps, according to prior optimization experiments. Concerning the best hopper size, one should also consider that some materials are shear-sensitive and a long residence time in the hopper can alter their flow behavior or other properties. In the case of feeding a premix, a long residence time in the hopper can also induce segregation.

The geometry of the hopper is also crucial. Rectangular hoppers often show problems with stagnation of powder flow in the corners. Symmetrical cylindrical hoppers with a sufficient hopper angle ensure mass flow of the material in the hopper. Asymmetrical hoppers are used for increasing the hopper volume while keeping the screw length short, which is beneficial for the material conveying in the screw. In such hoppers, mass flow is not possible, since the material has different velocities on the vertical and angular walls.

The agitator in the hopper has the task of breaking down bridges in the hopper and providing material flow from the hopper to the screw. The agitator usually consists of two to four arms moving through the material by rotation. The axes of the agitator can be horizontal or vertical. Alternatively, there are also inatallations of paddles pushing elastic walls of the hopper back and forth, or vibrating installations available. Most feeders have an agitator though and horizontal installation is more common, for reasons of construction (the motor of the screw can drive the agitator, so less motor power is needed) and handling reasons. For powders with poor flowability the agitator design is crucial. Especially, for small hopper sizes and high filling heights it can happen that a horizontal agitator builds a bridge around itself. Figure 10.5 shows such a situation schematically. If such a bridge is stable, this causes a process interruption since the bridge has to be broken down manually. We detected such bridges in feeding experiments with a twin-screw feeder (MTS-Hyg, Brabender, Germany) for very poorly flowing powders such as calcium stearate.

A prerequisite for accurate feeding is that material is continuously flowing from the hopper into the pitches of the screw. The state of material flow can best be evaluated by doing experiments in volumetric feeding mode. In the volumetric feeding mode, no controller interferes in the process and the influence of the feeder geometry and setup can be

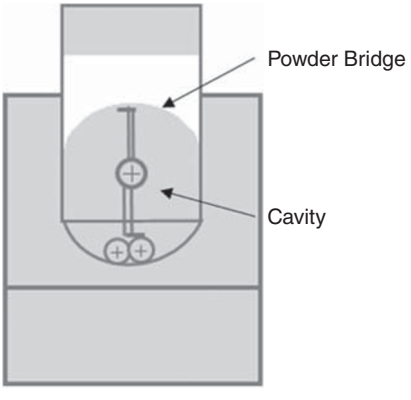

Figure 10.5 *Schematic illustration of bridge around the agitator.*

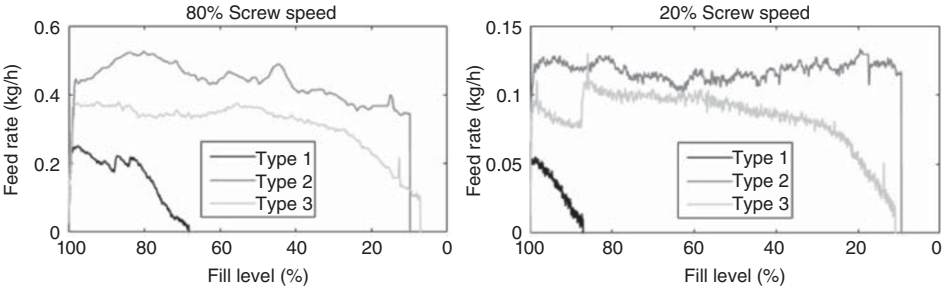

Figure 10.6 *Volumetric feeding experiments using calcium stearate (Lohmann) with different agitators. Left: 80% of nominal screw speed; right: 20% of nominal screw speed. Agitator "Type 1" shows stable bridging in the hopper. Agitator "Type 2" provides material flow in the hopper with little fill level influence on feed rate. Agitator "Type 3" shows the build-up of an unstable bridge at the beginning and a strong fill level dependence of feed rate.*

evaluated best. Figure 10.6 shows results of volumetric feeding trials with three different agitator geometries. The feed rate is shown dependent on the fill level in the hopper. The goal was to emty the hopper completely at two different screw speeds (20% and 80% of nominal screw speed). The black line "Type 1" shows stagnation of the material output from the feeder at a fill level close to 80% for both screw speeds. This indicates the formation of a stable bridge in the hopper above the agitator. The dark gray line "Type 2" shows constant material flow from the hopper to the feeder screw for both screw speeds. The pale gray line representing "Type 3" shows the formation of an unstable bridge above the agitator for the lower feed rate. After destruction of this bridge the hopper can be emptied completely though. From these experiments, feeder two could be identified as the optimal agiator geometry, since no bridging occurred, and the influence of the fill level on the feed rate was minimal. Thus, this agitator was able to provide the most consistent material flow into the feeder screw. With this agitator it is useful to investigate the feeding accuracy in gravimetric feeding mode, since a controllable behavior of the system can be expected. If the material flow in the hopper cannot be provided, even the best controller could not compensate the feeding variation.

Concerning the selection of the right screw, most manufacturers provide a list of feed rate ranges for each screw. The pitch of the screws determines how much free volume is available at each revolution of the screw. Thus, screws with a smaller pitch are used for smaller feed rates. Using a large pitch for low feed rates can result in strongly pulsing powder flow from the feeder outlet. Moreover, process control becomes more difficult at the extreme limits of the process. Therefore, the screw speed at the desired feed rate should be chosen between 20% and 80% of the nominal screw speed. In order to have little material adhering to the metal surface of the screw, the surface finishing can be important as well.

In the case of material lumping together at the feeder outlet, discharge screens are applied to homogenize the powder flow. For shear-sensitive materials, though, this can result in blocking of the screw due to the densification of the material in the screw channel. In addition, the control of the system becomes more complicated, since the controller cannot detect the system response (feed rate change) immediately after changing the control parameter (screw speed).

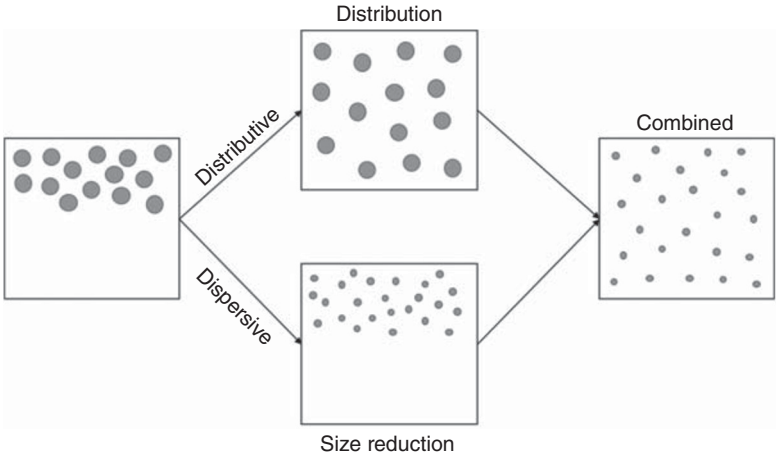

Figure 10.7 *Relationship between dispersive and distributive mixing.*

So far, no general rule for feeder selection based on material properties is available. Thus, it is necessary to select the possible setups based on experience and evaluate the best setup in feeding experiments. After the setup selection also a characterization of the feeder performance in typical processing phases (e.g. long-term performance, refilling, etc.) is necessary [5].

10.4 Twin-screw Extrusion

The process of mixing two or more different materials and/or immiscible compounds demands a high level of mixing capability. Such formulations are processed by using twin-screw extruders. The additional screw provides a larger interface between the unit and the material (e.g., for heat transfer, devolatilization, etc.) and more elongational and shear mixing in the intersection between the screws, as well as an increased backflow. Mixing in a twin-screw extruder is induced by relative physical movement of the single particles. As polymer flows are not turbulent, mixing is dominated by laminar flow. This laminar mixing occurs by shear and elongational components and includes distributive and dispersive mixing, as well as homogenization. Figure 10.7 shows the two mixing mechanisms and the resulting qualities [2].

Dispersive and distributive mixing are not spatially separated as there will be always distributive mixing in dispersive mixing [6].

Depending on the quality of the mixing machinery and/or components, there are several mixing conditions. If components are not soluble (e.g., crystals in a matrix) an ideal mixture on molecular level is not possible. The goal of HME is the production of the best possible material regarding homogeneity. While the melting and mixing processes demand energy input, the low thermal conductivity of polymers may lead to thermal degradation caused by viscous dissipation. Accordingly, the engine provides the amount of energy required, while the polymer sets the upper limit and the needed mixing quality the lower limit of the process window (see Section 10.5). For comparing various extruders the specific mechanical energy

(SME) is used, which is the energy consumption per unit weight of the processed material in Wh/kg [7].

$$\mathrm{SME} = \frac{\epsilon^* V^* I}{\dot{m}} \tag{10.1}$$

with ϵ being the motor efficiency, V the voltage, I the current and $\dot{m}$ mass flow.

In addition to the SME, the residence time distribution (RTD) has a major influence on product homogeneity and describes the time the material is exposed to the process environment (temperature and pressure, as well as mixing and shear). Therefore, it can influence the material properties both in a positive (homogenization) and a negative (material degradation) way [8, 9].

The RTD in an extruder depends significantly on screw pitch and speed in partially filled screw sections, and mainly on throughput in fully filled screw sections. A simple conveying element has a very narrow RTD, while a toothed mixing element or kneading block show a wider distribution [10].

A high level of mixing can be achieved by a variety of systems, such as kneaders, roll mills or planetary roller extruders [11]. However, one of the most frequently used types are twin-screw extruders. While co-rotating twin-screw extruders are well known in the pharmaceutical processing, the counter- rotating technology almost never appears though it has some very interesting benefits, such as very low residence time, pressure independence and low mass flow pulsation. Both twin-screw extruders and their differences are discussed below.

10.4.1 Counter-rotating Twin-screw Extruder

Counter-rotating twin-screw extruders are mainly used for temperature sensitive materials. Each screw segment forms a closed c-like chamber (see Figure 10.8) where the melt is conveyed from the hopper directly to the end of the screw without any exchange with neighboring chambers. Due to absent drag forces, only little viscous dissipation and therefore material heating occurs [2].

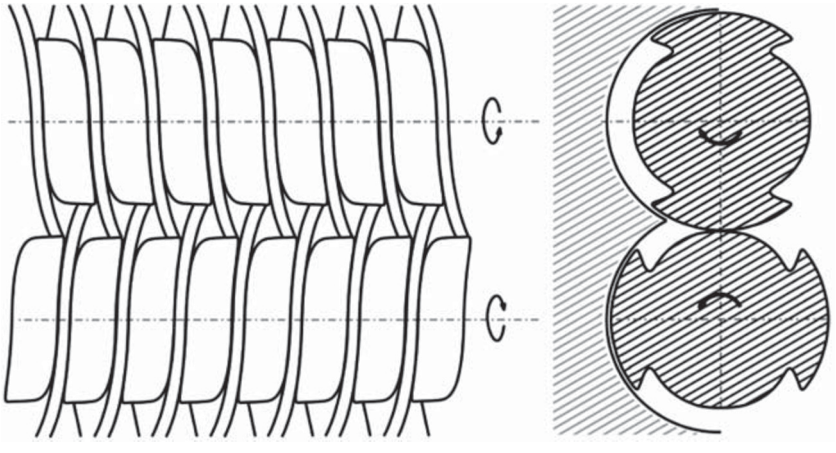

Figure 10.8 *Intermeshing counter-rotating twin-screw extruder (according to Hensen* et al. *[12]).*

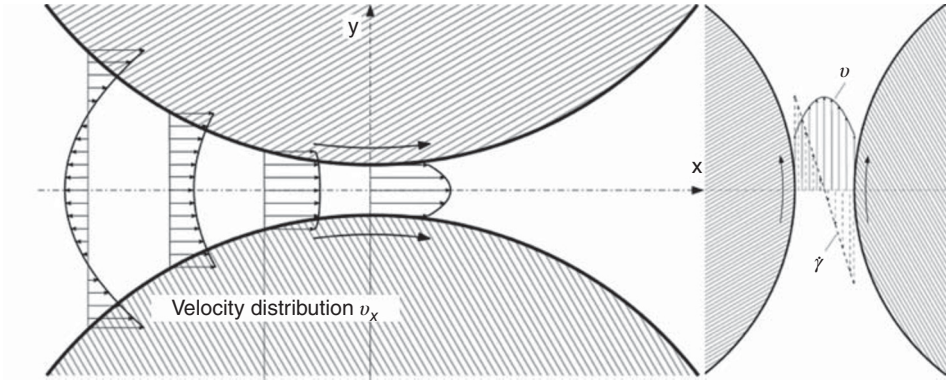

Figure 10.9 *Velocity and shear rate profile in a counter-rotating twin-screw extruder (according to Hensen* et al. *[12]).*

The mass is conveyed by forced transport, independently of its tribological properties and the counter pressure. The residence time spectrum is very narrow and the material stress (e.g., temperature, shear rate) is rather low. The conditions in the screw gap are shown in Figure 10.9. On the left side, the calendar flow between the screws and the corresponding pressure profile leads to high shear on the flight of the screw and no shear in the middle, as pictured on the right side.

10.4.2 Co-rotating Twin-screw Extruder

Co-rotating twin-screw extruders do not form closed chambers (axially open system) and hence do not have forced conveying. The melt is conveyed by drag force in channels, which surround both screws in a helix-shaped eight. Every revolution moves the melt one pitch in axial direction. The mass transport occurs in $2^* i–1$ partial flows, where i means the movement rate (two-flight = 2, three-flight = 3). Figure 10.10 shows the partial flows of a three-flighted respectively two-flighted screw.

The co-rotating twin-screw extruder provides a linear velocity distribution in the screw gap. Due to symmetry reasons, the pressure relations are equal on both sides of the gap and constant shear conditions across the gap width. Figure 10.11 shows the velocity and shear rate profile in the screw gap of a co-rotating twin-screw extruder.

The screw design itself can be adjusted by changing the numbers, length and types of screw elements along the shaft. This modular design enables a tremendous flexibility and allows specific optimization of screw and barrel geometry depending on the material and the application [14]. Figure 10.12 shows four possible elements exemplarily.

The use of kneading disks provides a very high level of induced shear energy, and therefore, mixing capability. The enhancement of mixing and the increase of applied energy are determined by the thickness of the disks and the offset angle (see Figure 10.13).

10.5 Operation Point

By evaluating the volume flow rate versus pressure drop curves for the extruder screw and the die in dependence on the process settings the point of operation can be determined (see

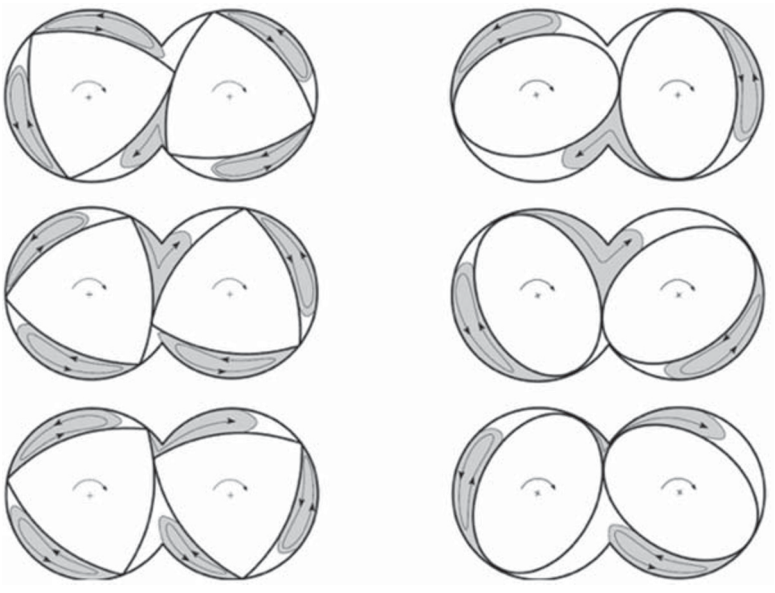

Figure 10.10 *Partial flows depending on the movement rate of a three-flighted (left) and two-flighted (right) screw (according to Hensen* et al. *[12]).*

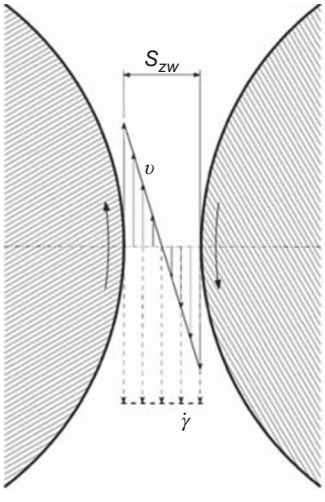

Figure 10.11 *Relationships in the screw gap of a co-rotating twin-screw extruder (according to Hensen* et al. *[12]).*

Figures 10.14 and 10.15). At the intersection of the corresponding screw and die curve (same temperature) the pressure and volume flow rate are equal at the screw tip and the die inlet. Variations in process settings such as melt temperature (T_1 and T_2), screw speed (n_1 and n_2) or flight depth (h_1 and h_2) lead to (significant) changes in the point of operations and therefore process behavior [1].

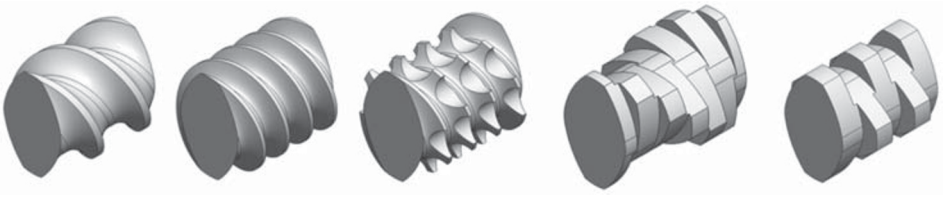

Figure 10.12 *Various screw elements.*

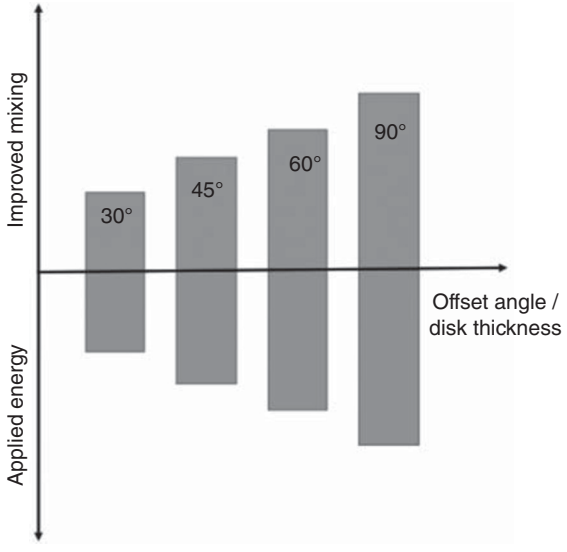

Figure 10.13 *Influence of the offset angle on the processing behavior of kneading blocks.*

Based on this, Figure 10.15 shows the operation area (and operation points A) of a conventional single-screw extruder. This area is limited in the region below by the economic border (E), which characterizes an economical process (e.g., by a minimum melt flow rate). Due to an increasing melt flow rate the residence time of the polymer in the extruder decreases, and therefore, the homogeneity (quality) of the melt decreases. This quality border (Q) limits the area above. Excessive heat (e.g., because of too much shear heating) can affect the melt quality as well. T_{max} shows this upper limit of the operation area [12].

10.6 Downstream Processing

The task of the extruder is to produce a homogeneous material (shaped or intermediate) in the range of few kilograms per hour. Depending on the target dosage form, the materials rheology, product purity, costs, the mass flow and the selected downstream process, the product can be in its final form (e.g., injection molding) or can be an intermediate product, such as sheets (e.g., film extrusion) or pellets (e.g., die face granulation) for capsule filling

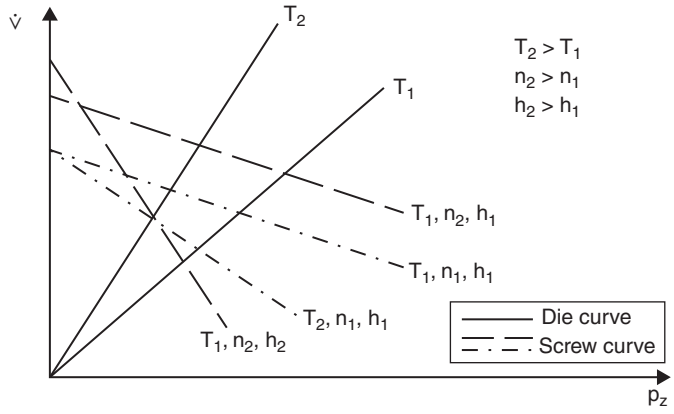

Figure 10.14 *Different operation points depending on the process parameters. Picture courtesy of Montanuniversitaet Leoben, Polymer Processing.*

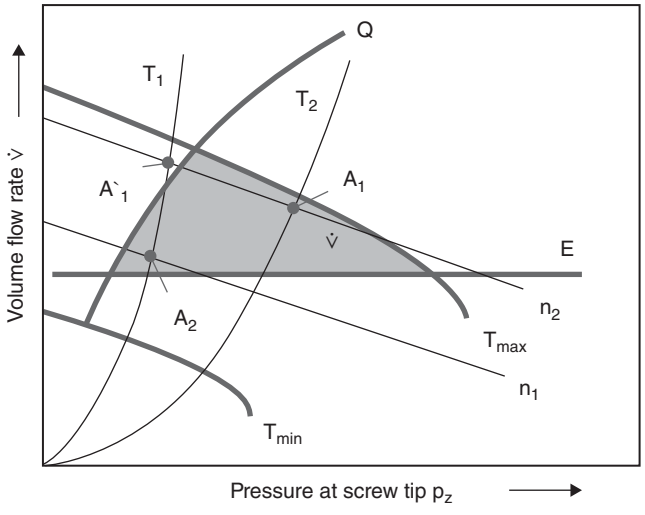

Figure 10.15 *Operation area of a conventional single-screw extruder. Picture courtesy of Montanuniversitaet Leoben, Polymer Processing.*

or tablet compaction. Figure 10.16 gives an overview of various downstream processing options and the resulting products [13].

10.6.1 Direct Shaping of Final Product

In pharmaceutical processing two continuous processes are applied. Both form the molten material directly into an applicable dosage form.

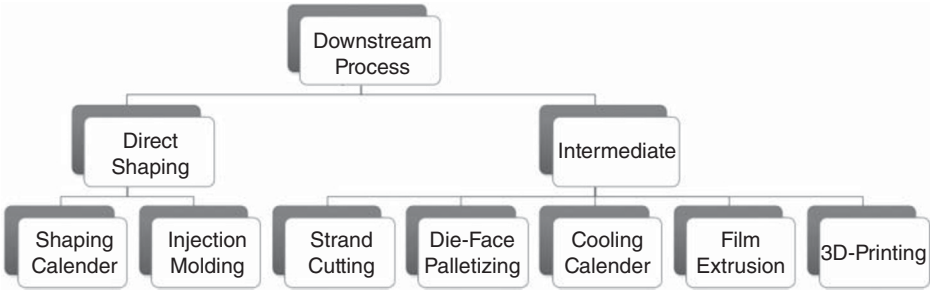

Figure 10.16 *Overview of possible downstream processes.*

10.6.1.1 Shaping Calender

A shaping calender consists of two narrow counter-rotating rolls with corresponding cavities. Using an extruded film (see Section 10.6.2.4), the melt is forced into the cavities to form tablets. Due to the process characteristics, a thin web remains on the tablets, which is removed in a following process (e.g., rotating drum).

10.6.1.2 Injection Molding

Injection molding (IM) is one of the most important production methods in polymer processing. Due to several benefits, this processing technique is suitable for various pharmaceutical dosage forms, such as tablets, capsules, implants, intravaginal inserts and multi-layer devices for controlled release applications [1, 12]:

- IM is easily implemented in a continuous line
- IM is a straightforward route from the material to the part
- With IM relatively high mixing capabilities are possible
- For IM no or only minimal machine finishing of the produced parts is necessary
- IM is easily run in automated mode
- IM exhibits excellent reproducibility

The injection molding cycle consists of several steps from the preparation of the raw material to the ejection of the finished part. Figure 10.17 shows the individual steps:

1. Plastification of the raw material by rotation of the screw. The pellets or powders are transported from the hopper to the screw tip and melted through dissipation by inner and outer friction as well as heat transfer from the heater bands on the cylinder. The melt cushion is compressed at the screw tip and pressure builds up
2. The mold is closed and the screw injects the material by axial movement. Hereby operating pressures of several thousand bar are standard but not suitable for all APIs
3. The screw holds the pressure in the mold to minimize shrinkage and to ensure a fully filled mold. Meanwhile the part is cooled until it is dimensionally stable
4. The mold is opened and the part ejected. Simultaneously, the plastification starts the cycle again by screw recovering and conveying of melt to the screw tip. This cycle time (and the number of parts per shot) defines the capacity of an injection molding machine

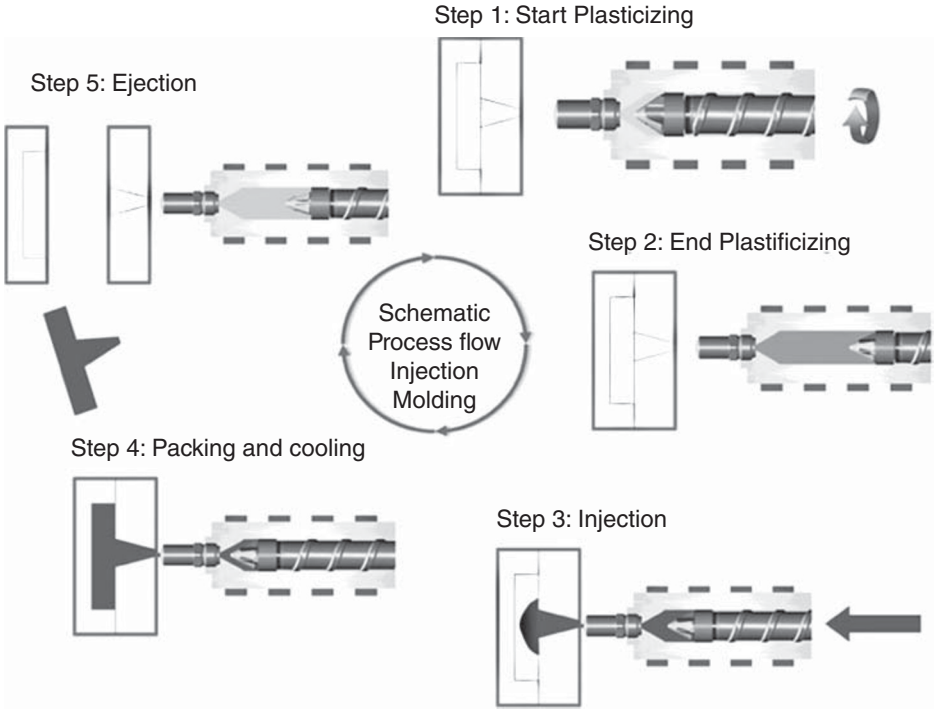

Figure 10.17 *Injection molding process – schematic flow illustration. Picture courtesy of Engel GmbH Austria and IPIM, Johannes Kepler University Linz, Austria.*

10.6.2 Intermediate Products

In many cases the continuous extrusion process is applied for making new material systems (solid solutions, solid dispersions or for embedding nano-particles in a melt [16]) and works similar to a granulation process by achieving concentration uniformity and flowability of the material and by suppressing segregation. Often the material is ground in a subsequent step or pellets are made. The pellets can be directly filled into capsules or fed to a tablet press. The downstream options usually used in the pharmaceutical industry for the production of intermediates are chosen based on requirements for the next production step and cuttability above the softening point [13].

10.6.2.1 Strand Cutting

Strand cutting (Figure 10.18) is used for sticky materials. Here, cylindrical strands are extruded and a conveyer belt with air knifes cools (solidifies) the strand and transports the material to the strand cutter. The strands move inside the feeding rolls and are cut by the cutting rotor. The obtained pellets are cylindrically shaped with a relatively narrow size distribution. The throughput has to match closely the extrusion flow with appropriate control of the strand cutter speed (both feeding and cutting) for a stable continuous process, resulting in uniform pellets [13].

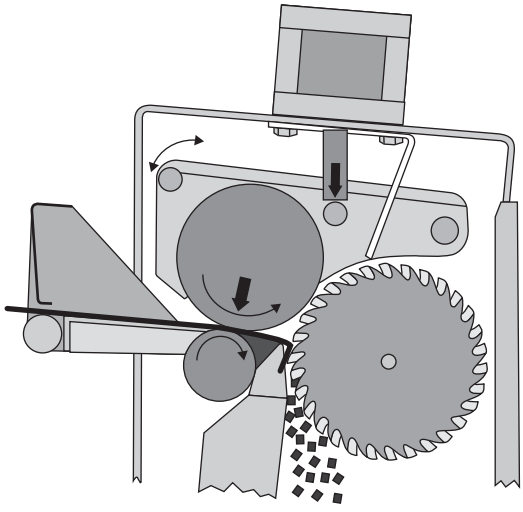

Figure 10.18 *Strand cutting. Picture courtesy of Automatik Plastics Machinery GmbH.*

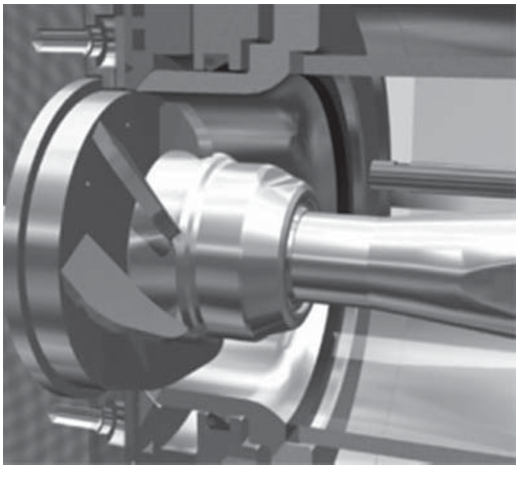

Figure 10.19 *Hot die face cutting. Picture courtesy of Automatik Plastics Machinery GmbH.*

10.6.2.2 Hot Die-face Cutting

In hot die-face cutting (Figure 10.19), the cutter is directly attached to the extrusion die. The extruder produces cylindrical strands and the cutting rotor cuts them directly at the die plate into pellets. In contrast to strand cutting, more spherically shaped pellets are formed due to surface tension and viscoelastic behavior of the material, resulting in a better flowability of the pellets [17, 18]. The challenge here is to cut above the softening temperature of the material, which needs the right rheological characteristics for the hot cutting. Otherwise, the product smears across the knives and die plate, which then can lead to lumps and sometimes to burnt material as well. The material is usually cooled with compressed

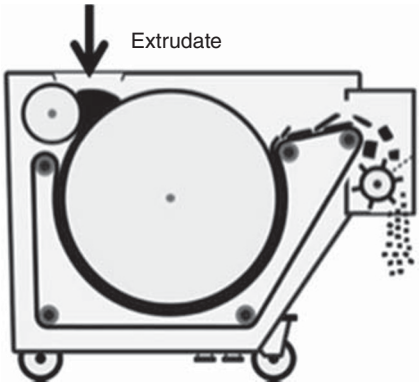

Figure 10.20 *Cooling calender principle. Picture courtesy of BBA Innova GmbH.*

air, as water is in most cases not suitable for pharmaceuticals due to the solubility of APIs and the product's purity requirements. Thus, the design and control of the cooling air flow is critical for achieving a robust process. An improved die-plate design may enable to hot die-face cutting of even sticky materials in a continuous process [13].

10.6.2.3 Cooling Calender

In a cooling calender, also termed drum cooler (Figure 10.20), a belt presses the extrudate onto a cooling drum to form a thin sheet. After solidification, the film detaches from the drum and breaks. A subsequent crusher reduces the fragments into smaller particles. The drawback of this technology is the broad particle size distribution. Thus, particles usually must be milled again before further processing [13].

10.6.2.4 Film Extrusion

Though the extrusion of strands is a well-accepted technology in pharmaceutical processing, laminar extrusion (e.g., films) is rarely used. Nevertheless, some applications, such as an alternative to organic or aqueous casting techniques [19, 20], or the production of transdermal drug delivery systems [21] are already under investigation. Compared to strand extrusion, in this process the extruder is equipped with a sheet die to distribute the melt homogeneously (regarding flow speed) and to form a first geometry, which then is cooled homogenously (from one or both sides) in a so-called chill-roll unit and transported to the finishing section. The most frequently used flat-film die is the so-called coat-hanger die (see Figure 10.21), with a rheologically designed flow channel to distribute the melt across the width. The melt enters a manifold and passes the throttle or island field. Flow adjustable components (e.g., barriers or lips) enable the manipulation of non-uniform discharges of the melt [2].

10.6.2.5 Co-extrusion

Products with a special property profile (e.g., different release rates or a diffusion barriers) or formulations with different APIs may be not achievable by producing a uniform material. To continuously make multi-layer structures, combining two or more

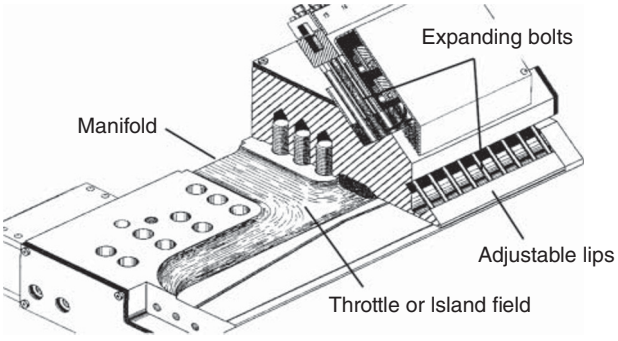

Figure 10.21 *Coat-hanger die (according to Hensen* et al. *[13]).*

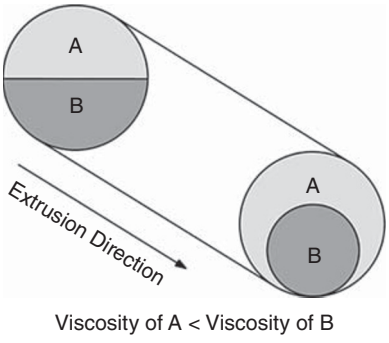

Figure 10.22 *Time-dependent migration of layer A into layer B during co-extrusion.*

materials, co-extrusion technology is applied, where every material requires its own manifold and extruder [22–25]. Generally, there are three concepts, depending on the flow of the single melt forming and layer consolidation [2]:

- Dual slot dies: the layers are formed separately and consolidated outside the die
- Multi-layer dies: the layers A, B and C are formed separately and merged inside the die
- Feed block dies: the melt streams are consolidated first and then a single film is formed

Depending on the materials and their processing temperatures and viscosities, the right system has to be chosen. Especially the ratio of the material viscosities is a significant parameter. In formulations, where this ratio is too high, specific defects in the final product depending on the process and die settings will occur. The most important consideration, when setting up a co-extrusion process, is to achieve a homogeneous layer distribution and to prevent flow instabilities [26, 27].

The layer distribution is mainly influenced by the time-dependent migration of one layer material into the other one. This phenomenon appears in the die, where the expected layer profile is changed due to melt flow operations (see Figure 10.22) [28, 29].

The multi-layer structure is more prone to an inhomogeneous distribution if the materials have strongly different viscoelastic properties. Depending on the position of a layer in the multi-layer laminate, it is exposed to varying shear stresses and shear rates, which influence the flow behavior. This leads to a series of dynamic loads during the flow through the die.

The more layers are combined, the higher is the impact of this effect. Another problem is a varying melt elasticity, as normal forces affect the layers' arrangement depending on their storage modulus. Formulations with a high storage modulus (for example) tend to show a rearrangement of the layers, even if they are processed with materials of the same viscosity. If the layers are processed with different extrusion speeds, the acceleration of one layer by the other can lead to interface instabilities.

Generally spoken, the material with the lower viscosity tends to coat the higher viscous material. This may be prevented by choosing the correct melt temperatures. Nevertheless, this interfacial instabilities can also be used to increase the interfacial bonding [26, 30].

10.7 Continuous Manufacturing with HME

Although HME is a fundamentally continuous process, there are several inherent challenges involved when it is integrated into a continuous work flow. Additionally, the most immediate implementation of continuous manufacturing in the pharmaceutical industry is likely to be heterogeneous, or linking continuous and semi-continuous unit operations together into a continuous production line. Accordingly, though HME is a well understood process having a long history in both polymer and food industry, subsequent topics regarding continuous manufacturing need to be considered as they are the key for successful implementation of this process technology.

10.7.1 Process Understanding

There is a large base of experience with HME in the polymer industry, so the process understanding is very well developed, and overall, is transferable to the pharmaceutical industry. Coming from a very efficient industry, simulation tools utilizing (predictive) process models, scale-up strategies as well as general process–property relationships are available and used to understand the dynamics of material flows through the machinery by utilizing, for example, RTD. Nevertheless, the claims to product quality attributes, traceability and property resolution scale are very different. Furthermore, the ability of measuring and predicting material propagation, distribution/stagnation or disturbances is not needed to that extent as it is in pharmaceutical industry. As an example, in the polymer industry, the main interest is to provide a homogeneous melt (in terms of temperature and mixedness) for downstream processes. The material stability, morphology, load of shear and so on is relevant only in a few types of processes (e.g., PVC production). The mainly used polymers, fillers and additives are very stable with a broad process window (e.g., polyolefines, talcum, colorants) or only sensitive to moisture (e.g., poly ethylene terephthalate or polyamide). Therefore, the quality considerations and the connected regulatory complexity differ to a large extent. The subsequent sections give short insights into specific aspects of HME in a pharmaceutical environment.

10.7.2 Control Strategy

HME as a continuous process is generally seen as a steady-state process with a narrow process window. Though this is true, extruders are a low-pass filter with possible long-term

drifts in temperature, throughput or similar. This also leads to the fact that process controls can have a slow response and even the best control system and strategy may not be able to stabilize the process and a diversion may be necessary to maintain product/intermediate quality. Therefore potential variations in the process, equipment or operating conditions are rather rare, while problems in the raw material stream (e.g., stoppage of feeders, input fluctuations, bridging or segregation) can have a significant impact not during extrusion but in the downstream. It is beneficial that some process parameters can be detected in-line during the extrusion process by, for example, NIR probes mounted in the extruder barrel. In conclusion, the level of control for the extrusion process itself can be rather low (Level 2 or 3) depending on the mixing behavior, while the raw material and downstream needs a higher Level such as 1 or 2, according to ASTM E2968-14.

10.7.3 State of Control

According to the ASTM E2968-14 standard, a state of control is a condition in which a set of controls consistently provides assurance of continued process performance and product quality. Operating under a state of control ensures the production of a product with the desired quality.

For Level 1 applied in HME this means that process variable such as screw speed, throughput or temperature are manipulated variables. Manipulated variables are automatically adjusted in response to the disturbance to keep the controlled variables within a specific range. A state of control can then be established by in-line monitoring. Finally an active process control system for a continuous HME line should be able to respond to disturbances both from the extruder (fast) or up- and downstream unit operations (slow).

For Level 2, the raw material attributes and the process parameter may vary within a specific range (design space) without impacting the product or intermediate quality. A state of control can be established similar to Level 1 by in-line moitoring of raw material attributes and process parameters. End or intermediate product testing or surrogate models are used for confirmatory purposes.

Level 3 systems require tight control of raw material attributes and process parameters in a very narrow process window. Process–property relationships are not fully developed for process monitoring, needing intermediate product testing to ensure a state of control.

10.7.4 Diversion of Material

The primary challenge for diversion in HME is detecting the out of specification materials. While start-up and shut-down scenarios are rather easily manageable, the detection of material in a running extrusion process, involving back-mixing with a typical residence time in the range of minutes, is quite challenging. Accordingly, the detection of material as well as adjacent portions with a limited set of measureable parameters may not be sufficient for the purpose of batch control. Thus, a combination of surrogate measurements (e.g., pressure, temperature and screw torque) and a comprehensive understanding of the process dynamics is necessary. The surrogate measurements, with sufficient spectral and temporal resolutions, can support end-point PAT solutions to maintain the product quality dynamically. However, to achieve the confidence level needed for real-time release, the measurements must be

related to the process dynamics itself in a deterministic manner. The multi-phase material transition (particle to semi-melt to melt) and physics (e.g., shear-induced heat generation and phase transfer) involved have considerable complexicity, so the best route for process understanding may be advanced, multi-physics modeling. Therefore, developing and validating appropriately simplified models that can be efficiently simulated to support process development is key for successful implementation of continuous HME. The physical separation of out of specification material can be done right after pelletization or by bypassing the die and collecting a separate melt stream.

Considering a manufacturing line for the production of tablets from HME pellets (see Figure 10.23) a possible process setup is shown. The line contains a feeding unit upstream of the extruder, a die-face pelletizer attached to the extruder and a blender with a second feeding unit before the tablet press. Since there is an interface between the extrusion/pelletization and the downstream unit (blending/tableting), a diverter flap (dark gray box) can easily implemented for out of specification material. Based on the quality target product profile (QTPP) the essential product or intermediate properties are given. Many of these properties can be determined inline during manufacturing. Partially, process parameters (light gray boxes), such as the flow rates of each component, or the SME in the extruder, are provided by single unit operations. Other properties, like pellet size and shape or melt composition are determined by additional PAT tools.

With no overall control concept applied to this manufacturing line, PAT tools are necessary for process monitoring. In principle, the product properties are already given by the processing parameters. If all feed rates from the feeding units are known (and proven to be trustworthy), a calculation of the melt composition is possible. The same is valid for the pellet size at a certain throughput volume and pelletizing speed. Nevertheless, a model correlating the pellet size to throughput volume and pelletizer speed work can only be achieved in very simple cases, since a production of agglomerated pellets cannot be predicted easily that way. If such a prediction is desired, the thermal state of the melt, the die plate and the pelletizer have to be monitored very closely. For this, very sophisticated sensor technology (measurement robustness, adequate sampling frequency, resolution) is required. Not applying additional PAT tools carries a very high risk, thus they are usually used as a redundant measurement.

Another crucial aspect concerning sensors is their sensitivity and measurement frequency. Especially for real-time release testing (RTRT), one has to ask the question, from which deviation level will an error be detected. Engish and Muzzio [31] discuss this extensively in their paper. The conclusion is that batch definition, traceability and monitoring frequencies should be investigated using the RTD along the manufacturing line. With the RTD it is also possible to select the start and duration of material segregation with the diverter flap. When a feed rate deviation is recognized, the flap will remain inactive for the dead time of the extruder. When the deviation is not visible in the feeding signal, but only in the concentration monitoring at the end of the extruder (e.g., in case of a deviation during refilling of a hopper), the flap must be activated after an accordingly shorter dead time. Moreover, the RTD depends on the momentary process parameters (e.g., screw speed, total throughput), which might be changed slightly for control reasons and thus must be determined for the whole process window. The duration of the material segregation depends on the width of the RTD. For example, the flap can be closed again after 99% (or other threshold level) of the out of specification material is ejected. In this

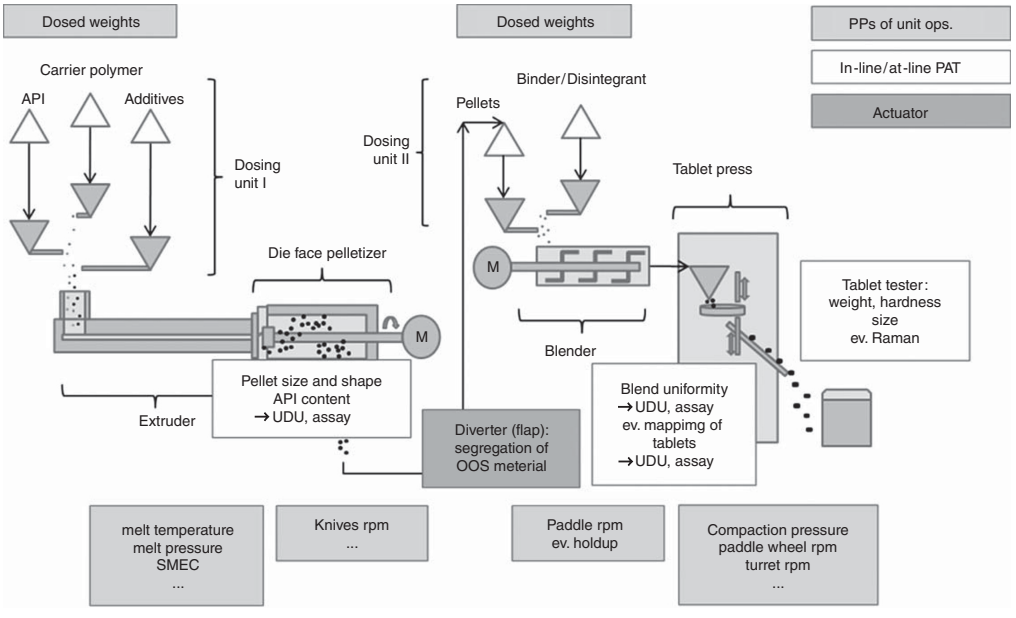

Figure 10.23 *Example process line with process parameters provided by the unit operations (light gray boxes), PAT tools (white boxes) and out of specification segregation spot (dark gray boxes).*

case the separation of the process into two sub-units makes the ejection easier, since the dosing unit in the second process part acts as a material buffer. The buffer fill level can be controlled with a slight increase, or decrease of the extrusion throughput. Moreover, the second feeding unit induces additional backmixing over the different refill cycles of the pellet hopper. With a thorough characterization of this backmixing, also the acceptance criteria for content uniformity in the intermediate pellets can be adjusted.

10.8 PAT for HME

The PAT initiative deals with real-time process analytics and data analysis (in contrast to traditional end of line testing) according to the FDA guidelines, promoting "a risk based approach" [32] in pharmaceutical processing. PAT enhances the understanding and control of production processes [33] aiming at the real-time release (RTR) of processed drug products. Generally said, a process is well understood, when: (i) all critical sources of variability are identified and explained, (ii) the encountered variability is managed by the process according to control strategies and (iii) the product quality attributes can be accurately and reliably predicted [32].

A PAT system is only as good as the sensor technology. Thus, a wide range of sensors is available, divided into their integration in the process (in-line, on-line) and the number of output variables (uni- or multivariate). The requirements for an extrusion PAT sensor are higher than for other purposes due to high pressures, high temperatures and possibly abrasive materials. Additionally, the location of the sensing device is critical for obtaining accurate information of the process status. In the following paragraphs the most commonly used technologies for extrusion are briefly described.

10.8.1 Near-infrared Spectroscopy

Near-infrared (NIR) spectroscopy is based on the attenuation of light by absorption. The sample is irradiated with light in the wavelength range of about 1000–2500 nm. The light photons are absorbed by the sample molecules, which accordingly excite higher vibrational states. Depending on the specific wavelengths of the absorbed light the molecular structure can be evaluated. Generally, only molecular vibrations which result in a change of dipole moment, can be excited [36]. Therefore, polar bonds and bonds with a pronounced difference in atomic mass show stronger absorption of NIR radiation. The most prominent bands belong to –CH, –OH and –NH functional groups [37]. In contrast to mid-infrared, the NIR region mainly shows overtones and combination vibrations of these functional groups [37, 38]. When applying NIR in an extrusion process, the spectrum will change along with the formulation and process settings, such as temperature, pressure and all factors influencing these parameters (e.g., screw speed, filling ratio, etc.). Thus, robust models need to be developed. In pharmaceutical extrusion NIR can be used for studying the API content and the polymer-API interactions directly in the die [39].

10.8.2 Raman Spectroscopy

Raman spectroscopy is based on frequency shifts in reflected light compared to incident monochromatic laser light. These shifts are due to inelastic scattering (i.e., shift of

frequency) of photons by a molecule, with induced transitions between vibrational states of the irradiated molecules. Most commonly 785 nm diodes or 1064 nm Nd:YAG lasers are used. The radiation excites the molecules to a non-stable virtual state which the molecules quickly relax, converting a part of the incident energy by shifting the scattered light to lower frequencies (so-called Stokes radiation). At room temperature this is the most commonly observed effect in Raman spectroscopy. At higher temperatures a certain fraction of molecules is already in an excited vibrational state, according to the Boltzmann distribution [40]. When they relax back to the ground state, the rotational energy is converted and the reflected light shifts to higher frequencies (anti-Stokes radiation).

Raman is well suited to measure non-polar bonds, that is C–C, C=C, S–S, N=N [36], like carbon chains and aromatic rings. The spectra are not affected by the presence of water, which is highly polar. As the NIR signal is strong for polar bonds, these two spectroscopic techniques can be used complimentary. However, the need for relatively high energy input and the fluorescence of many compounds is a disadvantage.

10.8.3 Chemical Imaging

Chemical imaging utilizes Raman and NIR sensors to obtain spatially resolved (two-dimensional) information of the chemical composition. This information can be accessed by filter techniques, the push broom principle or by rasterizing the surface. Depending on the complexity of the process mainly filter or push broom are used. While a filter is used for rather simple tasks such as moisture detection, complex formulations demand a push broom [40].

10.8.4 Particle Size Analysis

In a continuous process, information about the particle size distribution (PSD) and/or parameters such as sphericity are important for the product and to control downstream operations, such as pelletization. Several techniques, including image analysis, focused beam, laser diffraction or spatial filter velocimetry, have already been applied on- or in-line [34].

10.8.5 Optical Coherence Tomography

Optical coherence tomography (OCT) is a non-invasive optical imaging technique, which allows the analysis of multi-layered structures within a sample depth of up to 0.5 mm. OCT enables the acquisition of one-, two- and three-dimensional depth-resolved image data of subsurface regions. In OCT an optical beam (broadband light source) is focused onto the surface of the sample. The main part of the beam is directly reflected by the surface while a substantial fraction penetrates into the sample structure and is reflected by the interface of two media with different indices of refraction (e.g., coating and core material). By measuring the delay time of the reflections the coating structure and thickness can be determined. A number of studies have already demonstrated the application of OCT for continuously measuring the coating thickness [41, 42].

10.8.6 Data Processing

To extract the relevant data from the sensors, output data processing must be performed either by calibration models relating the raw data to product parameters (e.g. evaluation of spectra via projection to latent structures; PLS) or by automatic algorithms (e.g. layer detection in OCT cros-sectional images). Figure 10.24 shows such a data processing.

Calibration models are typically data-driven models [e.g., multiple linear regression (MLR), PLS or support vector machine (SVM)], which need to be developed *a priori* and are mostly applied for spectroscopic data.

Figure 10.24 shows NIR spectroscopy data of a molten material during HME [44]. The chemometric algorithm works in two steps. At first, the data are pretreated as they might contain variations due to parasitic measurement effects, such as light diffraction, positioning variations or the impact of material temperature and its opacity. Additionally, spectral regions with irrelevant spectral information regarding the specific parameter of interest need to be excluded. Second, the evaluation of the spectra is done by a scalar product of the pretreated spectrum vector with the regression coefficient (or loading) resulting in the numerical value of the parameter of interest (response) [45].

A different processing step (also shown in Figure 10.24), associated with automated algorithms without the need of an *a priori* model, is performed for imaging techniques, such as the already mentioned OCT, example shown in Figure 10.24 for film-coated pellets. Though this method enables real-time process monitoring, it requires an algorithm for the segmentation of the coating layer and the calculation of the thickness.

PAT as a toolbox provides a necessary link between monitoring and control, including: (i) the data collection and aggregation of all kinds of analyzers in-line and in real-time, (ii) extracting information from these data regarding the state of the system, (iii) checking for possible deviations and automatic root cause identification and(iv) deciding which process parameters must be manipulated to eliminate the deviation. Such a holistic control strategy of the entire process will ensure the appropriate product quality.

10.9 Process Integration into Computerized Systems

The tasks of the PAT toolbox mentioned above need to be done at a centralized location. Thus, the PAT tools are integrated into a computerized system [46]. The function of such a computerized system consist of course of tasks related to data collection, storage and processing and process control. Moreover, GMP requirements also have to be fulfilled, such as: (i) allocation of audit trails, (ii) generation of electronic records, (iii) secure application of electronic signatures, (iv) ensuring data integrity, (v) system security and (vi) incident management.

The regulatory authorities released guidelines and regulations defining these topics [47–49]. Moreover, the International Society for Pharmaceutical Engineering (ISPE) published *Good Automated Manufacturing Practices (GAMP5) Guidelines* [82], which have become the main point of reference for validation of computerized systems in the pharmaceutical industry [46]. In general, these guidelines consider the data acquisition and process control system with all PAT tools as another process step. Thus, also for these steps one has to do risk assessment by defining critical quality attributes (CQAs) and critical process parameters (CPPs) [50]. Based on this approach it is possible to identify

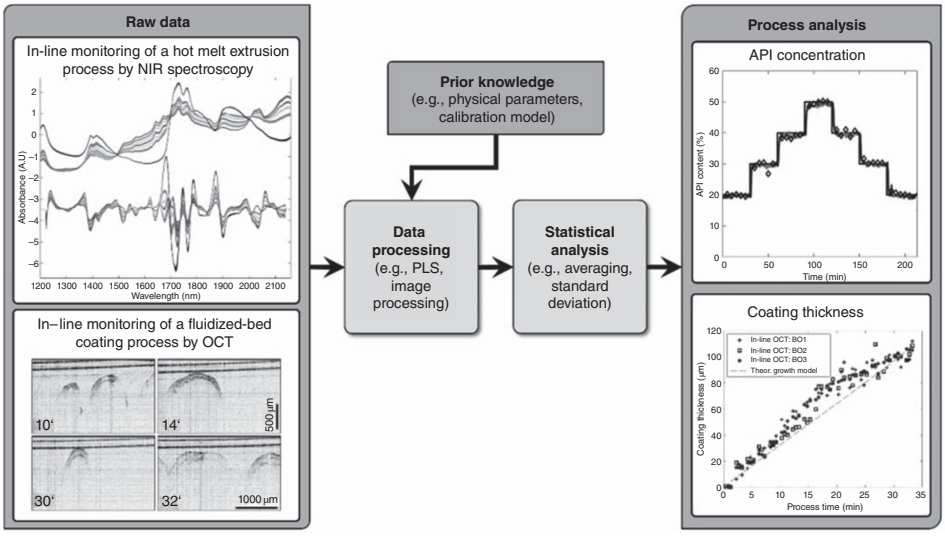

Figure 10.24 *Schematic overview of a typical sequence: from multivariate raw data (e.g., spectra, images) to product quality parameters (e.g., API concentration, coating thickness of pellets or tablets) [44].*

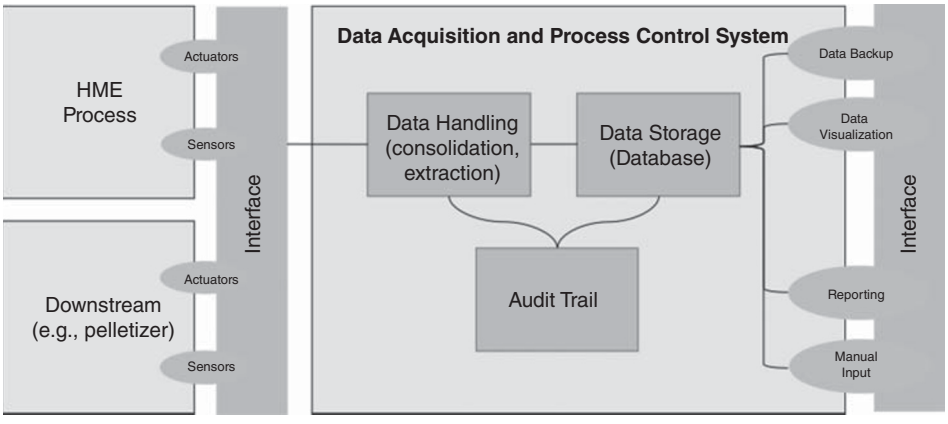

Figure 10.25 *Schematic of a basic data acquisition and process control system for a continuous HME line consisting of several processes (i.e., feeding, extrusion, pelletizing, etc.).*

these sub-processes in an automated system, which are most likely to fail and which have the highest impact in patient safety. The sub-processes declared critical are subsequently improved until the risk can be lowered to a non-critical level. Further information about the GMP aspects of a computerized system can be found in the guidelines and publications published by the agencies or associations such as ISPE.

10.9.1 IT Structure of Supervisory Control Systems

According to process and GMP requirements, an IT structure for process supervision and control of an HME process line contains the following basic units: (i) process sensors and actuators, (ii) interfaces, (iii) data processing units, (iv) a database and (v) an audit trail. Figure 10.25 shows a schematic illustration of a supervisory control system [14].

The process sensors deliver information about the state of different process units, whereas the actuators are used to control the process. The sensors and actuators are either integrated in the machines (e.g., feeder screw speed, extruder screw speed, melt temperature, pressures, torque, etc.) and equipment software or applied externally to the process (e.g., most spectroscopic methods). Thus, the equipment most likely comes from many different manufacturers using different communication protocols. Moreover, the data structures vary (uni- or multi-variate) depending on the type of measurement. Thus, the interfaces need to connect all of them into one computerized system. Since data integrity is a crucial aspect in GMP the interfaces have to be selected carefully. For example, the GAMP 5 guideline also contains an appendix dealing with software supplier evaluation [50]. The common approach is to use standardized interfaces, such as object linking and embedding for process control (OPC). Once the data are available at the data processing unit, several tasks are performed. One of the most important tasks is to aggregate the data from sensor interfaces with different sampling rates. Each sensor has its optimized sampling rate, based on relevant dynamics, its signal to noise ratio and computational performance limits. The data must be stored time aligned. Moreover, multivariate data are processed, for example, spectral data are interpreted using chemometric models in this

process step. The resulting data vectors are then stored time-aligned in a database. This way data are visualized in real-time during the process and are available for the operator later on for off-line analysis via a graphical user interface. For regulatory reasons all important activities and events must be traceable later on. This is realized with a service providing an accurate audit trail. Moreover, the generation of reports must be facilitated and data backup needs to be performed on a regular basis. Manual input must be provided to allow the operator to change certain parameter values or to add electronic signatures.

The information gained from continuous process monitoring should lead to increased process understanding. Meaning, all critical sources of variability are identified and explained, allowing an exact and reliable prediction and control of product quality [4].

10.9.2 Real-time Release Testing

So far PAT has been considered as a way of monitoring and controlling a system. Another big advantage of continuous processing is that information collected during manufacturing can be used to avoid end of the pipe testing of the product quality. RTRT allows the immediate release of products based on data obtained during the process. One has to consider, though, that the measurements and models used for process control are not necessarily also a good basis for RTRT decisions. While the parameters for process control relate usually to the process state, for RTRT the measurements and models need to test the critical properties in the QTPP. For an extrusion process, it is crucial to detect melt pressure, torque of the extruder screw or melt temperature for control reasons. None of these parameters must refer to the quality attributed to the product, though. The QTPP contains properties, such as assay, dissolution, microbiology and others. Considering the extrusion process, the API concentration in combination with pellet size could be used to predict the dissolution profile from the pellets via a mathematical model. Thus, additional models correlating, for example, different material or process parameters to quality attributes of the final product, have to be developed. Still, since for microbiological testing for example no “real-time” methods are currently available, it will not be possible to realize RTRT for every drug. Microbiological testing can be avoided, if it can be proven scientifically, that microbiological loading is not critical for the specific drug.

10.10 Conclusion

Coming from polymer processing, HME was introducted in pharmaceutical processing some decades ago. However, the equipment needs to be adapted to meet regulatory requirements and needs to be GMP-compliant. Meanwhile, HME is already used commercially by producing strands and films, which are then transformed into the desired dosage form [51]. According to Stankovic *et al*. [52] the application of HME in combination with a corresponding downstream process can form pellets, granules, spheres, tablets [53], oral fast dissolving films, transdermal and transmucosal DDSs [54], implants [55–57], stents and ophthalmic inserts [58].

These examples highlight the advantage of HME as a platform for the production of a large variety of dosage forms. Ozurdex (Allergan [59]), Zoladex® (AstraZeneca [60]) or

Eucreas® (Novartis [61]) are just examples of many already marketed products. The mentioned benefits of HME such as operation in continuous mode or the short residence and process time are contrasted by disadvantages (high shear rates, pressures and temperatures). Thus, extensive knowledge of the material, as well as the equipment and the processes is necessary. Following the experience of polymer engineering and science the roll-out to continuous pharmaceutical production is possible as a specialized high-tech production technique for tomorrows' drug products.

References

[1] Laske S., (2015) *Habilitation Thesis*, Montanuniversitaet Leoben, Leoben.
[2] Michaeli W. (1992) Carl Hanser Verlag, ISBN 1-56990-144-9.
[3] Rauwendaal C. (1986) Hanser Publishers, ISBN 3-446-14196-0.
[4] Schenck, L., Troup, G. M., Lowinger, M., Li, L. and C. McKelvey (2011) Achieving a hot melt extrusion design space for the production of solid solutions, in *Chemical Engineering in the Pharmaceutical Industry: R&D to Manufacturing* (ed. D. J. am Ende), John Wiley & Sons Ltd., London, pp. 819–836.
[5] Engisch, W. E. and Muzzio, F. J. (2012) Method for characterization of loss-in-weight feeder equipment, *Powder Technol.*, **228**, pp. 395–403.
[6] Rauwendaal C. (2001) Carl Hanser Verlag, ISBN 3-446-21774-6.
[7] Wildi, R. H., Maier, C. (1998) Carl Hanser Verlag, ISBN 3-446-18494-5.
[8] Barbas, J. M., Machado, A. V., Covas, J. A. (2013) *Chemical Engineering Science*, **98**, 77.
[9] Dennis, H. R., Hunter, D. L., Chang, D., Kim, S., White, J. L., Cho, J. W., Paul, D. R. (2001) *Polymer*, **42**, 9513.
[10] Laske, S., Witschnigg, A., Selvasankar, R. K., Holzer, C. (2013) *Journal of Applied Polymer Science*, **131**, 6, 39919–39924.
[11] Kohlgrüber, K. (2007) Carl Hanser Verlag, ISBN 1-56990-422-7.
[12] Hensen, F., Knappe, W., Potente, H. (1989) Carl Hanser Verlag München, Wien, ISBN 978-3446143395.
[13] Treffer, D., Wahl, P., Markl, D., Koscher, G., Roblegg, E., Khinast, J. G. (2013) *AAPS Advances in the Pharmaceutical Sciences Series*, **9**, pp. 363–396.
[14] Sarhangi Fard, A., Hulsen, M. A., Meijer, H. E. H., Famili, N. M. H. and Anderson, P. D. (2012) *Macromolecular Theory and Simulation*, **21**, pp. 217–240.
[15] Lei, X., Longjiang, S. and Bingyan, J. (2011) InTech, ISBN 978-953-307-169-5.
[16] Khinast, J. G. (2012) R1142GB: System for producing a solid preparation from a suspension. *European Journal of Pharmaceutics and Biopharmaceutics*, **860** 85–95.
[17] Bialleck, S. and Rein, H. (2011) *European Journal of Pharmaceutics and Biopharmaceutics*, **79**, 2.
[18] Roblegg, E., Jäger, E., Hodzic, A., Koscher, G., Mohr, S., Zimmer, A., Khinast J. (2011) *European Journal of Pharmaceutics and Biopharmaceutics*, **79**, 3.
[19] Repka, M. A., Gutta, K., Prodduturi, S., Munjal, M., Stodghill, S.P. (2005) *European Journal of Pharmaceutics and Biopharmaceutics*, **59**, 189–196.
[20] Mididoddi, P.K., Repka, M.A. (2007) *European Journal of Pharmaceutics and Biopharmaceutics*, **66**, 95–105.
[21] Wolff, H.-M. (2000) *Pharmaceutical Science and Technology Today*, **3**, 173–181.
[22] Müllers, K. C., Wahl, M. A., Pinto, J. F. (2013) *European Journal of Pharmaceutical Sciences*, 49.
[23] Vynckier, A.-K., Dierickx, L., Voorspoels, J., Gonnissen, Y., Remon, J. P., Vervaet, C. (2013) *Journal of Pharmacy and Pharmacology*, **66**, 167–179.

[24] Vynckier, A.-K., De Beer, M., Monteyne, T., Voorspoels, J., De Beer, T., Remon, J. P., Vervaet, C. (2015) *International Journal of Pharmacy*, **491**, 243–249.
[25] Vynckier, A.-K., Dierickx, L., Saerens, L., Voorspoels, J., Gonnissen, Y., De Beer, T., Vervaet, C., Remon, J. P. (2014) *International Journal of Pharmaceutics*, **464**.
[26] Prakash, O. (2007) *Comparative Materials Science*, **37**, 7.
[27] Prakash, O., Moitra, A. (2006) *Comparative Materials Science*, **37**, 12.
[28] Oliver, G. D. (2015) *Veröffentlichung Developments In Coextrusion Technology*. Available at: http://www.ptonline.com (accessed 24 January 2016).
[29] Han, C. D., Shetty, R. (1976) *Pollution Engineering Science*, **16**, 10, 697–705.
[30] Han, C. D., Shetty, R. (1978) *Pollution Engineering Science*, **18**, 3, 180–186.
[31] Engisch W. and Muzzio F. (2016) *Journal of Pharmaceutical Innovation*, **11**, 1, 64–81.
[32] US Food and Drug Administration (2003) *Pharmaceutical cGMPs for the 21st Century – A Risk Based Approach: Second Progress Report and Implementation Plan*. FDA, Rockville.
[33] US Food and Drug Administration (2004) *Guidance for Industry. PAT – a Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance*, US Department of Health, Rockville.
[34] Treffer, D., Wahl, P. R., Hörmann, T. R., Markl, D., Schrank, S., Jones. I., Cruise, P., Mürb, R.-K., Koscher, G., Roblegg, E. and J. G. Khinast (2014) *International Journal of Pharmacy*, **466**, 1/2, pp. 181–189.
[35] Leskinen, J. T. T., Simonaho, S.-P., Hakulinen, M. and Ketolainen J. (2013) *International Journal of Pharmacy*, **442**, 1/2, pp. 27–34.
[36] Reichenbächer M. and Popp J. (2007) Teubner, pp. 61–118.
[37] Siesler, H. W. (2007) Basic principles of near-infrared spectroscopy, in *Handbook of Near Infrared Analysis*, 3rd edn (eds D. A. Burns and E. W. Ciurczak), CRC Press, New York, pp. 7–20.
[38] Siesler, H. W., Ozaki, Y., Kawata, S. and Heise, H. (2002) *Near-Infrared Spectroscopy: Principles, Instruments, Applications*. John Wiley & Son, Ltd, London.
[39] Saerens, L., Dierickx, L., Quinten, T., Adriaensens, P., Carleer, R., Vervaet, C., Remon, J. P. and De Beer, T. (2012) *European Journal of Pharmaceutics and Biopharmaceutics*, **81**, 1, pp. 237–230.
[40] Hertel, I. V. and Schulz, C.-P. (2010) *Atome, Moleküle und optische Physik 2*, Springer, Heidelberg, pp. 1–88.
[41] Markl, D., Hannesschläger, G., Sacher, S., Leitner, M. and Khinast, J. G. (2014) *European Journal of Pharmaceutical Science*, **55**, pp. 58–67.
[42] Markl, D., Zettl, M., Hannesschläger, G., Sacher, S., Leitner, M., Buchsbaum, A. and Khinast, J. G. (2014) *Chemical Engineering Science*, **125**, pp. 200–208.
[43] Sacher, S. and Khinast, J. G. (2016) *Process Simulation and Data Modeling in Solid Oral Drug Development and Manufacture*, Springer, New York, pp. 311–383.
[44] Hiob, M. (2011) *GMP-Berater*, Maas und Peither AG, GMP-Verlag, Weiheim.
[45] Witschnigg, A., Laske, S., Kracalik, M., Feuchter, M., Pinter, G., Maier, G., Märzinger, W., Haberkorn, M., Langecker, G. R., Holzer, C. (2010) *Journal of Applied Polymer Science*, 117.
[46] Linz, T. and Seeger, S. (2006) *21 CFR Part 11 Revisited, Encyclopedia of Pharmaceutical Technology*, 3rd edn (ed. J. Swarbick), Informer Healthcare USA, Inc., New York.
[47] European Commission (2011) Annex 11: Computerized Systems, in *Good Manufacturing Practices for Medicinal Products for Human and Veterinary Use*, vol. **4**, European Commission, Brussels.
[48] European Commission (2011) Chapter 4: Documentation, in *Good Manufacturing Practices for Medicinal Products for Human and Veterinary Use*, vol. **4**, European Commission, Brussels.
[49] FDA (2011) *Guidance for Industry: 21 CFR Part 11; Electronic Records; Electronic Signatures, Glossary of Terms*, vol. **1**. FDA, US Department of Health, Rockville.

[50] ISPE (2008) *GAMP® 5: A Risk-Based Approach to Compliant GxP Computerized Systems*. ISPE, New York, p. 352.
[51] Ghebremeskel, A.N. and Spada, L.T. (2012) *Sustained Release Latanoprost Implant*. Patent, US 2012/0276186 A1.
[52] Stankovic, M., Frijlink, H. W. and Hinrichs, W. L. J. (2015) *Drug Discovery Today*, **20**, 7, pp 812–823.
[53] De Brabander, C. *et al.* (2003) *Journal of Controlled Release*, **89**, 235–247.
[54] Morales, J.O. and McConville, J.T. (2011) *European Journal of Pharmaceuticals and Biopharmaceuticals*, **77**, 187–199.
[55] Stankovic, M. *et al.* (2014) *European Journal of Pharmaceuticals and Biopharmaceuticals*, **87**, 329–337.
[56] Stankovic, M. *et al.* (2013) *European Journal of Pharmaceutical Science*,**49**, 578–587.
[57] Ghalanbor, Z. *et al.* (2013) *European Journal of Pharmaceuticals and Biopharmaceuticals*, **85**, 624–630.
[58] Lee, S.S. *et al.* (2010) *Pharmaceutical Research*, **27**, 2043–2053.
[59] Allergan (2010) *Ozurdex Implant – Product Characteristics. OZURDEX 700 Micrograms Intravitreal Implant in Applicator*. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_Product_Information/human/001140/WC500095499.pdf (accessed 4 May 2016).
[60] AstraZeneca (2010) *Zoladex (Goserelin Acetate Implant 3.6 mg) – Prescribing Information*. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/019726s054, 020578s032lbl.pdf (accessed 04 May 2016).
[61] Joshi, Y. *et al.* (2007) *Formulation Comprising Metformin and Vildagliptin*. World patent: WO/2007/041053.

11

Continuous Processing in the Pharmaceutical Industry: Status and Perspective

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11.1 Industry Drivers for Continuous Processing: Competitive Advantages

Pharmaceutical manufacturers face many challenges when developing new products and getting them to market in a timely, safe and cost-effective way. From formulating new molecular entities to improving generic drug production or extending the lifecycle of existing oral solid dosage (OSD) forms, all according to the remit of increasing patient safety, reducing the cost per tablet and optimizing the price/performance balance play a key role in determining the success and sustainability of any operation.

As previously described in great detail, continuous processing could provide a solution to these challenges. This chapter reviews the pharmaceutical industry's approach to continuous manufacturing (CM) and its current state of implementation.

Continuous processing is not a new concept. For many years, technologies such as spray drying, dry blending, granulation and extrusion, to name a few, have been recognized as continuous operations. Implemented as independent unit operations, however, the manufacturing process has traditionally functioned in a stepwise "bin to bin" or "powder to powder" manner. So what makes this new initiative and current focus on CM so different?

Continuous Manufacturing of Pharmaceuticals, First Edition.
Edited by Peter Kleinebudde, Johannes Khinast, and Jukka Rantanen.
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At first glance, it could be viewed as a simple link between unit operations, resulting in a "powder to tablet" flow. Looking more closely, early adopters, system integrators and regulatory agencies identified that this "logic" link is far more complex. Beyond mechanical integration, interfaces between control systems and monitoring strategies had to be established, and the integration of these continuous systems into existing facilities, along with logistical hurdles and implementation strategies within the lead-user organizations and product portfolios, were equally important challenges to overcome as the technology transfer itself.

Thus, the implementation of CM is a corporate-level "business excellence" decision as opposed to simply installing a technological solution to enhance certain product performance capabilities. If lead-users embark on such a venture, they soon learn that the decision to implement continuous processing in their portfolio involves a whole-organization paradigm shift.

Looking ahead and predicting that, in a decade, a significant number of major companies will have adopted CM, it is evident that this is not an easily accomplished task. It is a major undertaking for all parties concerned. This chapter provides an overview of the pharmaceutical industry's journey towards the implementation of fully integrated, continuous processes, from "powder to coated tablets," and the strategies involved. Aside from any regulatory pressure, the three main drivers of CM are:

- Improved quality control (QC) and reduced quality costs
- Cost reductions in research and development (R+D), product transfer and manufacturing (increased operational efficiency and productivity)
- Faster reactivity towards capacity needs (optimized and more flexible supply chains)

These are all typical "business excellence" initiatives, for which CM has become a major enabler. In addition, there are technological reasons to select continuous process technologies, such as spray drying or extrusion. Here, the rationale is slightly different, but includes factors such as:

- Enhanced solubility
- Preventing drug abuse
- Taste masking
- Sustained release capabilities

Given that extrusion is already a continuous process, it makes sense to shape the extrudate into the final drug form in the same process. In other words, both business excellence and increased product performance drivers are combining to intensify the competitive advantages offered by CM.

CM is no longer a niche trend. It is already happening. Early adopters will benefit from competitive advantages. And although implementation and knowledge transfer can be time-consuming, CM technologies are already improving, enabling those pioneers to keep apace with the paradigm shift, sustain their business excellence trajectory and stay ahead of the market.

Highly efficient production will be key to success as profit margins erode and the much-debated R+D pipeline continues to falter. The development of personalized medicines, products developed for specific populations or subgroups and/or treatments will certainly result in a decline in the need for batch-produced "generic" drugs and

may well instigate a completely new paradigm of supply chain practices throughout the pharmaceutical industry. Janet Woodcock, Director of the Food and Drug Administration (FDA)'s Center for Drug Evaluation and Research (CDER), asks: "Are you ready for the concept of continuous drug production?" If not, get ready, she advises [1].

And it is not only FDA that is supporting the implementation of CM; ASTM International has also introduced a "Standard Guide for Application on Continuous Processing in the Pharmaceutical Industry" [2]. This guide introduces concepts and principles designed to assist the development, selection and operation of continuous processing technologies for the pharmaceutical industry: from definitions of terminologies to process design principles, from product quality control to process control system design objectives, and what any user needs to know when establishing a CM system within a given company structure. This guide is a very useful manual for any CM project team working on drug substance (DS) and/or drug product (DP) processes.

11.2 Continuous Manufacturing in Bioprocessing

11.2.1 Continuous Bioprocessing Enablers and Guidance

Continuous bioprocessing (CBP) continues to grow in popularity and acceptance in the biopharmaceutical industry. Although most processes still run single-unit operations in a continuous manner, such as perfusion bioreactors, the ultimate aim is for entire process lines to function continuously.

Perfusion bioreactor systems have been used for decades and became particularly popular when the cell harvest step was made more reliable and contamination rates went down. Once the upstream process became more controllable, the focus shifted to the downstream steps, providing the motivation to advance the other unit operations used within the process and assess what needed to be done to be able to run a continuous purification system.

Single-use process technology became a major enabler, resulting in robust continuous processes that precluded the need for the lengthy cleaning and set-up cycles associated with traditional processing equipment (which commonly took 5–8 hours). Any upstream efficiencies gained, however, including the robust cell harvest step, were lost as soon as the process moved downstream. Product was often held up as a result of purification bottlenecks.

The introduction of single-use processing steps, followed by unit operations, accelerated the push for continuous biopharmaceutical manufacturing. The experience gained from the past helped to design the process components and interfaces of the future. As single-use process components can be switched and replaced quite easily, the "stop and go" modus operandi has been transformed into a continuous process flow.

And, as the fluid volumes processed are far lower than in traditional batch/fed-batch processes, analytical technologies – as well as the process equipment itself – also benefited from an innovation boost, resulting in integrated sensors for inline monitoring and control. The dual development of process equipment and novel analytical technologies was an important contributor to two of the foundations of CM: Quality by Design (QbD) and Process Analytical Technology (PAT).

This does not mean that every process step or technological breakthrough runs perfectly; a few continuous bioprocess steps still require improvement. However, advances in downstream processing have shown promising developments during the last few years. And, as more end users and suppliers realize the benefits and cost-effectiveness of CM, further technology advances are expected.

A number of approvals have been made for products manufactured in continuous (upstream) mode. This approval rate will no doubt accelerate during the next few years, as both industry and regulators become more confident and familiar with CM. A major mindset issue was the definition of a batch within a continuous process, which was needed for control, documentation and follow-up purposes.

Practices from current CM applications show that defining a batch within a continuous system can be done in a process-specific way. The EMA utilizes the ICH Q7 definition: "In the case of continuous or semi-continuous production, a batch may correspond to a defined fraction of the production. The batch size can be defined either by a fixed quantity or by the amount produced in a fixed time interval" [3]. Definitions such as these help to overcome any possible misconceptions about the utter fluidity of a continuous process. It must be recognized that continuous bioprocesses have an even stricter emphasis on process controls and product quality data. In addition, it is not enough for the process itself to be robust; the same criteria apply to the supply chain in and out of the process [4, 5]. FDA definitions of both lot and batch in 21 CFR 210.3 state: "(10) Lot means a batch, or a specific identified portion of a batch, having uniform character and quality within specified limits; or, in the case of a drug product produced by continuous process, it is a specific identified amount produced in a unit of time or quantity in a manner that assures its having uniform character and quality within specified limits" and mirror the ICH Q7 definition. In addition, FDA encourages continuous processing as a fundamental pathway to implementing QbD and risk management principles, as per the 2004 "*Pharmaceutical cGMPs for the 21st century – a risk-based approach*" [6].

To summarize, continuous bioprocessing (CBP) is maturing. It is no longer a question of "if it will prevail", but "when it will become a dominant processing modus". Modern process technologies and regulatory acceptance will support the acceleration of CBP implementation, which, respectively, will enable the future implementation of on-demand manufacturing platforms.

11.2.2 Process Technologies

11.2.2.1 Bioreactor Systems

The starting point of any CBP is the bioreactor system. Perfusion bioreactors are not necessarily new to the pharmaceutical industry and have been used for many years. However, perfusion is not a universally well-adopted process, accounting for approximately 10% of total cell culture systems and representing only one-third of new bioreactor installations [7]. This resistance to adopt probably derives from past experiences with high failure rates and overly complex set-ups. In addition, early protein expression rates restricted the application of perfusion as large volumes were needed to achieve the required yields.

Improved expression rates, higher cell densities and new innovations in bioreactors facilitated the commercial-scale use of perfusion processes. Perfusion bioreactor equipment is

now available as stainless steel, reusable or single-use polymeric systems. As the cell culture process runs for a prolonged period (30 days to 6 months), multi-use stainless steel systems are preferred, although single-use reactors do offer some efficiency advantages. As single-use systems improve, in terms of robustness, aeration, connectivity and sensor technology, the higher the conversion or implementation rate of single-use systems is likely to be. And, as perfusion cell culture bioreactor volumes are much lower than fed-batch processes, single-use bioreactors become even more attractive as an option.

Most perfusion bioreactor systems run at the 50–500 L scale, which is quite low compared with some of the large-scale, batch-based monoclonal antibody process volumes of 20 000 L or more. However, perfusion systems can achieve similar yields owing to the higher cell density rates and viability levels achieved. The constant exchange of fluids in and out of the bioreactor supports these increased cell densities and viabilities by keeping both parameters stable instead of being ramped up and down as in fed-batch processes. Furthermore, it also enhances the end-product target quality; the product is not retained in the cell culture environment for extended periods of time, which can potentially cause product degradation [8, 9].

11.2.2.2 Cell Harvest

Traditional cell harvest technologies were a major contributor of high failure or contamination rates in perfusion processes. The separation systems were not robust enough to run for the required amounts of time. As the reactor volume is cycled over the cell separation device, the system needs to be extremely reliable to ensure that contaminants are not brought back into the bioreactor system. Contamination and fouling of the cell harvest step were much more prevalent in the past, which did not necessarily encourage operators to switch to perfusion systems. Current cell harvest systems are far more robust in terms of total throughput and barrier technology.

The requirements for cell separation technologies in perfusion processes are:

- Reliable performance for long periods of time
- Retention of cell viability, product quality and stability
- Easy to clean, if not disposable
- Scalable
- Ability to separate at different cell densities

Current separation technologies include gravitational settlers, filtration, continuous centrifugation and acoustic systems [10]. Filtration and gravitational separation systems can be used within the bioreactor or as an external device. All other methods are external.

The various separation methodologies have distinct advantages and disadvantages, and the right one must be selected to fit the specific application. As with most processing steps, there is no “one size fits all” technology. Gravitational settling has been used successfully in a number of applications; however, the cell separation effectiveness causes some cells to be carried over, which means that additional purification steps are required. In addition, the cells tend to adhere to the settler, altering the separation dynamics, particularly at higher cell densities. Continuous centrifugation can be used to process high cell density cultures, but shear forces must be controlled to prevent cell losses or elevated host cell protein levels.

Furthermore, most continuous centrifugation processes have operational time limits and need to be stopped for cleaning, meaning that some redundancy is required to avoid stopping the overall process. Acoustic or ultrasonic separation is not widely used, but new sound-based separating technologies show promise and good results. These systems can run for long periods of time and the newer systems could be designed for single-use applications, obviating cleaning. Evaluations are required to assess cell separation efficiencies and possible cell damage before the separation step is implemented.

The oldest separation technology used in perfusion processes is filtration. Spin filters, for example, show excellent cell separation performance without influencing cell viability, but only within very specific operational parameters. If these operational parameters are not maintained or the feed stream composition changes, spin filters rapidly lose their functionality, which can result in premature fouling or possible contamination. Other filtration-based separation devices are tangential flow systems, which run in recirculation or single-pass modes. Once again, these systems show good cell separation performance and low shear forces. But, they become blocked with long-term use and therefore require cleaning. A newer tangential flow design is the alternating tangential flow (ATF) device, which incorporates a hollow fiber filter module within a filter holder utilizing a diaphragm to pulse fluid over the filter, which greatly reduces fouling [9]. The ATF system has a multitude of advantages, including excellent long-term performance, good scalability and is free from specific operating parameters. So far, this technology has shown the best design and performance results.

The cell harvest stage is probably the most critical aspect of achieving effective separation and keeping the bioreactor free from contaminants. This step requires a thorough evaluation to ensure that the right separation system is selected for the specific application and operating parameters.

11.2.2.3 Purification Processes

As mature as upstream processing is, continuous downstream purification is equally as new. Some of the technologies are just a few years old and a thorough understanding of the entire continuous downstream process remains to be acquired. According to the literature, encouraging technological advances have been made and certain continuous purification steps have either been abbreviated or reduced in size [5, 11–13]. Multiple intermediate processing steps can now be removed and simplified. Some process designs show the harvested fluid being directly transferred to the capture step, which would be configured as a serial or circular multi-column design (Figure 11.1). The column chromatography set-up would not have an idle mass transfer zone, but would be fully and rapidly used, helping to significantly reduce the processing time and, as a result, decrease product degradation, improve yields and deliver a more stable product.

Other process steps could be reduced by a factor of 50–100 [5]. Smaller equipment would reduce resin use (20%), buffer use (50%) and lower the hold-up volume. The hold-up volume is often neglected, but can rapidly accumulate to a large loss of product. The smaller and more compact the systems, the shorter the transfers and the lower the hold-up volume losses. In some instances, new technologies such as membrane chromatography for the anion exchange columns or UV viral inactivation systems have been suggested. Membrane chromatography utilizes surface-modified, microporous membranes with pore sizes

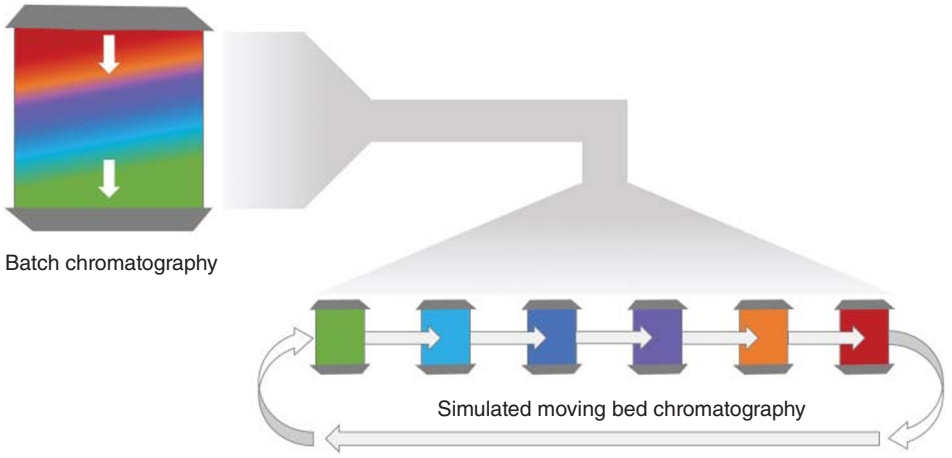

Figure 11.1 *Countercurrent multi-column chromatography system (courtesy of Jornitz Biosystems Inc.).*

ranging from 0.8 to 3.0 μm that drastically reduce diffusion-related mass transfer effects. The open pore structure enables the purification of large biomolecules (capturing) or the adsorptive removal of contaminants such as host cell proteins (HCP), DNA, endotoxins and viruses in flow-through mode (polishing).

The UV-C viral inactivation device is designed to use Dean Vortices to swirl the process fluid within the single-use fluid path to ensure that the entire fluid volume is subjected to irradiation (254 nm). The benefit of a UV-C system is the precise control of the irradiation dose per fluid volume, as UV-C can potentially affect the target protein; as such, appropriate process validation must be done to evaluate these potentially detrimental effects. Both have the benefit or higher processing speed and being available as single-use devices.

The increased speed of the purification processes enables the hold vessel amounts and sizes to be decreased. In one study, the tankage volume requirements were reduced 10-fold, which also lowers the footprint in the cleanroom [14]. In addition, the example showed that the processing time could be shortened to half that of a traditional process.

11.2.2.4 Analytical Tools

Process analytical technologies are vitally important to maintain a steady-state perfusion system and control its (continuous) output. Any variability would create havoc during the harvest and downstream steps. Robust inline controls must therefore be implemented. Cell density and viability are very much dependent on the input and consumption of gasses and feed streams, but are also dependent on the output of waste such as lactate or ammonia. Consumption and production must be monitored inline, in real time, to be able to control the cell culture and compensate for any potential excursions, such as pH corrections and/or cell harvest speeds.

These process analytics are highly dependent on the quality of the sensor technology, which has evolved to become more stable, compact and innovative [15, 16]. For example, sensor patches for dissolved oxygen (DO) and pH are available that can also be used as

single-use sensors on single-use bioreactor bags. This may be important when it comes to maintaining a contaminant-free environment in the bioreactor. In the past, some sensor probes were bypassed and microbial contaminants were able to enter the bioreactor, which is clearly not acceptable, especially in long-running perfusion systems. Furthermore, new sensor technology is not restricted to DO, pH or temperature, but includes a wide range of parameters and applications that are often single-use, including carbon dioxide, pressure, flow, cell size and density, conductivity, turbidity and redox potential.

Online *in situ* near-infrared spectroscopy (NIR) sensors are available for various applications and measurements, facilitating the measurement of glucose, lactate and ammonia during the cell culture process. These sensors are not just used for upstream processes, but also for downstream unit operations, as the specific operating parameters of each stage provide important feedback and enable optimal performance levels to be attained. It is important to be in control of the entire process to achieve acceptable levels of consistency and monitor the reliability of individual process steps.

In situ measurement technologies create an easily accessible picture of the state of the cell culture process. However, off-line measurements are often used as a data support function. Here, sampling is critical, as it could potentially introduce undesired contaminants. New technologies now allow automated sampling, off-line measurements and data acquisition. Once again, single-use technology systems have provided a routine sampling solution; these devices are pre-sterilized and reduce the risk of contamination or false-positive results.

The robustness and variety of sensor technology has made significant progress during the last few years. Yet, there are still hurdles to overcome regarding the control of operational parameters and product quality. And, data acquisition needs to be complemented with proper analysis, prediction models and decision systems, which will subsequently guide the user and help them to make the right processing choices.

11.2.3 Examples of Continuous Manufacturing

Most examples of continuous manufacturing focus on upstream processing. Experience to date and the available information mainly relate to perfusion bioreactor systems and, to a certain degree, cell-harvesting technologies. Commercially available products, such as Remicade, Rebif and Kogenate, have been produced using perfusion systems. However, entire continuous processes, not just the cell culture step, are seriously being evaluated for commercialization.

Having recognized the financial benefits, some processes have been modernized to accommodate CM; in other instances, new facilities have been designed to introduce (almost) end to end production lines. In both instances, benefits in terms of floor space, personnel and increased product output have been realized. One example showed how a nonfinancially viable drug manufacturing process was modernized to incorporate continuous processing and subsequently became sustainable [17]. Such examples are extremely encouraging, particularly if previously unavailable drug products can be made available by removing financial manufacturing obstacles. This would make drugs accessible, on demand, to a larger patient base and also enable the production of specialty medicinal products.

End to end processes are being developed and often supported by funds from pharmaceutical companies [18]. It demonstrates the industry's interest and need to turn entire

manufacturing processes into compact, highly efficient and flexible entities. The realization that the processes of the past may not be financially viable, and the increased industry competition, have accelerated the development of new continuous processes. But, it cannot be done by industry alone; it requires in-depth input from suppliers. Technological progress and case studies indicate that entire end to end process lines can be accomplished [13]. But, more work needs to be done and more data need to be published to convince the regulatory authorities to approve such processes.

11.2.4 Economic and Design Implications

11.2.4.1 Commercial Comparisons

Several publications are available that compare batch, fed-batch and perfusion cell culture processing. Most of the comparisons only consider the upstream performance of perfusion versus fed-batch. These comparisons highlight the benefits of continuous bioprocessing (Table 11.1), including:

- Higher cell densities and viabilities
- Higher product yields
- Better product stability
- Lower capital investments owing to smaller reactor footprints
- Better process control

The higher complexity of a perfusion system and the threat of secondary contamination during the prolonged cell culture process are noted disadvantages. Although, as new cell culture process technologies have been introduced, these two factors have also been minimized.

Table 11.1 shows the benefits of the perfusion cell culture process in terms of actual vessel volumes (footprint and capital expense) and increased output rates. Results vary from cell line to cell culture but the overriding themes of perfusion versus with fed-batch comparisons are higher yields, better product stability, better output rates and lower bioreactor volumes [12, 19]. As cell culture media is fed constantly into the perfusion process, media consumption is often thought to be greater than in fed-batch processes. However, because the bioreactor volume is so much smaller and fed-batch systems still require feed streams, media consumption is normally similar or, more often, lower.

Process controls for perfusion systems are more complex; but, the higher cost still outweighs the expense of the larger bioreactor systems required for fed-batch processes. And, regarding time to run, the delivery and validation process for a fed-batch bioreactor system takes much longer, which means that valuable manufacturing time is unavailable. In addition, some perfusion bioreactor systems exist as off the shelf products or can be bought with redundancy in mind to provide flexible operational capacities. Smaller systems offer more flexibility and shorter times to run, making them extremely valuable commodities for biomanufacturers.

The enhanced economies offered by CM are not limited to the perfusion cell culture, but also extend to the purification process. The amount and size of chromatography columns and ultra-/diafiltration steps is greatly reduced. For example, the size of a capture step in a continuous bioprocess stream may be 50–100 times smaller than in a batch process [4]. Not

Table 11.1 *Cell culture process comparison (courtesy of John Bonham-Parker)*

	Perfusion	Concentrated perfusion	Fed-batch	Concentrated fed-batch
Feed	Complete medium	Complete medium	Feed concentrate (multiple)	Complete medium
Environment	Constant	Constant	Constant	Changing
Osmolarity	Constant	Constant	Increasing	Limited or no change
Waste/toxic molecules	Removed	Removed	Accumulated	Removed
Product residence time	Low	Low	High	High
Stability of environment for product	High	High	Low	Moderate
Typical process duration	1–2 months	1–2 months	1–3 weeks	2–3 weeks
Typical cell concentration	$10–30 \times 10^6$	$60–120 \times 10^6$	$10–30 \times 10^6$	$70–200 \times 10^6$
Typical cell viability during production	75–95%	75–95%	30–95%	90–95%
Typical cell viability at harvest	75–95%	75–95%	30–70%	80–90%
Compatible with disposable bioreactors	Yes	Yes	Yes	Yes
Compatible with ATF-cellbanking?	Yes	Yes	Yes	Yes
Compatible with ATF-manufacturing	Yes	Yes	Yes	Yes
Seed train (liters)	Eight stages: 1 ml (vial), 5 ml, 25 ml, 125 ml, 600 ml, 3 L, 15 L, 75 L	Eight stages: 1 ml (vial), 5 ml, 25 ml, 125 ml, 600 ml, 3 L, 15 L, 75 L	10 stages: 1 ml (vial), 5 ml, 25 ml, 125 ml, 600 ml, 3 L, 15 L, 75 L, 400 L, 2000 L	Eight stages: 1 ml (vial), 5 ml, 25 ml, 125 ml, 600 ml, 3 L, 15 L, 75 L
Seed train with ATF-manufacturing platform (liters)	2 stages: 100 ml (bag), 10 L	2 stages: 100 ml (bag), 10 L	3 stages: 100 ml (bag), 10 L, 500 L	2 stages: 100 ml (bag), 10 L
Typical manufacturing vessel size	500 L	500 L	10 000 L	500 L
Media cost per litre	Moderate	Moderate	High	Moderate
Media volume required	High (1–2 vvd)	High (1–2 vvd)	Low (1 vv)	Moderate (10–15 vv)
Harvest	Daily/constant	Daily/constant	One per batch	One per batch
Process control requirements	High	High	Moderate	High
Operational skill required	High	High	Moderate	Moderate
Alkali addition	Low	Low	Moderate	Low
Compatible with continuous DSP	Yes	Yes	No	No

(*continued*)

Table 11.1 (Continued)

	Perfusion	Concentrated perfusion	Fed-batch	Concentrated fed-batch
Output from 1000-L reactor, per day	0.2 kg	0.8 kg	n.a.	n.a.
Output from 1000-L reactor, per run (CHO cell data)	6 kg (20×10^6 cells per ml; 30 days)	24 kg (80×10^6 cells per ml; 30 days)	1.2 kg (peak 20×10^6 cells per ml; 14 days)	17 kg (peak 100×10^6 cells per ml; 18 days)
Time to produce 10 kg of product	1–2 batches; ~7 weeks	1 batch; ~2 weeks	8–9 batches; ~22 weeks	1 batch; ~2 weeks
Yearly output from 1000-L reactor	60 kg (10 runs)	240 kg (10 runs)	24 kg (20 runs)	255 kg (15 runs)
Reactor size required to produce ~250 kg per year	4× 1000 L	1× 1000 L	1× 10 000 L	1× 1000 L

only does that reduce capital investment, it also decreases operational expenses: less buffer and smaller amounts of resins are required, and less cleaning and sterilization are needed. Costs are also reduced in the process and facility layout owing to the smaller footprint of the equipment, which subsequently impacts operating expenditure as the cleanroom areas are smaller and less energy is required.

11.2.4.2 Process and Facility Design Comparison

Large-volume biopharmaceutical blockbusters are very much in decline, which means that capital-intensive, product-dedicated facilities are being replaced with more flexible and agile plant. Flexibility is an ambiguous term and will be defined differently depending on the product and production process. It can mean the ability to process multiple products, to scale the process volume up and down, on demand, or to be able to move the site. Single-use technologies are enablers that fulfill this need; but, this flexibility also needs to reflect the facility design requirements. The benefits of single-use technology – mobility, ease and speed of set-up – only become apparent in multi-product production possibilities when those single-use components are not restricted by their surroundings, the facility itself.

Continuous bioprocessing is another great enabler of flexibility, owing to its smaller process and facility footprint. The number of processing steps is reduced and the equipment used is much smaller than in large-scale batch/fed-batch processes. Depending on the process design, some CBP designs require just half the footprint of traditional processes, and they are expected to become smaller still. This means that the overall cleanroom space requirement is much smaller, which enables the implementation of these processing steps into prefabricated, mobile cleanroom units or ballroom designs.

Prefabricated cleanroom systems not only create true flexibility, they also represent robust containment of the various processing steps without affecting the rest of the cleanroom (Figure 11.2) [20]. The units have their own air handling system and are

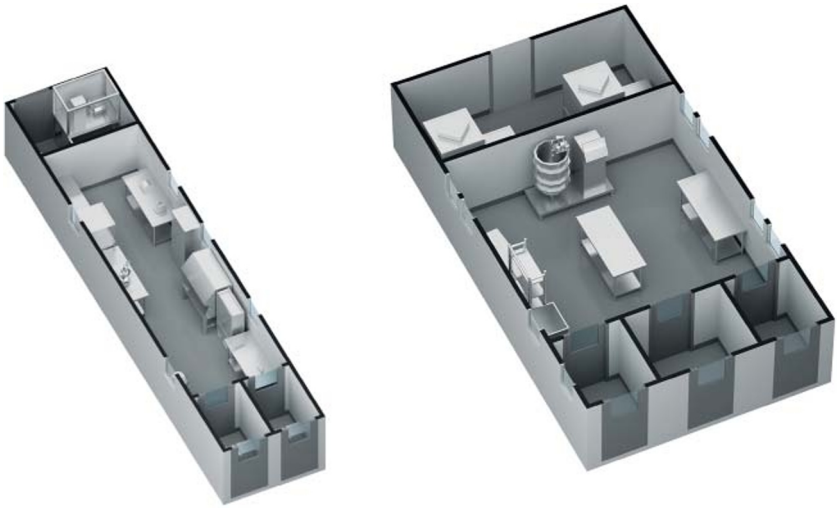

Figure 11.2 *Prefabricated, autonomous cleanroom units (courtesy of G-CON Manufacturing Inc.).*

not interconnected with each other via a convoluted ductwork system. Most traditional cleanroom designs, including modular and container-based systems, are supplied with a central air handling system and are interconnected. Any change requires requalification or means that the entire cleanroom structure has to be rebalanced. With time being so critical and requalification making the processing area inaccessible, the concept of what is truly flexible becomes an important consideration.

Encouragingly, the different cleanroom and containment options currently available are designed with mobility, flexibility and reusability in mind. Whether it is isolators, cleanroom cabinets or totally contained cleanroom pods, the common theme is the ability to create a viable end-user solution that can accommodate either a CM line and/or single-use systems. This not only results in the fast deployment of facilities, it also reduces engineering and qualification timelines, as well as providing a familiar environment for the auditing regulator. True flexibility comes with autonomous cleanroom space, which can be easily decontaminated and sanitized, controlled and reused. The cleaning and repurposing of autonomous cleanroom space makes these facilities ideal for continuous or multi-product processing.

Another cleanroom concept, enabled by continuous processing in conjunction with single-use processing equipment, is the ballroom design [4]. Here, the entire process is located in one cleanroom space – from cell culture to media and buffer preparation, from purification to bulk preparation. Small footprint CBP operations could be run in a single ballroom, meaning that fluid transfers – if not entire processes – could be controlled and set-up by very few people.

The personnel, material and waste flows are very simple in a ballroom design. Ballroom cleanroom designs can be established as mini-sites and could be used for multi-product purposes (as long as the entire ballroom system can be sanitized, especially if an excursion occurs). The use of single-use processing equipment for multiple unit operations in the same

cleanroom space indicates a high level of confidence in the robustness of this technology [21]. However, leaks and/or human error would severely jeopardize any ballroom-based process. The ultimate vision for the future is the use of flexible mini-site facilities that can be utilized in any region of the world, as in-country/for-country supply systems, which can be built and run within months to fulfill local healthcare requirements. Continuous bioprocessing and single-use equipment are enablers of such flexible sites and can now be augmented with autonomous cleanroom modules.

11.3 Continuous Manufacturing for Oral Solid Dosage Forms

11.3.1 Industry Approaches to the Implementation of CM

When new technologies are making their way from concept to reality, "old believers" and "early adopters" can respectively hinder or drive their progress. At the same time, a highly regulated and globally organized supply chain is an additional hurdle to any fast paradigm shift in the pharmaceutical industry. What with the discrete steps of API production, primary formulation, secondary packaging and final distribution, the dominance of batch-based processing has led to high inventories and slow response times; it can take months to go from the first manufacturing step to final delivery.

Some of the key players have started to challenge this central dogma with a number of different strategies. Novartis and MIT, for example, boast a fully integrated primary/secondary pilot plant driven by the MIT Center for Continuous Manufacturing in Boston (Mass., USA) [22]. Another example is Vertex, who developed, transferred and manufactured an FDA-approved OSD product with a continuous (powder to coated tablet) secondary manufacturing rig and real-time release (RTR) strategy [23].

One of the most prominent "old beliefs" is that CM cannot be used for small-scale or low-volume manufacturing. As we know, however, it is simply a matter of the value and cost of an API. At the same time, it is also argued that CM is not economically viable for high-volume, blockbuster products either. Given that GSK recently built and invested in a US$ 50 million commercial-scale continuous system in Singapore, this "old belief" could well be dismissed. "It will be large enough to produce up to eight billion tablets and one billion capsules a year," stated CEO Andrew Witty, who went on to say that this project would result in a 50% reduction in costs and a 50% reduction in carbon footprint. Furthermore, he stated that between one-third and one-half of the company's current portfolio of drugs could be made using CM [24].

Pfizer came to another conclusion. Having been involved in CM solutions for several well-known products for decades, Pfizer suggested that it does not matter if the end product is small volume/high value or a cheaper medium to high volume product. The scalability, flexibility and, last but not least, portability of CM will provide significant competitive advantages in tomorrow's pharmaceutical supply chain [25].

To address this contradiction, the value of the product must be taken into account, as well as a deep analysis of the supply chain. Although many isolated continuous processes have existed for years, there are very few fully integrated continuous-flow operations. As such, the full economic benefits of CM are difficult to assess.

To make a meaningful cost-benefit assessment, it is normal procedure to review a portfolio of products to determine which one represents the best business case: the value of a

product can strongly influence expected revenue figures, as does market demand, production volumes and the effects of amortization on the investment and/or implementation of CM (see Section 11.3.3.2). The next step is to analyze the process steps and collect cost data from the existing production process. Section 11.3.3.1 offers some guidelines regarding identifying the best business candidate for CM implementation.

Another point to consider is the business environment or market segment. Is the company producing ethical or prescription-free pharmaceuticals? Is it a generic manufacturer or a contract development and manufacturing company (CDMO)? Depending on the business model, the "needs and wants" to implement a CM solution might play a key role.

It should be noted, as well, that the first contract manufacturing organizations to invest in CM technologies were Catalent, Aesica and, lately, Patheon, who recently embarked on a 50 kg/h powder to tablet CM system [26]. As these companies start to move into the CM space, more will follow, to benefit from the competitive advantages enjoyed by early adopters.

Any business decision is essentially based on Equation (11.1) [27]:

$$C_0 = -A_0 + \sum_{t=1}^{n} (E_t - A_t) \cdot (1+q)^{-t} \tag{11.1}$$

C_0 is capital value or net present value (NPV).
A_0 is the initial investment in year $t = 0$.
E_t is revenue (cash effecting).
A_t is expenses (cash effecting) at the time/year t following $t = 0$.
q is the interest rate.

Section 11.3.3.1 lists and analyzes typical arguments to support continuous processing, to assess which of those savings are really important for the NPV as an investment decision.

In commerce and business, theoretical scenarios are used in the same way as applied science models to predict certain results while important parameters are changing. By comparing alternative business scenarios, Equation (11.2) derives information about the dominating drivers for any investment:

$$C_0^N - C_0^A = -\left(P^N - P^A\right) + \sum_{t=1}^{n} \left[\left(E_t^N - E_t^A\right) - \left(A_t^N - A_t^A\right)\right] \cdot (1+q)^{-t} \tag{11.2}$$

Which alternative is the most favorable investment proposition? A or N? This established technique, as used in business schools and research centers, like MIT [28], will be applied in Section 11.3.3.1 to demonstrate that CM offers benefits in a variety of different business cases and can be used as a basis for investment decisions [29].

Any NPV can only be assessed if the value of the product is known; the "cost per tablet" is not enough. It is, of course, a valid measure, but is not sufficient to support any time-based, long-term strategy [27]. The NPV calculation is a dynamic method that takes the investor's business target into account; that is, the expected payback against the capital market interest rate. Based on a finance and cash flow plan, this method also enables alternative propositions to be compared but is better suited to calculating scenario outcomes. With CM, as in any investment decision, time and timing is critical, highlighting once more why cost per tablet is only a minor factor in the overall evaluation.

There are many examples of underutilized equipment and facilities in stagnant pharmaceutical markets, or where healthcare costs are strictly controlled, and also examples in emerging markets where companies suffer from a lack of capacity. Before any company owner or CEO decides to invest in a new technology, all of the above must be assessed and appraised. In some instances, a less than watertight business case will support the decision to implement CM. The competitive situation may convert a "want" to a "need." That is, the "need" to implement continuous processing!

11.3.2 Typical Installation Layouts

Once the unit operations have been defined by the process engineers, the next steps involve the process flow diagram, the layout plan and logistics; that is, the integration of continuous processing equipment into an existing facility or the development of a "greenfield" installation. To take such an important step, one important piece of information is needed: the definition of the product portfolio and requirements to be able to manufacture that product. This will determine the flow rate of the materials through the process and the throughput capacities of each unit operation.

At this stage of CM implementation, the new ASTM standard provides certain process design principles, such as: "6.1.3. Hence when designing a continuous processing system, consideration should be given to the process conditions experienced by the materials as they flow through the system" [22]. This principle is important, as mechanical, control and process engineers need to work hand in hand to define the optimal layout for the product portfolio. Another important paragraph relates to material handling and conveying between each unit operation: "Careful consideration should be given to the design of transport and flow control elements within a continuous system to ensure that materials will flow in a predictive way without adversely impacting product quality" [2].

This shows just how sensitive the interface between the different unit operations can become, and it should be determined at the beginning of each CM implementation project which party is responsible for process and equipment integration. Both level of control and level of product quality are critical: effective system integration is an absolute priority during any CM project.

Before a detailed functional specification can be written, these preliminary activities must be completed. And, as the control strategy is often based on the functional specification as well, elements such as state of control, raw materials and intermediates, equipment, uniform quality and character of the product, product collection or rejection, traceability, process monitoring and sampling, risk assessment and failure modes, scale-up and RTR testing specifications must also be considered [23].

Having mentioned scale-up, it is important to describe how to increase production in the overall strategy. The ASTM standard cites the following alternatives: "To increase process capacity from development to commercial production, consider (1) scaling-up the duration of the process, (2) increasing the production rate, (3) adding parallel processing lines or (4) adopting a risk-based approach to scaling-up a continuous process" [2].

Another important topic in today's pharmaceutical industry is reducing transfer times and costs between R+D and commercial production. In future manufacturing environments, the system layout for R+D-scale production will be exactly the same, and dedicated equipment will be used to eliminate any transfer risks between different sites in the world [25].

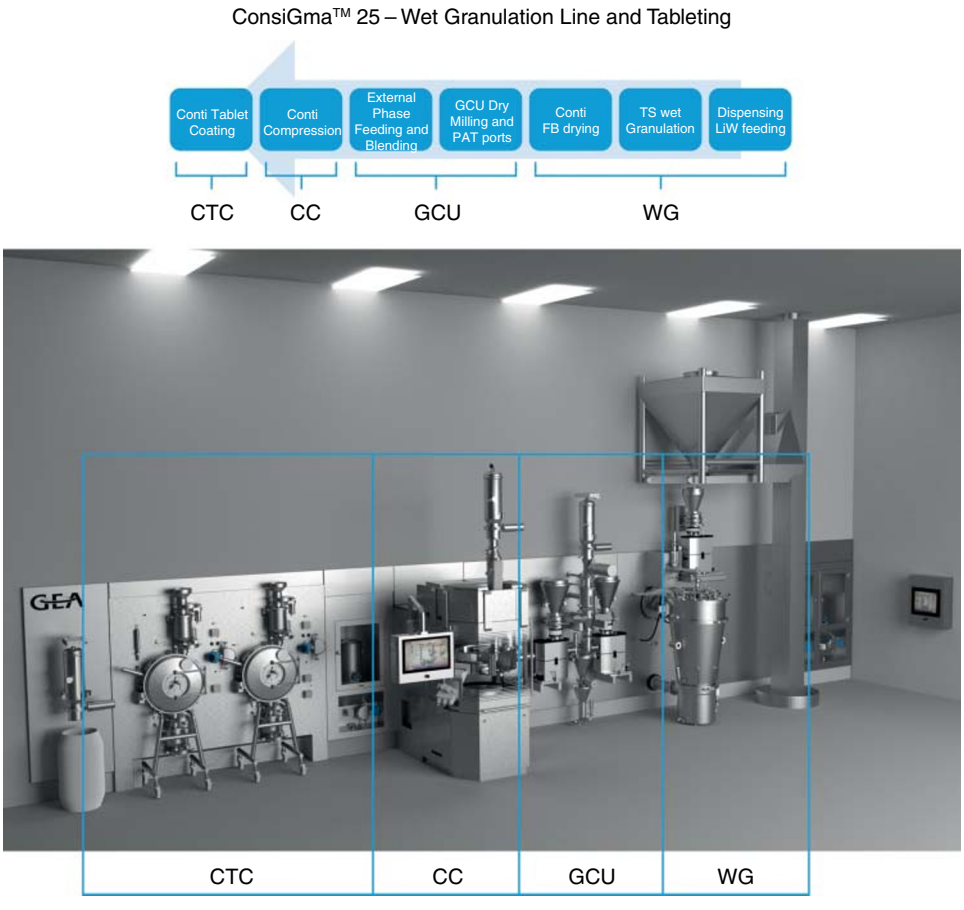

Figure 11.3 *A horizontal wet granulation line, including compression and coating equipment (courtesy of GEA).*

The very important aspect of this concept is the "miniaturization" of the equipment, which is a unique property of continuous processes. It provides the additional freedom and flexibility to design manufacturing set-ups that are mobile, as described in the following section.

11.3.2.1 Horizontal Layout

A typical horizontal layout configuration is shown in Figure 11.3. The unit operation modules are positioned alongside each other and, although the material flow is horizontal, there are still elements wherein gravimetric flow is essential (from the outlet of the loss in weight feeder into the dry blending units or the wet granulation system).

A more challenging procedure is the transfer of wet granules. The wet granulation unit could potentially be placed above the fluid bed dryer to eliminate, as much as possible, any transfer problems with the wet granules. Another key requirement is to get the outlets and

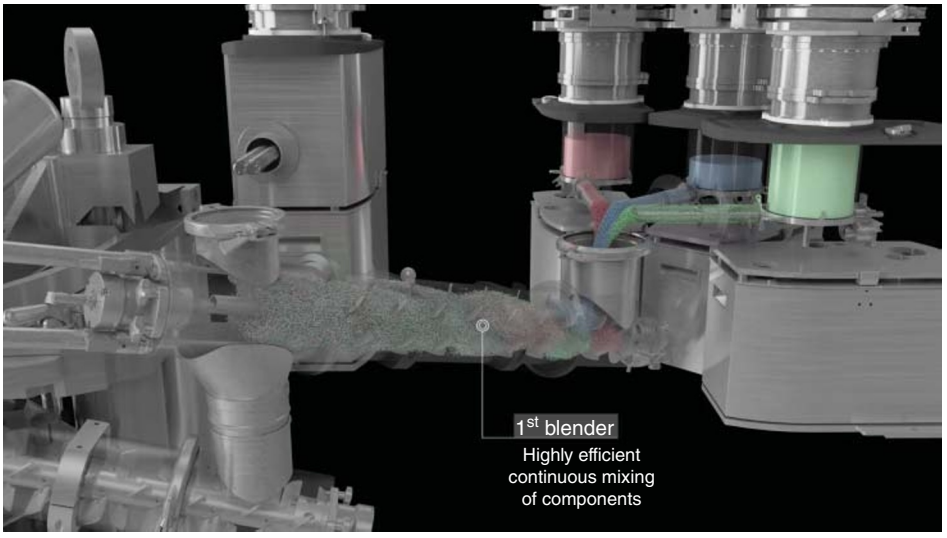

Figure 11.4 *Gravity flow in a horizontal set-up (courtesy of GEA).*

inlets of each unit operation as close to each other as possible; any material or buffer "hold up" should be minimized.

Future developments will result in even more miniaturization as the control panels begin to merge and the unit operations progressively become more mechanically integrated. For example, combining material handling, wet granulation and direct compression in a horizontal layout could offer throughput capacities of 5–50 kg/h, depending on the formulation.

It is important to mention that in any so-called horizontal layout, gravimetric flow modules still play a key role. Every loss in weight feeder discharges powder by gravity into the next unit operation (such as dry blending or wet granulation). And even when feeding and blending occurs directly above a tablet press, the material flow is controlled by gravity (Figure 11.4).

11.3.2.2 Vertical Layout

Often defined by logistics or the physical structure of the facility, a vertical set-up may offer certain advantages. For example, no intermediate material handling equipment – such as vacuum conveying or a screw transportation system – is needed for gravimetric flow to link the process unit operations together.

Because of the risk of segregation and to reduce the potential of material plugs forming during transportation within physical transfer systems, vacuum conveying is not recommended for dry powders. Granulated or melt extruded product can, however, be vacuum transferred, as long as the material is not buffered or held up at any stage without constant flow. It should be noted that typical pneumatic conveying systems are prone to plug flow behavior and back-mixing effects should not be expected. In addition, when using a vertical set-up, certain material streams or product intermediates may need to be elevated between process levels; suitable conveying systems will need to be selected and defined.

Figure 11.5 *IBC docking station and contained material handling (courtesy of GEA).*

In some facilities, one floor may be dedicated to material transport, wherein only IBCs, big bags or drums are moved (manually or by autonomous vehicles). In such instances, a docking station is required to connect the material transport system to the continuous process equipment inlet (Figure 11.5). The docking station provides a number of important functions:

- It enables the operator to position the IBC, in a safe manner, at the correct infeed port
- It facilitates product identification and process tracking for the batch records
- It enables effective powder discharge from the IBC (intermediate bulk container) without material bridging, blockages or operator intervention
- It provides a constant feed from the material handling system
- It provides a containment (valve) interface between the IBC and the powder feed to prevent contamination in the good manufacturing practice (GMP) area and guarantee maximum operator safety
- It is clean in place (CIP) compatible

Beyond unit operation layout, material handling and the actual logistics of the process are a critical aspect of CM performance (Figure 11.6). End-product quality – and patient safety – begins with the input material. Any CM system is only as good as its material handling capabilities; none of the downstream unit operations can compensate for interruptions and fluctuations of the inbound material.

Another important criterion to consider when selecting the best possible system layout is cleanability and the use of short product transfer chutes between operational levels. Easy operator access and handling are key elements of rapid cleaning and fast changeover times, which are impacted by the overall amount of product touching equipment surface areas, the level of process integration and the amount of miniaturization within the system.

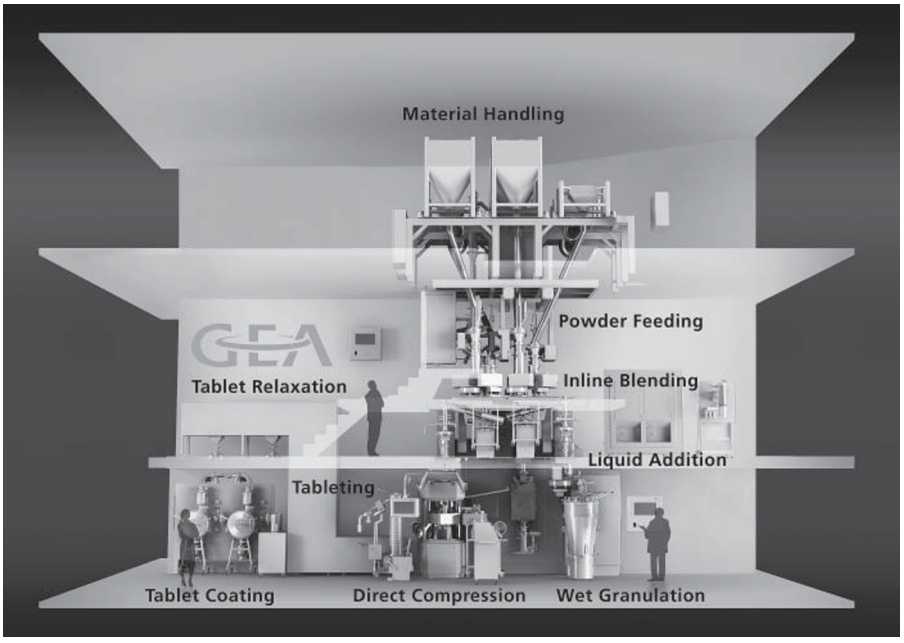

Figure 11.6 *From powder to coated tablets in a vertical set-up (courtesy of Vertex and GEA) [23].*

As continuous technologies, by definition, process smaller quantities of product in a fast and highly intensified way, the equipment has much-reduced product contact areas.

Cleaning, including product changeovers, contributes to both downtime and the overall equipment effectiveness (OEE) evaluation of the whole system. Needless to say, it is important to assess downtime as a significant contributor to the economical/NPV justification for CM implementation. The cleaning procedures need to be based on real product and equipment tests, and prepared together with the equipment vendor, the system integrator and the user group, and be specified in the URS. Another argument to support highly integrated systems is product yield, particularly for high value APIs.

11.3.3 Economic Justification and Business Excellence

As described previously, each company has its own business environment and competitive arena. As such, there is no "typical" business case. Here, however, a structured approach is used to generate an example business case for CM implementation. It has been stated that an in-depth analysis of current processes [29] and the extant product and pipeline portfolio is needed to determine the best drug candidate, as well as the most appropriate location for a CM installation. NPV can be used to compared alternative solutions; but, the process begins with the following questions:

- Why CM?
- What is CM?
- How can CM be implemented?

The "why" is basically a business question: apart from regulatory issues, the main drivers, as previously described, have been to support the pharmaceutical industry's adoption of CM.

In addition, the regulatory agencies vocally support the continuous supply of high quality drugs to patients in their political and legal territories, and also encourage agility, flexibility, reduced manufacturing and distribution costs, and a reliable pharmaceutical supply chain. It is a potential threat to public health if the supply of high quality medicines is hindered by any constraints. For a more detailed review of "why," a cost driver analysis must be done; a checklist of the industry's typical arguments is presented in the following section. The "what" has been addressed previously; so, let us talk about the "how."

11.3.3.1 Factors for Economic Success

Having previously defined the pharmaceutical business environment, this chapter will present a number of different scenarios using the NPV as a benchmark. The order of categories listed in Table 11.2 is not a ranking of importance or priority; these factors are dependent on the specific business environment. They are, however, universal and "typical."

All of these parameters affect the NPV and, as they vary widely, specific scenarios must be examined to identify the most influential parameters or compare different investment strategies. First, however, key factors affecting revenue and expenses – the manufacturing cost per tablet – need to be defined.

Factors that influence revenue and cash-in relate to optimizing productivity and increasing the manufacturing output of a plant. These are also short-term effects compared with those that help to gain market share by supplying new regions or implementing a faster and more agile supply chain.

Looking at the manufacturing costs more closely, there are two categories: variable and fixed. Also, CM implementation can cause immediate operational cost-saving effects.

There are also savings and cost advantages to be gained at the R+D stage. Those R+D savings are, however, difficult to assess; they are heavily dependent on the product and the therapeutic class. For rare disease drugs, for example, the material saving in DoE work might justify and return any investment in a year, which may not be a realistic scenario for the majority of current pharmaceutical products.

As a starting point, a basic scenario can be used to show how the NPV calculation model and the technique works, comparing a traditional batch-based direct compression set-up and a continuous direct compression system. Figure 11.7 shows the unit operations and the typical layout of a manufacturing site.

This business case is based on a throughput of 500 000 000 tablets (400 mg) per year. The typical batch size in this example is 500 kg. The main question to address is whether the existing batch system is still economically viable and how a CM process can improve the cost per tablet and, consequently, the NPV [30].

The first step is to assess the cost structure and, based on the parameters listed above, calculate the effect of CM implementation. The second step is to analyze the cash flow effect, allowing for whole-investment depreciation with time. To calculate the NPV, some input from marketing is required to predict demand and accommodate changes in the supply chain.

Table 11.2 *Factors of economic success*

Category	Effects
Reduced inventory WIP	Reduced number of smaller, flexible manufacturing campaigns Reduced inventory between production batches Reduced inventory value of WIP (Work in Progress) in the supply chain
Reduced cycle times	Less downtime: easier handling and faster cleaning (smaller equipment with less product touching surfaces, wash off line [WOL] principle) Reduced QA time
Increased OEE level	Higher overall equipment availability and 24/7 operation
Direct labor costs	Reduction of direct labor costs by multi-machine operation: more unit operations controlled by one operator No dispensing activity needed: less material handling
Indirect labor costs	Less offline QC testing Less maintenance
Reduced capital investment	In the case of POD-based installations: less depreciation than traditional systems; less infrastructure required Reduced risk of investment as systems are more flexible/reusable Reduced delivery time and engineering costs for highly standardized systems
Reduced operational costs	Reduced GMP area and service area footprint Reduction of IBCs (including cleaning and storage) Reduced utility consumption (power, water and compressed air)
Savings in product transfer	API savings during R+D and product transfer Operational expenses to execute R+D, transfer and registration batches Less labor cost: reduced time for DoE and analytical support Less time and cost for analytics, reduced number of samples
Reduced QA costs	Less batch failure No re-work Fewer quality checks Faster batch release by RTR testing

The results shown in Figure 11.8 indicate a clear preference for CM, whereby the main cost per tablet savings derive from reduced quality costs, lower labor costs, reduced footprints and lower manufacturing-related utility costs.

The graph also highlights CM's flexible batch size functionality too, showing the product value benefits and throughput capacities that can be gained with this type of equipment and process layout for this particular site. It also confirms the system's flexibility, which is mathematically defined by the areas under the curves.

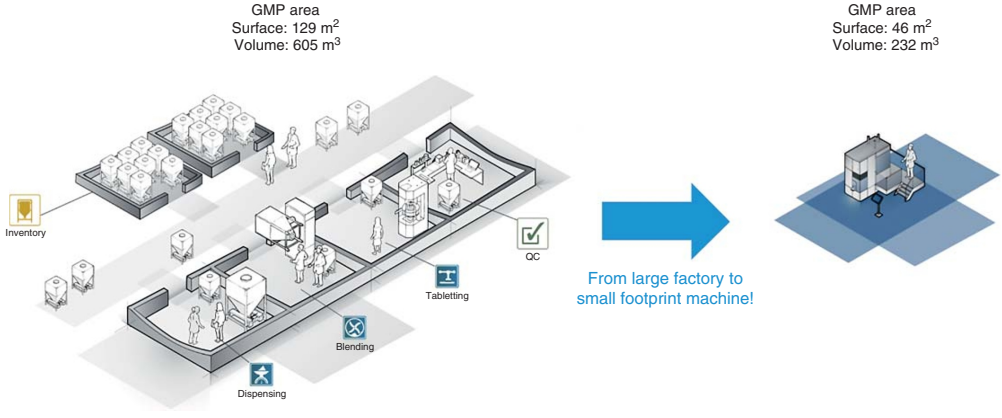

Figure 11.7 *Batch versus continuous: integration and space reduction (courtesy of GEA).*

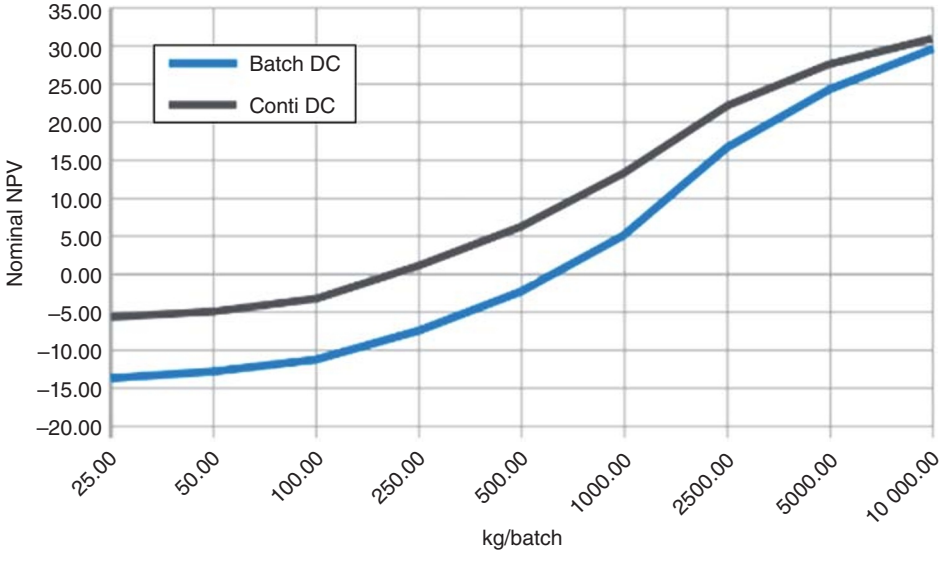

Figure 11.8 *Nominal NPV after six years: batch (Batch DC) versus continuous (Conti DC) processing (courtesy of GEA).*

It also confirms at what point, or at what batch sizes, the equipment gets too small and becomes limiting to the business case. Lastly, it also includes the interest rate at which the investment provides a 10% per annum return for the investor [30].

Often, decisions must be made regarding whether a manufacturing site has reached its capacity limits and needs to further increase productivity within certain space limitations. The amount of space gained by implementing CM can help in those instances to increase throughput capacity (including multi-machine operation by a single operator).

11.3.3.2 Time to Market Effects and New Product Launches

Another scenario reflects the market launch of a new pharmaceutical product. A key driver for CM is reduced time to market – resulting from "rapid DoE" and the elimination of scale-up – in early stage development, product transfer and production for products that are on a critical registration path. The following chart compares a market launch with a traditional batch-based direct compression set-up with a continuous direct compression system (Figure 11.9).

The assumptions that have been made are R+D-based time savings, derived from faster DoE work, as well as obsolete product transfer (the DoE work was done on an identical continuous processing system).

With cash flow shown on the time axis (per year), it is clear that the continuous system not only offers a faster return in investment, it also displays a higher post-implementation cash flow. In the first couple of years, the investment is not used until the product is validated and approved for production.

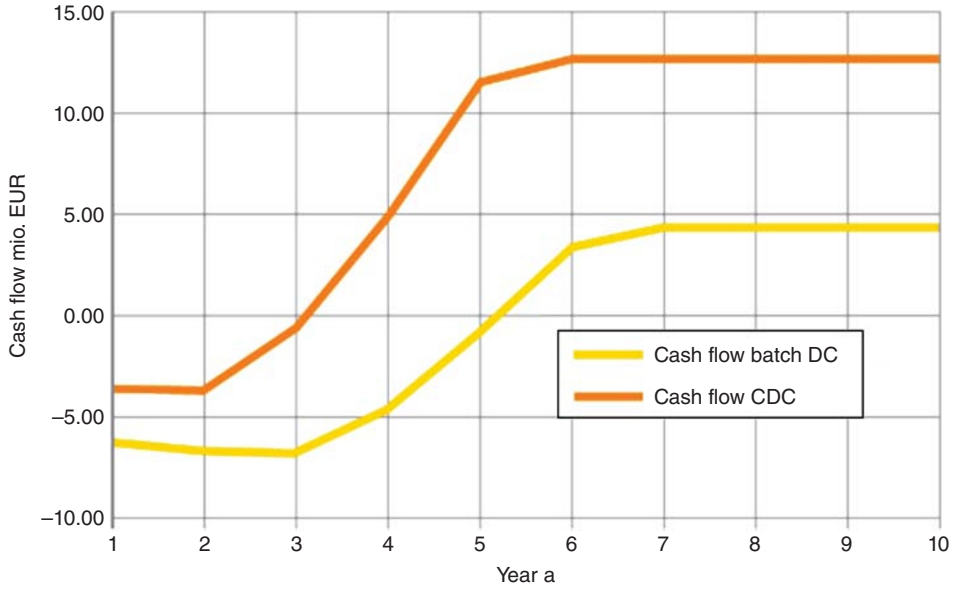

Figure 11.9 *Product launch cash flow: batch (Batch DC) versus continuous (CDC) processing (courtesy of GEA).*

11.3.3.3 High Volume/Low Value Versus Low Volume/High Value

Another question to be considered is whether CM is better suited to high volume/low value or low volume/high value products. The short answer is both, although the implementation of CM in each instance varies. The line layouts are different and the R+D system for the DoE phase is extremely important. Particularly for high value products based on very small quantities of extremely expensive new drug entities, the in-process material must be used as efficiently as possible. The ability to process large batches at the highest OEE levels – without unforeseen interruptions – is crucial. Cleaning times and full product changeovers must be optimized and are best developed as a holistic cleaning and control strategy with the operators.

Of note is the fact that, even with small batch sizes, CM demonstrates positive NPV values, even when the machine is not fully utilized. By contrast, for large batches of low value/high volume product, batch-based systems offer very similar NPV values. But, given the range of batch sizes, the continuous system always, in all examples, delivers a better NPV (Figure 11.10).

As expected, the CM system shows the greatest advantage for small batch sizes (25–250 kg). For some products, allowing for process times of 1–24 h, this would enable a supplier to meet quarterly market demand. In addition, owing to API savings of 70–90% accrued during DoE (compared with batch-based processing), the NPV remains positive, even for an underutilized R+D system [30].

For large-scale production, which means manufacturing big batches, the OEE level is crucial, and an important aspect of that is material logistics. Real continuous systems operate in an OEE range of greater than 90%, which makes optimized cleaning and maintenance

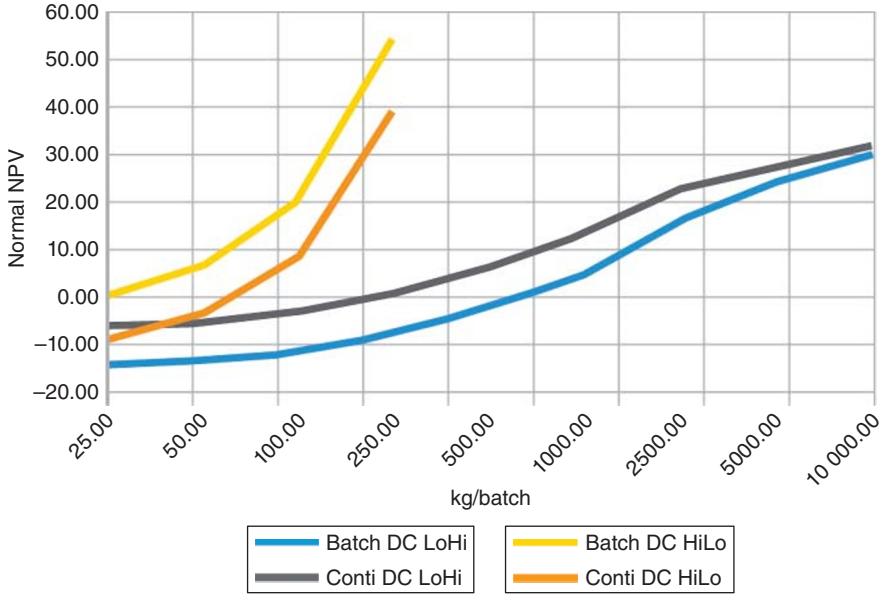

Figure 11.10 *Nominal NPV after 6 years: batch (Batch DC) versus continuous (Conti DC) production of high volume/low value and low volume/high value product (courtesy of GEA).*

schedules an absolute necessity. All initial investments for the above examples include the construction of cleanroom suites, utilities and cleaning. The scenario technique also helps to identify major cost drivers such as downtime, quality control and quality assurance costs.

11.3.3.4 Implementation Strategies

Implementing any new organizational structure or technology does not just affect the product portfolio and/or the staff; it also presents a corporate culture shock and a supply chain hurdle for the entire company. M.E. Porter described it well in Figure 11.11 and, at the same time, suggests just how complex it might be to implement a CM system in a batch-thinking, value-adding organization. This chapter will provide some background, and some practical ideas, regarding how to succeed with such a paradigm-shifting project [31].

Continuous processing starts in the Operations department of any value adding chain. To boost the operational excellence of a company, Operations is the "heartbeat" and CM initiatives, along with the supply chain, are the "pacemaker."

Similarly, both inbound and outbound logistics are affected: these activities are required to feed or charge the material at one of the process and, simultaneously, manage or discharge the outcome at the other end. Supply chain management in a CM paradigm means monitoring the residence time and throughput capacity of the entire process.

The supply chain needs to guarantee that enough material is delivered, in time, at the right time, to the correct inbound feeding stations. The supply chain "bullwhip" effect, mentioned earlier, describes larger and larger swings in inventory in response to changes in customer demand (Figure 11.12). The further away (upstream) you get from the customer

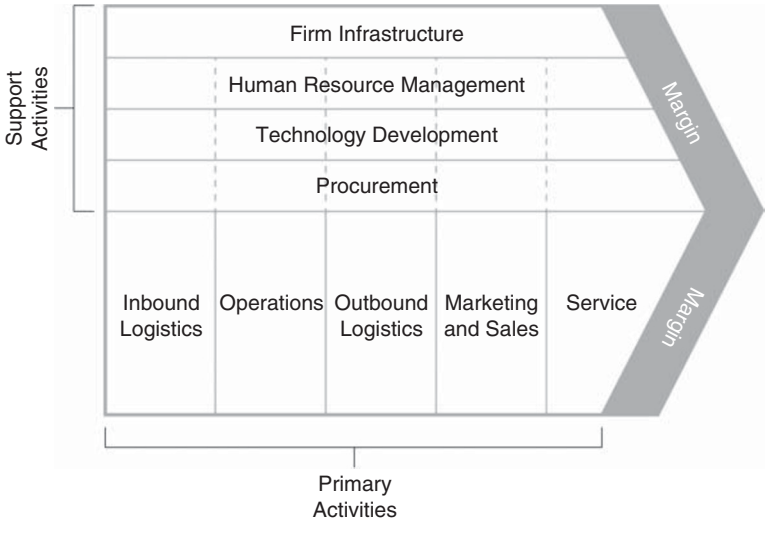

Figure 11.11 *M.E. Porter's value chain.*

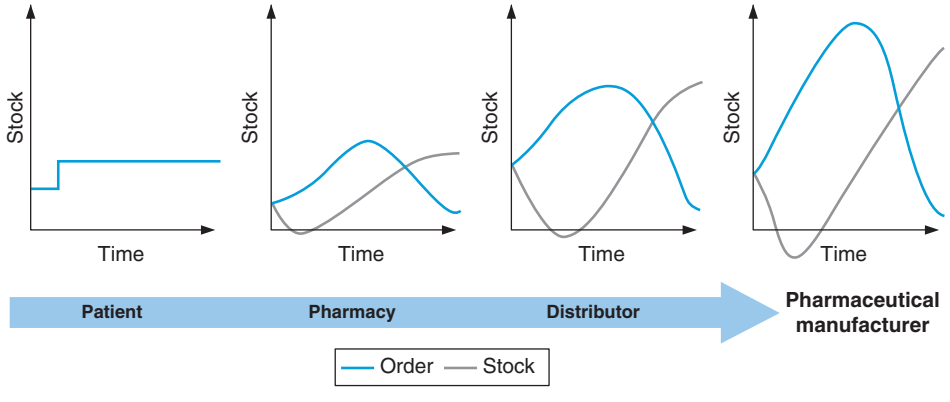

Figure 11.12 *The bullwhip effect [32].*

or final point of consumption, the greater the oscillation. In the manufacturing process, the greatest distance away from the deliverable is the raw material supply chain.

The same phenomenon can be found in today's pharmaceutical value chain as capital tied up in warehouses. CM is the solution [32]. In other words, it does not matter if we look at a highly integrated process comprising many linked unit operations or an entire supply chain. The same principles can be applied and the process engineer/supply chain manager will observe the same effects. The further upstream we go, the more material we will find waiting to be used. Any buffer, hopper or material storage solution represents an inefficient material flow path. It also highlights the robustness and in-depth understanding of a continuous process and its functional dynamics.

From this perspective, it is clear that meaningful CM implementation requires a joint team and organizational effort: it is a cross-functional process that adds value to the whole

company. If driven by one department or a single group of engineers, implementation will not succeed. It affects all levels of the organization and needs to be steered by the company's top management.

Of course, there are numerous continuously operating unit operations in existence, including tableting and roller compaction, but to benefit from the full business excellence effects of continuous processing, the whole supply chain needs to be engaged and involved. An isolated approach, at any stage of the process, will fail to deliver the full revenue generating and cost-saving potential of CM.

According to M.E. Porter's "five forces of competitive advantage," the long-term business strategy of a company can be built on continuous processing to gain advantages in five areas: client negotiation power, vendor negotiation power, an expanded product portfolio, better service and, last but not least, an enhanced competitive position in new markets or against newcomers in existing markets [33].

A fully efficient and more agile supply chain will boost your business performance, increase patient safety and help to overcome any drug shortages, notwithstanding the ability to provide medicines to treat patients with rare diseases at very short notice.

An implementation strategy not only needs a comprehensive business plan, profound market intelligence and a solid financial foundation, it also requires a cross-functional team with project management experts and subteams replete with top-tier process engineers, control, software and quality control engineers, for example, who have the skills and a proven track record of handling similar-scale projects. Finally, any external stakeholders, including regulatory agencies and vendors, need to be involved at an early stage to launch a successful CM implementation project.

11.4 The Pharmaceutical Supply Chain of the Future

11.4.1 Portable, Continuous, Miniature and Modular

The development of small-scale, continuous manufacturing systems will be one of the most significant changes in the pharmaceutical industry in the next 10 years (Figure 11.13). Flexible development options will facilitate the commercial manufacturing process and enable greater process understanding to be achieved with smaller quantities of material.

M.E. Porter's "five forces" describe a strategic environment in which any value adding company is challenged by, and early adopters can gain market share, by implementing continuous processing and agile supply chain management [33].

To face these challenges, flexibility is key; the solution is to establish flexible plant, the main drivers of which are:

- A product portfolio and R+D pipeline of personalized, high value and orphan drug products
- Lifecycle management of blockbuster/established products using fast, flexible R+D and manufacturing processes that shorten times to market
- Increased responsiveness to customer demand: agile supply chains with low inventories
- Market entry and growth in emerging markets by rapidly deploying standardized and pre-qualified process technology
- Reduced CAPEX risk by using adaptable manufacturing and construction units as well as shared utilities and service areas

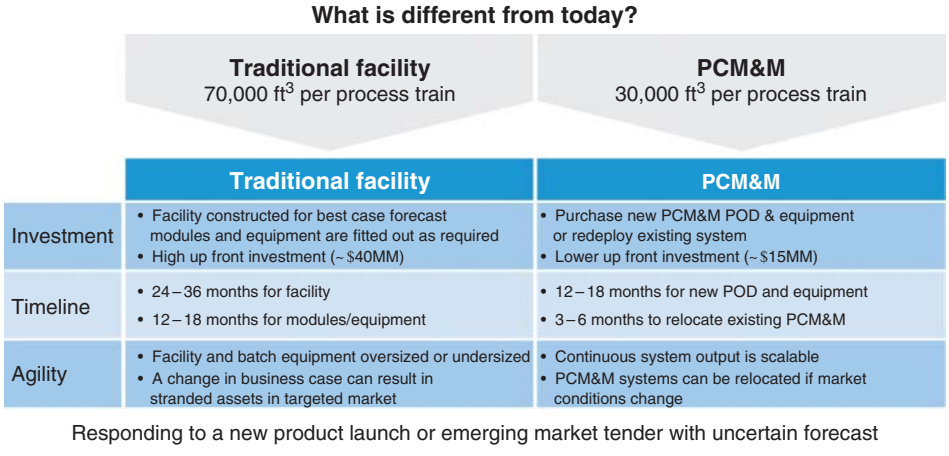

Figure 11.13 *Continuous manufacturing, today and tomorrow (courtesy of Pfizer).*

The following case story presents an example of how continuous processing, and continuous process equipment, enables modern flexible manufacturing concepts. Beyond the general challenges facing the pharmaceutical industry, drug manufacturers also need to follow specific quality and compliance rules. Notwithstanding the financial and competitive hurdles that affect every manufacturing sector, pharmaceutical companies are under constant pressure to optimize performance and maximize output. "As players recognize the problem of reliability in the drug supply chain, they will gravitate toward the most reliable suppliers and, ultimately perhaps, to an entirely different supply chain model," notes Janet Woodcock, Director of the FDA's Center for Drug Evaluation and Research (CDER) [1, 34].

This section describes the introduction of small-scale flexible CM plant into the pharmaceutical industry: the portable, continuous, miniature and modular (PCMM) concept, developed by a consortium of Pfizer, G-Con and GEA and, recently, GSK [35] is flexible, mobile and takes the pharmaceutical industry a significant step closer to on-demand tablet production.

"This innovation comes at a time when the pharmaceutical industry has been trending toward lower-volume products, driven by an increased focus on precision medicine approaches to develop and commercialize new therapies," noted Pfizer [36].

11.4.2 The PCMM Concept

11.4.2.1 General Description of PCMM

To create the next generation of oral solid dosage processing technologies and address the rapidly changing requirements of drug manufacturers, Pfizer, GEA and G-Con Manufacturing created a consortium to design and build a portable, autonomous manufacturing environment for continuous OSD production using GEA's ConsiGma™25 system and G-CON's modular POD system.

Continuous processing enables entire lines to be miniaturized and made both modular and portable. Furthermore, CM provides advanced process control and results in more consistent and higher quality products. New and advanced technologies, such as CM, can help to transform today's pharmaceutical business processes into a future market environment driven by global megatrends, such as ageing populations, growing middle classes in emerging markets, increased patient safety, cost reductions in public and private healthcare and increased regulations.

The result is PCMM-based development and manufacturing. PCMM is a standardized production technology platform that is used for product development and commercial production. A key advantage of this platform is the ability to use the same equipment throughout the entire product lifecycle. The PCMM platform offers a PAT-compatible process control solution for continuous wet granulation and continuous mixing/direct compression, enabling efficient transfer from development to clinical and commercial production without scale-up. The system is easy to deploy and ship. In addition, the PCMM platform combines equipment design, PAT, advanced process control and engineering expertise to deliver a fully integrated cGMP facility using PODs (see Section 11.2.4.2). PODs are prefabricated, autonomous cleanroom units.

The process begins with the design and build of the POD and the process equipment. After onsite FATs, the PODs and equipment are then transported to the desired location for onsite integration, installation and final qualification. The process equipment and the PODs can be also pre-qualified before shipment to reduce onsite start-up times. As the design is based on standardized equipment and processes, process validation can also be simplified and expedited.

Being mobile, the system can operate in "gray space" or a warehouse. The finished product includes processing space, technical space, raw material dispensing, material/personnel airlocks and a washroom. Walkways and support areas can be incorporated into the same design concept, as well as complete manufacturing areas.

PCMM embodies the idea of portability in pharmaceutical development and manufacturing. Continuous processing enables miniaturization, which increases the amount of accessible locations, reduces energy consumption and enables modularity, which subsequently enables rapid processing and product changeover. PODs offer a truly portable "plug and play" system. And, with further miniaturization possible, the portable POD structures can be classified as "equipment," making accelerated depreciation available.

They also enable rapid deployment and redeployment, reduced capital investment, enhanced safety and environmental isolation; multi-company POD installations – "POD Farms" – could also be created, providing greater opportunities for localized pharmaceutical manufacturing.

This new OSD paradigm will generate significant cost savings and greatly simplify transfer/scale-up from R+D to commercial manufacturing. Using the same equipment for development, clinical supply and commercial production will maximize manufacturing efficiencies, providing the following benefits:

- Improved quality control (QC)
- Improved time to market
- Improved operational efficiency
- Improved supply chain agility

11.4.2.2 PCMM Components

11.4.2.2.1 POD Systems

The design and layout of the G-CON POD modules was described previously in Section 11.2.4.2. As a component of the PCMM project, they reduce both budgetary and facility constraints by providing readily deployable, mobile, scalable and fully self-contained cleanrooms. The overall benefits of the PCMM POD design can be summarized as follows:

- Integrated process, facility and utility systems within a self-contained unit
- Fast and efficient onsite installation and assembly, allowing for rapid start-up
- Capability to transport and redeploy PCMM PODs to new location(s) in the future

11.4.2.2.2 ConsiGma™ Continuous Processing Platform

GEA's contribution to the PCMM project is the powder to tablet process equipment (Figure 11.14). ConsiGma™ is a multipurpose platform that has been designed to transfer powder into tablets in development, pilot, clinical and production volumes in a single compact unit. The system can perform dosing and dry blending of raw materials, wet granulation, drying, tableting, direct compression (going directly from the dry blend to compression) and quality control, all in one line. And, as it can produce liquid–solid blends, granules and dry blends continuously, using a novel continuous mixing technology (CMT) inline blending system, there is minimal waste during start-up and shutdown and the batch size is determined simply by how long you run the machine. Quality is measured throughout the process and, as such, drastically reduces the cost per tablet.

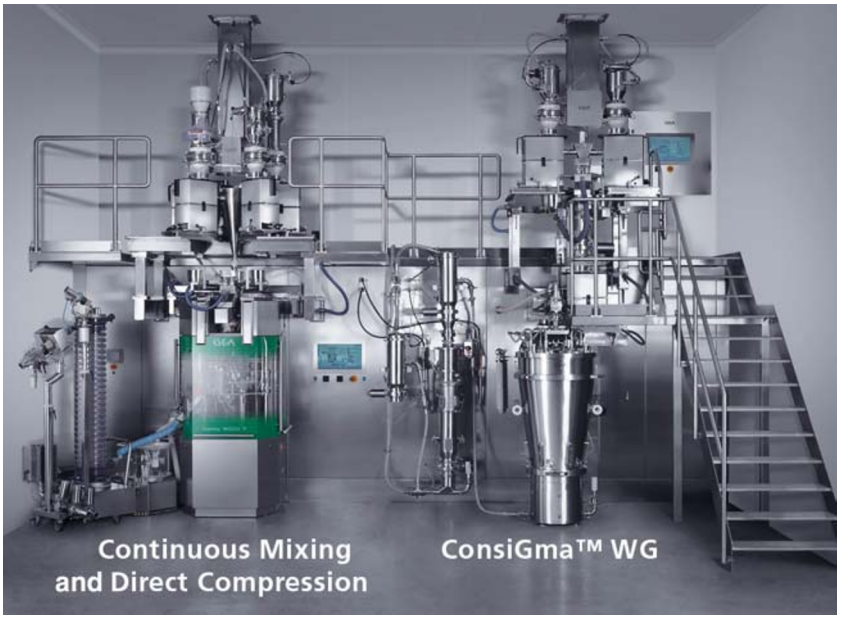

Figure 11.14 *Material handling, wet granulation and direct compression in one horizontal layout (courtesy of GEA).*

The whole system is designed to process material capacities of 10–30 kg/h, depending on the formulation, and operate 24/7 at the highest possible OEE level, depending on the at-site conditions, in- and outbound logistics and the user's requirements.

This novel technology provides a standardized OSD development and commercial production platform. The complete "containerized" POD-based facility is pre-engineered and assembled in the field for rapid deployment. The POD and can be disassembled, relocated and redeployed to a different location, reducing the risk of stranded assets.

The PCMM POD layout has a 60–70% smaller footprint than a conventional production facility (including the service area) [25, 36].

Advanced process control and PAT tools enable monitoring during production, so quality can be designed into products from the start. Thanks to this second by second process control, the online PAT sensors and the small amount of product in process at any time, the production of out of specification material is minimized.

11.4.3 Discussion

Regulators are increasingly supportive of CM and manufacturers recognize that current quality assurance costs are disproportionately large compared with other industries, wherein the production, detection and removal of out of specification product is vanishingly small. Potential API savings of more than 60% and time to market reductions of more than a year have been identified by companies using small-scale CM systems. In 10 years, the vast majority of tablets will be produced on CM lines that are installed in modular facilities that are a fraction of the size of current plants.

PCMM embodies the idea of portability in pharmaceutical development and manufacturing. Continuous processing enables miniaturization, which increases the amount of accessible locations, reduces energy consumption and enables modularity, which subsequently enables rapid processing and product changeover. The concept answers many of the flexibility needs discussed by Van Kranenburg *et al.*, 2015 [37], including:

Capacity flexibility: Continuous processing means that production volumes can be adjusted to meet demand. So-called batch sizes no longer depend on the scale of the equipment, but on the amount of time you run it. In addition, the same equipment can be used for both development and commercial manufacturing, dramatically reducing the effort, cost, time and risk associated with tech transfer.

Furthermore, the time and work that goes into modeling, PAT and advanced process control are actually concentrated within the platform technology as opposed to being diluted across a variety of equipment designs and scales. Using a common technology platform for clinical, stability, registration and process understanding batches promotes knowledge management intensification, offering better production rates that are more closely aligned to the annual production volumes of the personalized medicine/post-blockbuster era. Plus, new inventory management approaches can be adopted to respond to market fluctuations. As such, PCMM offers a rational approach to rapid formulation and process development, as well as efficient and sustainable commercial manufacturing.

Product flexibility: Thanks to the modularity and flexibility of the ConsiGma™ platform, several processes can be combined into one manufacturing unit: dry blending, wet

granulation and drying, dry granulation, melt granulation, direct compression and coating.

Location flexibility: PODs are constructed with the flexibility to be easily relocated or repurposed for the next drug product release or alternative applications. PODs can be placed in an existing warehouse space or a brown/greenfield site, allowing for easy facility expansion or the cloning of facilities in multiple locations for fast track facility build-up.

Feedstock flexibility: Although feedstock flexibility in the pharmaceutical industry is a lesser concern, given the regulatory restrictions involved in switching API and excipient sources, a certain amount of pliability is still required. A manufacturing technology needs to be able to handle any variation in raw material quality. The CM technology platform is a very robust system that is capable of doing this; the unique dry blending system used, for example, allows a wide operational window and can be adjusted second by second. Online monitoring provides instant feedback and control of final product quality, compensating for any variation in the incoming material.

In addition, the PCMM concept also answers the specific needs of the pharmaceutical industry for enhanced quality and compliance. Throughout the collaborative design process, innovative approaches have been incorporated into the project to increase speed, enhance quality and reduce overall project cost. Timelines of 12–18 months can be achieved for a POD-based installation, compared with 24–36 months for a traditional "bricks and mortar" facility [24]. The design of the air bearing and lifting system enables both PODs and process equipment to be positioned and installed into a gray space warehouse within a week, without the need for extensive onsite rigging equipment.

The integration of five PAT sensors in the continuous wet granulation and continuous mixing/direct compression process equipment enables efficient transfer from development to clinical and commercial production without scale-up. Plus, the use of an advanced process control (APC) system provides real-time monitoring and control by integrating feedback from process and PAT sensors.

With lower upfront investment costs compared with traditional design and build approaches, lower energy and resource requirements, and enhanced quality, PCMM is the solution to many of the pharmaceutical industry's flexibility needs. Additional benefits include increased OEE, optimized R+D (10 times less material use, 10 times faster than conventional batch equipment), multiple formulations and flexible batch sizes, and reduced cleaning costs and materials.

11.5 Conclusion

A multifaceted concept that can be used to produce a wide range of biologics, small molecules, APIs and drug products, PCMM is the factory of the future [25, 34, 37]. For more than 20 years, the batch-based production of blockbuster solid dosage forms dominated the industry. Profitability was such that companies were not incentivized to innovate or risk developing new manufacturing technology. However, in the post-blockbuster era, it is increasingly recognized that material costs during drug development are significant, new drug products are likely to be manufactured in much smaller quantities and that, for novel treatments, the development of a commercial manufacturing process is not guaranteed.

Such pressures have put the costs, risks and timelines associated with traditional batch-based development and manufacturing under scrutiny. In most industries, CM is seen as the low-cost solution to producing low value, high volume products in which there is little need to focus on the cost of materials used in process development and, often, little need for product changeover.

Process intensification in the pharmaceutical industry has led to the development of smaller and more compact equipment. With the goal of achieving more consistent process control and, ultimately, higher quality end products, manufacturers are increasingly moving away from batch-based systems and switching to CM. Providing increased yields, lower utility consumption and reduced waste, continuous manufacturing presents a paradigm shift in drug production and meets the industry's demands for faster product development, reduced costs, improved production economics and increased manufacturing flexibility.

Acknowledgments

Pfizer, G-CON Manufacturing, GEA.

References

[1] Koberstein, W. (2014) Janet Woodcock's quality agenda at CDER, *Pharmaceutical Online*. Available at: www.pharmaceuticalonline.com/doc/janet-woodcock-s-quality-agenda-at-cder-0001 (accessed 2 February 2016).

[2] ASTM E2968 (2015) *Standard Guide for Application of Continuous Processing in the Pharmaceutical Industry*, American Society for Testing and Materials, West Conshohocken, USA.

[3] ICH Harmonized Tripartie Guideline (2004) Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients, Q7, ICH, Geneva, Switzerland.

[4] Allison, G. (2014) Regulatory and quality considerations for continuous manufacturing. Presentation at: *International Symposium on Continuous Manufacturing of Pharmaceuticals: Implementation, Technology and Regulatory*. Harvard, Cambridge, USA.

[5] Rios, M. (2012) Developing an integrated continuous bioprocessing platform: a discussion with Genzyme's Konstantin Konstantinov. *BioProcess International* **10**(11), doi: 10.1002/biot.201100464.

[6] FDA (2012) *Pharmaceutical cGMPs for the 21st Century – a Risk-based approach*, US Food and Drug Administration, Rockville, USA. Available at: www.fda.gov/ohrms/dockets/ac/03/briefing/3933B1_02_Pharmaceutical%20cGMPs.pdf (accessed 2 February 2016).

[7] Langer, E. (2012) *Ninth Annual Report and Survey of Biopharmaceutical Manufacturing Capacity and Production – a Study of Biotherapeutic Developers and Contract Manufacturing Organizations*, Bioplan Associates Inc., Rockville, USA.

[8] Ozturk, S.S. and Kompala, D. (2006) Optimization of high cell density perfusion cultures, in: *Cell Culture Technology for Pharmaceutical and Cell-Based Therapies* (eds S.S. Ozturk, W.-S. Hu), CRC Press, Boca Raton, USA, pp. 387–416.

[9] Bonham-Carter, J. and Shevitz, J. (2011) A brief history of perfusion biomanufacturing: how high concentration cultures will characterize the factory of the future. *BioProcess Intl* **9**(9), 24–31.

[10] Voisard, F., Meuwly, F., Ruffieux, P.A. *et al.* (2003) Potential of cell retention techniques for large-scale high-density perfusion culture of suspended mammalian cells. *Biotechnology and Bioengineering* **82**(7): doi: 10.1002/bit.10629.

[11] Jungbauer, A. and Peng, J. (2011) Continuous bioprocessing: an interview with Konstantin Konstantinov from Genzyme, *Biotechnology Journal* **6**, 1431–1434.

[12] Sinclair, A. (2014) *Continuous Manufacturing: an Overview*. Presentation at PDA Europe, Modern Biopharmaceutical Manufacturing, PDA, Lyon, France.
[13] Mueller-Spaeth, T. and Morbidelli, M. (2009) Continuous chromatography for the purification of monoclonal antibodies, in *Process-Scale Purification of Antibodies* (ed. U. Gottschalk), John Wiley and Sons, Inc., Hoboken, USA.
[14] Brower, M., Hou, Y. and Pollard, D. (2015) Monoclonal antibody continuous processing enabled by single use, in *Continuous Processing in Pharmaceutical Manufacturing* (ed. G. Subramanian), John Wiley and Sons, Inc., Weinheim, Germany.
[15] Ratcliff, A. and Preisig, C. (2013) Advances in sensor technology improve biopharmaceuticaldevelopment, *Bioprocess International* **11**(4). Available at: www.bioprocessintl.com/upstream-processing/fermentation/advances-in-sensor-technology-improve-biopharmaceutical-development-341848 (accessed 2 February 2016).
[16] Thomas, P. (2009) Bioprocess sensors: PAT means proliferation, *Pharmaceutical Manufacturing*. Available online at: www.pharmamanufacturing.com/articles/2009/189/ (accessed 2 February 2016).
[17] Hemispherx Biopharma (2015) Hemispherx Biopharma announces the completion of the newly upgraded alferon facility: commercial production of alferon is in the final stage integrating continuous flow manufacturing technology. *Press Release*. Available at: www.hemispher11.net/content/investor/default.asp?goto=818 (accessed 2 March 2016).
[18] Wallack, T. (2007) Novartis to give MIT $65m to find new way to produce drugs. *The Boston Globe*. Available at: www.boston.com/business/articles/2007/09/28/novartis_to_give_mit_65m_to_find_new_way_to_produce_drugs/?page=full (accessed 28 September 2015).
[19] Carsten, J.N., Clarke, H.R.G. and Jensen, J.P. (2009) Perfusion! Jeopardy or the ultimate advantage? Bioprocess International *Online Educational Series*. Available at: www.cmcbio.com/Portals/0/CMC/docs/perfusion.pdf (accessed 2 February 2016).
[20] Holtz, B. and Powers, D. (2012) Integration of a single-use platform process within an innovative facility design. *BioPharm International*. Available at: www.biopharminternational.com/integration-single-use-platform-process-within-innovative-facility-design (accessed 2 February 2016).
[21] Wolton, D.A. and Rayner, A. (2014) Lessons learned in the ballroom: predicting pharma disposable facilities. *Pharmaceutical Online* **34**(4). Available at: www.pharmaceuticalonline.com/doc/lessons-learned-in-the-ballroom-0001 (accessed 2 February 2016).
[22] Trout, B. and Bisson, W. (2009) *Continuous Manufacturing of Small Molecule Pharmaceuticals*. Available at: www.qbd-dtc.com/wp-content/uploads/continuous-manufacturing.pdf (accessed 2 February 2016).
[23] Warman, M. (2014) *Control Strategy in Continuous Manufacturing of Drug Product*. Presentation at IFPAC, Washington, DC, USA.
[24] Witty, A. (2013) *Glaxo Use New Technology at India Plant*. Available at: www.fiercepharmamanufacturing.com/story/glaxo-use-new-technology-india-plant/2013-11-18 (accessed 2 February 2016).
[25] Mitzner, R. (2014) *PCMM Portable, Continuous, Miniature and Modular Oral Solid Dosage Technology*. Presentation at ISPE Annual Meeting, Las Vegas, USA.
[26] Closs, S. and Heidel, S. (2014) *Small-scale Process Design to Facilitate Commercialization of a Wet Granulation Process using Continuous Manufacturing and Bringing Continuous Manufacturing to OSD*. Poster presentation at AAPS, San Diego, USA.
[27] Kleinaltenkamp M. and Plinke W. (eds) (1995) *Wirtschaftlichkeitsrechnung als Grundlage industrieller Beschaffungsentscheidungen, Grundlagen Technischer Vertrieb,* Springer Verlag GmbH, Heidelberg, pp. 496–500.

[28] Schaber, S.D., Gerogiorgis, D.I., Ramachandran, R. *et al.* (2011) Economic analysis of integrated continuous and batch pharmaceutical manufacturing: a case study. *Ind. Eng. Chem. Res.* **50**(17), 10083–10092.

[29] Plötner, O., Spekman, R.E. and Rese, M. (2007) *Bringing Technology to Market, Cost Decisions and Pricing Decisions in Times of Value-based Management*, John Wiley and Sons, Inc., Hoboken, USA, pp. 167–175.

[30] Schoeters, K. and Steiner, R. (2015) *How to Achieve Operational Excellence by Continuous Processing? The Implementation of Continuous Manufacturing in the Pharmaceutical Industry*. Presentation at the ISPE/FDA/PQRI Quality Manufacturing Conference, Washington, DC, USA.

[31] Porter, M.E. (1999) The structural analysis of industries, in: *Competitive Strategy*. Available at: https://courses.washington.edu/imt584/sp08/pdfs/porter.pdf (accessed 2 February 2016).

[32] Knolmayer, G., Mertens, P. and Zeier, A. (eds) (1999) *Supply Chain Management on Basis of SAP-System: Perspective of an Order Processing in the B2B Industry,* Springer-Verlag GmbH, Berlin.

[33] Porter, M.E. (2000) *The Competitive Advantage of Nations*. Available at: hbr.org/1990/03/the-competitive-advantage-of-nations (accessed 2 February 2016).

[34] Brennan, Z. (2015) *FDA Calls on Manufacturers to Begin Switch from Batch to Continuous Production*. In-Pharmatechnologist.com. Available at: www.in-pharmatechnologist.com/Processing/FDA-calls-on-manufacturers-to-begin-switch-from-batch-to-continuous-production (accessed 2 February 2016).

[35] Pfizer (2015) *Pfizer Announces Collaboration with GSK on Next-generation Design of Portable, Continuous, Miniature and Modular (PCMM) Oral Solid Dose Development and Manufacturing Units*. Available at: www.businesswire.com/news/home/20151029005733/en/Pfizer-Announces-Collaboration-GSK-Next-Generation-Design-Portable (accessed 2 February 2016).

[36] Nixon P. (2015) *Broad Implementation of Continuous Manufacturing for Solid Oral Drug Products: What can the Future Look Like?* Presentation at the 50th Arden Conference, Baltimore, USA.

[37] Van Kranenburg, K., Sofra, S., Verdoes, D. *et al.* (2015) Small-scale flexible plants. towards a more agile and competitive EU chemical industry. In: *TNO Innovation for Life*. Available at: www.tno.nl/media/5699/small-scale_flexible_plants.pdf (accessed 2 February 2016).

12

Design of an Integrated Continuous Manufacturing System

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12.1 Introduction

As mentioned in other chapters of this book, the last five years have been witness to an unprecedented level of innovation in pharmaceutical manufacturing, driven primarily by a rapid growth in interest in continuous manufacturing, and to a lesser, but important extent, in precision manufacturing.

While powder-based continuous manufacturing has been practiced for decades in other industries (including consumer products, detergents, food, minerals processing, construction materials, ceramics, polymers, and metal powders), it is relatively new to the pharmaceutical industry, and only a few continuous facilities have been implemented to this date. Importantly, continuous manufacturing enables supervisory closed-loop process control and real time quality assurance. This capability, which has enabled superior process controllability and quality performance in many other industries, requires a significant effort to design and integrate not only the process equipment, but also the sensing and control capabilities.

In this chapter we present a systematic, 12-step approach for designing, implementing, integrating, optimizing, and validating a continuous manufacturing system. Wherever appropriate, we also discuss the regulatory relevance of the technology integration effort.

Continuous Manufacturing of Pharmaceuticals, First Edition.
Edited by Peter Kleinebudde, Johannes Khinast, and Jukka Rantanen.
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The discussion reflects our understanding as of January 2016, but the reader is cautioned that the field is evolving rapidly and many sections of this chapter are likely to require updating in the near future.

12.2 Step 1: Rough Conceptual Design

When considering the development of a continuous manufacturing facility, the industrial practitioner is well advised to consider very carefully not only the short-term intended use of the facility, but also other needs and demands that are likely to emerge. A multiplicity of situations can lead to evolving requirements and constraints that can be difficult to address if proper up-front planning is inadequate: Is the main use product and process development, or is it intended as a clinical and/or commercial manufacturing facility? Is the facility intended for a single product or does it require flexibility to accommodate many, as yet unknown, products? If so, how many ingredients, and in which proportions, need to be processed? What type of formulations and manufacturing methods will be needed? What is the optimum flow rate range – and how much flexibility is needed, given unknown market demands? It is critically important to consider these issues very early in the process, because continuous processes, requiring integration and synchronicity of many process components, are significantly less flexible than batch systems. As has been recently, and painfully, realized by some companies that launched efforts to build continuous systems without paying proper up-front attention to these issues, flexibility is expensive, but lack of flexibility, when needed but absent, is much more expensive.

Thus, the first step of the 12-step design process constitutes the development of a conceptual design strategy for the given process development project. Step 1 advocates long-term thinking in process design, not only from a technical perspective but also from a commercial viewpoint. This includes the creation of a blueprint of the design strategy, advocating minimal retrospective high-impact changes. No perceptible development is performed in the step and the step can thus be considered to be Step 0 of the entire effort; however proactive planning can improve the likelihood of long-term success. There are at least six considerations that need to be addressed. These have been detailed below.

12.2.1 Type of Product

For the sake of this chapter we will assume that the product to be manufactured has been targeted for delivery as a solid dosage form. In that case, the type of product must first be defined to begin to decide what options for continuous manufacturing are feasible. For many products, this decision is often made very early in the product development cycle. However, when considering the design of a flexible continuous manufacturing system, one might want to have the ability to manufacture either tablets, or capsules, or both. The decision of whether to manufacture a tablet or a capsule will not only dictate the type of equipment needed for preparing the final dosage form, but will also begin to bring constraints, such as what is the overall throughput the process can be designed for. Similarly, aspects of the formulation such as whether the intended product is high drug content or low drug content (or whether the facility needs to be able to manufacture both types) will have an effect on equipment selection and process throughput.

It is likely that the process constraints are different for batch and continuous manufacturing and that a product intended or previously manufactured by one batch methodology, for example, wet granulation, may be manufactured continuously using an inherently more efficient route like direct compaction. Therefore, it is important to examine the formulation(s) of the product(s) to be manufactured when designing a continuous manufacturing process, particularly when it has been formulated for batch manufacturing. The difficulties that may be associated with developing a specific type of product for a given formulation in batch mode may be easily overcome by manufacturing the same product continuously. On the other hand, the product might have been registered using a certain formulation and type of manufacturing process and the company might need to keep those parameters unchanged, even at the cost of a more expensive, lengthier, and a less efficient process.

12.2.2 Type of Manufacturing Route – Direct Compaction, Wet Granulation or Dry Granulation

The next level of specification for putting together a rough conceptual design of the continuous manufacturing process is to decide on the mode(s) of pharmaceutical product manufacturing that will be required.

In batch manufacturing of pharmaceutical solid dosage forms, the limited understanding of, and control over the process design space has necessitated the use of more intensive manufacturing processes than may be required when applying advanced pharmaceutical manufacturing design and continuous manufacturing principles. However, process robustness and the related operational design space must be taken into account as part of a risk analysis with any pharmaceutical process design, and it is therefore likely that we will continue to utilize both wet and dry granulation techniques within continuous pharmaceutical manufacturing for the foreseeable future.

In batch processing, direct compaction is often considered a risky production route, due to risk of blend segregation, among other factors. As a result, formulations that have a tendency to segregate are often granulated to ensure a consistent content uniformity [65, 66] of the active ingredient in the final product [67]. Properly designed continuous systems, including the use of efficient mixers, minimization of internal lags (such as hoppers), and elimination of semi-continuous steps, have demonstrated an excellent ability to achieve homogeneity even when dealing with materials with high segregation tendencies [68], paving the road for such formulations to be manufactured via direct compaction.

Another factor that promotes the use of granulation in batch processing is when active ingredients in the product have a strong tendency to agglomerate. Such products often display (active pharmaceutical ingredients) API lumps despite repeated de-agglomeration attempts. This case is commonly seen when a product contains a small percentage of highly cohesive API in the formulation. Once again, a properly designed continuous system can mitigate this problem, for example, by using a combination of high shear co-milling of the API and other ingredients, followed by low-shear blending with shear-sensitive ingredients (such as lubricants), immediately followed by compaction. When using a well-designed transition between the blender and the tablet press, the powder blend, within seconds, finds itself in the die of the tablet press. In a continuous process, unlike for a batch process, the material lacks the time, and the environment, to re-agglomerate.

12.2.3 Flexible or Dedicated

An important factor that needs to be considered, prior to beginning the process design and development, is whether the production line will be dedicated to one formulation, or if it will flexible and intended to be used for the manufacturing of several products. In principle, the same manufacturing line (hardware components) can be used to manufacture multiple products, provided that the operational range of equipment components has been properly specified to accommodate multiple formulations. If the process train is intended for the manufacturing of multiple products, then a design that is amenable for all process materials should be pursued. The optimal design of a continuous process line that is capable of manufacturing a wide range of products is a challenging topic that will not be pursued in this chapter. However, it is an important topic that needs to be carefully addressed early-on in any continuous facility design project.

Another factor that should also be addressed in this step is the desired degree of modularity of the process equipment. If the line is of limited functionality (i.e., only direct compression), it is possible, and even likely, that the process for which the production line is being designed, will only run intermittently, and therefore it will have large downtimes. A more flexible line, for example one that could function as a wet granulation line *and* a dry granulation line *and* a direct compression line, would be more likely to be utilized more efficiently. While a flexible line requires a higher upfront investment, the additional flexibility might provide a good return on this investment. Importantly, to be easily reconfigured between modes of manufacturing, the equipment needs to be mounted in modules that can be connected flexibly to enable easy reconfiguration. Moreover, during manufacturing downtimes, modular equipment dedicated to the one process could be used for another production line. In this case, the design of the connections, sensors, and controls should be such that it allows for easy assembly and disassembly of the process equipment. The flexibility of the line is also important because a faulty piece of equipment can be quickly and easily swapped with a functional device.

12.2.4 Feeding Multiple Ingredients, Including Pre-blends

Ingredients in a formulation are chosen depending on the material (powder) properties of the active ingredient and desired nature of the release of the active ingredient (among other factors). It is not uncommon for a product formula to contain up to six or more ingredients. The choice of the number of ingredients and their relative proportion affects the process design in a number of ways.

First, if an ingredient is a very minor component (in weight ratio), there may be issues with being able to feed it accurately and mixing it homogeneously. This can be addressed sometimes by scaling up the overall process to higher throughput, but if this is not a desirable or practical solution, pre-blending the minor ingredient(s) with a major ingredient into a well-mixed blend via batch mixing prior to continuous feeding may be a solution. Take for example the case of an ingredient at less than 0.1% w/w going into a process designed to run at 50 kg/h. That equates to 50 g of material being required to be introduced into the system over the span of 1 h, or less than 1g/min. Performance of screw feeders often degrades at low feed rates [1]. In such scenarios, it may be advisable for the minor ingredients to be premixed with major ingredients and introduced in the process as a pre-blended binary mixture.

Pre-blending may also be a logical process choice if the number of ingredients would require a large number of individual feeders that would become cost prohibitive, or overly complicated for implementation or control. Clustering more than six feeders around a single transition is difficult, and also expensive.

Also, some ingredients, irrespective of the feed rates, are difficult to feed accurately using screw feeders [2]. For example, silicon dioxide is observed to electrostatically adhere to the feeder parts leading to "bearding." It is advisable for such ingredients to be introduced in the process by pre-blending them with major ingredients.

Finally, if the line is intended for multiple products, the proportions of major and minor ingredients will change from formulation to formulation. Careful selection of feeders, and design of a line that enables fast and convenient replacement of feeders, are required to enable such flexibility.

12.2.5 Strategy for Sensing and Control

Typically, quality by design (QbD) methods are predicated on identifying critical raw material attributes (CMAs), critical process parameters, and critical finished product quality attributes (CQAs). In a line that is intended for a single product, perhaps an existing product, where CMAs and CQAs are known, the design problem might be limited to understanding, and translating, critical process parameters from the batch process onto those of the continuous process. In such cases, definition of the required process analytical technology (PAT) capabilities is relatively straightforward.

A more complex situation arises if the line is intended for multiple products or for new products yet to be developed. While CQAs tend to be similar between products (and are mainly driven by regulatory expectations), the need to assure quality for a new product necessarily requires same flexibility in measurement capabilities. For example, the frequency of measurements and the quality of sensors needed to ensure content uniformity might be different for blends containing various amounts of different APIs and excipients.

However, in a continuous process, we also have the opportunity (and in some cases the need) to monitor properties of intermediate blends in order to ensure efficient processing and high product quality. In addition, as mentioned, continuous manufacturing can enable real time quality control, thus paving the way for real time release. To enable a line with such capabilities requires a significant amount of effort and resources, and needs to be carefully considered.

Thus, a general strategy on the desired depth of sensing and control should be agreed prior to Step 2. Characterization of individual unit operations and open loop experiments on the entire process will reveal the relationship between critical process parameters (CPPs) and the CQA of the process. However, the required level and control implementation may be defined by regulation, likely to be based on a risk-based analysis of the product and the process. Low dose formulations with highly potent APIs will likely require a higher degree of sensing and control. Similarly, a higher degree of sensing and control will be needed for the development of a real-time release strategy if that is desirable.

12.2.6 Regulatory Strategy

As mentioned previously, the field of continuous pharmaceutical manufacturing is evolving rapidly, as at the present time many companies and universities are participating in research

and development efforts. This evolution also includes regulatory agencies, led by the United States Food and Drug Administration (FDA), which have both expressed a keen interest in continuous manufacturing, and a need to develop and communicate regulatory expectations regarding the minimum conditions required to approve a continuous process. At the present time, it is widely expected that as experience with continuous processes increases both in industry and in the regulatory bodies, a set of "best practices" will emerge, with input from multiple stake-holder including academia, and that these best practices, perhaps in the form of guidelines or guidances, will help determine the requirements for converting an existing product from batch to continuous processing or for registering a new product.

In the meantime, companies should develop a strategy for filing with regulatory agencies that should include, at a minimum, the same type of information filed for a batch process, but with a substantial additional amount of information demonstrating the capability of the continuous process, and the ability of the sensing and control infrastructure to detect and mitigate sources of variability and to ensure product quality. While in principle the regulatory requirements for a continuous system should not exceed those of a batch system, in reality the current lack of experience with continuous manufacturing creates a certain degree of anxiety that is likely to lead to increased regulatory scrutiny. The authors of this chapter have the opinion that these issues can be addressed by effective communication. At the present time, the FDA is actively inviting companies to hold frequent meetings with their "advanced technology team" to discuss methodologies for development and implementation of continuous systems. This creates an excellent opportunity for detecting concerns early and correcting them efficiently.

12.3 Step 2: Material Property Screening

A thorough understanding of raw materials and intermediate blends is crucial to the successful design of a robust continuous process, wherein achieving and maintaining a steady operation is paramount. In addition, relationships between material properties and process performance facilitate quality by design and process control. Material information helps to accurately tune analytical sensors and process models, but more importantly, it paves the road for the development of an adaptive, self-learning material database, which aids in future process development.

As the simplest example, let us consider a continuous direct compaction process, where powder is subjected to several unit operations, including feeding, de-lumping, mixing, and compaction. As a result, the powder is exposed to different levels of shear, normal stress, charging, and temperature changes. For example, in a mixing unit operation, the powder particles move relative to the mixer blades and vessel walls, as well as relative to each other, leading to the development of frictional forces. These conditions can cause some powders to experience attrition and to partially coat other ingredients in the blend. Such a "dry coating" process modifies the nature of particle surfaces, and can directly affect many powder material properties, for example, flowability, cohesion, density, hydrophobicity, electrostatics, agglomeration, and segregation tendency [3]. Changes in material properties that may occur during processing can affect the process performance, both beneficially and adversely and, ultimately, the final product quality [4]. For this reason, an understanding of material

properties *as they evolve along the process* is paramount to the development of robust processes. Moreover, not only should raw materials be characterized, but also the intermediate blends that form during the process should be thoroughly characterized. The intermediate blends can possess significantly different properties than the individual components.

While processes have an impact on material properties, it is also true that material properties affect process performance. For example, a material with good flow properties will be fed accurately by a gravimetric feeder; however a material that is likely to charge electrostatically will flow irregularly and adhere to the walls of the system [3]. Another example that is well known, the residence time distribution of a material in a blender is a function of its bulk density and flow properties [5].

Understanding the effects of material properties on process performance, and the effect of the process on material properties, enables quality to be built into the manufacturing process, and consequently into the product, by design. Knowledge about the behavior of the materials, as they evolve in each unit operation within the process, enhances process understanding and facilitates diagnoses when the process does not behave as desired.

Another important need for characterizing raw materials and intermediate blends is to develop accurate calibration models for analytical sensors. Sensors like NIR, Raman, X-ray, or microwave are affected by the packing density of the material, degree of shear, and particle size and morphology, among other factors. It is important that calibration models be used to tune these sensors using materials whose properties most closely match those in the real process. This requires the characterization of the material at certain locations within the actual process. Although, at first thought, this appears to be an impediment, once tuned, sensors can accurately predict not only intended properties but also secondary material properties. For instance, in addition to predicting composition, appropriately calibrated NIR spectrometers can also predict density of the material [6], degree of imparted shear, and dissolution behavior of the final product [7]. This predictive ability is a critical facilitator in enabling real time release of the product, but it clearly requires that the materials used to develop the calibration models be representative of the materials in the process, not only in terms of composition, but also in terms of these additional physical variables, both to avoid confounding effects, and to enable accurate prediction.

Information about properties of raw materials and intermediates are also necessary for the accurate tuning of process models. The use of process models in the design of continuous processing will be detailed in Step 4. These models can be fairly mechanistic, and it is thus imperative that they are tuned using accurate material property information for satisfactory performance.

It is thus clear that a thorough characterization of raw and intermediate material properties is essential for the development of a robust process. Due to the complex nature of bulk material properties, there are numerous measurement techniques, each one quantifying a specific aspect of behavior, and under specific conditions. There are ongoing efforts, both in industry and academia, aimed at using statistical methods to identify material properties which will best characterize the performance of a certain unit operation, and those which will be most affected by a certain processing condition. The role of individual material properties in unit operations will not be discussed here. They can be found in [2, 8] along with an introduction to the statistical methods to optimize powder flow measurements and predict powder processing performance.

12.4 Step 3: Characterizing Unit Operation Using Actual Process Materials

Once the properties of individual materials have been examined, the next step in the design and development of a continuous process is the characterization of individual unit operations using the actual, characterized process materials.

All process equipment can be physically configured in several different ways. For example, screw feeders can be fitted with a variety of screws and screens, each combination yielding different performance, blenders can use different blade configurations, and so on. In addition, all process equipment can be operated under a variety of conditions. Thus, this step constitutes performing rigorous testing on individual unit operations to understand the relationship between settings and operating parameters and equipment performance for the actual materials of interest. Also part of this step is considering the effect of an immediately upstream unit operation on the performance of the operation which is being studied. For example, a continuous blender should be examined to understand the effect of blending parameters on blending performance and also how the blender responds to different types of flow rate variability from the feeders.

A final task in this step is the characterizing the residence time distribution (RTD) of each unit operation with the process configuration, operational parameters, and materials that will be used in the process. Evaluating the residence time distribution of a unit operation is critical for material traceability and process control. The use of unit operation RTDs in conjunction with the RTD of the entire process is vital to establish a materials traceability strategy. Although traceability is addressed much later in the development process, a thorough quantification of the residence time distribution of the material in an individual unit operation is recommended to be performed before the physical integration of the unit operation in the line. It is thus encompassed in this step.

As our main case study we focus on the design of a continuous direct compaction process. Thus, characterization of loss in weight feeders and continuous blenders will be discussed in detail. A mill and a tablet press, the other two pieces of a common direct compaction process, are equipment which are also employed in batch manufacturing and have thus been well studied. They will not be discussed here. Although the discussions focus on characterizing equipment for a direct compaction process, the general premise of this design step is translatable. The focus is to agree upon a tooling configuration for a unit operation which optimizes its performance given the properties of the incoming feed stream and characterizing the RTD of the unit operation.

12.4.1 Loss in Weight Feeders

A loss in weight feeder is a sophisticated machine which introduces granular material into a process from an emptying hopper. All loss in feeders consists mainly of three parts, namely, a volumetric feeder, a weighing platform and a gravimetric controller (Figure 12.1). The volumetric feeder consists of a single screw or a pair of screws situated at the base of a feed hopper. The material enters the flight of the rotating screws and is transported to the other end of the barrel which houses the screws. The exit of the barrel can also be fitted with screens of different mesh sizes. The screen helps to de-lump the outgoing material and ensures a more steady flow. The material in the hopper enters the flight of the screws due to gravity, while in some feeders, scraper blades are employed to assist the pushing the material into the screw flights.

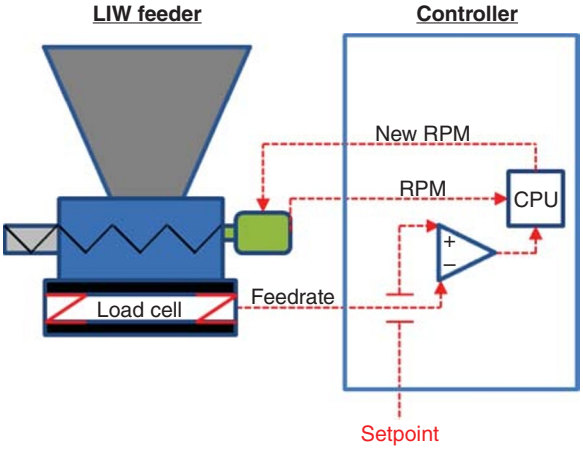

Figure 12.1 *Diagram of the main components of a loss in weight feeder. A volumetric feeder is mounted on a load cell with a feedback controller monitoring and controlling the feed rate.*

The volumetric feeder is mounted on top of the weighing platform which measures the weight of the powder in the hopper. During the feeding operation, the gravimetric controller acquires a signal from the load cell of the weighing platform. Using the differences in weight over time, the controller can compute the instantaneous mass rate. It compares the instantaneous mass rate with the desired set-point and adjusts the feed rate to achieve the set-point by changing the speed of the rotating screws.

Due to its granular nature, material exits the feeders as discrete packets rather than a continuous stream. There is therefore an intrinsic amount of variability associated with the total feed rate. This noise, suitably averaged over time, can be quantified by computing the relative standard deviation of the feed rate. The challenge in configuring a feeder is to arrive at a screw and screen configuration which minimizes this relative standard deviation.

Another important consideration in the characterization of a feeder is to develop a suitable refill strategy. As the feeder delivers the material, the hopper begins to empty. If the operation is to continue, then the material in the hopper must be replenished. A refill results in a sudden increase in the pressure experienced by material at the base of the hopper. This causes an increase in its bulk density resulting in a higher overall mass rate delivered by the feeders until the gravimetric controller takes the necessary corrective action. The intensity and the duration of the over-feeding are dependent on the amplitude and the frequency of the refill. Determining the quantity and frequency of the refill is encompassed in this step.

We will now discuss both these considerations in brief. Additionally, we will also visit methods to determine the residence time distribution of the material in loss in weight feeders.

12.4.1.1 Feeder Sizing and Tooling

The first step in configuring a feeder is choosing the appropriate feeder size. Feeders are available in different sizes; the diameter of the barrel that houses the screws determining the size of the feeder. A design of experiment based approach is recommended to select an appropriately sized feeder and a screw–screen combination that provides the best

performance. To determine the appropriate feeder size, the feeders should be run in volumetric mode at all screw–screen combinations. The feeder for which the highest numbers of screw–screen combinations operate appropriately between 20% and 80% of the screw speed range is the right sized feeder. Once the appropriate feeder size is selected, the next step is to select the screw–screen combination that delivers the best performance. A method to quantify the performance of a tooling configuration using an external catch-scale was proposed by Engisch and Muzzio [9]. The central idea is to measure the standard deviation of the feed rate. That screw–screen combination which results in the smallest standard deviation of the feed rate should be the tooling of choice. The long-term stability of the screw–screen combination should be also be tested by running the feeder for extended periods of time and comparing the standard deviation over time. If the standard deviation of the feed rate increases over time, the suitability of the screw–screen combination for feeding that particular material becomes questionable. Two commonly encountered reasons of failure are the accumulation of material on the screws (also discussed in Step 2) and the choking of the feeding barrel due to the presence of the screen. Self-cleaning screws can often address the material adhesion on the screws. Screens typically do not provide a tangible improvement in performance for feeding free-flowing materials. Use of screens with larger mesh sizes or absence of a screen can address the choking of the feeder barrel during feeding of cohesive materials.

12.4.1.2 Feeder Refills

To ensure uninterrupted operation of the process, feeders have to be periodically refilled. As previously mentioned, refilling a feed hopper causes the feeder to deviate from its original set-point. One reason for this deviation is the feeder switching to volumetric mode during refill. In volumetric mode, the feeder is blind to changes in screw filling and changes in powder density. Another potential source of variation is material aeration during refill causing it behave like a liquid and flood the feed screws. A final source of variability is the change in density of powder at the base of the hopper due to the pressure exerted by the material added during refill. The frequency of the refills and the amount of material added during each refill dictate the extent of deviation from the target feed rate during refill of the feeder. The objective of development of a refill strategy is to minimize these deviations by developing a refill schedule that is technologically plausible and sustainable.

Engisch and Muzzio [10] investigated the effect of frequency and amplitude of refills on feeder performance. One strategy is to refill the feeder more frequently with less material. This strategy causes deviations which are smaller but more frequent. An alternate plan is to refill the feeder less frequently but with larger quantity of material. Although this causes deviations to occur less frequently, the deviations are large and can move across the entire process, causing product to be out of quality specification. The best refill strategy is the one that minimizes the number of refills as well the deviations caused by the refill. The quantity of material added during a refill should consider the ability of the downstream blender to smoothen the deviation caused by this refill to an acceptable level. This requires an understanding of the downstream process and acceptable variability. Ability of blender to smooth deviations from a feeder is discussed in Section 12.4.2.

12.4.1.3 Residence Time Distribution in Loss in Weight Feeders

The amount of time that an individual particle spends within the unit operation is defined as its residence time. The residence time of the particle is dependent on the path it traverses within the unit operation. There are millions of particles in a unit operation at a given point in time and each particle traverses a different path. Particles thus spend different times inside the unit operation. This leads to a distribution of residence times. Characterization of the RTD of a unit operation, as previously mentioned, is a key enabler for material traceability. This is because back-tracking a product to its lot will require information about *when* the lot was in the system and whether the lot inter-mixed with its leading or trailing lot of material, both of which can be identified if the residence time and residence time distribution of the system are known.

The RTD of any operation can be measured by introducing an instantaneous pulse of a tracer material in the system and measuring the concentration of the tracer in the outlet stream as a function of time. Alternatively, the tracer could also be introduced as a step function and the response of the system can be measured as a function of time. The output to a step or a pulse change can be modeled in several ways. Details can be found in the literature [11, 12, 69]. The two extreme cases are when the unit operation behaves as an ideal plug flow reactor (PFR; no axial mixing) or an ideal continuous stirred tank reactor (CSTR; instantaneous axial mixing over a given volume). Typically, all real systems exhibit a behavior between the two extreme scenarios (Figure 12.2).

The RTD of material in loss in weight feeders is the convolution of its RTD in the hopper and the feed screw. The feed screw can be considered to be performing under almost ideal plug flow conditions, and the challenge is thus distilled to understanding the RTD of the material in the feed hopper. The RTD of the material in the feed hopper is further complicated by the presence of bridge breakers or agitators within the hoppers of certain feeders. Agitators are typically in the form of a rotating blade situated at the base of the hopper and help to ensure that material gets pushed into the feed screws. They also prevent rat-holing of hoppers and prevent lump formation. The agitation results in mixing of powder along the depth of the hopper. If a refill is performed, especially with a material from a different lot, understanding the intermixing of the lots becomes critical for material traceability.

12.4.2 Continuous Blenders

Continuous powder mixing is not new to the process engineering community. Continuous mixers have been widely used in the food, mineral processing, detergents and the catalyst industry for decades. However, in a recent review by Pernenkil and Cooney [13], the following statement highlights the state of continuous mixing for pharmaceutical applications. "*It is interesting to observe that pharmaceutical powders have not been reported in continuous blenders*." However, with the recent surge in interest in continuous processing, both industry and academia have begun to research a variety of classes of continuous blenders. A short summary on the different continuous blenders can be found in Oka and Muzzio [14].

Tubular blenders have become the most popular class of continuous blenders for pharmaceutical mixing applications. Thus, although there are several classes of continuous blenders, characterization of only tubular blenders will be discussed in this chapter. These

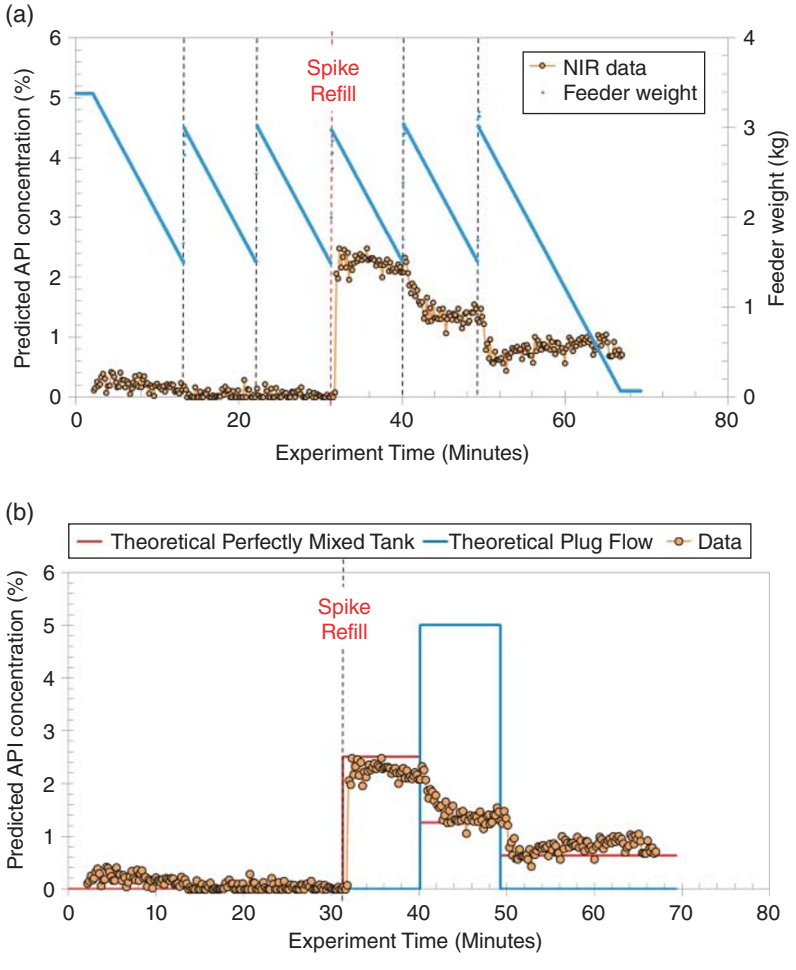

Figure 12.2 *(a) RTD response of a K-Tron KT-20 feeder to a pulse of tracer material (acetaminophen). The solid lines show the weight of the material in the feed hopper as a function time. The spikes indicate hopper refills. (b) Fit of the data to standard CSTR and PFR models. It can be observed that mixing inside the feeder mimics a perfect CSTR, characterizing substantial back mixing.*

blenders are characterized by a cylindrical tubular section with a diameter ranging from three to six inches (1 in = 2.54 cm) and an axial length of 6–36 in. Fitted along the axial centerline of the tube is a motor-driven agitator. The impeller (agitator) has a number of blades distributed along its length. The speed of the impeller, type of blades, number of blades, and their orientation can be adjusted, all of which have implications on the performance of the blender. Powder ingredients enter the blender at one end of the tube and are pushed forward by the blades and by the powder behind it. The powder mixture exits the blender at the opposite end of the tube.

The primary objective of characterizing a blender is to converge on a configuration which ensures thorough mixing of powder ingredients. Vanarase and Muzzio [15] found that the

degree of mixedness of the powder stream exiting the blender bears a direct correlation to the number of blade passes that the material experiences inside the blender. A higher number of blade passes resulted in a higher degree of homogeneity of the exit powder stream. The key challenge in configuring a blender for optimum performance is to thus arrive at configuration that maximizes the number of impeller passes. The number of blade passes is given by:

$$\text{Number of impeller passes} = \tau \text{ (in min)} \times \text{Impeller speed (in rpm)} \tag{12.1}$$

where τ is the mean residence time. The mean residence time of the material can be expressed as follows:

$$\tau \text{ (in min)} = \frac{\text{Material holdup (kg)}}{\text{Total mass rate (kg/min)}} \tag{12.2}$$

Equation (12.1) can thus be rewritten as:

$$\text{Number of impeller passes} = \frac{\text{Material holdup (kg)}}{\text{Total mass rate (kg/min)}} \times \text{Impeller speed (in rpm)} \tag{12.3}$$

It is important to note that the material holdup inside the blender is a function of the impeller speed. The number of impeller passes is thus not a product of two independent variables (the total mass rate is fixed and is usually not a variable in process design). Moreover, the material holdup is inversely proportional to the impeller speed (Figure 12.3a). The highest number of impeller passes thus could occur at intermediate rotation rates where the product of the material holdup and the impeller speed goes through a maximum. Vanarase and co-workers [15] observed and validated this phenomenon for a Gericke GCM-250.

As can be observed from Figure 12.3, parts (b) and (c) respectively, the highest number of blade passes and consequently the best performance is obtained at intermediate impeller rotation rates for an all forward blade configuration in the Gericke GCM-250 blender [15]. Similar observations were made at all blade configurations.

The material holdup inside the blender can also be modified by performing certain design alterations, specifically to the exit of the blender tube. For example, in a Glatt GCG-70, the angle of the outlet weir can be modified to increase material holdup, a higher angle of exit results in a higher holdup. Similarly, the degree of openness of the exit gate in case of the Gericke GCM-250 can be adjusted to alter the material holdup inside the blender. In case of some blenders, the angle of inclination of the entire tube can be changed to modify holdup. Portillo *et al*. [16, 17] studied two such blenders by GEA. The material holdup and blade passes increased at high degrees of inclination, resulting in superior performance.

A final means to modify material holdup is changing the blade configuration. Blades attached on the impeller can be changed to push the material forward or backward to varying extents based on their angle of orientation. The choice of the blade configuration is not only critical for maximizing blade passes, but equally importantly, for smoothening incoming noise of the feed stream. To fully understand the effect of blade configuration on blender performance, it is worthwhile to examine the mechanisms of mixing in continuous tubular blenders.

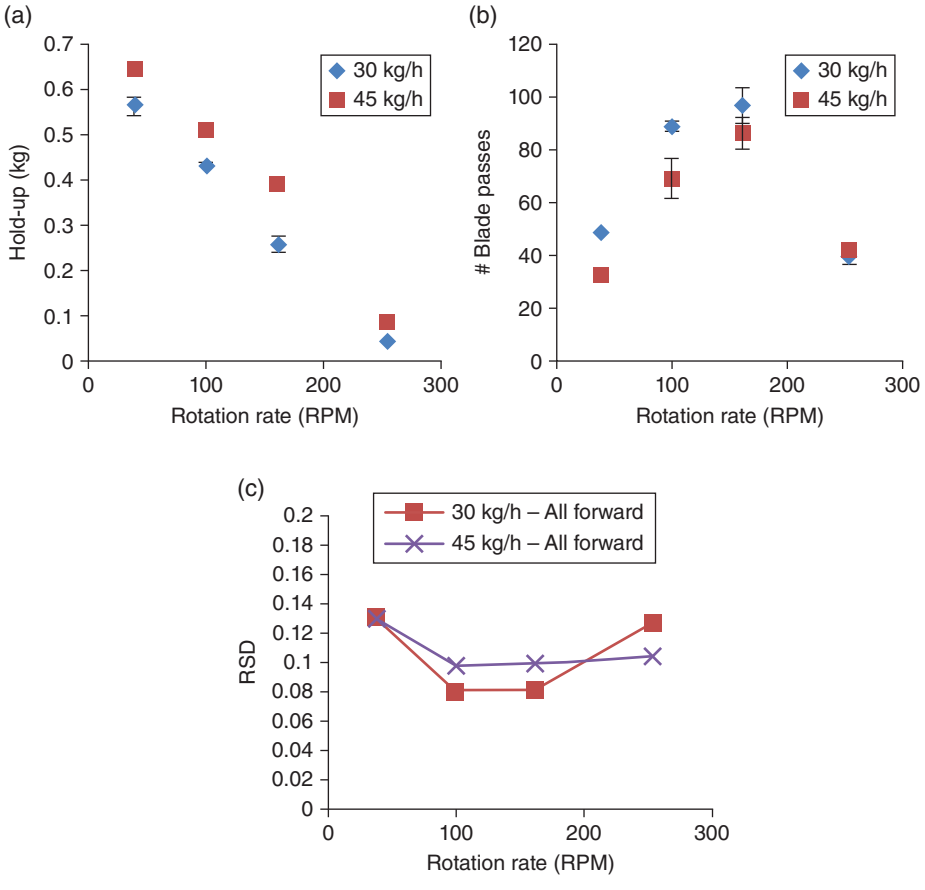

Figure 12.3 *Effect of impeller speed on (a) mass-holdup, (b) number of blade passes, and (c) relative standard deviation of the active concentration in the outlet stream for an all forward blade configuration.*

12.4.2.1 Mixing Mechanisms in Continuous Tubular Blenders

Powder mixing in continuous tubular blenders can be categorized into two mixing modes: axial and radial. Consider two powders, A and B (Figure 12.4), being fed into the blender. For the sake of argument, consider them to be completely unmixed at the entrance of the blender as shown in Figure 12.4, which illustrates a radial cross-section at the mouth of the tube. The blades of the impeller lift the powder settled at the bottom of the tube and tumble it over, leading to mixing in the radial direction. In an ideal case, the powder components at the exit of the blender will be completely mixed. At steady state, radial mixing can be considered to be largely time independent. Each radial cross-section in the blender exhibits the same arrangement of components over time but subsequent cross-sections do not. In a blender that operates under complete plug flow conditions, the radial mixing is the only mode of mixing.

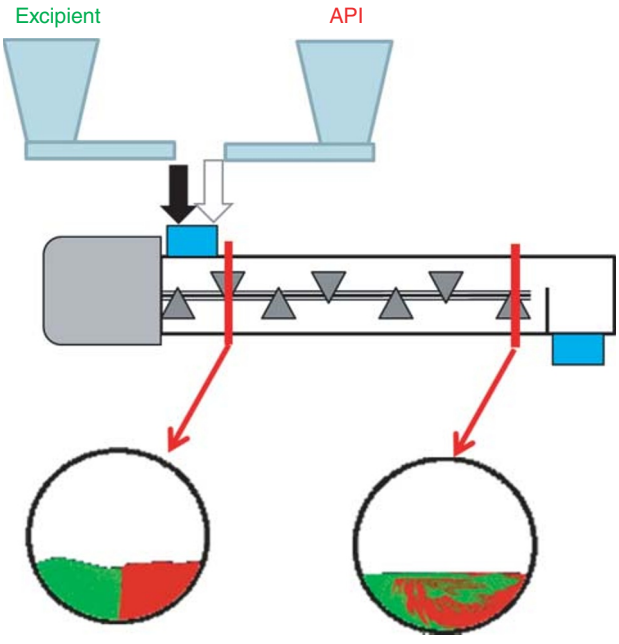

Figure 12.4 *Illustration of radial mixing phenomenon in a continuous tubular blender along the blender length. Each radial cross-section in the blender exhibits the same arrangement of components over time but subsequent cross-sections do not.*

It is, however, close to impossible (and not desirable) to setup a blender to operate under complete plug flow. When the blades of the impeller lift and tumble the powder in the radial direction, a part of the material is also pushed forward and backward depending on the orientation of the blades. The degree to which the blade configuration encourages backward vs. forward *pushing* determines the extent of axial mixing in the blender. For example, if all the blades in the blender are oriented in the forward direction, then the blender will be expected to have the least amount of axial mixing while the extent and number of blades which are angled backwards will dictate back mixing. This intuitively suggests that orientating the blade backwards results in increased material holdup inside the blender resulting in a higher number of blade passes.

An additional advantage of having a degree of back mixing configured in the blades is smoothening high frequency noise from feeders. The granular nature of all powders makes steady feeding challenging. All powder feeders have a degree of noise associated with them. If the blender is configured for complete plug flow, the noise from the feeders will pass through the system unfiltered and will be a feature of the final product thereby leading to content uniformity variations in the final product. Both these factors suggest that a blender must be configured to have a sufficient degree of back mixing. However, one must realize that the angling the blades backwards results in material being pushed in a direction opposite to the direction of the incoming feed stream. This may result in reduction in capacity or in a worse case; the blender can become clogged or choked.

A final consideration in configuring a blender is the over-shearing of shear sensitive components. Excipients like lubricants, waxes, low melting point polymers and alcohols, fume silica, and weak granules are shear sensitive, and the application of excessive shear could result in these materials dry-coating the bulk ingredients [18, 70]. Thus, as discussed in Step 2, this may result in the major ingredients becoming extremely hydrophobic. This can lead to deterioration of tabletability [19] of the bulk ingredients and poor dissolution performance of the final product [18, 20].

Considering all the above factors, a strategy to configure a blender can be summarized by the three steps presented below:

1. Choose an exit weir which maximizes material holdup.
2. Choose a blade configuration that maximize material holdup and can sufficiently smoothen incoming feeder noise.

Selections from steps 1 and 2 should not result in excessive reduction in capacity of the blender or blender choking/clogging.

3. Choose an impeller speed that maximizes the total number of blade passes without resulting in excessive shearing of the material.

The objective function that underlies these three steps is achieving a highly homogenized exit stream.

12.4.2.2 Residence Time Distribution in Continuous Blenders

Measuring residence time distribution in continuous blenders is similar to the procedure described in Section 12.4.1.3. A step change or pulse of tracer is introduced at the input of the blender and the output concentration of tracer is measured as a function of time. In addition to quantifying the residence distribution of the blender for material traceability, evaluating the residence time distribution of the blender is critical to ensure smoothening of high frequency feeder noise.

As previously mentioned, the granular nature of the material makes consistent feeding very challenging. Each feeder is intrinsically associated with a high frequency feeding noise. However, the blade arrangement in the blender can be tuned for a RTD behavior such that this noise can be smoothened.

One strategy of ensuring that the feeding noise will be smoothened is to perform the study for the worst case scenario; poorest feeding scenario coupled with a blade arrangement that provides minimum back mixing. If satisfactory smoothening is observed, then sufficient performance can be assured for all other scenarios. Alternatively, the blade arrangement may be changed to incorporate further back mixing. Figure 12.5 shows a worst case feeding scenario convoluted with the RTD of a blade configuration with minimum back mixing. While the relative narrow nature of this particular RTD (Figure 12.5a) does limit its ability to filter frequency approaching its natural width (Figure 12.5b), the noise from the feeder is at a higher frequency (see upper line in Figure 12.5d). As a result, the actual effect on the exiting concentration of the material in the blender is minimal (see lower line in Figure 12.5d). Data in Figure 12.5 refers to magnesium stearate, which was fed using a K-Tron KT-20 into a Glatt GCG-70 at the mid-point of the blending tube. The blades were arranged such that the

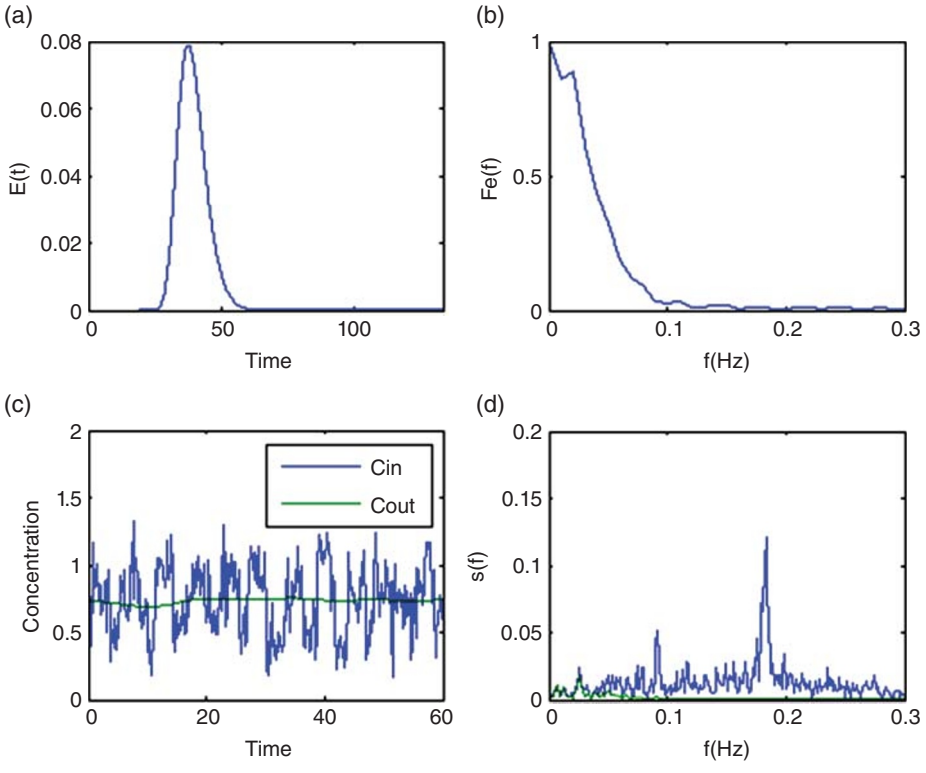

Figure 12.5 *Noise analysis of KT-20; worst case noise coupled with worst case RTD for filtering noise. (a) Normalized RTD of the blender. (b) Filtering ability of the blender. (c) Concentration in versus predicted concentration out after axial mixing in blender. (d) Noise spectrum of the raw feeder (upper line) versus effective frequency filtering done by the blender (lower line).*

middle one-third blades in the blender were alternated forward and backward. The impeller speed was 286 rpm and the total mass rate was 40 kg/h (magnesium concentration was 0.74% w/w).

Residence time distribution in continuous blenders has been studied in great detail [12, 21, 22]. A thorough theoretical background and several experimental case studies can be found in [23].

This step is the foundation for the successful operation of the physical components of the process. Poor execution of this step will result in less than satisfactory performance of the process, irrespective of the level of sophistication of the PAT and control architecture. At the end of this step, the design engineer must have decided the tooling configurations and the setting at which the unit operations will be run during the actual process. The engineer should have knowledge of the residence time distribution of individual unit operations at these configurations and settings for the actual process materials.

The process designer is now ready to physically integrate the individual unit operations to build the process train.

12.5 Step 4: Develop and Calibrate Unit Operation Models Including Process Materials

Interest, development, and application of mathematical tools in pharmaceutical manufacturing have surged dramatically due to the benefits they bring to process development. Some of the major challenges in the development of these tools are the accurate description of processes due to the lack of understanding of granular material behavior and the limitations in measuring their properties in a meaningful and reliable manner. Characterization efforts undertaken in Steps 2 and 3 (i.e. materials and unit operations characterization) aim at building process understanding. This knowledge can then be translated into a collection of multiple process inputs and outputs, related to each other via equations that describe the process. These mathematical models are the first step in developing and applying quantitative process engineering tools, which can be used to design, study, control, and optimize manufacturing processes. In this step we discuss the major concepts for developing models for unit operations.

12.5.1 Application of the Model Development Algorithm in Pharmaceutical Problems

The general strategy to analyze complex systems, with the goal of model development, consists of a series of steps that require both observation and mathematical analysis. Several authors have discussed different algorithms for model development, in order to systematically guide the efforts and provide a framework for model development [24–26]. In brief, the framework can be presented in four major steps: (1) problem formulation, (2) inspection and classification, (3) variable selection and model compositions, and (4) evaluation and verification. In problem formulation, the goals are to clearly delineate the model purpose as well as clarify its inputs and outputs. During the inspection and decomposition step the aim is to decompose the system studied (e.g., unit operation or group of units) into several subsystems in order to clearly understand the equipment fundamentals. Once the system is decomposed interactions between the subsystems can be formulated as inputs for (i.e., or outputs from) a set of mathematical equations (i.e., models). Finally, in the evaluation and verification stages, the model is tested in order to evaluate how well the set of mathematical expression represents the real process. Several methods for verification can be implemented to ensure model validity [25–28]. Continuous evaluation and verification with experimental data throughout its application ensures that the model will remain valid and relevant. This last step can create a loop for the process, as it requires the model development process to review the objectives and evaluation criteria set out in the first objective [29].

In the aforementioned framework, lack of knowledge about the product and equipment can limit the inspection and classification step, which in turn, affects variable selection and equation building. In pharmaceutical regulatory initiatives, a set of definitions are established in order to help model developers overcome these challenges [30]. Below, the individual components of the framework are presented with their analogous definition in the pharmaceutical industry.

12.5.1.1 Inspection and Classification

Since the pharmaceutical industry is risk-adverse in nature, the regulatory body's approach of the classification and analysis of variables is based on risk management and assessment.

Variables, inputs, parameters, units, or processes are evaluated based on their impact to the final product and, most importantly, the patient. Risk assessment categorizes potential adverse events based on probability, severity, detectability, and sensitivity [31, 32]. This approach, along with sensitivity analysis methods, provides a framework for decomposing and classifying the different component and inputs in a process. For example, Hlinak *et al*. [33] have provided a list of raw material properties and their potential effects on process performance and product quality. Such approaches can then be used as a starting point for identifying the variables and performance metrics that relate to material properties effects.

12.5.1.2 Variable Selection

Variable selection is pivotal in model development in order to minimize computational cost and maximize model information. For this reason, variables that have a significant impact on process responses should be selected. Given the risk management approach, variables deemed as potential sources of change to the process are considered critical process parameters (CPPs). The designation of CPPs is highly related to the extent that changes in this value will affect product quality or process goals [34]. In the initial stages of pharmaceutical research model development, these variables are selected based on heuristic methods and by observation of experimental data. Examples of potential CPPs include unit operation parameters such as screw speed, throughput, compaction force, and powder hold-up.

Characterizing the effect of potential CPPs on product material properties through the process is one of the goals of process development. These product material property responses are important to correlate with the product performance *in vivo*. Material property responses that are associated with *in vivo* performance include both chemical and physical properties and are known as critical quality attributes (CQAs). Generally speaking, any variable that can cause product rejection is a CQA. More specifically, drug content and uniformity indicators with respect to API content (e.g., assay, content uniformity) and drug release profile (dissolution specifications) are always considered CQAs [35, 36].

12.5.1.3 Evaluation and Verification

Model evaluation and verification requires understanding of the effects that input variability has on model outputs. As part of model formulation and variable selection, the inherent variability of the model should be captured in order to more accurately represent the system and avoid oversimplification of the model. To this end, data collected for the process must include an internal verification set, in order to test the ability of the model to capture both, the expected changes in the process and the system variability. Model maintenance is also a key and fundamental step for pharmaceutical models, which has been heavily discussed in several regulatory guidance reports [37–39].

12.5.2 Recommendations for Developing a Unit Operation Model that Incorporates the Effects of Material Properties

The integration of material properties as an input and as an output to the model is critical for further process modeling, as it allows for the predictions to include the effects these will properties have in the system. Nevertheless, it is important to take into account certain factors when including material properties into the modeling framework.

12.5.2.1 Determine the Material Properties of Interest for First Pass Model Development

In order for a material property (whether for a raw ingredient or an intermediate blend) to be defined as a critical material attribute, it must be able to be tested reliably. For this reason, specifications on physical properties are typically limited to bulk powder properties, which are more straightforward to test. These include bulk density, particle size distribution, flow factor, cohesion, and compression behavior [40]. Therefore, experiments intended for the design and development of models need to include materials for which these properties are known or are easily measurable. Two of the material properties that need to be critically evaluated for model development are bulk density and flowability. These material properties are easy to measure and have a very high impact of several of the design and operating parameters. For example, bulk density has a high impact on mass flow rate given that material flow along the unit is driven by volumetric displacement [33, 41, 42]. Nonetheless, the vast majority of raw material properties have not been associated with experimentally observed blend and product properties and equipment responses.

12.5.2.2 Examine the Range of Material Properties that Need to be Evaluated

Selection of materials for experimental designs is often based on heuristics or the material availability. For this reason, several efforts for model development do not capture the full range of material properties that are observed in the unit, limiting the application of models to a small subset of scenarios. Understanding the typical ranges of material properties entering the unit is a valuable piece of information that can help minimize experimental efforts, as well as improve model development. Critical understanding of the materials commonly observed for a specific unit (e.g., raw materials for feeders, or blends for feed frames) can aid the process of model development.

12.5.2.3 Evaluate Modeling Strategies to Predict Material Property Effects

One way to address material properties effects is using reduced order models [71]. The goal is to provide a methodology in which the phenomenological and residence time distribution model constants (e.g., mean residence time, exponential decay coefficients) are correlated with material properties. This proposed methodology will be evaluated here using examples of other chemical industries.

Unit operation models that take into account material properties provide a valuable tool that can be used to determine which process parameters can be used to mitigate the changes of material properties in a process. Furthermore, this method can be used for control strategies and systems that take into account the variability in material properties in order to maintain product critical quality attributes.

12.6 Step 5: Develop an Integrated Model of an Open Loop System

After the formulation of individual unit operation models is completed based on the methodology described previously, the next step is their integration into a single dynamic model of the entire line. Similarly to a continuous process, where multiple unit operations are linked

in series, the individual mathematical models are connected so their inputs and outputs contain the relevant information needed to simulate the whole process. The integrated model, also known as a flowsheet model, can be used to determine the interactions between unit operations and evaluate the performance and design space of the entire process at a global level. Integrated process models allow process engineers to obtain information about conditions that would lie outside the range of acceptable outcomes, and thus, narrow the scope of subsequent experimental investigations. This information naturally leads to more focused development efforts, which could eventually lead to a higher level of process understanding and accurate determination of the "design space" (which should more appropriately be called the "acceptable operational space"). The reduction in experimentation due to *in silico* evaluation reduces materials usage (e.g., API, excipients), waste, development time, cost, and personnel exposure, while helping improve process understanding, controllability, flexibility, and product quality. During process optimization, flowsheet models can be used to determine optimal values for critical process parameters.

12.6.1 Model Integration Basics

The primary requirement in developing an integrated model for an open loop system is being able to transfer the information from one unit operation model to the next in a manner that resembles the actual continuous manufacturing process. Although it is possible to connect individual unit operation models in series using available modeling software (e.g., MatLab®, Mathematica®, Python®), this process may be tedious and require a high degree of modeling knowledge. Several process simulation software companies (e.g., Aspen Technology Inc., Process Systems Enterprise Ltd, Wolfram Alpha Ltd) have developed software that can be used to easily create integrated simulations using blocks of equations, each representing an individual process model, as the base structure of the model. Blocks can be connected in such a way that variables are passed between them using inlet and outlet ports, and a variety of property connection types, mimicking the transfer of material from one unit to another in a manufacturing process. Figure 12.6 shows an example of the integrated process modeling components based on the use of unit operation models as building blocks connected via ports and property connections.

Selecting the order of each individual unit operation block depends on the system configuration. All unit operations should be able to accept information from a previous unit and provide information to a subsequent one using the connection ports and channels. Variable types within these systems (e.g., particle size, bulk density) must all be expressed in consistent units of measure in order to avoid integration issues downstream of the process. This, while an easily fixed problem during model development, becomes one of the most common issues during integration.

12.6.2 General Algorithm for Building an Integrated Model

Modern flowsheet model environments are equipped with robust dynamic solvers that can readily resolve complex process models containing tens of thousands of differential, algebraic, and integral equations [43]. However, it is still important to ensure that these problems are well posed. Once the individual unit operation models have been developed, integration

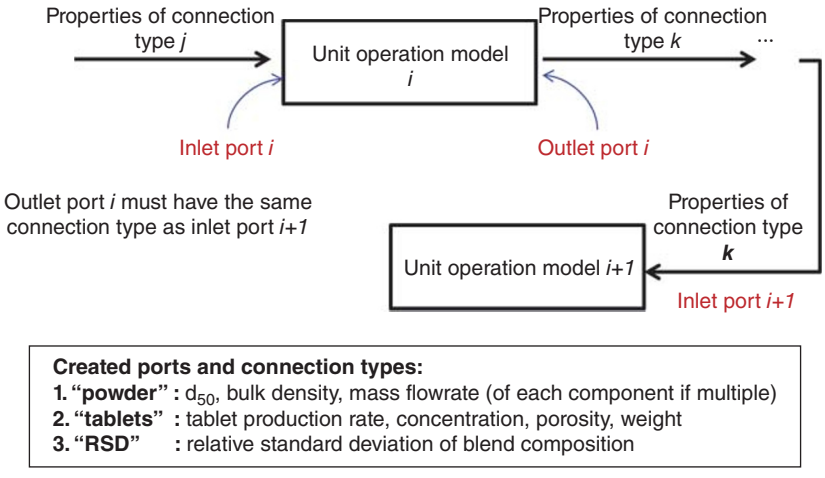

Figure 12.6 *Model integration for a multi-unit operation process. Each block represents an individual unit operation model connected to a subsequent model using an information transfer port and an information connection. Both the port and connection type transfer specific information between units, which will become part of the calculations inside that unit. "Powder" connections and ports contain information regarding how each unit operation affected the powder stream properties such as flow rate, particle size, and bulk density.*

can be easily performed using process simulation software. The steps for integration are presented below.

12.6.2.1 Select the Unit Operation Models for a Specific Process

Selection and organization of the models is based on the design of the system being studied. At this stage all the unit operations can be selected and placed on the simulation environment with the goal of understanding which are the model inputs required for the simulation, and also to understand what are the connectivity requirements between unit operations. Modifications of the model based on the needs for integration can be performed at this stage in order to avoid further integration issues.

12.6.2.2 Select the Ports and Connection Types for Information Transfer

If several connection types and ports are available, selection of the appropriate ones for the units selected is critical before integration. Connection types and ports should to be able to accept all the information for the properties being considered or transferred between unit operations, even if those properties do not change in the individual unit operation model. For example, although a unit may not directly affect a property of a stream (e.g., particle size is largely unaffected by the blender) its information still needs to be carried over the connection type so that a subsequent unit (e.g., a roller compactor) can use the data for its calculations. It is also important to consider the variable types and what units of measure (e.g., meters for length, liters for volume) are being used in order to minimize integration

issues. Furthermore, valid initial conditions must be provided for all differential equations and that the information transferred from one block to another must contain valid operating conditions for any systems of equations.

12.6.2.3 Connect the Individual Unit Operation Models

Once connection ports and types have been resolved, the individual unit model blocks can be connected. At this stage, it is also recommended to connect and run the simulation after each unit operation is integrated. For example, if a system containing more than three units is being modeled, after the integration of the first two units, the simulation should be run to ensure that there are no issues. After the two units have been integrated and modeled, the third should be connected and the simulation re-run. This approach will minimize the number of errors in integration, and avoid the need to debug a large simulation, by ensuring that at each step the simulation is running.

12.6.2.4 Run Complete Process Model and Test Results

After the simulation is complete, the information from previous units should show the influence at the outlet of a subsequent unit. These changes should be tested and verified similarly to an individual process model, specifically taking into account the presence of delay times between units and the dynamics of each unit.

For further information about the development and application of integrated process models, refer to Chapter 2 where a more in-depth discussion and evaluation of continuous direct compression flowsheet are performed.

12.7 Step 6: Examine Open Loop Performance of the Process

Characterization of individual unit operations, described in Step 4, is a key component in overall process development. However, the performance of the overall process is not an elementary addition of the performance of individual unit operations. The performance of the overall process is a function of interaction between unit operations, in addition to their individual performances. The CPPs of a certain unit operation affect not only its own performance, but also the performance of unit operations further downstream, the performance of unit operations upstream if distributed feedback control is used, and the CQAs of the final product. Thus, although characterization of individual unit operations is critical, it is equally important to understand the effect of integrated dynamics of unit operations in series.

In order to properly design a distributed control architecture, it is important to first understand the intrinsic dynamics of the integrated system in the absence of distributed control actions. This step constitutes understanding the effect of perturbations and critical process parameters of certain unit operations on product stream further downstream, and on CQA the final product. This is also the first time that the entirety of the process is run, end to end, after it has been mechanically integrated. Thus, this step allows to test if the process parameters at which the process is designed to run can produce the final product with acceptable quality attributes. This step is critical to reveal inconsistencies between operational ranges of different unit operations (e.g., can all unit operations handle the desired flow rates?).

It also provides the opportunity to test the design of the physical transitions between unit operations and quantify the residence of the material in the transitions. Finally, it allows for testing the long-term stability of the process.

The chronological series of actions to be performed during this step are listed below.

1. Mechanically integrate all unit operations – feeders to the tablet press.
2. Identify CPPs. These should be determined from studies in Step 4.
3. Identify CMAs of the process stream.
4. Install PAT tools to ensure that the above identified CMAs can be evaluated. Except for final blend homogeneity, capability to monitor CMAs online and in real-time is *not* a requirement at the present time. The key need is the ability to evaluate these CMAs. The necessary analysis can be performed offline based on samples extracted from the process. However, as discussed later, ability to monitor CMAs of the process stream is likely to be a process requirement for the purpose of implementing an effective distributed control methodology.
5. Design and execute a DOE to quantify the effect of CPPs from 1., on the CMAs from iii and on final product CQAs.
6. Test the long-term stability of the process at the design midpoint conditions at which the final process is expected to run.
7. Quantify residence time of the material in the transitions and in the entire system.

Steps 1. to 6. also find synonymity to a certain degree in batch processes, or have been well debated. A transition, on the other hand is unique to a continuous process. Quantifying the RTD of a transition is thus discussed below.

Transitions connect two unit operations and transport material from one unit operation to the next. Figure 12.7 shows the time required for a blend after exiting the blender to travel the length of the transition and manifest itself into tablets, compressed by a tablet press situated immediately after the blender.

The experiment was performed at a total mass rate of 30 kg/h, the transition was perfectly vertical and transported material as a packed vertical bed. In order to quantify the residence time in the transition, a step change in the concentration of acetaminophen in the blend was made and its response was monitored. As shown in the Figure 12.7, it took about 9 min for the perturbation after having exited the blender to manifest itself in the tablets. Knowing the residence time of the material in the feed frame, the residence time of the material in the transition can be calculated. Neglecting such a long delay would lead to an inaccurate model. Thus, residence time characterization needs to be performed for all the transitions of the process.

The completion of this step results in the mechanical integration of all unit operations. It allows the experimenter to understand the effect of various CPPs on CMAs of the process stream. It also confirms the ability of the system to create the final product with the desirable quality attributes, and quantifies the effect of CPPs on these attributes. It allows for testing the long-term stability of the process. Finally, it charts the residence time profiles for transitions which connect the unit operation in the process. We are ready to move on to the next step of the process: development and implementation of PAT methodologies for online sensing.

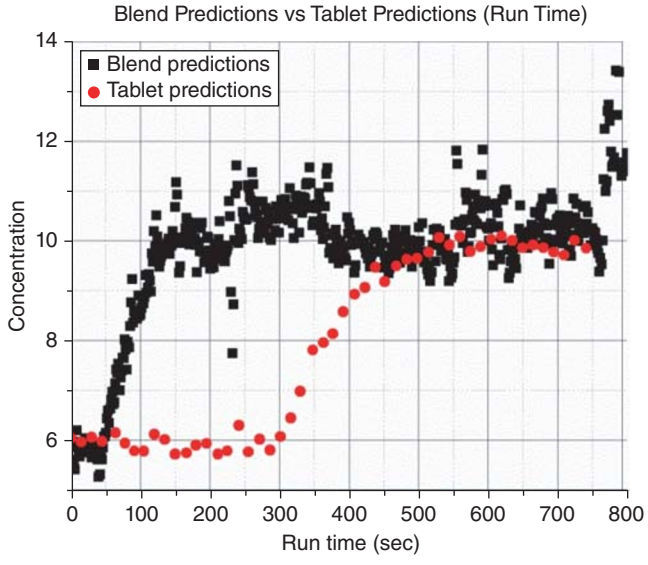

Figure 12.7 *At time 0, feed ratio was changed from 6% APAP to 10% APAP. The series of squares is the in-process spectra of the material post the blender. The series of circles represents NIR measurements on tablets sampled at the exit. It takes about 9 min after the perturbation having exited the blender to manifest itself into tablets.*

12.8 Step 7: Develop/Fine Tune PAT Methods for Appropriate Unit Operations

The DOE exercise performed in Step 6, and the characterization of unit operations performed as part of Step 3, result in the identification of material attributes of the process stream that are critical to the successful operation of the continuous process. These CMAs, or attributes correlated to the CMAs, should be monitored in real time to enable process control and predictability of the final product. This requires the development of appropriate sensing methods that monitor these material attributes (or their correlatives) in real time. The development of PAT methods that can accurately sense a representative sample of the process stream, or of the final product, and can take meaningful measurements, is a key step in the design of a robust and efficient continuous process.

Sensing technology for pharmaceutical materials has seen a surge in innovation over the past few years after the FDA introduced the PAT initiative [44] for the manufacture of pharmaceutical products. However, the majority of these technologies have been developed for batch manufacturing processes, where the powder material, or final product, is static and can be measured multiple times. The challenge is to reconfigure the sensing tools for a continuous framework, where the powder stream is dynamic and is moving with respect to the sensors.

The dynamic nature of the powder stream brings with it challenges; such as, the identification of sample size, the tuning of PAT tools to sense that sample size, and representative sampling. For example, consider a NIR probe that is monitoring a mixed powder stream exiting the blender. The powder stream is moving past the sensing window at a certain

velocity (volumetric flow-rate divided by the cross-sectional area of the chute). The sensor is scanning the moving powder at a certain frequency, and averaging a prescribed number of scans. Sampling theory dictate that the scanning frequency and averaging should be adjusted such that a single unit dose of material is sensed per the averaging operation for the given penetration depth. This requires the evaluation of the certain properties of the powder stream, such as the velocity. As previously mentioned, the velocity of the powder stream depends on its volumetric flow rate. Since the total mass rate, and not the volumetric flow-rate, is available, a test is required to determine the packing density of the powder stream in the chute. Once the flow velocity is known, the averaging frequency can be adjusted to ensure that an appropriate sample size is sensed.

A second concern is the need to achieve representative sampling of the powder stream. Representative sampling implies that a small sample sensed by the probe possesses the same properties as the overall powder stream. Consider the same example of the powder stream exiting a blender, which is being monitored by a NIR probe. If the probe is mounted on a transition, there is a possibility that the material, as it drops into or when is flowing through the transition, may rearrange itself such that there exists a gradient in its content. The separation can occur going from the outside to the inside or across the transition's cross-section. The NIR probe thus senses material that is not representative of the material throughout the cross-section and will consequently lead to erroneous measurements. This must be avoided, for example, by redesigning the geometry of the chute that houses the probe in order to ensure representative sampling.

Several researchers have exhibited the applicability of NIR-based sensing to monitor the content uniformity of a dynamic, dry powder stream [21, 45, 46]. A comprehensive review on the use of NIRs to evaluate contents of a powder sample can be found in Beer *et al*. [47].

The above discussion has focused on NIR spectroscopy to highlight sensing and sampling considerations. However, the criteria discussed above for sensing and sampling apply to all sensors that are employed to monitor the numerous CMAs of the process stream. Silva and coworkers have written a comprehensive review on the state of online sensing technology for particle size measurements [48]. Davies *et al.* [49] recently proposed a method to measure the density of the powder stream using a direct weight–volume measurement, while Romanach *et al.* [6] exhibited the use of NIR for measuring powder density. NIRs have also been widely used to determine, in real time, moisture content and the end point of drying operations. Irrespective of the sensing methodology, it must be ensured that measurements made on the attributes of the process stream should be meaningful, representative, and accurate.

12.9 Step 8: Implement Open Loop Kit with PAT and IPCs Enabled

This step consists of installing the previously developed PAT tools onto the continuous line, and validating their performance. This also involves quantifying the open loop system dynamics of the process.

PAT tools and methods developed in Step 7 should be tested by mounting them online and evaluating their in-process performance. Certain phenomena, like material adhering to probe windows upon extensive operation, can become evident during online testing of these probes. If this issue occurs, it will need to be addressed. The construction of the hardware that mounts the PAT probes is also detailed in this step. The nature of the material, or the

process, may demand the frequent cleaning of PAT tools, or process equipment, which may require the PAT probes to be dismounted and mounted several times, until the final position can be determined. Attention should be paid to the modularity of the mounting framework. The PAT models should also be tested online, by running materials, with known properties, through the process, and confirming the ability of the models to accurately predict these properties. Finally, the long-term stability of the PAT tools should be tested as a part of this step.

With the proper PAT infrastructure enabled, the step provides a good opportunity to verify the open loop dynamics of the system. For the case study introduced earlier, from Steps 3 and 6, the residence time distribution of all the individual components was quantified. In Step 5, information from these steps was used, and an integrated model of the entire process was developed. Also performed in Step 5, was the evaluation in the response of the system to simulated perturbations. This step provides a good opportunity to validate the integrated model. Perturbations simulated in Step 5 should be re-created in the actual process. The response of the system should be observed by evaluating the data from the appropriate PAT sensors in the process. The simulated responses and physical responses should be compared for similarity.

The source of perturbations in an actual process, which can be numerous, cannot always be predicted. However, almost all perturbations can be imitated experimentally, either by adding an instantaneous pulse, or by introducing a step change. Once the system response to an imitated perturbation is monitored, the underlying arithmetic of evaluating the response is identical to that of evaluating the RTD of a unit operation, detailed in Step 3. The response can mimic an ideal PFR, one or several ideal CSTRs, or most likely, somewhere between these two ideal cases.

Time constants achieved from the exercise above can now be used to design the control architecture. In principle, the control action should be such that the perturbation does not cause product to be out of specification. This can be achieved by spreading the effects of the perturbation (i.e., more back mixing) so that its impact is diluted without causing product failure. Alternatively, if producing out of specification product is unavoidable, a control option would be to predict which product would be out of specification, and divert such product to scrap or recycle. In such an event, we want to spread the perturbation as little as possible (i.e., less back mixing) to minimize the amount of product to be discarded. The design of the control architecture of the system is explained below in Step 9. Alternatively, if the amplitude and duration of the perturbation is very large, and outside the limits of the control system, the design parameters of the system (for example, size of the blender, blade angles of the blender) might need to be modified to increase the ability of the system to mitigate its effects. A change in the design parameters also requires appropriate change in the process models. The strategy that should be pursued also depends on the likelihood of the perturbation to occur. At this point, for a well- designed system, there should be a minimal chance of the latter scenario, and changing design parameters should be a final resort.

At the end of this step, all the PAT tools in the system have been installed and validated. The open loop dynamic of the system has also been characterized, and necessary time constants and dimensionalities have been estimated. One can now begin work on designing the control architecture for the process, and implementing the control architecture to enable closed loop control.

12.10 Step 9: Design of the Control Architecture

When a continuous process is integrated with a real time distributed control system, it is called a "closed-loop process." A closed-loop process consistently insures the achievement of desired predefined product quality. Under closed-loop operation, the raw and intermediate CMAs, the CPPs and the final product CQAs are measured in real time. Since these values are recorded in real time, the corrective actions are taken in real time, using a feedback, and/or feedforward controllers. A controller can be defined as a mathematical equation or algorithm able to calculate the quantitative actions.

Importantly, closed loop control is *not* new to the pharmaceutical industry, as many unit operations have, and have had for decades, "in process control" (i.e., "IPC"). For example, force and speed controllers in the tablet press have been used for many years; however, these local controllers only act on individual process units, and concern themselves primarily with mechanical parameters (as opposed to quality attributes). In contrast, a distributed control system acts on a unit operation to modify the outcome of another unit operation, and to ensure efficient operation of the entire system.

The concept of open- and closed-loop process is illustrated in Figure 12.8 [50]. If there are no variations in the raw material properties, and if there are no process disturbances, then one may be able to manufacture the product with the desired quality by running a steady process. The assumption that such an operation is possible is, in fact, one of the underlying assumptions, often inaccurate, of classic "process validation." In this open-loop operational scenario, the product quality can be fitted, but cannot be guaranteed. In practice, there are always variations in raw material properties, as well as in process disturbances. In some cases, these variations do not affect product quality significantly; however, in other cases, it is very difficult to achieve the desired product quality for open-loop operation, and one must take corrective action to achieve consistent quality. In closed-loop operation, accurate sensors for real time monitoring of critical process variables are placed in the optimal locations, and therefore, appropriate controllers are added so that the critical process variables can be controlled automatically in real time. The goal is to achieve the desired product quality irrespective of variations in raw material properties and process disturbances. The control system is also useful to manufacture the product safely, to satisfy flexible market demands, to reduce manufacturing expenses (e.g., labor cost), and to assure regulatory requirements.

The overall control architecture of a continuous pharmaceutical manufacturing process includes a local level control system and a supervisory control system. As mentioned, the local level control system (IPC) is unit operation centric, while the supervisory control system governs the overall plant in an integrated manner. The local level controllers are normally built into the unit operations, but their performance needs to be evaluated. A supervisory control system is externally added and its function is more complex; therefore, more attention needs to be paid to its design and evaluation.

The control architecture needs to be designed carefully before implementing it into the manufacturing plant. The design of the control architecture involves the identification of critical control variables, pairing of control variables with suitable actuators, selection of a real time monitoring tool for each control variable, selection of controllers and tuning of controller parameters, implementation of control loops into a process model, and performance evaluation of the control system [51]. The process flowsheet model is an important tool that can be used to design and perform preliminary tuning of an efficient, and robust

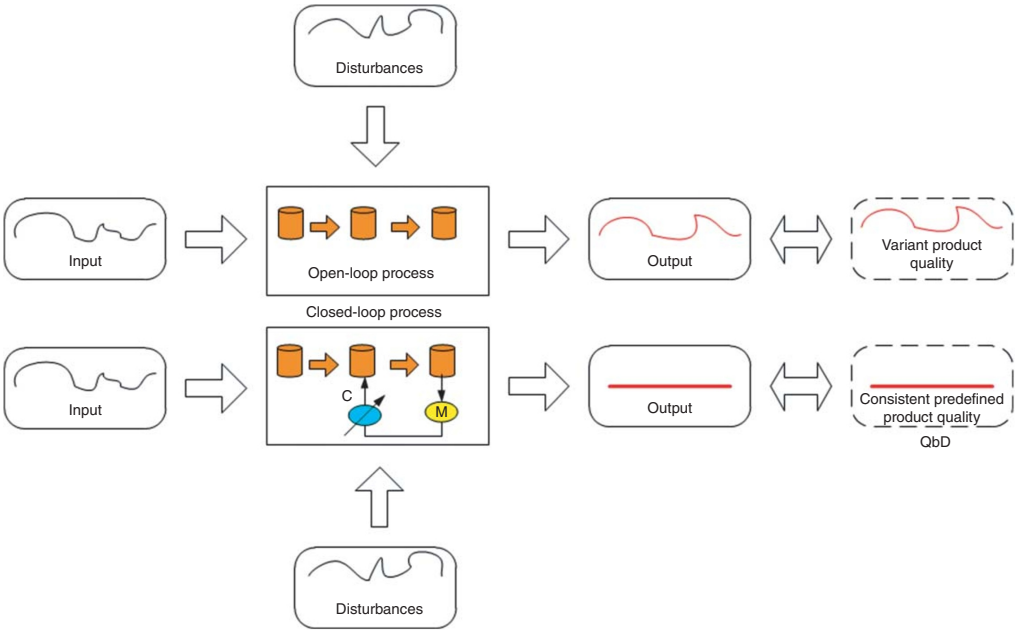

Figure 12.8 *Illustration of closed-loop and open-loop operation (adapted from [50]).*

control architecture. The different steps required for designing a control architecture are described in the following paragraphs.

The first step is to identify the critical process variables that need to be controlled. The critical control variables can be selected based on sensitivity analysis combined with process understanding. Sensitivity analysis can be used to analyze the sensitivity of CQAs to process variables. The process variables that have the most significant impact on CQAs should be controlled. The variables that are not self-regulating must be kept within the equipment and operating constraints. If a specific variable, or variables, significantly interact with controlled variables, then the former should also be controlled. The set points of control variables can be obtained from design space analysis. The design space can be generated through optimization.

The next step is to select an actuator for each control variable. The general criteria to select an actuator is that it should have a large effect on the corresponding controlled variable. The controlled variable should be most sensitive to the selected actuator with respect to other actuator candidates. The selected actuator should rapidly affect the controlled variable, and if possible, it should also affect the controlled variable directly, rather than indirectly, and there should be minimum delay time. The relative gain array (RGA) method can be used to pair the controlled variables with corresponding actuators [52]. In the RGA method, the relative gain should be calculated for each pair of controlled variables and actuators, and then a relative gain array matrix should be constructed. Relative gain is the ratio of open-loop gain and closed-loop gain. The open-loop gain can be obtained by partial differentiation of a control variable function with respect to an actuator candidate, while assuming that other actuator candidates are constant. This calculation is virtually identical to performing sensitivity analysis. Similarly, the closed-loop gain can be calculated by partial differentiation of the control variable function with respect to an actuator candidate, while assuming that all other controlled variables are constant. The elements of the relative gain array matrix are the relative gains. The values in the array describe the relationship between the inputs (actuators) and outputs (control variables). Negative values indicate an unstable relationship, while a value of zero indicates no relationship. A value of one indicates that the specific input variable is the only influence on that output variable. A value between zero and one indicates an interaction among the control loops.

Subsequently, the possibility of cascading the control loops needs to be investigated. In cascade arrangements, the inner and outer loops need to be integrated such that the outer loop provides the set point for the inner loop. The inner loop is called the slave loop while the outer loop is called the master loop. Cascade control loops can improve performance in many instances. For example, when a large time delay is involved and/or when disturbances affect a measurable intermediate that directly affects the controlled variable. The cascade control system however is more difficult to tune and requires a larger number of variables to be measured in real time. In a cascade arrangement, the dynamics of the inner (slave) loops should be significantly faster than the outer (master) loop.

It is often desired to couple a feedback control system with feedforward control capabilities. The next step is to thus identify the feedforward control loops [53]. The basic concept of a feedforward control is to measure important disturbance variables and take corrective action before the disturbances upset the process. The feedforward controller therefore takes into account the known and predictable effect of raw material variabilities and process disturbances proactively. The precise control of the quality of the pharmaceutical

product requires corrective actions in the process/raw material variability before product quality can be influenced. The capability of using both feedforward and feedback control to respond to real time disturbances throughout the multiple unit operations is one of the key advantages of continuous manufacturing [54]. An illustrative example of combined feedforward/feedback control loops is shown in Figure 12.9. As shown in the figure, the measured disturbance is the input to a feedforward controller. The output of feedforward controller has been integrated with the feedback control loop. The feedforward controller is a mathematical model relating input (disturbance) with output (actuator). The feedforward control loops requires additional sensors for real time monitoring of process disturbances.

The next step in the design of the control architecture is the selection of real time monitoring tools for critical control variables, slave control variables, and feedforward variables. The selection of sensors is important in the design phase of the control architecture because the performance of various sensors could vary from manufacturer to manufacturer. These sensor specifications can have significant impact on control loops performance. Therefore, on changing the sensors, the control loops might need to be re-tuned. Furthermore, since sensors typically introduce both error and delays, sensor models needs to be integrated with the process model before testing the control architecture. Different performance criteria (e.g., accuracy, precision, operating range, response time, resolution, sensitivity, drift) and cost need to be considered before selecting a sensor [55]. Many pharmaceutical processes require the implementation of spectroscopic techniques to monitor different process variables [56].

After identifying control variables, actuators, and sensors, the decision on the type of controllers to be used for each control loop needs to be made. There are two main classes of controllers available, proportional integral derivative (PID) controllers and model predictive controllers (MPC). Within the PID structure, P, I, and D can be used individually or in any combination as per requirement.

A PID controller is simpler, easier to implement, easier to use, and in most cases (but not all) works very well. The performance of PID controllers can be substantially limited by process nonlinearity, process dead time, process interactions, and process constraints. A dead time compensator (e.g., Smith predictor) might need to be integrated with PID controller if the process is dead time dominated.

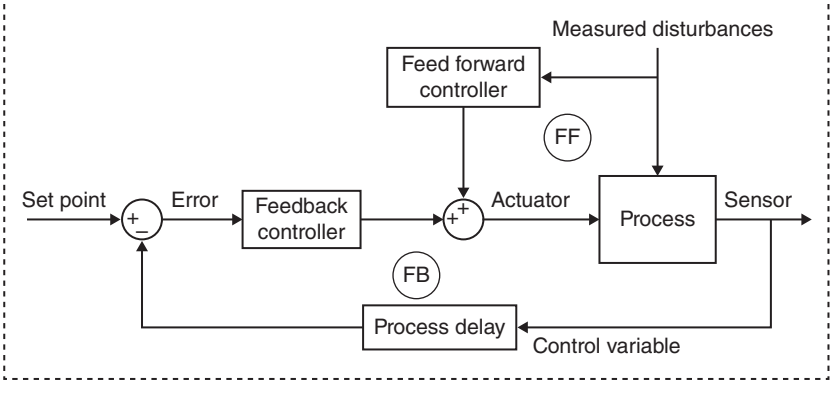

Figure 12.9 *Combined feedforward/feedback control.*

MPC refers to a family of control algorithms that employ an explicit model to predict the future behavior of a given process over an extended prediction horizon [57]. These algorithms are formulated as a performance objective function, which is defined as a combination of set point tracking performance and control effort. This objective function is minimized by computing a profile of controller output "moves" across a control horizon. The first controller output move is implemented, and then, the entire procedure is repeated at the next sampling instance [57]. MPC has proven to be a very effective control strategy and has been widely used in oil refining and chemical manufacturing. There are several advantages of using MPC. For example, MPC is better than PID when handling multivariable control problems, process constraints (e.g., actuator limitations, constraints on controlled variable, system constraints), process delays, system disturbances, equipment (sensor/actuator) failure, and process variable interactions. It is important to note, both PID and MPC need to be tuned using appropriate methods. Of the two, MPC is easier to tune. The Ziegler and Nichols [58] method can be used for the tuning of a PID controller, while an optimization based method (e.g., integral of time absolute error; ITAE) can be employed to tune MPC [57]. After designing the control architecture, it needs to be implemented into the process model for *in silico* performance evaluation before implementing it into the plant.

12.11 Step 10: Develop Integrated Model of Closed Loop System

The control architecture, previously developed in Step 9, needs to be implemented into an integrated process flowsheet model of the continuous pharmaceutical manufacturing process. This integration will allow the user to obtain an integrated closed-loop model of the system [57, 59, 60]. The integrated closed-loop process model is required to tune the controller parameters and evaluate the performance of the control architecture. gPROMS, a software developed by PSE, has been used as a simulation platform to demonstrate the development of an integrated model of a closed-loop continuous pharmaceutical manufacturing process. The control architecture designed in the previous step, together with the integrated open-loop process flowsheet model, is the starting point for this development step.

To integrate the controller inputs/outputs with the integrated flowsheet model, the first task is to create input/output control ports in the unit operations, wherever needed. The purpose of the input/output control ports is to transmit the information between the process model and the controllers. An output port is the location where a sensor needs to be integrated and an input port is the location where an actuator needs to be placed. In the case of local level control, the input/output ports will be in same unit operation, while in case of supervisory control, the input/output ports could be in different unit operations.

The second task is to add the controllers and to create feedback loops by connecting the input/output ports with the controllers input/output. The integration of a control loop with the process model is illustrated in Figure 12.10. As shown in the figure, the sensor outlet is connected with the controller inlet, and the controller outlet is connected with the actuator inlet. Within the controller, there is a port to integrate external set point signals obtained from the master controller (e.g., when using cascade control loops). When using a model to simulate the action of the control architecture, the sensor input signal comes from the process model, while the actuator output signal goes back to the process model. This

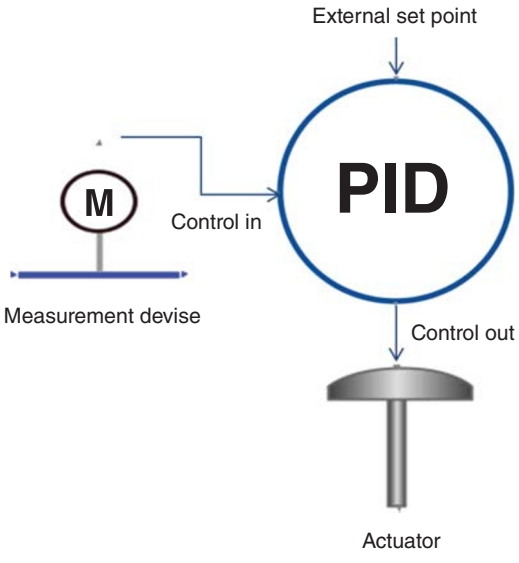

Figure 12.10 *Integration of a control loop with the process model.*

integration resembles the actual implementation of control loops in a real-world processing plant.

The third step is to provide the controller parameters and constraints. In the case of a PID controller, gain, reset time, and rate are the tuning parameters. The controller parameters can be tuned using either a heuristic based method (e.g., Ziegler and Nichols [58]) or an optimization-based method [61]. In the case of an optimization based method (e.g., ITAE) an objective function needs to be minimized using the optimization routine of gPROMS, and the controller parameters that give the minimum error need to be identified. The objective function can be formulated as in Equation (12.4), where n is the total number of control loops, V^i is the ith controlled variable, and V^i_{set} is the set point of the ith controlled variable.

$$\text{OBJ} = \sum_{i=1}^{n} \left(\int_0^t t|V^i - V^i_{\text{set}}|\text{d}t \right) \tag{12.4}$$

In addition to tuning controller parameters, there are other control parameters that need to be specified appropriately to achieve the ideal controller performance. These parameters are minimum and maximum limits of controller inputs (control variables), minimum and maximum limits of controller outputs (actuators), bias (controller offset used for smooth switching), and rate limits [57].

The closed-loop process flowsheet model of continuous pharmaceutical manufacturing process has been reported elsewhere [53, 57, 59, 60]. Singh *et al.* [60] described the design of control architecture for a continuous tablet manufacturing process via roller compaction. The control architecture was implemented into an integrated process flowsheet model and the controller parameters was tuned. The performance of the control system was evaluated for set point tracking and disturbance rejection. Singh *et al.* [57] developed a hybrid

MPC-PID control architecture for direct compaction continuous tablet manufacturing process. MPC was implemented in MATLAB and PID was implemented with the model simulated in gPROMS. Matlab and gPROMS communicated via gOMATLAB tool of gPROMS. The design, implementation, and evaluation of control architecture for continuous tablet manufacturing via wet granulation was studied by Singh *et al.* [59]. Additional feedforward/feedback control architecture was also design, implemented, and evaluated [62].

12.12 Step 11: Implementation and Verification of the Control Framework

This step constitutes the implementation in the physical line and the experimental verification of the control architecture developed in Steps 9 and 10. A detailed, step by step procedure to implement and verify the control architecture in an actual plant has been presented by Singh *et al.* [56]. The key challenge is enabling communication between the real time process monitoring sensors, their software, the data management tool, the control platform and the plant actuators. Each component of the sensing and control framework communicates through its own language. Discussed below is a gist of what constitutes facilitating these multi-lingual components to communicate accurately and efficiently, thereby enabling closed loop control.

The physical sensor measures a material attribute (e.g., blend composition) or a process parameter (e.g., compression force) and creates a representative signal. In the case of spectroscopic sensors, the generated signal is multivariate in nature and thus needs to be regressed to an ordinary number. The regressed signal is sent to a data management software. The data management tool communicates this signal to the control system, typically through an OPC (OLE process control) protocol, in addition to performing several other functions. The control system assimilates this signal and decides on the necessary corrective actions. The process hardware or the actuators receive directions from the control system and implement the corrective action to the plant, to bring the CQA/CPP back to its set point. We will briefly discuss each of these communication steps, considerations during implementation of each step, and commonly available platform technologies to set up each communication junction.

At the beginning of the control loop is the *sensing probe*. The probe senses the material and creates a representative signal. This signal is typically stored in the sensor's proprietary software. For some probes, the signal could be a simple number. For NIR and some other spectroscopy-based sensors, the signal is multivariate in nature. In such cases, the multivariate signal must be converted to one (or a few) ordinary number(s). This is because most control algorithms are designed to assimilate ordinary numerical or binary numbers as input. Multivariate signals are converted to ordinary digits in the *online prediction tool* with the help of previously developed calibration models. The chemometric models are not developed in the online prediction tool but have to be developed using commercially available, *multivariate data analysis software*, such as Unscrambler X by Camo or Simca P+ by Umetrics. These models are then imported to the online prediction tool. The online prediction tool receives the multivariate signal from the sensor and converts it to an ordinary number using the imported calibration model. The predicted value of the CQA/CPP is

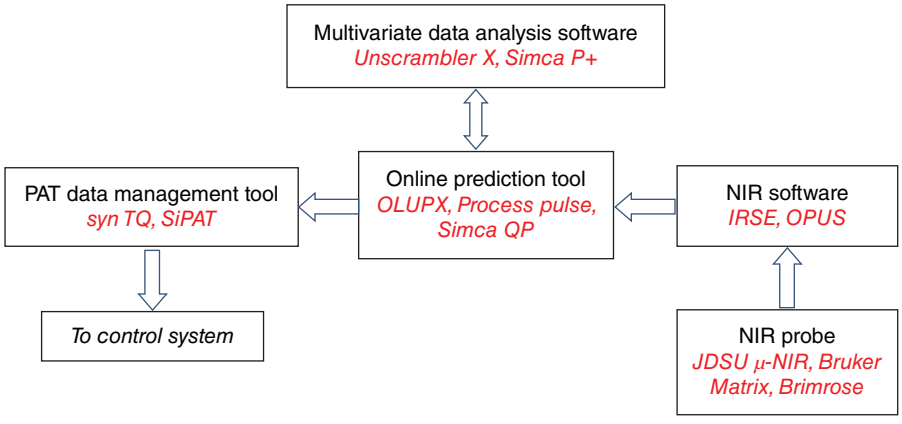

Figure 12.11 *Flow of communication from a sensor to the data management tool. Examples of each tool from different vendors are also given.*

communicated to a *PAT data management tool*. A schematic illustrating the flow of communication is shown in Figure 12.11.

The PAT data management tool receives the predicted value of the CQA. This tool is a software for systematic data collection and storage. Moreover, the tool has an OPC communication protocol and can thus communicate with the control platform, which too, is OPC compliant. The data management tool allows data to be stored, protected and plotted. It allows for alarms to be created. synTQ from Optimal Industrial Automation Limited and SiPAT from Siemens are common commercially available PAT data management platforms.

The control system receives data from the PAT data management toolbox via an OPC protocol. The control system is the component of the control framework which takes the input signal, and decides on the necessary corrective action based on a previously developed algorithm. It communicates this action to the actuators, which make physical changes to ensure the CQA/CPP returns to its set point. The control system has hardware and software components. The software component is tasked with data reception, analysis and decision making. The hardware component is tasked with communicating with the actuators. This is typically done via a standard industrial communication protocols like Fieldbus or Ethernet. The flow of communication is illustrated in Figure 12.12. DeltaV from Emerson Process Management and PCS7 by Siemens are commercially available control platform which are geared for pharmaceutical processes.

Once the implementation of the control system is complete, the next step is to verify it in order to ensure that all its components are performing as expected. As an illustrative example, Singh *et al.* [56] performed a verification exercise on a ratio controller for two feeders. The example is described in brief here. Two feeders, one feeding semi-fine acetaminophen (Mallinckrodt) and the other feeding silicified microcrystalline cellulose (Prosolv, JRS Pharma) were linked by a ratio controller. The feeders fed into a Comil which fed into a continuous blender. The blender output was discharged into a chute, on which was mounted a JDSU micro-NIR. The NIR monitored the acetaminophen concentration. A previously developed calibration model in Unscrambler X was imported to Process Pulse.

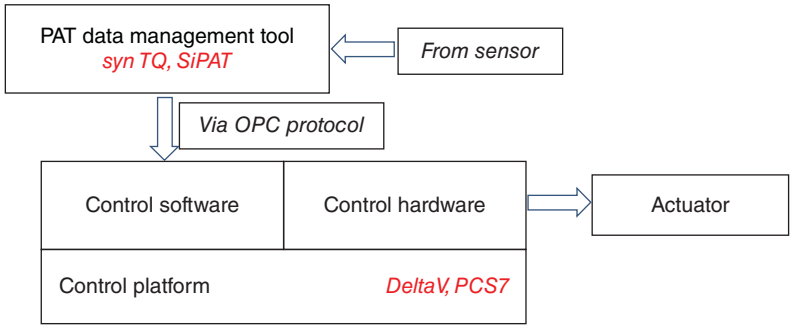

Figure 12.12 *Flow of communication from the PAT data management tool to the actuator.*

OLUPX, an online prediction engine, was integrated with Process Pulse. The APAP concentration was communicated to the DeltaV control system via a MATLAB OPC toolbox. A model predictive control (MPC) algorithm analyzed the input and communicated the corrective action to the actuators, the feeder screws. The results were previously reported elsewhere [56, 63].

The operating and control user interface for a direct compaction continuous tablet manufacturing pilot plant is shown in Figure 12.13. As shown in the figure, four feeders (one API feeder, two excipient feeders, one lubricant feeder), mill, blender and tablet press has been connected with the control platform. Note that each unit operation can also be run individually, if deemed necessary. Operational parameters (e.g., set points and actual values) have been displayed in real time for each unit operation.

12.13 Step 12: Characterize and Verify Closed Performance

This step constitutes characterizing and verifying closed loop performance of the entire process. An exercise similar to the one performed in Step 6 should be repeated, albeit this time with the control system enabled. This involves changing certain process parameters and observing the response of system to this change. This allows the experimenter to quantify the sensitivity of the system to process inputs in the presence of the control system, whose objective is to ensure that CQAs do not deviate from their prescribed set point. Such characterization increases process knowledge, facilitating quality to be built into the product by design. The exercise also confirms that the highest quality product is produced at the optimum process parameters.

Step 11 involved the implementation of the individual control loops and their verification. However, when running the entire process, all control loops operate simultaneously, which may create unanticipated interactions that must be understood and conflicts that might require resolution. Thus, a thorough characterization of the effect of process parameters on the CQAs of the final product is necessary. Moreover, running the process under the supervision of the control system allows one to understand the system performance not only at the set point but also around the set point. For instance, consider a scenario where the effect of the blender speed on the final product is being tested. At a certain design point of the DOE, the blender speed is set at a given value, for example, 100 rpm. During

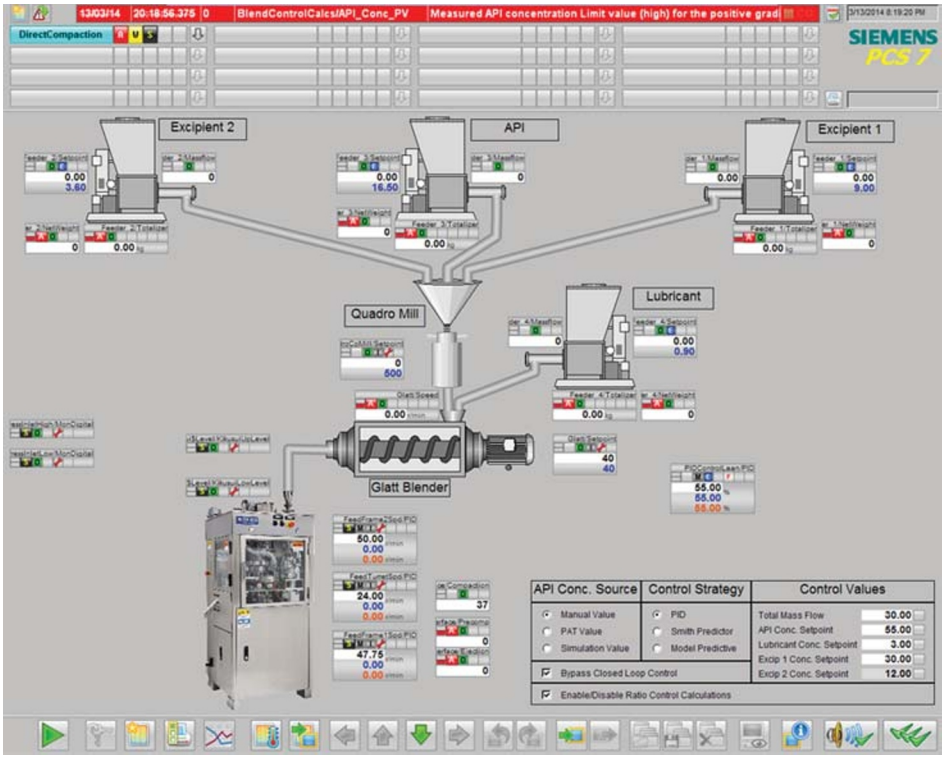

Figure 12.13 *Plant operating and control user interface.*

Step 6, when this design point was tested, the blender speed, in the absence of a control system always stayed constant at 100 rpm. With the control system enabled, the blender speed may vary depending upon the CQAs that are linked to the speed. This allows for the population of the response surface near the blender speed of 100 rpm.

Interaction between control loops, as previously mentioned, may also create unprecedented interaction effects. Consider the previous example, where the blender speed is set at 100 rpm. Fluctuations in this speed occur if the speed is linked in a control loop. Consider a scenario, where the speed increases from 100 to 105 rpm. The slight increase in the speed results in a decrease in the blender holdup. The excess material is ejected from the blender and is added to the chute following the blender. A level sensor detects an increase in the holdup level within the chute. The system, to maintain its set point, might then increase the speed of tableting. An increase in tableting speed could result in a change in properties of the final product (example, hardness and dissolution properties of tablets), triggering new control actions. The process, if allowed to continue evolving, might then become unstable. Thus, it is highly recommended that the DOE performed in Step 6 should be repeated in the presence of the control system. It enables one to characterize the effect of control loop interactions on the CQAs of the process stream and the final product.

Finally, the long-term stability of the system, in the presence of the control system, should also be tested as a part of this step. This helps to ensure that process does not drift with

time, and in case it does, the control system can detect this and take corrective action. It also ensures no physical changes to the system occur as result of extended operation, for example, sticking of powder material to surfaces over time, choking of hoppers, coating of blender and mill blades with material, and so on.

The step is designed to enhance the experimenter's understanding of the system and enhance process knowledge. It helps to understand sources of variability and establish control over the variability. It also helps to establish relationships between CMAs, CPPs, and CQAs. Finally, it facilitates process optimization to ensure the highest quality product. This step is the key enabler for successful implementation of QbD [64].

12.14 Conclusions

As of the date when this chapter was written (December 2015), the pharmaceutical industry has a large and rapidly growing degree of interest in implementing continuous manufacturing plants, but little actual experience with fully integrated, distributed control capabilities. Questions such as "do we really need closed-loop control?" and "what is the value of models?" continue to be asked. While in a general sense these questions are legitimate, in the narrow context of continuous manufacturing facility they actually reveal that as a community of practice, the pharmaceutical industry is still trying to understand how to use these technologies. Many other questions remain, including what is the appropriate regulatory framework for "process validation" and for quality assurance for continuous processes, how to standardize materials, equipment, and operations in order to make adoption faster, more reliable, and less expensive, and how to accelerate and optimize product and process development. These remain areas of active research, and as experience is gained and best practices emerge, the answers to these questions will have a profound impact on the management of the pharmaceutical product pipe line and supply chain.

Many efforts are currently under way to collect and align best practices between academics, regulators, users, and suppliers of continuous manufacturing technology. Generally speaking, the initial excitement is now being tempered by a growing recognition that a properly implemented facility is a major task, and that the mechanical integration is perhaps the easiest part of the job – the integration of sensing and control and the implementation of capabilities for real time quality assurance is a much larger, and much less intuitive undertaking. This is a welcomed development, one that greatly increases the probability of harvesting the full benefits of advanced manufacturing while minimizing the probability of disappointments.

In the meantime, another critical issue is worth pointing out – the skill set. The implementation and efficient operation of an integrated continuous facility requires a heavy dose of "process engineering" skills. Process engineering is a large component of product and process development in many industries, such as petroleum processing, petrochemicals, specialty chemicals, and others. It has a well developed toolbox, including the ability to develop and use a wide range of models to maximize process understanding while minimizing Edisonian "trial and error", and capabilities to perform science-based process scale-up and scale-down. As the pharmaceutical industry makes progress in adopting advanced manufacturing methods, including continuous manufacturing, it will need the equivalent toolbox. Some of the components needed can be readily "translated" from toolboxes in other

industries, but some of the tools are specific, because both materials and quality requirements are specific to pharma. In the next decade, we will make major progress in this direction, providing exciting career opportunities for young scientists that are currently choosing where to apply their talents.

It should prove exciting.

References

[1] Engisch, W., and F. Muzzio (2015) Loss-in-weight feeding trials case study: pharmaceutical formulation. *Journal of Pharmaceutical Innovation.* **10**(1): 56–75.

[2] Muzzio, F., S. Oka, and W. Engisch (2010) *Addressing Material Properties in the Design of a Direct Compression Continuous Manufacturing System*. Springer, Heidelberg.

[3] Portillo, P.M., et al. (2010) Investigation of the effect of impeller rotation rate, powder flow rate, and cohesion on powder flow behavior in a continuous blender using PEPT. *Chemical Engineering Science.* **65**(21): 5658–5668.

[4] Muzzio, F.J., T. Shinbrot, and B.J. Glasser (2002) Powder technology in the pharmaceutical industry: the need to catch up fast. *Powder Technology.* **124**(1/2): 1–7.

[5] Vanarase, A.U., J.G. Osorio, and F.J. Muzzio (2013) Effects of powder flow properties and shear environment on the performance of continuous mixing of pharmaceutical powders. *Powder Technology.* **246**: 63–72.

[6] Singh, R., et al. (2015) Real time monitoring of powder blend bulk density for coupled feed-forward/feed-back control of a continuous direct compaction tablet manufacturing process. *International Journal of Pharmaceutics.* **495**(1): 612–625.

[7] Hernandez, E., et al. (2016) Prediction of dissolution profiles by non-destructive near infrared spectroscopy in tablets subjected to different levels of strain. *Journal of Pharmaceutical and Biomedical Analysis.* **117**: 568–576.

[8] Koynov, S. (2015) *Using Statistical Methods to Optimize Powder Flow Measurements and to Predict Powder Processing Performance*.Rutgers University, Graduate School, New Brunswick.

[9] Engisch, W.E. and F.J. Muzzio (2012) Method for characterization of loss-in-weight feeder equipment. *Powder Technology.* **228**: 395–403.

[10] Engisch, W.E. and F.J. Muzzio (2015) Feedrate deviations caused by hopper refill of loss-in-weight feeders. *Powder Technology.* **283**: 389–400.

[11] Froment, G.F., K.B. Bischoff, and J. De Wilde (1990) *Chemical Reactor Analysis and Design*, vol. **2**. John Wiley & Sons, Inc., New York.

[12] Gao, Y., et al. (2011) Characterizing continuous powder mixing using residence time distribution. *Chemical Engineering Science.* **66**(3): 417–425.

[13] Pernenkil, L. and C.L. Cooney (2006) A review on the continuous blending of powders. *Chemical Engineering Science.* **61**(2): 720–742.

[14] Oka, S. and F. Muzzio (2012) *Continuous Powder Blenders for Pharmaceutical Applications*. Springer, Heidelberg.

[15] Vanarase, A.U. and F.J. Muzzio (2011) Effect of operating conditions and design parameters in a continuous powder mixer. *Powder Technology.* **208**(1): 26–36.

[16] Portillo, P.M., M.G. Ierapetritou, and F.J. Muzzio (2008) Characterization of continuous convective powder mixing processes. *Powder Technology.* **182**(3): 368–378.

[17] Portillo, P.M., M.G. Ierapetritou, and F.J. Muzzio (2009) Effects of rotation rate, mixing angle, and cohesion in two continuous powder mixers — A statistical approach. *Powder Technology.* **194**(3): 217–227.

[18] Pingali, K., et al. (2011) Mixing order of glidant and lubricant – Influence on powder and tablet properties. *International Journal of Pharmaceutics.* **409**(1/2): 269–277.

[19] Mehrotra, A., et al. (2007) Influence of shear intensity and total shear on properties of blends and tablets of lactose and cellulose lubricated with magnesium stearate. *International Journal of Pharmaceutics.* **336**(2): 284–291.
[20] Pingali, K., et al. (2011) Evaluation of strain-induced hydrophobicity of pharmaceutical blends and its effect on drug release rate under multiple compression conditions. *Drug Developement and Industrial Pharmaceuticals.* **37**(4): 428–435.
[21] Vanarase, A.U., et al. (2010) Real-time monitoring of drug concentration in a continuous powder mixing process using NIR spectroscopy. *Chemical Engineering Science.* **65**(21): 5728–5733.
[22] Vanarase, A.U. (2011) *Design, Modeling and Real-time Monitoring of Continuous Powder Mixing Processes*. Rutgers University, Graduate School, New Brunswick.
[23] Osorio, J.G., et al. (2015) Continuous powder mixing. *Pharmaceutical Blending and Mixing.***2015**: 101–127.
[24] Himmelblau, D. and K. Bischoff (1968) *Process Analysis and Simulation: Deterministic Systems*.John Wiley & Sons, Inc., New York.
[25] Sargent, R. (2010) Verification and validation of simulation models. in *Proceedings of the 2010 Winter Simulation Conference*,SCS, Miami.
[26] Balci, O. (2010) Golden rules of verification, validation, testing, and certification of modeling and simulation applications. *SCS M&S Magazine.* **4**.
[27] Sargent, R.G. (2005) Verification and validation of simulation models, in *Proceedings of the 37th Conference on Winter Simulation*. Winter Simulation Conference, Orlando, pp. 130–143.
[28] Arlot, S. and Celisse, A. (2010) A survey of cross-validation procedures for model selection. *Statistics Surveys.* **4**: 40–79.
[29] Min, F.Y.Y. and Wang, Z.C. (2010) Knowledge-based method for the validation of complex simulation models. *Simulations and Models in Practice.* **19**: 500–515.
[30] Lee, S., et al. (2015) Modernizing pharmaceutical manufacturing: from batch to continuous production. *Journal of Pharmaceutical Innovation.* **10**(3): 191–199.
[31] Nosal, R. and T. Schultz (2008) PQLI definition of criticality. *Journal of Pharmaceutical Innovation.* **3**(2): 69–78.
[32] Rogers, A. and M. Ierapetritou (2004) Challenges and opportunities in pharmaceutical manufacturing modeling and optimization, in *Computer Aided Chemical Engineering*, (eds J.D.S. Mario R. Eden and P.T. Gavin), Elsevier, New York, pp. 144–149.
[33] Hlinak, A.J., et al. (2006) Understanding critical material properties for solid dosage form design. *Journal of Pharmaceutical Innovation.* **2006**: 12–17.
[34] Leopore, J. and Spavins, J. (2008) PQLI design space. *Journal of Pharmaceutical Innovation.* **3**(2): 79–87.
[35] Airaksinen, S., et al. (2005) Role of water in the physical stability of solid dosage formulations. *Journal of Pharmaceutical Science.* **94**(10): 2147–2165.
[36] Lionberger, R.A., et al. (2008) Quality by design: concepts for ANDAs. *AAPS Journal.* **10**(2): 268–276.
[37] US FDA (2002) *Pharmaceutical cGMPs for the 21st Century: a Risk-based Approach*, FDA, Rockville.
[38] US FDA (2004) *Guidance for Industry: PAT — A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance*, FDA, Rockville.
[39] US FDA (2014) *Guidance for Industry Current Good Manufacturing Practice*, FDA, Rockville.
[40] Ng, K.M. (2002) Design and development of solids processes – A process systems engineering perspective. *Powder Technology.* **126**(3): 205–210.
[41] McKenzie, P.K., S. Tom, J. Rubin, E., and Futran, M. (2006) Can pharmaceutical process development become high tech? *AIChE Journal.* **52**: 12.

[42] Boukouvala, F., et al. (2012) An integrated approach for dynamic flowsheet modeling and sensitivity analysis of a continuous tablet manufacturing process. *Computers and Chemical Engineering.* **42**: 30–47.

[43] Tolsma, J.E., J.A. Clabaugh, and P.I. Barton (2002) Symbolic incorporation of external procedures into process modeling environments. *Industrial Engineering and Chemical Research.* **41**: 3687–3876.

[44] US FDA (2004) *PAT Guidance for Industry – a Framework for Innovative Pharmaceutical Development, Manufacturing and Quality Assurance*, FDA, Rockville.

[45] El-Hagrasy, A.S., et al. (2001) Near-infrared spectroscopy and imaging for the monitoring of powder blend homogeneity. *Journal of Pharmaceutical Sciences.* **90**(9): 1298–1307.

[46] El-Hagrasy, A.S. and J.K. Drennen (2006) A process analytical technology approach to near-infrared process control of pharmaceutical powder blending. Part III: Quantitative near-infrared calibration for prediction of blend homogeneity and characterization of powder mixing kinetics. *Journal of Pharmaceutical Sciences.* **95**(2): 422–434.

[47] De Beer, T., et al. (2011) Near infrared and Raman spectroscopy for the in-process monitoring of pharmaceutical production processes. *International Journal of Pharmaceutics.* **417**(1/2): 32–47.

[48] Silva, A.F.T., et al. (2013) Particle sizing measurements in pharmaceutical applications: Comparison of in-process methods versus off-line methods. *European Journal of Pharmaceutics and Biopharmaceutics*. **85**(3, part B): 1006–1018.

[49] Davies, C.E., R.C. Lankshear, and E.S. Webster (2011) Direct measurement of the bulk density of cohesive particulatematerials by a quasicontinuous in-line weighing method. *International Journal of Pharmaceutics.* **417**(1/2): 21–27.

[50] Singh, R. (2009) Model-based computer-aided framework for design of process monitoring and analysis systems, in *Chemical and Biochemical Engineering*, Technical University of Denmark, Copenhagen, p. 296.

[51] Singh, R., K.V. Gernaey, and R. Gani (2009) Model-based computer-aided framework for design of process monitoring and analysis systems. *Computers and Chemical Engineering.* **33**(1): 22–42.

[52] Bristol, E. (1966) On a new measure of interaction for multivariable process control. *IEEE Transactions on Automatic Control.* **11**(1): 133–134.

[53] Singh, R., Muzzio, F., Ierapetritou, M., and Ramachandran, R. (2015) A combined feed-forward/feed-back control system for a QbD based continuous tablet manufacturing process. *Processes.* **3**: 339–356.

[54] Myerson, A.S., et al. (2015) Control systems engineering in continuous pharmaceutical manufacturing. *Journal of Pharmaceutical Science.* **104**: 832–839.

[55] Singh, R., K.V. Gernaey, and R. Gani (2010) An ontological knowledge-based system for the selection of process monitoring and analysis tools. *Computers and Chemical Engineering.* **34**(7): 1137–1154.

[56] Singh, R., et al. (2014) A systematic framework for onsite design and implementation of a control system in a continuous tablet manufacturing process. *Computers and Chemical Engineering*, 2014. **66**: 186–200.

[57] Singh, R., M. Ierapetritou, and R. Ramachandran (2013) System-wide hybrid MPC–PID control of a continuous pharmaceutical tablet manufacturing process via direct compaction. *European Journal of Pharmaceutics and Biopharmaceutics*. **85**(3, part B): 1164–1182.

[58] Ziegler, J.G. and B. Nichols (1942) Optimum settings for automatic controllers. *Transactions of the ASME.* **64**: 759–765.

[59] Ravendra, S., et al. (2014) Closed-loop feedback control of a continuous pharmaceutical tablet manufacturing process via wet granulation. *Journal of Pharmaceutic Innovations.* **9**: 16–37.

[60] Singh, R., M. Ierapetritou, and R. Ramachandran (2012) An engineering study on the enhanced control and operation of continuous manufacturing of pharmaceutical tablets via roller compaction. *International Journal of Pharmaceutics.* **438**(1/2): 307–326.
[61] Seborg, D.E., T.F. Edgar, and D.A. Mellichamp (2004) *Process Dynamics and Control*, 2nd edn, John Wiley & Sons, Inc., New York.
[62] Singh, R., et al. (2015) A combined feed-forward/feed-back control system for a QbD based continuous tablet manufacturing process. *Processes.* **3**: 339–356.
[63] Singh, R., et al. (2014) Implementation of an advanced hybrid MPC–PID control system using PAT tools into a direct compaction continuous pharmaceutical tablet manufacturing pilot plant. *International Journal of Pharmaceutics.* **473**(1/2): 38–54.
[64] Yu, L.X. (2008) Pharmaceutical quality by design: product and process development, understanding, and control. *Pharmaceutical Research.* **25**(4): 781–791.
[65] Oka, S., et al. A quantitative study of the effect of process parameters on key granule characteristics in a high shear wet granulation process involving a two component pharmaceutical blend. *Advanced Powder Technology*. **26**: 315–322.
[66] Oka, S., et al. The effects of improper mixing and preferential wetting of active and excipient ingredients on content uniformity in high shear wet granulation. *Powder Technology*. **278**: 266–277.
[67] Oka, S. Effects of powder cohesion and segregation on pharmaceutical mixing and granulation. Retrieved from http://dx.doi.org/doi:10.7282/T30R9RM8
[68] Oka, S., et al. Diminished segregation in continuous blenders. *Powder Technology*. **309**: 79–88.
[69] Oka, S. and F. Muzzio. Using residence time distribution to understand continuous blending. *Powder and Bulk Engineering*. April 2017.
[70] Oka, S., et al. Lubrication in continuous tubular blenders. *Pharm Technology*. **40**: 44–45.
[71] Barrasso, et al. Population balance model validation and prediction of CQAs for continuous milling processes: toward QbDin pharmaceutical drug product manufacturing. *Journal of Pharmaceutical Innovation*. **8**: 147–162.

13

End to End Continuous Manufacturing: Integration of Unit Operations

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13.1 Introduction

True continuous manufacturing (CM) of a pharmaceutical is more than just a method of manufacturing in which materials are continuously being fed and removed from a process. It is the ultimate application of quality by design, in which the process is developed as an integrated whole with a systems approach, together with model-based design and control. Tremendous benefits can be obtained when realizing this type of fully continuous process for pharmaceuticals, similar to what has been obtained for other industries. Examples of such potential benefits include improved control over process and product quality, highly reduced quantities of intermediate compounds, the ability to continuously recycle material, substantial cost savings, and reduced footprint. However, important technological

Continuous Manufacturing of Pharmaceuticals, First Edition.
Edited by Peter Kleinebudde, Johannes Khinast, and Jukka Rantanen.
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and organizational challenges have to be met in order to realize CM across the board for pharmaceuticals.

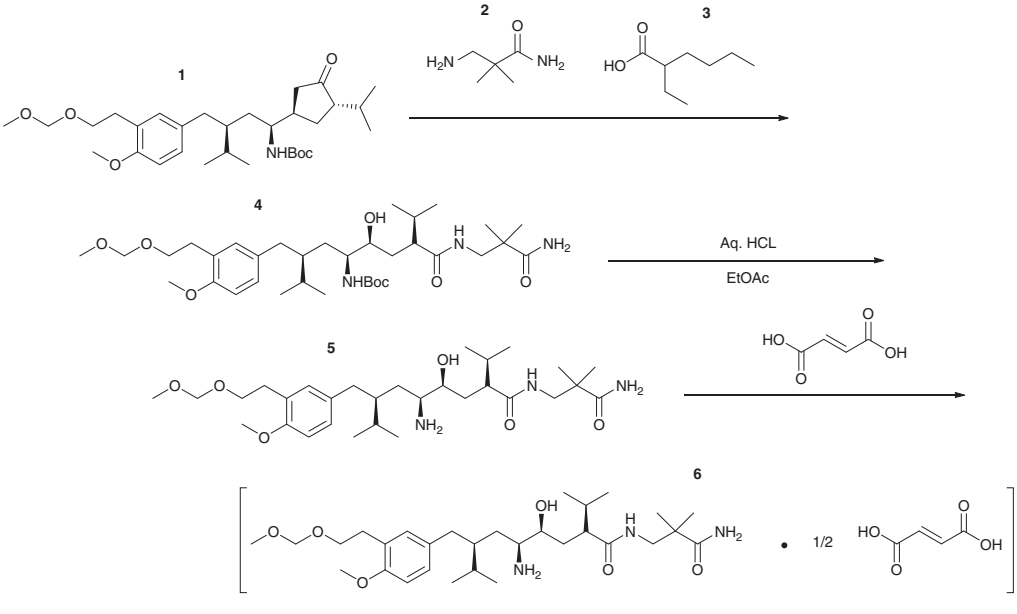
The objective of this chapter is to discuss the challenges and opportunities when fully integrating a continuous process for pharmaceuticals from end to end. A realistic case study will be used throughout the chapter to support the discussion with real-life examples from pilot plant experiments. The pilot plant produces a pharmaceutical (aliskiren hemifumarate) from start (advanced chemical intermediate) to finish (tablet with final dosage) in continuous flow. This chapter has a detailed description of the pilot plant in Section 13.2. A special focus will be on those parts of the plant where new technologies were used that are difficult to operate batchwise, which highlights the idea that the development of a CM process should not simply be seen as an exercise to run batch technologies in continuous flow, but rather as an opportunity to develop novel technologies that are only operable within a continuous environment. Section 13.3 discusses the role of system dynamics. In Section 13.4, the role of process analytical technology (PAT) in the studied pilot plant is discussed. The development of advanced PAT can be seen as one of the main enabling technologies of CM for pharmaceuticals. In addition, Section 13.4 briefly discusses the relation between PAT and process models to estimate unknown process variables for monitoring and automated control. The pilot plant that is discussed in this chapter exhibits significant benefits compared to the existing batch process. Moreover, novel technologies that are currently under development are expected to further enhance CM of pharmaceuticals. Examples of such future technologies are discussed in Section 13.5. The chapter ends with a chapter summary and discussion of benefits and challenges of CM of pharmaceuticals.

13.2 Process Description

We previously reported [1] a process to continuously manufacture aliskiren hemifumarate, **6**, containing tablets starting from an advanced intermediate, **1** (Scheme 13.1). This section provides a brief overview of the key unit operations in the process (Figure 13.1) for completeness.

The two starting materials **1** and **2** enter the process as solid powders that are melted separately and dosed into the first reactor, R1, along with the liquid catalyst **3**. The reactor consists of a static mixer, M1, to initially mix the three streams followed by a tube reactor with a nominal residence time of 4 h. The mixer and reactor are contained in an oven to maintain the temperature at 100 °C. The solvent-free reaction product is then dissolved in a mixture of ethyl acetate and water to form a two-phase stream. The streams are separated by membrane-based liquid–liquid phase separators. The aqueous phase containing the catalyst and excess **2** leaves the process either as waste or can be used as a potential recycle stream. The organic phase proceeds to a series of crystallizers, Cr1 and Cr2.

The crystallization is performed to purify the stream of reaction product **4** by removing leftover starting material **1** which was known to form a critical impurity in the final product if processed further. The crystallization is carried out in a series of two mixed suspension, mixed product removal (MSMPR) crystallization vessels. Each crystallization vessel is controlled at a constant level with a nominal residence time of 4 h in which the output slurry of crystallizer Cr2 is conveyed to a continuous filter, W1. The filter removes the mother liquor and washes the crystals with additional solvents. The concentrated wet cake is then diluted with additional solvent in a mixed vessel, D1. The concentration of solid in D1 is



Scheme 13.1 *Synthetic route to aliskiren hemifumarate starting from advanced intermediate* ***1*** *using continuous processes.*

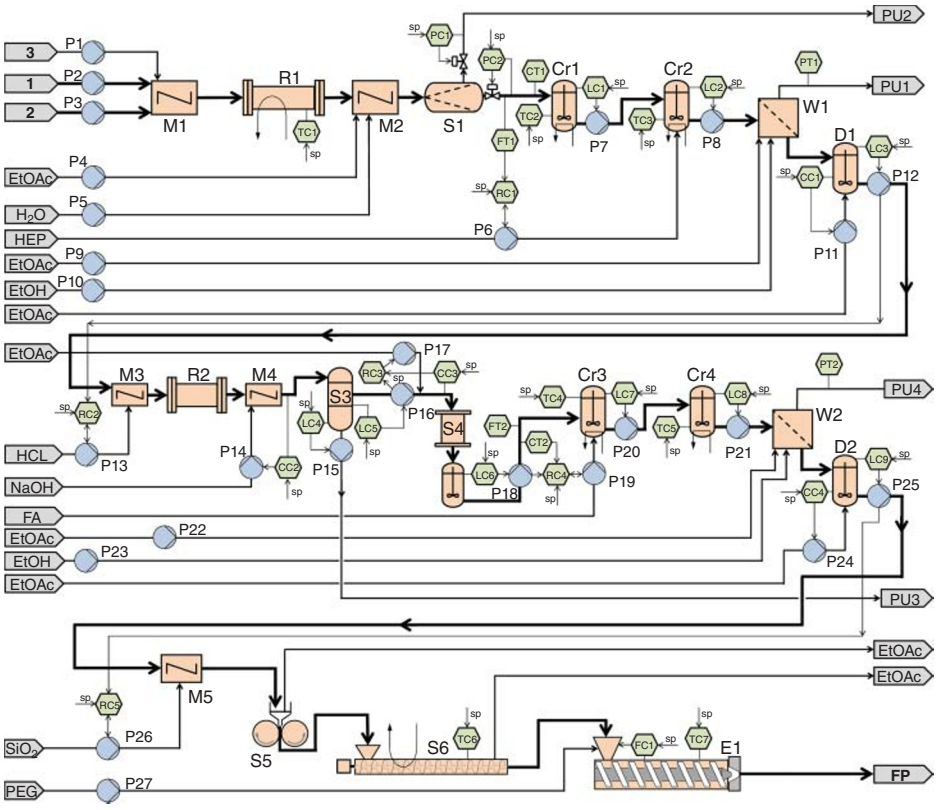


Figure 13.1 *Process flow diagram with control loops. P – pump; M – mixer; R – reactor; TC – temperature controller; PC – pressure controller; CT – concentration transmitter; FT – flow transmitter; RC – ratio controller; S – separation; Cr – crystallization vessel; LC – level controller; PT – pressure transmitter; W – filter/wash; D – dilution tank; CC – concentration controller; FC – flow controller; E – extruder; MD – mold; sp – control set point. Adapted from [1]. Copyright 2013 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim.*

controlled by adjusting the solvent flow rate into the vessel using a density flow cell (CC1) to monitor the mixture composition.

Following dilution of the purified **4** slurry, a second reactor performs the deprotection reaction to form the active pharmaceutical ingredient aliskiren **5**. A concentrated stream of aqueous HCl is mixed with the slurry in the second tube reactor. Instead of using a static mixer to combine the two streams, gas from the generated CO_2 mixes the streams within the tube reactor. The reaction is rapidly quenched at the reactor outlet by a stream of NaOH using a static mixer to ensure the reaction is halted. The addition of NaOH is controlled by an inline pH probe (CC2) following the mixer. The reaction is highly exothermic with the heat handled by the small reaction volume and high heat transfer in the static mixer followed by a small diameter tube – a process that would be difficult to carry out batchwise. The pH of the reaction product is controlled via automated feedback control with the NaOH stream

as a manipulated variable. The two-phase reaction product flows into a settling tank, S3, where the aqueous phase is sent to waste and the organic phase is fed forward towards a crystallization operation.

The concentrated organic phase is diluted with additional ethyl acetate solvent and then clarified with microfiltration membranes, S4, to remove salt particles that form from dilution, which produces a clear stream that is conducive to concentration measurement of **5** by an ultraviolet (UV) flow cell (CC3). The UV measurement is fed back to a flow ratio controller (RC3) that controls the ethyl acetate dilution stream. A column of molecular sieves dry the organic phase prior to metering into an MSMPR crystallizer, Cr3. Fumaric acid is metered into the crystallizer by a ratio controller (RC4) supported by another UV sensor (CT2) to monitor the concentration of **5** entering the crystallizer. The hemifumarate salt of aliskiren **6** forms and precipitates to form a slurry. A second crystallizer, Cr4, operated at lower temperature is used to increase the recovery of **6**. The outlet flow rate of each crystallization vessel is controlled by a level sensor connected to a pump to maintain a nominal residence time of 4 h. The outlet of the second crystallizer, Cr4, is then fed to a second continuous wash and filter, W2. The wet cake is then diluted with ethyl acetate in a second slurry tank, D2, using a density flow cell (CC4) to monitor and control slurry concentration.

Finally, a slurry of SiO_2 is mixed in line with the purified **6** slurry stream prior to entering a two-stage drier. The first stage, S6, evaporates the bulk solvent using heated drums which evaporate the solvent and press the slurry into a thin cake which is flaked and drops into a second stage, a screw vacuum drier, S7. The remainder of the solvent is removed in the screw dryer producing a dry powder. Subsequently, the powder is pneumatically conveyed into a gravimetric feeder which meters the powder into a twin screw extruder, E1. Polyethylene glycol is metered into the extruder as the main excipient. The extruder mixes the active ingredient with the excipient which is then directly sent into a compression mold, MD. The mold forms the tablets, which are ejected and collected at the end of the process. The produced tablets met tests for product quality related to dissolution behavior and composition [1].

The continuous system has been designed in a highly modular fashion, which allows for processing units to be exchanged easily. Physically, a modular design has been realized by placing closely related unit operations into single enclosures that can exchange material and information with each other enclosure. Individual panels allow for all communication hardware to be mounted in the relevant enclosure such that all information streams from a single enclosure can interact with a central control system (Siemens Simatic PCS7). The software of the control system has also been designed in a modular fashion by using different operating screens for different parts of the process. In general, a modular design for CM is important to enhance process development and equipment utilization. Furthermore, a modular design enables the process to operate between selected unit operations without the need to operate the entire process. The crystallization tanks and dilution tanks following filtration can act as holding vessels so the first or section reaction can be run in isolation. Typically, holding a slurry will result in changing crystal size distribution which can have an effect on the final product performance; however, the slurries are all dissolved in subsequent unit operations. The second reaction involves dissolution into an organic solvent phase while the final active ingredient crystals are melted in the presence of the PEG excipient by the melt extrusion unit operation.

13.2.1 Specific Benefits Obtained as a Result of CM

The continuous manufacture of aliskiren hemifumarate tablets makes use of several benefits derived from the integration of continuous unit operations. The upstream synthesis of the active ingredient makes use of chemical steps motivated by operation in a continuous manner [2]. Existing batch synthesis of **4** involve long reaction times under dilute conditions [3–6]. In order to operate in flow, a faster synthesis performed as a melt is used, a synthesis that would be difficult to mix effectively in a stirred batch reactor [2]. The second reaction is also run under concentrated conditions relying on the fast mixing and increased heat transfer of the tube reactor to operate successfully [7]. The downstream unit operations are also streamlined compared to typical tablet production processes involving milling, powder blending, granulation, and tablet compression. The continuous process employed makes use of a melt extruder that produces the formulated drug product and is directly coupled to the tablet formation process, which significantly reduces the footprint and processing time required to go from drug substance to the final tablet.

Integrating multiple units together allows for unique process conditions not available when manufacturing occurs sequentially in discrete batch units. By operating continuously and linking unit operations together, the quantity of intermediate compounds can be minimized substantially. This benefit is found specifically in the second reaction, which involves a rapid quench following the reactor. The low pH within the reactor results in degradation of **5** if the reaction is not quenched soon after completion, which is relatively simple to achieve in a continuous process by locating the quench at the end of a reactor with a well-defined residence time. In the event of a process upset, the only material at risk is the small amount located in the reactor. For a batch process, the entire batch would be at risk, which would be many times the volume of the continuous process given the lower equipment utilization for a rapid reaction (<5 min) requiring more loading and unloading time relative to the reaction time [8].

13.3 System Dynamics

13.3.1 Model-based Design and Control are the Governing Concepts in CM

Quantitative understanding of the dynamics of a continuous pharmaceutical process is essential, not only of the dynamics of individual processing steps, but also of the dynamics of the system as a whole. Process simulations are more important for the development of continuous pharmaceutical processes as various long-term experiments to study system-wide behavior may not be well attainable. Process simulations can be used to, at least partially, fill that gap by predicting the short- and long-term behavior of an integrated process with relatively low investment. Experimental efforts can be directed towards the understanding of single unit operations, which allow for mathematical models of single unit operations to be constructed, with quantified uncertainty. The behavior of the complete system can, subsequently, be predicted by connecting all models of single unit operations in an integrated process model. Such methodology based on unit operations is well established within the chemical industry. Consequently, software to support dynamic process simulations of complete plants and a range of analysis tools are readily available. In the remainder of this section, some key concepts related to system dynamics applied to the CM process described in Section 13.2 will be discussed. Data obtained from both pilot plant experiments and process simulations are used to support the discussion, which highlights the essential role of process models for CM of pharmaceuticals.

13.3.2 The Absence of True Steady-state Operation and the Implications for Product Quality Control

A process is said to be operating in steady state when the values of all process variables do not change with time within a certain tolerance. On the other hand, process variables do change during transient process operation. The ability to operate a continuous process around steady state offers opportunities for simplified process control, because critical quality attributes (CQAs) do not significantly change over time anymore. In particular, in the case of batchwise processing, which is by definition transient, control of product quality is complicated by the need to predict the dynamic course of the processing step such that the *anticipated* final product quality meets specifications. In the case of continuous processing, when startup and shutdown are excluded, product quality control can be focused around steady-state operation, which involves only a single operating point. In addition, knowledge on the final product quality is always available as product is being produced continuously, which allows for corrective action to be taken when trends in product quality are undesired. Therefore, operation around a steady-state operating point offers advantages for product quality control. However, as will be demonstrated in this section, in practical terms it is not always clear when a CM process is operating in (or near) steady state. Fortunately, this is not a problem since the objective of CM is to maintain CQAs within a desired range, which does not necessarily require the process to be in steady state. Model-based control is a key concept of CM, which can greatly enhance the control of CQAs when operating outside steady state.

There are several, mainly practical, difficulties in evaluating whether a CM process operates near steady state, which makes it impractical to design a system to only produce product under clear steady state conditions. First, the precise transition between startup behavior and steady-state behavior may be ambiguous. For example, Figure 13.2 demonstrates the values of two process variables during startup of the pilot plant. Clearly, the holdup of the illustrated tank approaches steady state rapidly after startup. However, the concentration of **4** in the liquid phase in the same tank does not approach steady state within the same time, as a minimum is reached after approximately 18 h, and the concentration stabilizes

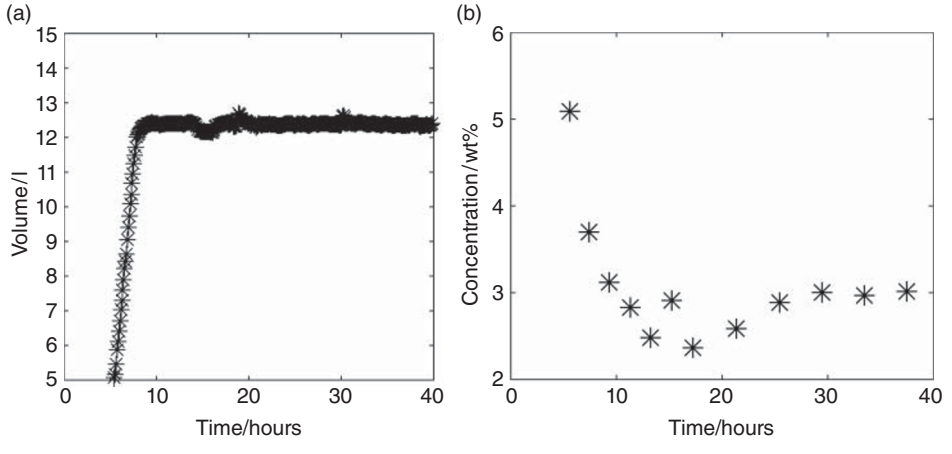


Figure 13.2 *Dynamic development of the level in crystallizer Cr2 during startup (a) and concentration of **4** in the mother liquor in crystallizer Cr2 obtained from HPLC analysis during the same period (b).*

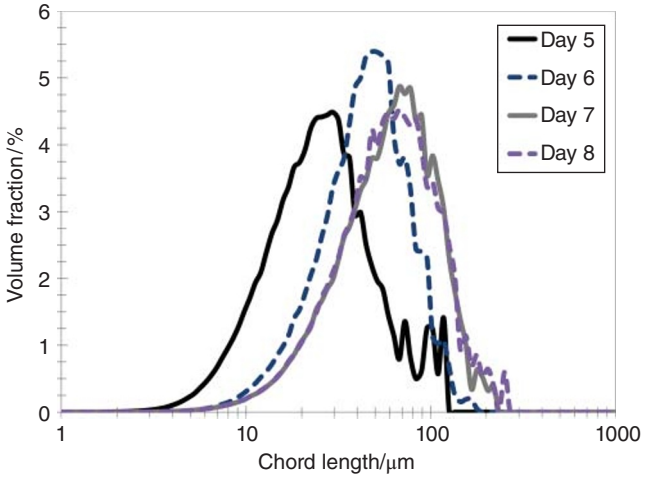


Figure 13.3 *Dynamic development of the chord length distribution of API crystals during an experimental run of an integrated CM pilot plant. Reprinted (adapted) with permission from [37]. Copyright 2014 American Chemical Society.*

only after 30 h. Even small differences in concentration of **4** in crystallizer Cr2 can have a significant impact on the material attributes of the produced crystals, because the concentration determines the driving force for crystallization kinetics. In general, this small example demonstrates that certain process variables, and thus CQAs, may still vary significantly after startup whereas other variables may rapidly approach nearly steady-state values. Depending on the availability of PAT, certain dynamics after startup may not be visible. Figure 13.3 illustrates another example of a process variable that approaches steady state slowly. The illustrated dynamic development of the chord length distribution is a fingerprint for the development of the crystal size distribution of the API crystals in crystallizer Cr4. A number of residence times are needed before the crystal size distribution approaches steady state. Since the crystal size distribution affects downstream operations (e.g., filtration, drying, mixing), transient effects can be expected downstream even after the crystallizers approach steady state due to the delay in response of downstream units. Second, variations of the input variables to the process (e.g., properties of feedstock or solvents) and disturbances (e.g., faltering valves or pumps) acting on the process will continuously push the operating point in different directions as discussed in more detail in Section 13.3.5. Third, delays in measurable outputs of a CM process can translate directly into a delay in being able to observe when the process has reached a new steady state.

The ambiguous transition between startup and steady state and the absence of true steady-state operation long after startup calls for a flexible control strategy that is focused on maintaining CQAs within a certain range rather than on operating at steady state. Such a strategy is also required to be able to use material manufactured during startup and shutdown as material for sale. Loosely speaking, steady state is not necessarily desired and often not needed. Rather, a reliable "state of control" should be the aim during the process operation of CM processes for pharmaceuticals, in which CQAs are satisfied and operations are not necessarily at a steady state [9].

13.3.3 Plant-wide Control for CM: Disentanglement of Times Scales and Control Objectives

The previous section illustrates that time scales with different orders of magnitude determine the dynamic behavior of a CM process. When fully integrating all unit operations, very long time scales can determine the input–output behavior of a CM process for pharmaceuticals. For example, several days may be needed before an inert compound in the feed has been recovered at the outlet of the process (see Section 13.3.4). On the other hand, on the level of individual unit operations, very fast processes exist. Examples of fast processes are the rapid quench following the second reactor or the formation (nucleation) of new solid particles in the final crystallizers. Although not formally analyzed here, it is clear that the process behavior is determined by time constants that span several orders of magnitude. Such broad range of time scales poses challenging questions for the development of a plant-wide control strategy, which, fortunately, is a well-studied problem within chemical engineering for over half a century [10]. Plant-wide control is concerned with the control of a complete plant [11]. The question is what variables to measure, control, manipulate and how to connect them in automated control loops. Obviously, the theoretical number of automated control loops that can be constructed is tremendously large. Fortunately, the vast majority of those theoretical control loops can easily be rejected based on process insights. Furthermore, designing the best control structure is often not needed. Rather, all that is needed are systematic design procedures for control structures that guide decision making and prevent designs of control structures that are bad.

Various researchers have proposed systematic procedures to design such plant-wide control structures [10–14]. Typically, some sort of hierarchical decomposition is applied and a classification between control objectives is proposed. For example, a distinction can be made between control objectives that aim to achieve stable plant operation (i.e., the ability to operate within the bounds of the equipment in terms of, for example, temperature, pressure, flow rate) and control objectives that aim to improve the performance of the plant (quality control). The design of automated control loops that aim to achieve stable plant operation has priority over the design of control loops for quality control. In the case of the discussed pilot plant, the level control loops provide process stability and essentially regulate the throughput of the process in an automated way. In general, there are at least two ways in which such throughput control can be achieved. In the first scheme, chosen for the pilot plant that is discussed in this chapter, the feed flow rate to the plant is set at a fixed value and all the output flow rates of unit operations with a pump are used as a manipulated variable in an automated level control loop (the so-called *push scheme*). In the second scheme, the product flow rate is set at a fixed value and all input streams to unit operations with a pump are used as manipulated variables in automated level control loops (the so-called *pull scheme*). Changes in throughput are often implemented with a slow rate. In such way, quality control loops have time to "catch up" with changes in throughput and adverse effects from interactions between both control layers are minimized. Subsequently, a hierarchical quality control layer has been designed on top of the existing stability control layer. Hierarchical decomposition aims to support decision making by decomposing a large complicated problem into a sequence of smaller subproblems. Furthermore, hierarchical decomposition disentangles in a natural way the various time scales that are present in the process [13].

An example of possible hierarchical viewings of the pilot plant discussed in Section 13.2 is illustrated in Figure 13.4 [15]. At the coarsest level, only the streams that enter the pilot plant and the streams that leave the pilot plant are visible. Since the time scales between the inputs and outputs can be very large, typically no automated control loops are designed at this level. Rather, a classification is made between input streams that have a significant long-term impact on the final product quality and input streams that do not affect output streams significantly via process simulations. Such classification can be used to define constraints when designing automated control loops at further stages of the design approach. For example, it should be avoided to utilize input streams that have a long-term effect on final product quality to address control objectives involving short time scales on a local scale. In a subsequent hierarchical viewing, more details are added to the representation of the pilot plant and streams with key intermediate materials appear. Process simulations and insights can be used to define the properties of those streams that have a significant impact on the final product quality. Subsequently, automated control loops can be designed to control those properties in the presence of uncertainties and disturbances. For example, in case of the pilot plant discussed in Section 13.2, unit operations that either involve synthesis and workup steps of selected compounds or that involve the formulation of the final product can be grouped together (Figure 13.4). Two of the dilution tanks of the integrated pilot plant (D1, D2) are installed to monitor and control the key properties (concentration) of such key intermediate streams. In the cases where recycle streams would be present, a subsequent hierarchical viewing could reveal the recycle structure of the plant. Finally, remaining automated control loops are designed by viewing the pilot plant at the most detailed level. Since design decisions that are taken at a higher level restrict decisions taken at a lower level, a natural disentanglement of process time scales can be achieved. Furthermore, a large and complicated design problem is reduced to a consistent sequence of smaller design problems, which structures decision making.

For example, consider decomposition Level 2 of the decomposition of our process (Figure 13.4), the properties of the main process stream going from block 2A to 2B ($F_{D1\rightarrow M3}$) that have the largest impact on the final product quality can be determined using process simulations (i.e., this step determines intermediate CQAs). In our case, for example, the fraction of **4** in stream $F_{D1\rightarrow M3}$ has a large impact on the final product quality. Subsequently, the properties of the input streams towards block 2A that are visible at Level 2 and that have a large impact on the identified CQAs can be determined (i.e., this step determines the CPPs). In our case, for example, the composition and feed flow rate of the stream with compound **1** has a large impact (CPP) around the nominal operating point whereas the stream with compound **2** does not. Finally, a control strategy can be developed that utilizes CPPs at Level 2 to control CQAs at Level 2 either via automated control loops and/or by defining constraints for the CPPs. When increasing the level of detail when proceeding to Level 3 of the decomposition, more CQAs and CPPs will be visible for which a suitable control strategy can be developed. The control strategy developed at Level 2 acts as a constraint for the control strategy at Level 3.

13.3.4 Residence Time Distribution of a CM Process: Impact of Recycling

Chapter 1 of this book explains the concept and importance of a residence time distribution (RTD) for CM. The final product is a mixture of material that exits the process at a

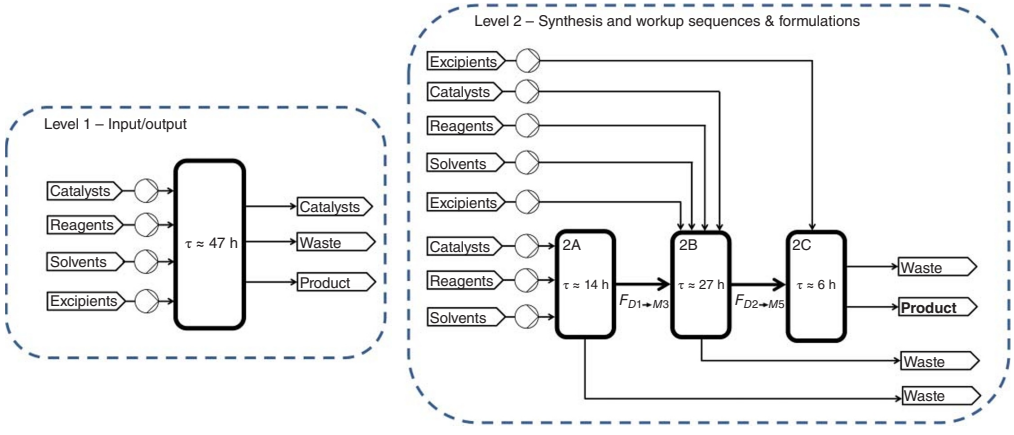


Figure 13.4 *Examples of hierarchical viewings for the continuous pharmaceutical pilot plant.*

certain time. The RTD provides information about the statistical difference in the history of the material that forms this mixture. A narrow residence time distribution is desirable to achieve easier traceability of produced products. However, such a process does not allow the use of recycling to increase yield and reduce materials costs, and the deliberate design of back mixing into a CM process can also ease the control for particularly challenging unit operations.

An RTD of a single unit operation is measured traditionally by introducing a tracer as a pulse or step input and, subsequently, by measuring the concentration of the tracer at the outlet as a function of time. For an integrated process, such procedure is complicated by the presence of various exits that may exist for the tracer and practical difficulties related to the measurement of the RTD of a complete process. However, knowledge of the RTD of individual unit operations can be used in a process model to obtain information related to the RTD of a CM process via process simulations. For example, the mixing behavior of a certain amount of impurity that enters the process, or is created within the process, can be predicted using process simulations, which provides important information for process design and control. When RTDs of individual unit operations are not available, basic assumptions regarding mixing can be used to estimate the RTD of individual unit operations. In this section, characteristics of the RTD of the integrated process described in Section 13.2 are analyzed via process simulations. The dynamic process model is inspired by the pilot plant and is described in more detail in literature [16]. In particular, the impact of inert impurities in the main feed stream on the final product quality will be analyzed. A special focus will be on the impact of a major recycle stream, which introduces mixing on a systems level.

Figure 13.5 illustrates the concentration of an inert impurity in the final product as function of time when an impurity enters temporarily the process. The impurity has been introduced as a step input in the feed of compound **1** at the beginning of the process. In particular, the feed stream with compound **1** (P2 in Figure 13.1) is enriched with 1.0 wt% of an inert compound for 6 min in the simulation, which could represent a contamination in a feedstock lot. The inert impurity is assumed to remain in the organic phase in both liquid–liquid extractions and then stay in the mother liquors and become partially removed from the process at the two washing and filtration stages. Only the amount of impurity in the mother liquor that is assumed to adhere to the crystals propagates to the subsequent stage from the filters. Cases with and without recycling are simulated. In the case with recycling, part of the permeate stream from filter W1 (labeled "PU1" in Figure 13.1), which still contains unreacted **1**, is sent back to reactor R1 to increase the overall yield of the process. Prior to mixing of the recycle stream and feed stream, part of the permeate stream is removed (10%) as a purge as a general strategy to prevent accumulation of impurities in the recycle stream and excess solvent is removed via evaporation. The recycle stream was not implemented in the actual pilot plant, but dynamic process simulations are used to analyze the behavior of the pilot plant extended with such a recycle stream.

Since the pilot plant features several unit operations that approach plug–flow behavior, a considerable delay time (about 1 day) is present before the first response is visible at the outlet of the pilot plant (Figure 13.5). The maximum concentration of the inert impurity is predicted after about 3 days for both cases. Furthermore, both distributions are skewed towards the right, which indicates that a longer time is needed before all of the impurity is removed from the process. When comparing the case with and without material

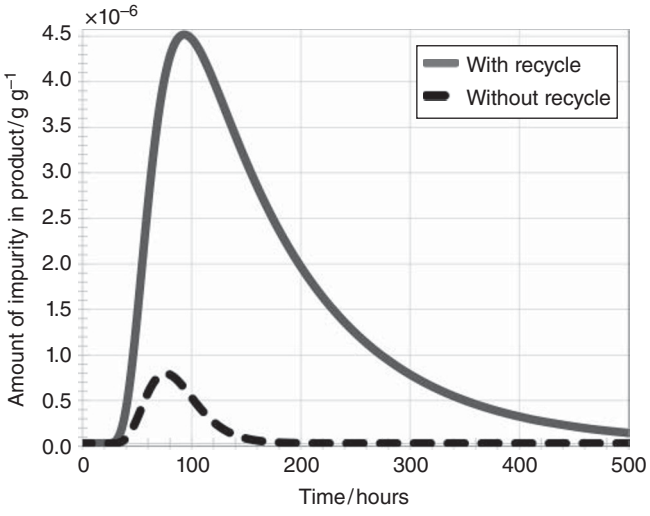


Figure 13.5 *The concentration of an inert impurity at the outlet of an integrated continuous pharmaceutical pilot plant, which was introduced as a short pulse at the inlet of the process. The data have been obtained from simulations using a state of the art process simulator (JACOBIAN®, Res Group Inc.).*

recycling, two main differences can be observed. First, the concentration of impurity in the final product is higher at any point in time when recycling is used. Second, the distribution broadens significantly when the material recycle is present. The latter observation can easily be understood as mixing on a systems level is introduced via recycling. The former observation is perhaps less intuitive, but can be explained by considering the impact of the recycle stream on the impurity levels in the first part of the process (i.e., up to dilution tank D1). In case of no recycling, most of the impurity will leave the process as a solute in the permeate stream of filter W1 (i.e., in stream "PU1" in Figure 13.1). In case of recycling, the impurity will be brought back to the beginning of the process together with the unreacted reagent. As a result, the overall level of impurity in the first part of the process will go up when recycling is being used, which will increase the amount of impurity that propagates to the remaining part of the process. Since the remaining part of the process is operated identically for both cases, the total amount of impurity that exits the process through the product stream is predicted to be higher in case of recycling.

It should be noted that quantitatively modeling for the prediction of trace amounts of impurities is often challenging. A sufficient amount of an impurity in isolated form is typically not available during development, which would be needed to conduct experiments to understand the physical and chemical behavior of an impurity (e.g., adsorption behavior or thermodynamic properties) in the various unit operations. Nevertheless, process models can still provide useful information in such cases by estimating orders of magnitude or by giving insights into the impact of certain design decisions. For example, in the illustrated case in this section, although the presence of a recycle does increase the peak value of an impurity in the final product, the absolute value remains very low and may very well be orders of magnitude below threshold values related to acceptable product quality.

Furthermore, the data from the process simulation clearly illustrate the impact of a certain design decision (recycling of compound **1**) on the way in which an inert impurity in the feed stream would propagate throughout the process. Finally, by choosing model assumptions in a specific way, a worst case scenario can be simulated, which may provide a reliable basis for robust design and product quality control.

In general, knowing the range of properties of key intermediate materials that can safely be processed further is important for a control strategy of a CM process for pharmaceuticals. In case an impurity is not expected to be diluted sufficiently in the system, a considerable time may be needed before all of this material has exited the process. In such a case, storage of small amounts of intermediate products in combination with quality control is important to prevent a future product that does not meet quality specifications. Alternatively, material can be strategically purged and throughput can be adjusted to speed up the cleaning process. In case such purge stream would contain valuable reagents or products, novel technologies (see Section 13.5) such as nanofiltration membranes are of interest to selectively remove impurities from a recycle stream [17]. For example, in case of the simulated process, selective removal of impurities from the recycle stream to reactor R1 would combine the benefit of an increased overall yield due to recycling of unreacted **1** with the benefit of a reduced total amount of impurity in the final product comparable to the case without recycling due to selective removal of impurities from the recycle stream.

13.3.5 Disturbances, Nonlinearities, and Delays: Implications for Control

Disturbances can be defined as all inputs to a process that cannot be manipulated but influence the process variables to be controlled [18]. The aim of automated control loops is to mitigate the effect of disturbances on controlled variables. In case disturbances can be measured, feedforward control can be very effective to compensate for the expected impact of disturbances via a process model. The CM pilot plant discussed in Section 13.2 features several examples of effective use of feedforward control. Ratio control is a form of feedforward control where the ratio of two flow rates is kept constant. For example, Figure 13.6 illustrates the dynamic profile for dosage of HCl in the second reactor for an illustrative period of time, which is a simple example of a ratio controller. The variations in flow rate are quite significant due to the level controller upstream, which illustrates that using a constant set point for this flow rate would likely not be acceptable. The outlet flow rate of dilution tank D1 is a manipulated variable of a level control loop.

In case disturbances cannot be measured, feedback control can be used to mitigate the effect of disturbances. Feedback control is based on the comparison of a measured controlled variable with a desired set point. Automated adjustments of one or more manipulated variables aim to bring the controlled variable closer to the set point. Feedback control is effective against both measured and unmeasured disturbances and can be implemented without any predictive model. The disadvantage of feedback control is that, by definition, a deviation from a desired value is needed before the controller takes any action. The CM pilot plant contains many feedback controllers. In all cases, the value of the manipulated variable is determined by multiplying the error (deviation of controlled variable with set point) with a constant (gain) and, possibly, in addition by integrating the past error over time (so-called PI feedback control).

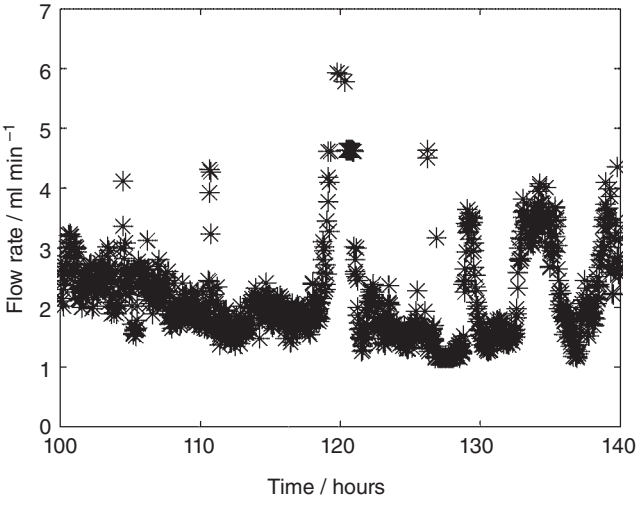


Figure 13.6 *Flow rate of HCl added to mixer M3 (manipulated variable of ratio control RC2).*

Figure 13.7 illustrates the dynamic development of the concentration of **4** and **6** (API) in two buffer tanks. A feedback controller manipulated the fresh solvent flow rate to control the density of the suspension close to a desired value. The controller cannot actively increase the solid concentration. Therefore, the controller may saturate in case the concentration in the vessel drops below the set point and upstream material has a low concentration, which causes the process to operate in an open-loop mode (see inset of Figure 13.7b). Nevertheless, in general, although a number of significant disturbances can be seen in Figure 13.7 on short time scales, both controllers are highly capable of maintaining the concentration close to a desired set point for a sustained period of time including during changes in set points.

Feedforward and feedback control are complementary in nature. Feedforward control takes anticipative action and a feedback controller takes corrective action. Therefore, the *combination* of feedforward and feedback control in an extended control loop is particularly strong. The studied CM pilot plant contains an example where feedforward and feedback control are combined in a cascade configuration. The concentration of **5** at the inlet of the dehydration column has to be maintained at a specified value to optimize downstream operations. A fresh solvent flow rate is used as the manipulated variable in a mixer to obtain the specified concentration via dilution. Several disturbances are acting on the mixer. First, the feed stream with concentrated **5** acts as a manipulated variable in an automated level control loop and thus varies with time, which can result in relatively fast variations. Second, the concentration of **5** in the feed stream may change over time, which is expected to be a relatively slow process. An inline UV sensor measured the concentration after the mixing point. Two control configurations are compared in Figure 13.8. The first scheme uses the UV sensor for observation, but manipulates the fresh solvent flow rate via a ratio controller. Clearly such a control strategy mitigates the impact of the variations in flow rate towards the controller. However, variations on a longer time scale can still be observed when

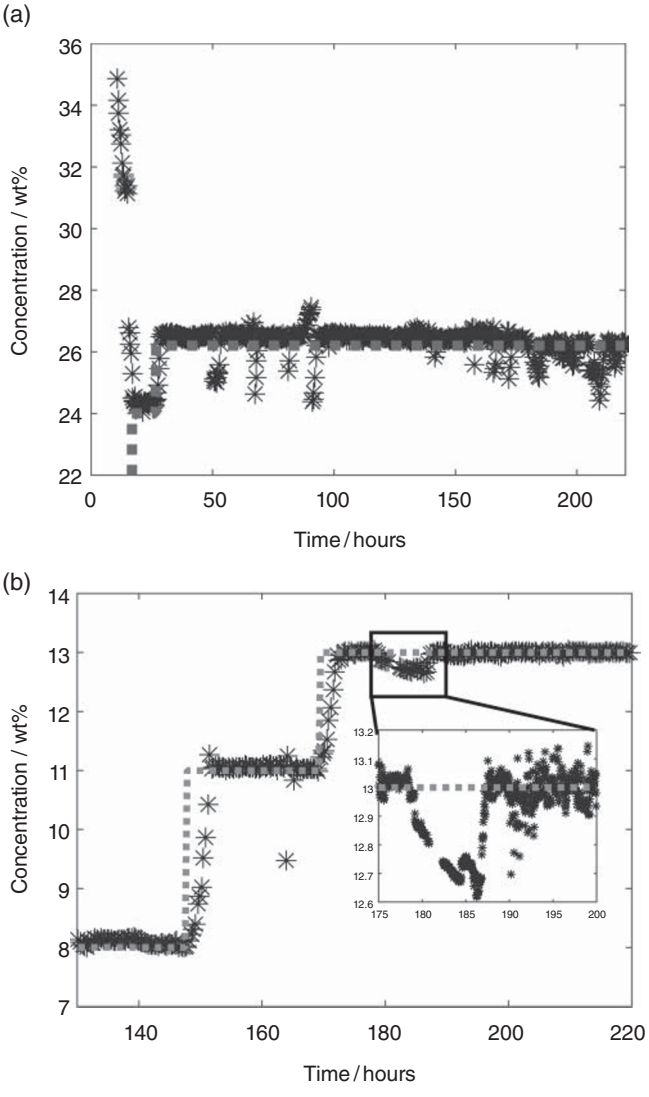


Figure 13.7 *Dynamic development of the concentration of key intermediate compounds: (a) compound* ***4*** *in dilution tank D1; (b) compound* ***6*** *in dilution tank D2. Both concentrations are obtained via a density measurement. The dotted gray line is the set point of the automated feedback controllers. Reprinted (adapted) with permission from [53]. Copyright 2014 American Chemical Society.*

implementing such a control scheme (Figure 13.9a). The second scheme uses the UV sensor to measure the controlled variable, which allows for feedback control to be employed in a cascade configuration. Instead of directly manipulating the fresh solvent flow rate, the controller adjusts the set point of the ratio controller. In this way, a fast inner loop mitigates disturbances related to variations in flow rate and a slower outer loop mitigates disturbances

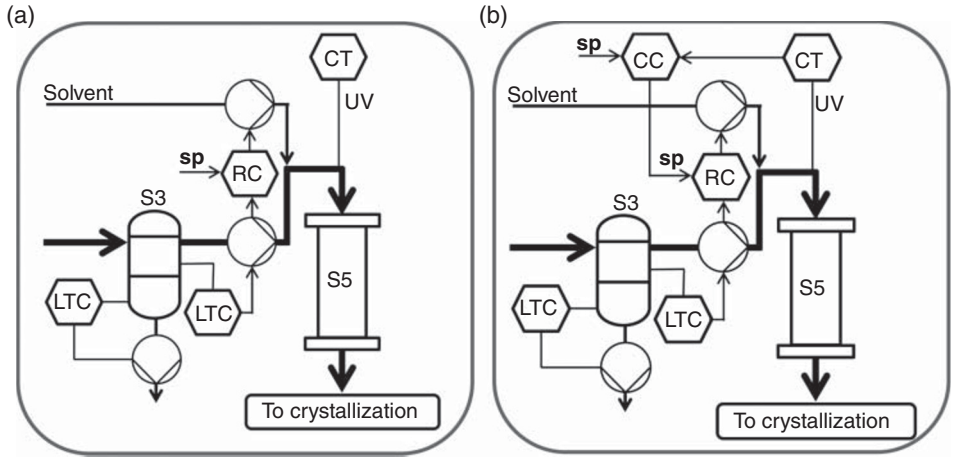


Figure 13.8 *Process flow sheet for two possible configurations to control the concentration of an intermediate compound within the CM process (salt filters are not shown). In scheme (a), the UV sensor (CT) is used for monitoring and the fresh solvent flow rate is the manipulated variable of a ratio control loop (RC). In scheme (b), the UV sensor (CT) is a controlled variable within an outer concentration control loop (CC) that manipulates the set point of an inner ratio control loop (RC).*

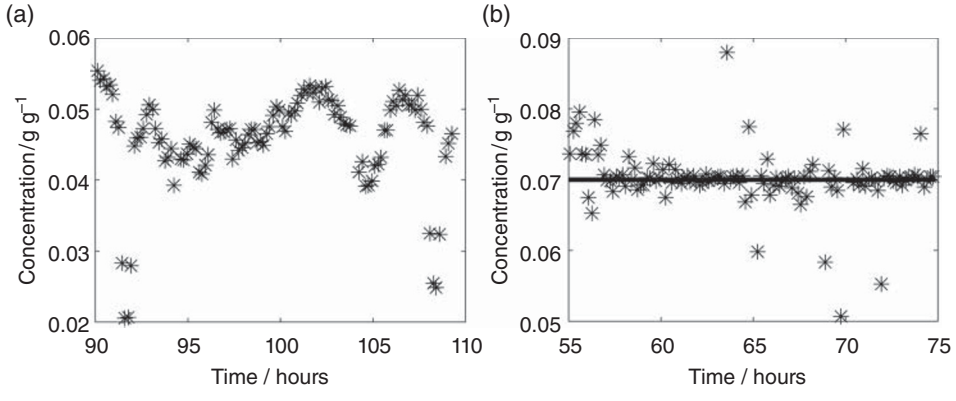


Figure 13.9 *Dynamic development of the concentration of compound **5** before entering the dehydration column (S5) for two tested control schemes: (a) ratio control only [configuration (a) in Figure 13.8]; (b) ratio control with an outer feedback concentration control loop [configuration (b) in Figure 13.8] including set point (solid line). Reprinted (adapted) with permission from [53]. Copyright 2014 American Chemical Society.*

related to changes in concentration of **5** in the feed stream to the mixer. Such an extended control scheme demonstrated superior performance in experiments (Figure 13.9b).

The design of the concentration control loop discussed above is further complicated by the presence of a significant time delay in the response of the measured variable towards a change in the manipulated variable. This delay can be explained by the presence of a

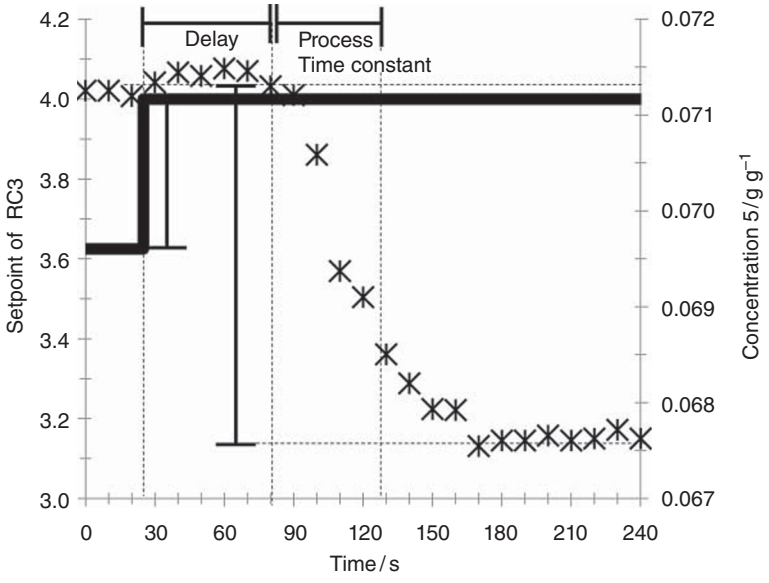


Figure 13.10 *Measurement of time delay and approximation of the measured response with a first order plus dead time process.*

number of salt filters between the mixing point and the UV sensor. Salt has to be removed before the sensor to obtain a signal of sufficient quality. To account for the time delay, experimental tests were conducted prior to the run to quantify the time delay and approximate the dynamic behavior via a first-order process. Figure 13.10 illustrates the response of the UV sensor when a step input in the set point of the ratio controller is implemented. It takes about 1 min before any response in the measured concentration can be observed. Furthermore, it takes about 2 min to reach a new steady state for this part of the process. The curve can be modeled as a so-called first order plus time delay process, which has two key parameters that characterize the dynamics. The delay time is the time needed before any response in output signal can be seen. The process time constant is the time it takes to reach 63% of the new steady-state output. Once those key parameters of the response curve are identified, recommended settings from literature, see for example well-known textbooks such as [18–20], can be used to design the outer feedback PI control loop, that is, to choose a suitable controller gain and integral time constant.

13.3.6 Startup and Shutdown Procedures

CM processes for pharmaceuticals may operate for a limited amount of time only due to a small required production capacity. This can be the case, for example, when a process is designed for high capacity, but used to produce the relatively small amount of product needed for clinical trials. The time needed for startup and shutdown is, in that perspective, relatively large compared to the rest of the operating time, and processes must be designed with almost zero product waste. Producing in-specification material during startup and

shutdown is, therefore, important to improve the economics of a CM process. For startup of the CM plant described in Section 13.2, a relatively conservative strategy was chosen. At distinct points within the process, material was accumulated and disposed of when necessary until the intermediate material attributes met certain specifications. The selection of those intermediate points loosely followed the hierarchical viewing as illustrated in Figure 13.4 (Level 2). The material in dilution tanks D1 and D2 were first brought to specification before being sent to subsequent unit operations. In this way, the CQAs at various points within the process were brought within a desired range in a stepwise fashion (i.e., section by section). The advantage of such a startup approach is that unit operations downstream will directly have well-controlled material as input material, which will minimize the required time to bring those CQAs within a desired range as well. Furthermore, the range of operating conditions where detailed process understanding is required is reduced when following such stepwise startup strategy. The downside is, obviously, that potentially valuable material is lost by disposing of the intermediate material. Also note that such a stepwise approach becomes more complicated when recycle streams are present. An alternative approach is to simply send all material directly to subsequent unit operations without disposing of material with an intermediate quality that is potentially far from a desired range. Such an approach has the potential to achieve a higher yield for the complete run, but introduces risks related to increased uncertainty with respect to startup dynamics. Dynamic process models are important in such analyses. Dynamic process simulations can be used to study different startup strategies [16]. Furthermore, dynamic optimization of a process model offers the opportunity to identify an *optimal* startup profile for a given objective function. The importance of startup and shutdown for CM is an important topic for future research as few real applications to pharmaceuticals have been reported.

13.3.7 Buffering

The addition of buffer tanks into a CM pilot plant does not alter the steady-state behavior of the process, but may significantly influence the dynamic behavior of the process. Buffer tanks allow for intermediate material to be stored, which offers opportunities for quality control. The downside is that the dynamic behavior of the process becomes more sluggish and the total holdup, and thus the working capital, of the plant increases. Buffering increases the mean residence time of the process and the time for startup and shutdown of the plant.

Buffer vessels can reduce variations in flow rate throughout the process by storing additional material when throughput increases temporarily. Figure 13.11 illustrates the dynamic development of the level in crystallizer Cr2 in the presence of severe disturbances. Note that this level is a controlled variable in an automated feedback control loop. The holdup in crystallizer Cr2 varies significantly due to a series of plugging events at the outlet of the crystallizer. In the case of such severe disturbances – such as plugged tubing – manual intervention is required. Once the plug has been removed, the automated level control loop brings the holdup of the tank gradually back to the set point. The speed at which the automated level control loop brings the holdup back to the set point can be manipulated via design of the control loop (i.e., via a certain choice of the controller gain in this case). This particular control loop was designed for a sluggish response so that a sudden increase in the outlet flow rate is avoided. The aim was to minimize propagation of this disturbance in throughput to downstream units at the expense of a larger residence time in the crystallizer.

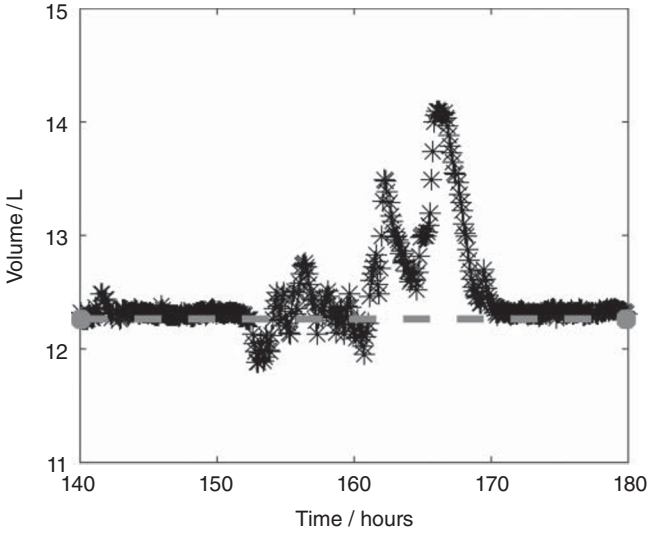


Figure 13.11 *Dynamic development of the level in crystallizer Cr2 during a period of operation where the influence of disturbances was clearly visible (set point is indicated by the gray dashed line).*

Averaging level control aims to obtain a suitable compromise between obtaining sufficient flow filtering (by diverting variations in flow rate to holdup) and minimizing investment costs related to the size of equipment (by pushing excess material to the next unit operation). Averaging level control can be achieved by applying rules of thumb for the selection of the controller gain [18] or by more sophisticated methods such as *optimal* averaging level control [21]. The latter explicitly considers an optimization problem for minimization of the variations in the outlet flow rate. Furthermore, rather than controlling the level in the buffer tank at a specific value, an upper and lower limit can be defined between which the level is allowed to vary. Loosely speaking, the level controller only takes drastic corrective actions when the level approaches such upper or lower limit.

Figures 13.12 and 13.13 illustrate a comparison between two strategies to obtain averaging level control to mitigate a disturbance, plugging of an outlet tube, that was observed during plant operation [22]. First, pilot plant data were used to estimate the parameters in a plant-wide dynamic model to simulate the process behavior. Figure 13.12 illustrates an example of how model-based simulations compare to experimental data after parameter estimation. Similar graphs can be made for any measured process variable in this part of the process. In general, the dynamics of the pilot plant based on total mass balances were captured well. Second, the impact of replacing the existing level controllers with more advanced level controllers based on *optimal* averaging was studied. Figure 13.13 illustrates one example of a comparison between different control strategies. Clearly, optimal averaging level control uses available buffer capacity in a more intelligent way to minimize the effect of incoming flow rate variations on the outlet flow rate. Essentially in the case of optimal averaging level control, the controller takes almost no action for the illustrated case

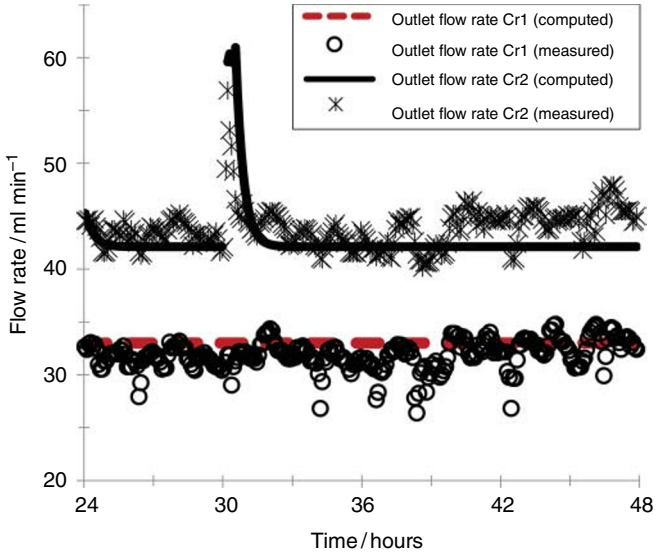


Figure 13.12 *Example of a comparison of experimental pilot plant behavior and simulated pilot plant behavior after parameter estimation [22].*

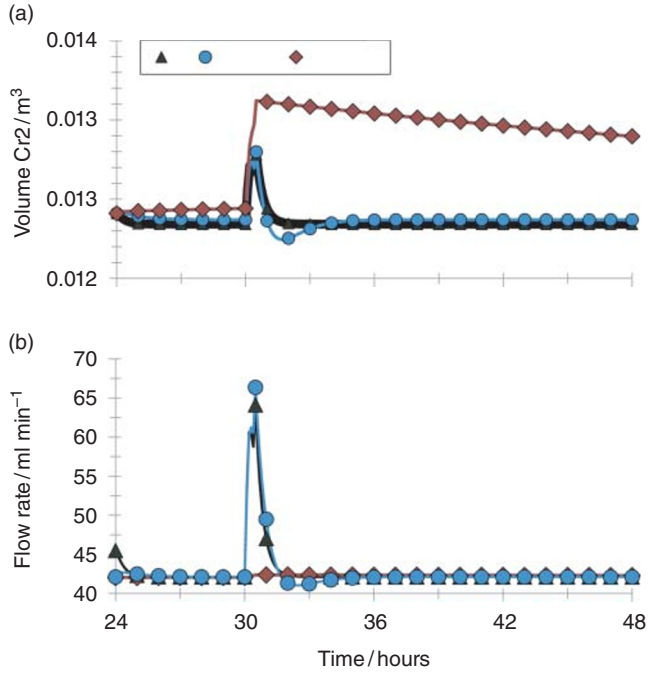


Figure 13.13 *Predicted behavior of optimal averaging level controllers for a selected disturbance that occurred during pilot plant operation. The triangles illustrate the simulated process behavior with a proportional feedback controller as implemented during pilot plant operation. The circles illustrate a proportional–integral feedback controller with tuned parameters that are recommended for averaging level control [18]. The diamonds illustrate the simulated behavior in the case of optimal averaging level control [21] would be implemented [22].*

as the disturbance in flow rate can be fully accommodated by excess volume in the tank. If the volume in tank would approach an upper or lower limit, the optimal averaging level controller would take action more aggressively. When deciding on the allowable upper and lower limits of well-mixed tanks, requirements for residence time have to be taken into account for vessels that are not solely used for buffer capacity. For example, when processing units such as well-mixed crystallizers or reactors are considered, variations in volume (and thus variations in residence time under conditions with nominal flow rates) may be restricted by crystallization or reaction kinetics, respectively.

13.4 Process Monitoring and Control

13.4.1 PAT Use in the Integrated Continuous Manufacturing Process

The availability of PAT is often mentioned as a key enabling technology for the design and operation of CM processes for pharmaceuticals. Several reviews on the importance and development of PAT for upstream pharmaceutical processes have recently appeared in literature [23, 24]. Selection of the appropriate PAT to implement on the CM process that is discussed in this chapter was driven by three different objectives: (1) provide key process measurements to integrate into the online control system, (2) collect data to understand the process performance on a detailed level to assist in process improvements and modeling, (3) enable early detection of abnormal events. Measurements to maintain inventory in the system such as by using level sensors provide quick feedback (capable of < 1 s response) which can then be linked to pump rates to control the overall mass flow rate through the process. Stoichiometry control was also important for several steps such as entering the second reactor or the second crystallization. In both cases, a concentration measurement was linked to a controller to maintain a constant composition. Controlling the concentration of **4** entering the second reaction was done with a density cell on D1 while the concentration of **5** entering Cr3 was controlled with a UV sensor. Both of these measurements provide a univariate output, meaning that only one concentration was estimated, which means that those streams needed to be relatively pure. D1 was located immediately after the filtration and wash of a crystallization product resulting in a stream containing only **4** and solvent. The second reaction was a deprotection and was selective enough to generate a stream of **5** where small levels of impurities were insignificant compared to the tolerance on stoichiometry for fumaric acid.

Additional samples were collected to validate that the selected measurement points and control loops were sufficient to control the process. Sample points were located throughout the process around each unit operation either from a tank or inline, which allowed direct sampling of material for detailed high-performance liquid chromatography (HPLC) analysis. These measurements were not directly integrated into the control system since the delay between when the sample was taken and when the analyzed values were available could be up to an hour including sample preparation times and replicate injections. In order to provide more rapid feedback for earlier tests of the system before all the online sensors were fully implemented, higher throughput LC methods were developed. Methods developed on 1.8-μm particle and fused-core columns permitted three- to fivefold reduction in elution times with minimal impact on sensitivity and resolution, which permitted feedback

within 10 min if a sample was prepared and immediately queued up for injection. Using LC for fast feedback required locating LCs near the process and dedicating them for process monitoring. In a production environment, this approach would mean these LC would need to be set up separately solely for process monitoring, requiring different method development objectives focused on speed and measurement of specific analytes (starting material, product, key impurities) rather than final quality control of isolated intermediates.

The increased sampling for LC analysis was done to ensure increased observability of the process during development. Once the process control strategies were validated, the additional samples were no longer necessary for normal operation of the process. For longer runs, periodic samples could be designed into the control strategy to provide validation of the performance over long time periods and for recalibration of measurement devices. Periodic samples could be chosen to be at only a small number of key points in the process, in our case tanks D1 and D2 are points where high purity streams are expected and required for acceptable overall performance (Level 2 in Figure 13.4). The use of online HPLC could enable regular, high sensitivity measurements to be integrated into the control system. Sampling these points infrequently for LC analysis would provide validation that the upstream steps were operating correctly and downstream steps were fed with the proper materials. Sampling of high purity streams such as for LC is likely unavoidable even with the increasing use of other online PAT such as infrared (IR) or mass spectroscopy (MS), which lack sufficient sensitivity to detect impurity levels required for monitoring trace impurities to a limit of 0.2% required for impurities without additional characterization.

The integrated nature of CM raises the importance of intelligent alarm management and detection of abnormal events using PAT [25]. The objective is to improve safety and economic performance of the CM plant. In general, the topic has been well studied within chemical industry as failures related to alarm management have often been cited as contributing factors to major accidents in chemical industry [18] and standard handbooks on the topic exist [26]. The CM process discussed in this chapter was equipped with various PAT devices to detect abnormal events during operation. The corresponding alarms were implemented in a single control system. For example, plugging of transfer lines with solid particles that are suspended in a solution is an important operational risk for CM (e.g., see Figure 13.11). Typically, the derivative of the level with respect to time changes instantaneously during a plugging event, which makes this derivative suitable to detect this particular abnormal event. Alternatively, in-line pressure sensors can be used to detect the onset of plugging (Figure 13.14). Filtering of a signal is often required to trigger an alarm at the right moments only. In general, care has to be taken to avoid an abundance of alarms. An in-line pressure sensor is another example of a measurement device that was installed in the pilot with the sole purpose of abnormal event detection to detect saturation of the salt filter (S4). More sophisticated techniques, such as principal component analysis, may be required to detect other abnormal events that are less easily observed or require various measurements at different points within the CM process to be detected [27].

13.4.2 Soft Sensors and Prediction of Future Performance

As discussed in the previous section, fast online measurements that can be utilized in automated control loops are not always (economically or technically) feasible for every process

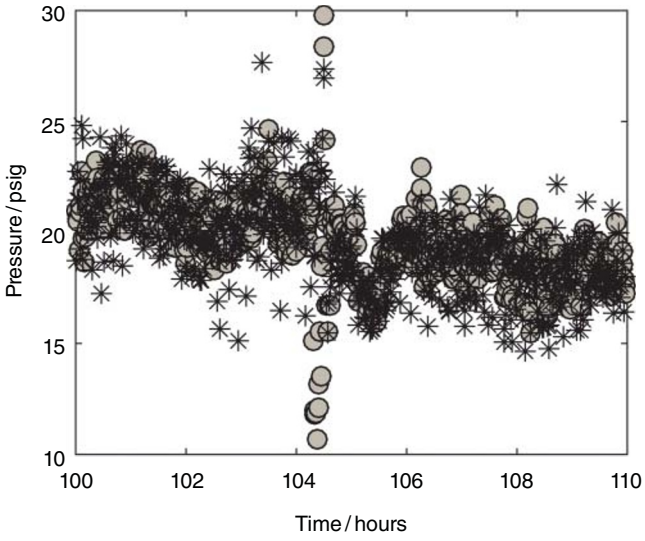


Figure 13.14 *Dynamic development of in-line pressure around two parallel reactors (R2). The sudden increase in pressure just after* t = *104 h triggers an alarm for the operator.*

variable. The development of so-called soft sensors can serve as an intermediate solution. Soft sensing involves the inference of a process variable of interest from other measured process variables that are related to the variable of interest. A process model is required to infer the value of the process variable of interest from the available measurements. Examples of soft sensors for CM of pharmaceuticals are reported in literature [24, 28–31]. An example of soft sensing for the discussed pilot plant in this chapter would be the estimation of a reaction rate by closing the energy balance around a reactor with temperature measurements. Computations are often fast, which means that as long as the secondary measurements are also fast, soft sensors can be used in automated control loops. Obviously, care has to be taken that the model–plant mismatch does not lead to excessive errors in the estimated process variable. Fortunately, the problem of estimating unknown process variables from a certain set of known process variables in the presence of uncertainty is a well-studied problem within process control.

The idea of estimating unknown process variables through model-based calculations at a present time can be brought one step further by estimating process variables in the future. Moreover, future control actions can be anticipated such that a certain performance indicator is optimized. Model predictive control (MPC) is an advanced control technique in which suitable input variables are calculated based on both current measurements and predictions [18]. A key advantage of MPC in the context of pharmaceutical processes is that process constraints can be taken into account explicitly. In other words, optimal input variables can be calculated while taking into account that certain process conditions cannot be violated in future plant operation. Such constraints restrict the allowable input variables, and as such may compromise optimal plant operation, but align well with QbD concepts. For example, a plant-wide MPC controller could be used to optimize input variables while complying with established design spaces of individual unit operations.

The effectiveness of MPC has been studied for a process model that was inspired by the pilot plant presented in this chapter [32, 54]. A comparison has been made with a conventional control structure consisting of only feedforward and feedback controllers and simple extensions to that such as cascade controllers in which inner control loops are nested within an outer control loop. The results demonstrate that the MPC control structure effectively regulates CQAs, outperforming the conventional control structure for studied disturbances, and allows for flexible process operation. Furthermore, the implemented control actions in the case of MPC did not violate defined process constraints related to product quality for the studied case, which could not be guaranteed in the case of the conventional control structure. The latter is important when taking into account regulatory requirements. Finally, combinations of MPC with conventional control structures have also been demonstrated to improve the efficiency of continuous pharmaceutical processes [33]. In general, even small improvements in throughput and product quality during periods of operation when major disturbances act on the system may significantly improve the economic performance of the plant taking into account the high added value of products within the pharmaceutical industry.

13.5 Outlook: Opportunities for Novel Unit Operations and System Configurations

The emergence of CM for pharmaceuticals provides unique opportunities for the development and application of radically new technologies within the pharmaceutical industry. Typically, pharmaceutical companies have been highly concentrated on developing products and often had little time to investigate the generation of technologies for manufacturing drug products that have a high potential but may only have a moderate chance of being successful. Since small modifications to existing technologies have little chance to result in significant breakthroughs, one of the strategies employed at the Novartis-MIT Center for Continuous Manufacturing is to spend significant efforts on novel tableting processes that can generate drug products with enhanced functionality and/or lower risk while reducing the number of unit operations. As described in Section 13.2 and more in depth in the literature [1], the CM pilot plant employed a lower risk option of hot-melt extrusion with coupled injection molding to produce the aliskiren hemifumarate tablets. Other technologies that are investigated at the center at the time of writing include various crystallization projects, and tableting of thin films and electro-processed materials.

Once the API has been fully synthesized, crystallization is often one of the most critical steps in efficiently producing the final dosage form – regardless of whether operating in batch or continuous mode. A well designed and executed crystallization is vital in the active compound's yield, chemical purity, polymorphism, particle size and potentially shape (and related properties such as flowability and tendency to agglomerate). For safety and regulatory reasons, purity and polymorph are of upmost importance in pharmaceuticals and no compromise can or should be considered. Yield is, of course, critical for an economically viable product.

Particle size and shape are known to be critical attributes but can be sensitive to small variations in the feed solutions, mixing conditions, and other disturbances and are not fully optimized in the crystallization step. Many of the downstream processes employed in a typical tableting process are to correct the size and shape of the API. These processes include

but are not limited to milling, sieving, wet granulation followed by drying (or dry granulation), spray drying, and blending with excipients such as glidants. A poorly designed and executed crystallization can negate a great synthesis pathway, potentially resulting in overall poor yield, failing molecular purity, undesired polymorphic forms, and an ultimate increase in the complexity and cost of tableting.

Due to the importance of crystallization, numerous projects are underway at the time of writing at MIT and a few are briefly discussed here. Several projects have been optimizing crystallization of APIs in MSMPR crystallizers. In these crystallizers, a concentrated solution is typically continuously being added while suspended crystals are being removed. To reduce large loses of material, the mother liquor can be recycled. As also briefly discussed in Section 13.3, material recycling can be important to improve the economic potential of a CM process. Recycling minimizes the amount of feedstock or (intermediate) product that is sent to waste. In addition, recycling also offers the opportunity to optimize chemistry for selectivity rather than yield as recycling of unreacted reagents can drive up the yield of the process as a whole. In the case of the CM process described in Section 13.2, the mother liquor from the second filter can be concentrated (such as by partial evaporation) and returned to the crystallizers for further crystallization of the API. To prevent the accumulation of impurities in this process, the impurities can either be removed via a purge stream or be *selectively* removed using, for example, nanofiltration membranes [17, 34]. Also, in addition to recycling raw materials, intermediates, and API, the high potential of catalyst recycling for CM has also been demonstrated [35].

Optimizing a multi-stage MSMPR crystallizer's performance with regard to yield, molecular purity, polymorphic form, and particle size can result in better control over the crystallization process and higher yields [36, 37]. Often the optimal conditions to achieve the best balance of all four of these properties are not intuitive. Modeling the process can quickly yield the optimized processing conditions with a minimum of experiments and amount of material. For example, we found that the polymorph dynamics in an MSMPR crystallizer can be controlled to selectively produce metastable or stable polymorphs of L-glutamic acid by manipulating the crystallization temperature and residence time [38].

The high dissolution rate and solubility of nanocrystals makes them very appealing for challenging APIs with low aqueous solubility. One novel concept being developed at the Novartis-MIT Center involves crystallizing a hydrophobic drug in an emulsion embedded in a polymer matrix [39]. The drug (fenofibrate in this case) is first dissolved in a volatile organic solvent and an oil in water emulsion is prepared. The emulsion is dispersed in an alginate mixture. Small macro-droplets of the mixture are crosslinked by controlled dripping into a calcium bath to create drug emulsion loaded beads (see Figure 13.15). The beads are dried – removing both the water and the organic solvent and crystallizing the fenofibrate. The crystal size was found to be dependent on the drug concentration in the organic solvent and the emulsion droplet size. The crystal size could be well controlled between 330 nm and 420 μm with up to an impressive 85% (w/w) drug loading (dry).

The first process to decrease the crystal size was to decrease the emulsion droplet size at constant drug concentration (saturation limit of fenofibrate in anisole). The dissolution of the fenofibrate from the hydrogel particles was highly dependent on the crystal size (Figure 13.16). To achieve submicron crystals, the concentration of the fenofibrate in the anisole was decreased while maintaining constant emulsion droplet size of 1.1 μm. The dissolution rates of both set of crystals are plotted in Figure 13.16 and compared to the release

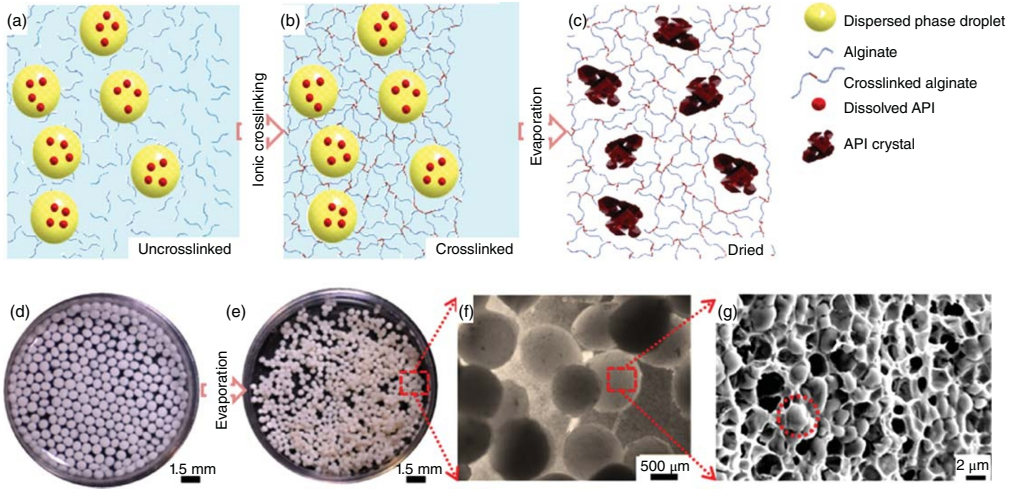


Figure 13.15 *(a) Emulsion droplets with a dissolved hydrophobic API are dispersed in an aqueous solvent containing the uncrosslinked alginate. (b) Upon cross-linking in a calcium bath, the nano- or macro-emulsion droplets are entrapped in the hydrogel matrix. (c) Upon evaporation, the dissolved API in emulsion droplets crystallizes to form crystals that are embedded in the dried hydrogel matri13. Panels (d) and (e) show hydrated "cross-linked" and "dried" composite hydrogel particles, respectively. (f) Microscopy images of "dried" composite hydrogels and (g) SEM image of "dried" composite hydrogel sliced open with embedded API identified (dotted circle). Reprinted with permission from [39]. Copyright 2014 American Chemical Society.*

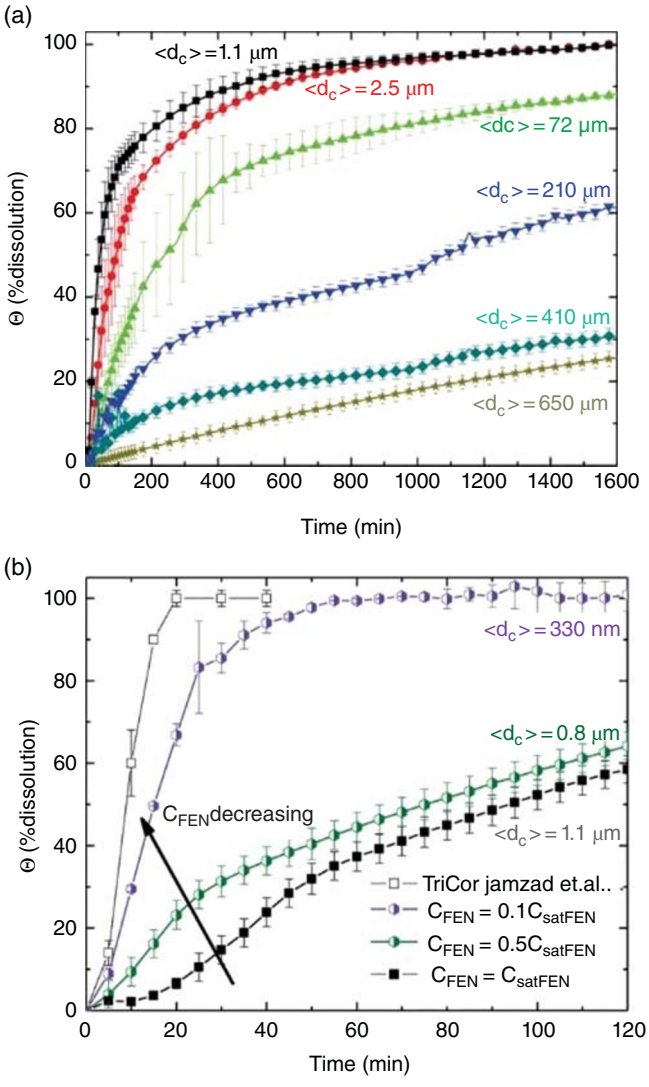


Figure 13.16 *(a) Dissolution profile of dried composite hydrogel particles with different crystal sizes prepared by controlling the emulsion droplet size at fixed API concentration (saturated fenofibrate in anisole). (b) Dissolution profile of smaller crystals in hydrogel particles compared to the commercial drug product Tricor tablets. Reprinted (adapted) with permission from [39]. Copyright 2014 American Chemical Society.*

rate of the commercial Tricor tablet data from the literature. The 330-nm nanocrystals had a similar release rate as the nanomilled drug in the Tricor product (Figure 13.16b). Once dried, the hydrogel particles can undergo direct compression into tablets (Figure 13.17).

Another process to continuously and efficiently tablet APIs is to create tablets from thin films. Crystallized or dissolved API is mixed in a wet mass. The wet mass is coated and dried

Figure 13.17 *Tablets made from composite hydrogel particles containing fenofibrate crystals (d = 1.1 μm) and final drug loading of 40%. Reprinted with permission from [39]. Copyright 2014 American Chemical Society.*

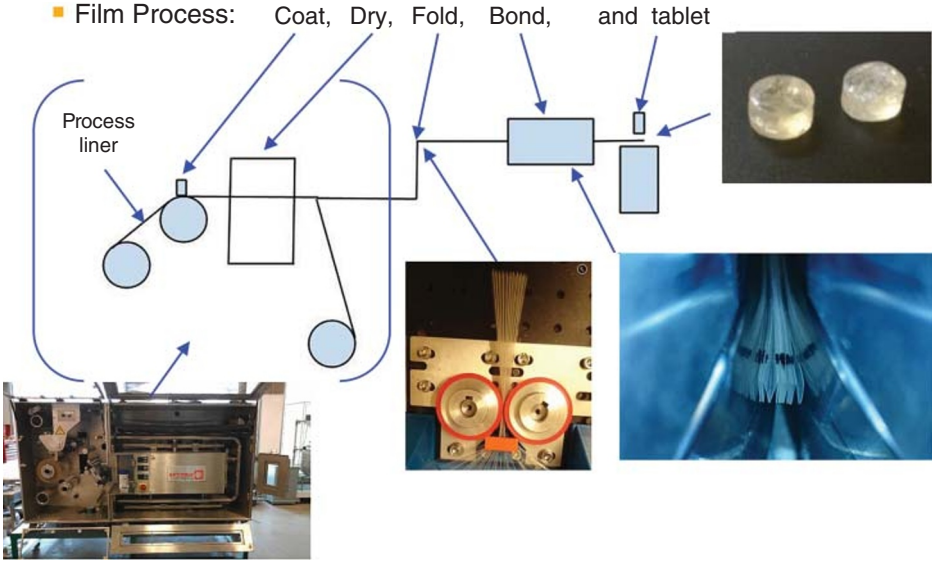


Figure 13.18 *Schematic and photos of making and processing thin films into tablets. A wet mass is made with dissolved or crystallized API. The wet mass is coated and dried in a commercial coater, folded, bonded, and tableted.*

to give a film with a uniform distribution of API, which would then be folded, bonded, and tableted (Figure 13.18). The process can potentially reduce the number of unit operations for tableting by roughly half. Even if the individual unit operations of tableting films would be more costly than the usual unit operations for tableting, the greatly reduced number of operations could result in an overall more economical process.

We are also working on another crystallization technology that involves films. Films are designed so as to interact with drug molecules during crystallization such that the nucleation rates are increased by orders of magnitude. In addition, crystallization of the desired

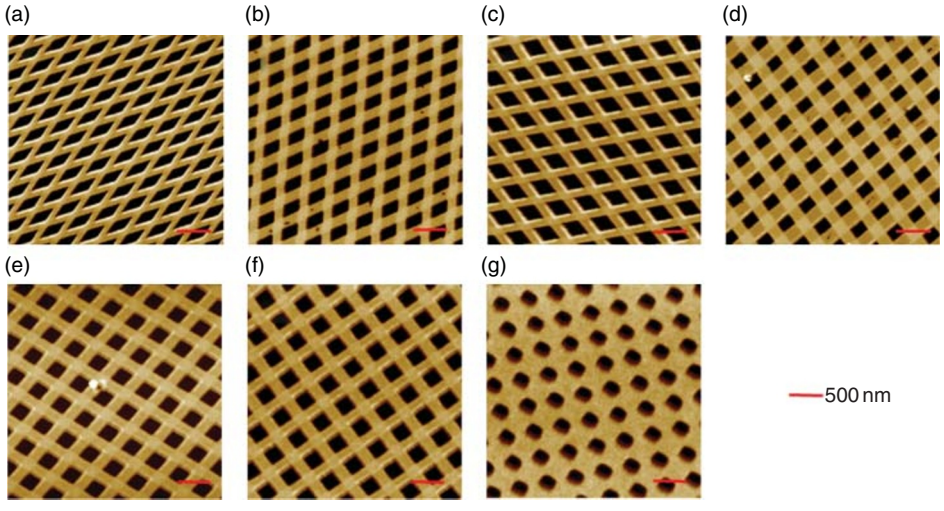


Figure 13.19 *AFM images of PVA films containing nano-indentations with (a) 40, (b) 60, (c) 65, (d) 80, (e) 85, and (f) 90 degree angles, as well as (g) round indentations. Reprinted with permission from [40]. Copyright 2015 American Chemical Society.*

polymorph can also be influenced. The process involves imprinting patterns on a film surface. The pattern is selected based on the calculated angles between major crystal faces for the desired polymorph resulting in dramatically increasing the nucleation rate of the desired polymorph [40]. Figure 13.19 shows various patterns imprinted on PVA films and tested to determine the nucleation rate. The induction rates of aspirin without film, with unpatterned (flat), and with the various patterns were measured (Table 13.1). The induction time was reduced by about one order of magnitude by introducing an unpatterned film to the system and up to another order of magnitude by using the best patterned film, 85° for aspirin.

Table 13.1 *Average nucleation induction times, their standard deviations and* r^2 *values for cooling crystallization of aspirin in ethanol conducted at supersaturation ratios of* $S = 1.8$ *and* $S = 2.4$*. Reprinted with permission from [40]. Copyright 2015 American Chemical Society*

	$S = 1.8$ τ (min)	r^2	$S = 2.4$ τ (min)	r^2
Homogeneous	29 900 ± 1140	0.964	3140 ± 110	0.968
Flat film	3090 ± 160	0.931	222 ± 17	0.940
Round	1035 ± 59	0.921	187 ± 10	0.977
40°	828 ± 34	0.966	158 ± 13	0.953
60°	799 ± 24	0.982	126 ± 11	0.934
65°	751 ± 16	0.992	130 ± 9	0.959
80°	340 ± 9	0.985	91 ± 6	0.981
85°	215 ± 18	0.907	48 ± 5	0.965
90°	400 ± 18	0.977	100 ± 11	0.939

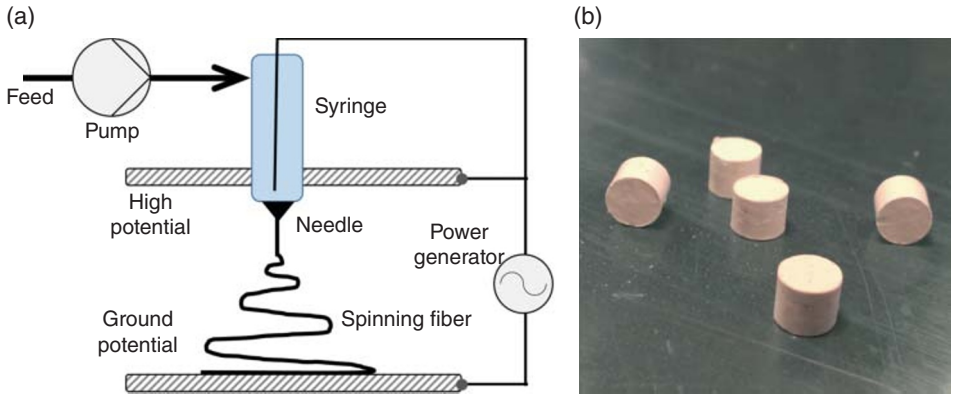


Figure 13.20 *(a) Schematic of electrospinning. (b) Tablets made from electrospun materials.*

A computational analysis of the crystal lattice information from the Cambridge Structural Database and the attachment energy method found that the best angles for enhancing nucleation of aspirin were 84.1°, 87.0°, and 59.6° (in decreasing order of largest family of faces) matching the experimental results. Similarly good results were also obtained for indomethacin [40]. Once the API has crystallized, tablets can be quickly and efficiently made by folding, bonding, and tableting the film – similar to the process for the films described above.

In addition to making tablets out of thin films, another novel tableting technology that we are investigating is the tableting of electrospun materials [41]. Electrospinning drugs involves dissolving or suspending drug particles in a liquid polymer mixture. We explored free surface electrospinning from a wire that has been coated with the drug mixture. A high potential (20–80 kV) is applied across a gap, causing jetting of the mixture and creating nanofibers containing the drug. The fibers are collected and processed into a tablet. Figure 13.20a shows a schematic of the electrospinning process to turn polymer mixtures into nanofibers and the final tablets are seen in Figure 13.20b. A higher magnification SEM micrograph can reveal the structure of the drug particles in the electrospun fibers (Figure 13.21).

13.6 Summary and Closing Thoughts

The last decade of research has delivered numerous convincing cases where CM offers inherent technological advantages for manufacturing of pharmaceuticals with, undoubtedly, many more to follow from future research. These advantages are realized not by simply translating an existing batch process to operate in continuous flow, but by seizing the opportunity to use improved technology that simply does not work well in batch mode. Examples of individual processing steps where such improved technologies are reported span the complete CM plant discussed in this chapter (i.e., from synthesis in flow to formulation in flow). Integrating all those unit operations into a single seamless CM process for pharmaceuticals is a natural next step for pharmaceutical industry to fully benefit from CM as other industries have done in the past.

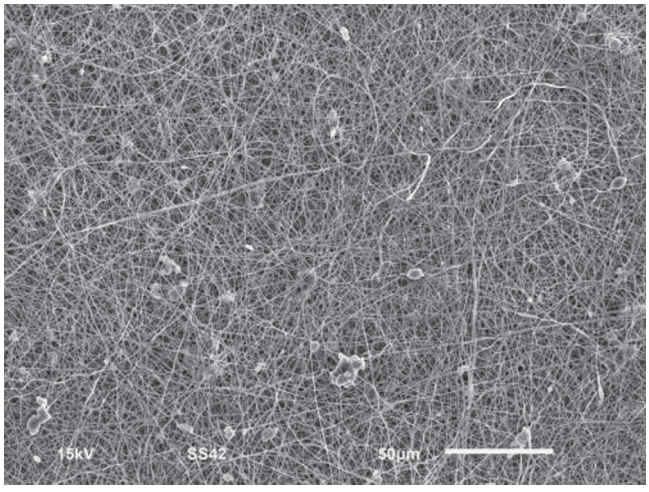


Figure 13.21 *SEM micrographs of drug particles (fenofibrate) on electrospun PVA fibers.*

In this chapter, we aimed to discuss the benefits and challenges related to the design and operation of CM processes for pharmaceuticals. A realistic case study has been used throughout the chapter to illustrate some specific benefits and challenges that we encountered in addition to more general thoughts on how to fully benefit from CM for future processes. The main focus of the discussion has been on technology development and application. However, it is also widely recognized that a change in mindset throughout pharmaceutical industry is required to break the old paradigm of batchwise manufacturing [42]. Early adoption of CM in the complete cycle from the discovery of active molecules to the final stages of manufacturing is essential such that CM is the natural point of departure for future research and development within pharmaceutical industry. The combined efforts of industry, academia, and regulatory authorities have spurred research and development into novel CM technologies in a broad sense and at various scales rapidly, which is a highly encouraging trend [43–50]. Such novel technologies and regulatory frameworks strengthen the foundation for endorsing CM as the core technology from the discovery of active molecules to the various phases of pharmaceutical manufacturing. Furthermore, the early adoption and use of state of the art process modeling and related tools can be seen as a crucial support tool for future CM processes, similarly as have been for other branches of the chemical industry [28]. More broadly looking ahead, access to a wide variety of unit operations for CM at a small scale is also important to gain learning earlier in development in addition to producing trial lots continuously.

The flexibility to manufacture different quantities of material is a key factor for success in pharmaceutical process development. CM offers the opportunity to simply run a process longer instead of only bigger (the latter being the practice for batchwise process development). Furthermore, simplified process control offers opportunities for easier scaleup. CPPs can be used as manipulated variables in automated control loops to control CQAs directly (instead of indirectly via control of CPPs). A control strategy based on feedback offers inherent advantages compared to a strategy where a fixed design space is

identified *a priori*. A control structure that works well on a small scale usually also works well on a larger scale. On the other hand, design spaces that are established on a small scale may not translate predictably to a larger scale. Furthermore, regions of design space that are not explored *a priori* cannot be used during operation [51]. Effective development of future CM processes of pharmaceuticals may, therefore, very well be tailored towards direct measurement of CQAs with PAT and revealing a suitable control structure for feedback to parameter space rather than only establishing a fixed design space *a priori*. In that perspective, the availability of flexible and modular control hardware and software that can be utilized throughout all the phases of process development of CM of pharmaceuticals is needed [52].

Section 13.3 illustrated some examples of the importance of identifying local and system-wide dynamics of future CM processes for pharmaceuticals and how to manipulate dynamics. Dynamic process modeling is useful to supplement experimental work for improved understanding of the process dynamics. For example, data that have been obtained from process simulations demonstrate in Section 13.3 how an inert impurity in the feeding material is expected to propagate throughout the process. Dynamic process simulations allow for a systematic evaluation of the impact of different control or design strategies (e.g., the presence of major recycle streams) on the presence of the impurity in the product as a function of time. In general, although a stable CM process will move towards a steady operating point, transient behavior is important to optimize the economic performance of a CM process through maximization of the overall yield and judicious mitigation of disturbances via automated process control. Fortunately, a control strategy solely based on the presumption of steady-state operation is not needed. Rather, a control strategy of future CM processes should be based on maintaining CQAs within their permissible range [37].

The availability to measure CQAs directly (instead of CPPs) with PAT is most effective for any control strategy based on feedback [51]. Section 13.4 provides a discussion on PAT that has been used in the CM process discussed in this chapter. In our case, different objectives were targeted by installing on-line PAT. First, PAT allowed us to improve our understanding of the process, which is important during development. Second, some PAT has also been integrated in the automated control system, which is important during operation. Third, PAT also allowed for early detection of abnormal events, which is crucial for efficient and safe process operation. Although the development of advanced PAT has seen spectacular development during the last decade, the majority of all process variables are not well measurable, at least from an economic point of view. Process modeling again offers opportunities since unknown process variables can be estimated using a validated process model and known measurements of other variables. Ultimately, the aim is to combine the capabilities of a process model to both estimate the full state of the system and to predict future behavior to support automated decisions for process control. This so-called model predictive control (MPC) is well established for various applications within chemical industry and CM of pharmaceuticals is an interesting future field of application. MPC for CM of pharmaceuticals has the inherent advantage that MPC explicitly allows for process constraints to be taken into account, which allows for optimization of control objectives related to economics while safeguarding established boundaries on process variables. The latter aspect clearly favors regulatory requirements.

Finally, Section 13.5 has highlighted some research directions that are being pursued at the Novartis-MIT Center for Continuous Manufacturing at the time of writing. The pilot plant discussed in this chapter already demonstrated significant advantages compared to batchwise processing [1]. These advantages are obtained at several places within the process where the inherent advantages of CM are exploited. Nevertheless, completely novel technologies tailored for CM can still dramatically improve the performance of the discussed process and future CM processes for pharmaceuticals in general.

References

[1] S. Mascia, P. L. Heider, H. T. Zhang, R. Lakerveld, B. Benyahia, P. I. Barton, R. D. Braatz, C. L. Cooney, J. M. B. Evans, T. F. Jamison, K. F. Jensen, A. S. Myerson, and B. L. Trout (2013) End-to-end continuous manufacturing of pharmaceuticals: integrated synthesis, purification, and final dosage formation, *Angewandte Chemie International Edition*, **52**, 12359–12363

[2] M. A. Foley and T. F. Jamison (2010) Amide bond formation via reversible, carboxylic acid-promoted lactone aminolysis, *Organic Process Research and Development*, **14**, 1177–1181.

[3] A. Dondoni, G. De Lathauwer, and D. Perrone (2001) A convergent synthesis of the renin inhibitor SPP-100 using a nitrone intermediate, *Tetrahedron Letters*, **42**: 4819–4823.

[4] S. Hanessian, S. Guesné, and E. Chénard (2010) Total Synthesis of "Aliskiren": The first renin inhibitor in clinical practice for hypertension, *Organic Letters*, **12**: 1816–1819.

[5] H. Rüeger, S. Stutz, R. Göschke, F. Spindler, and J. Maibaum (2000) A convergent synthesis approach towards CGP60536B, a non-peptide orally potent renin inhibitor, via an enantiomerically pure ketolactone intermediate, *Tetrahedron Letters*, **41**, 10085–10089.

[6] D. A. Sandham, R. J. Taylor, J. S. Carey, and A. Fässler (2000) A convergent synthesis of the renin inhibitor CGP60536B, *Tetrahedron Letters*, **41**, 10091–10094.

[7] P. L. Heider, S. C. Born, S. Basak, B. Benyahia, R. Lakerveld, H. Zhang, R. Hogan, L. Buchbinder, A. Wolfe, S. Mascia, J. M. B. Evans, T. F. Jamison, and K. F. Jensen (2014) Development of a Multi-Step Synthesis and Workup Sequence for an Integrated, Continuous Manufacturing Process of a Pharmaceutical, *Organic Process Research and Development*, **18**, 402–409.

[8] A. Sundaramoorthy, J. M. B. Evans, and P. I. Barton (2012) Capacity planning under clinical trials uncertainty in continuous pharmaceutical manufacturing, 1: Mathematical framework, *Industrial and Engineering Chemistry Research*, **51**, 13692–13702.

[9] A. S. Myerson, M. Krumme, M. Nasr, H. Thomas, and R. D. Braatz (2015) Control systems engineering in continuous pharmaceutical manufacturing. May 20−21, 2014 Continuous Symposium, *Journal of Pharmaceutical Sciences*, **104**, 832–839

[10] P. S. Buckley (1964) *Techniques of Process Control*, John Wiley & Sons, Ltd, London.

[11] G. Stephanopoulos and C. Ng (2000) Perspectives on the synthesis of plant-wide control structures, *Journal of Process Control*, **10**, 97–111.

[12] T. Larsson and S. Skogestad (2000) Plantwide control – a review and a new design procedure, *Modeling, Identification and Control*, **21**, 209–240.

[13] M. Morari, Y. Arkun, and G. Stephanopoulos (1980a) Studies in the synthesis of control structures for chemical processes: Part I: Formulation of the problem. Process decomposition and the classification of the control tasks. Analysis of the optimizing control structures, *AIChE Journal*, **26**, 220–232.

[14] M. Morari and G. Stephanopoulos (1980b) Studies in the synthesis of control structures for chemical processes: Part II: Structural aspects and the synthesis of alternative feasible control schemes, *AIChE Journal*, **26**, 232–246.

[15] R. Lakerveld, B. Benyahia, R. D. Braatz, and P. I. Barton (2013a) Model-based design of a plant-wide control strategy for a continuous pharmaceutical plant, *AIChE Journal*, **59**, 3671–3685.
[16] B. Benyahia, R. Lakerveld, and P. I. Barton (2012) A plant-wide dynamic model of a continuous pharmaceutical process, *Industrial and Engineering Chemistry Research*, **51**, 15393–15412.
[17] S. Ferguson, F. Ortner, J. L. Quon, L. Peeva, A. G. Livingston, B. L. Trout, and A. S. Myerson (2014) Use of continuous MSMPR crystallization with integrated nanofiltration membrane recycle for enhanced yield and purity in API crystallization, *Crystal Growth and Design*, **14**, 617–627.
[18] D. E. Seborg, D. A. Mellichamp, T. F. Edgar, and F. J. Doyle III, (2011) *Process Dynamics and Control*, John Wiley & Sons, Inc., Hoboken.
[19] B. A. Ogunnaike and W. H. Ray (1994) *Process Dynamics, Modeling, and Control*, Oxford University Press, Oxford.
[20] G. Stephanopoulos (1984) *Chemical Process Control: An Introduction to Theory and Practice*, Prentice-Hall, London.
[21] K. A. Mcdonald, T. J. Mcavoy, and A. Tits, Optimal averaging level control, *AIChE Journal*, **32**, 75–86.
[22] R. Lakerveld, B. Benyahia, P. L. Heider, H. Zhang, and P. I. Barton (2013b) Averaging level control to reduce off-spec material in a continuous pharmaceutical pilot plant, *Processes*, **1**, 330–348.
[23] A. Chanda, A. M. Daly, D. A. Foley, M. A. LaPack, S. Mukherjee, J. D. Orr, G. L. Reid, D. R. Thompson, and H. W. Ward (2014) Industry perspectives on process analytical technology: tools and applications in API development, *Organic Process Research and Development*, **19**, 63–83.
[24] L. L. Simon, H. Pataki, G. Marosi, et al. (2015) Assessment of recent process analytical technology (PAT) trends: A multiauthor review, *Organic Process Research and Development*, **4**, 67–77.
[25] A. Gupta, A. Giridhar, V. Venkatasubramanian, and G. V. Reklaitis (2013) Intelligent alarm management applied to continuous pharmaceutical tablet manufacturing: An integrated approach, *Industrial and Engineering Chemistry Research*, **52**, 12357–12368.
[26] B. R. Hollifield and E. Habibi (2011) *Alarm Management: A Comprehensive Guide : Practical and Proven Methods to Optimize the Performance of Alarm Management Systems*, International Society of Automation, Chicago.
[27] L. H. Chiang, R. D. Braatz, and E. L. Russell (2001) *Fault Detection and Diagnosis in Industrial Systems*, Springer, London.
[28] K. V. Gernaey, A. E. Cervera-Padrell, and J. M. Woodley (2012) A perspective on PSE in pharmaceutical process development and innovation, *Computers and Chemical Engineering*, **42**, 15–29
[29] A. Mesbah, A. N. Ford Versypt, X. Zhu, and R. D. Braatz (2013) Nonlinear model-based control of thin-film drying for continuous pharmaceutical manufacturing, *Industrial and Engineering Chemistry Research*, **53**, 7447–7460.
[30] R. Singh, M. Ierapetritou, and R. Ramachandran (2012) An engineering study on the enhanced control and operation of continuous manufacturing of pharmaceutical tablets via roller compaction, *International Journal of Pharmaceutics*, **438**, 307–326.
[31] R. Singh, D. Barrasso, A. Chaudhury, M. Sen, M. Ierapetritou, and R. Ramachandran (2014) Closed-loop feedback control of a continuous pharmaceutical tablet manufacturing process via wet granulation, *Journal of Pharmaceutical Innovation*, **9**, 16–37.
[32] Paulson, J. A., Mesbah, A., Streif, Stefan, Findeisen, Rolf, and Braatz, Richard D. (2014) Fast stochastic model predictive control of high-dimensional systems, *Proceedings of the 53rd IEEE Conference on Decision and Control*, pp. 2802–2809.

[33] M. Sen, R. Singh, and R. Ramachandran (2014) A hybrid MPC-PID control system design for the continuous purification and processing of active pharmaceutical ingredients, *Processes*, **2**, 392–418.

[34] S. Y. Wong, A. P. Tatusko, B. L. Trout, and A. S. Myerson (2012) Development of continuous crystallization processes using a single-stage mixed-suspension, mixed-product removal crystallizer with recycle, *Crystal Growth and Design*, **12**, 5701–5707.

[35] P. Li, J. S. Moore, and K. F. Jensen (2013) A microfluidic system for the continuous recycling of unmodified homogeneous palladium catalysts through liquid/liquid phase separation, *ChemCatChem*, **5**, 1729–1733.

[36] A. J. Alvarez, A. Singh, and A. S. Myerson (2011) Crystallization of cyclosporine in a multistage continuous MSMPR crystallizer, *Crystal Growth and Design*, **11**, 4392–4400.

[37] H. Zhang, J. Quon, A. J. Alvarez, J. Evans, A. S. Myerson, and B. Trout (2012) Development of continuous anti-solvent/cooling crystallization process using cascaded mixed suspension, mixed product removal crystallizers, *Organic Process Research and Development*, **16**, 915–924.

[38] T. T. Lai, S. Ferguson, L. Palmer, B. L. Trout, and A. S. Myerson (2014) Continuous crystallization and polymorph dynamics in the L-glutamic acid system, *Organic Process Research and Development*, **18**, 1382–1390.

[39] H. B. Eral, M. O'Mahony, R. Shaw, B. L. Trout, A. S. Myerson, and P. S. Doyle (2014) Composite hydrogels laden with crystalline active pharmaceutical ingredients of controlled size and loading, *Chemistry of Materials*, **26**, 6213–6220.

[40] L. Tan, R. Davis, A. S. Myerson, and B. L. Trout (2015) Control of heterogeneous nucleation via rationally designed biocompatible polymer surfaces with nanoscale features, *Crystal Growth and Design*, **10**, 392–400.

[41] K. M. Forward and G. C. Rutledge (2012) Free surface electrospinning from a wire electrode, *Chemical Engineering Journal*, **183**, 492–503.

[42] K. Plumb (2005) Continuous processing in the pharmaceutical industry – Changing the mind set, *Chemical Engineering Research and Design*, **83**, 730–738.

[43] G. Allison, Y. T. Cain, C. Cooney, et al. (2015) Regulatory and quality considerations for continuous manufacturing, *Journal of Pharmaceutical Sciences*, **104**, 803–812.

[44] C. Badman and B. L. Trout (2015) Achieving continuous manufacturing, *Journal of Pharmaceutical Sciences*, **104**, 779–780.

[45] I. R. Baxendale, R. D. Braatz, B. K. Hodnett, et al. (2015) Achieving continuous manufacturing: Technologies and approaches for synthesis, workup, and isolation of drug substance, *Journal of Pharmaceutical Sciences*, **104**, 781–791.

[46] S. Byrn, M. Futran, H. Thomas, et al. (2015) Achieving continuous manufacturing for final dosage formation: Challenges and how to meet them, *Journal of Pharmaceutical Sciences*, **104**, 792–802.

[47] K. B. Konstantinov and C. L. Cooney (2015) White paper on continuous bioprocessing, *Journal of Pharmaceutical Sciences*, **104**, 813–820

[48] K. Nepveux, J. P. Sherlock, M. Futran, M. Thien, and M. Krumme (2015) How development and manufacturing will need to be structured – Heads of development–manufacturing, *Journal of Pharmaceutical Sciences*, **104**, 850–864.

[49] T. Page, H. Dubina, G. Fillipi, et al. (2015) Equipment and analytical companies meeting continuous challenges, *Journal of Pharmaceutical Sciences*, **104**, 821–831.

[50] J. S. Srai, C. Badman, M. Krumme, M. Futran, and C. Johnston (2015) Future supply chains enabled by continuous processing – Opportunities and challenges, *Journal of Pharmaceutical Sciences*, **104**, 840–849.

[51] R. A. Lionberger, S. L. Lee, L. Lee, A. Raw, and L. Yu (2008) Quality by design: Concepts for ANDAs, *AAPS Journal*, **10**, 268–276.

[52] S. V. Ley, D. E. Fitzpatrick, R. Ingham, and R. M. Myers (2015) Organic synthesis: March of the machines, *Angewandte Chemie International Edition*, **82**, 30–38.

[53] R. Lakerveld, B. Benyahia, P. L. Heider, H. Zhang, A. Wolfe, C. J. Testa, S. Ogden, D. R. Hersey, S. Mascia, J. M. B. Evans, R. D. Braatz, and P. I. Barton (2014) The application of an automated control strategy for an integrated continuous pharmaceutical pilot plant, *Organic Process Research and Development*, **4**, 41–48

[54] Mesbah, A., Paulson, J. A., Lakerveld, Richard, and Braatz, Richard D. (2015) Plant-wide model predictive control for a continuous pharmaceutical process, *Proceedings of the American Control Conference*, pp. 30–34.

14

Methodology for Economic and Technical Comparison of Continuous and Batch Processes to Enhance Early Stage Decision-making

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14.1 Introduction

Along with the technological advances in pharmaceutical engineering and technology, there is an increasing expectation that pharmaceutical manufacturing should be modernized as well. Compared to other industries, the gap between world-class factories and the pharmaceutical industry still leaves room for significant improvements across all major manufacturing indicators such as stock turn, on time in full (OTIF), right first time (RFT), CpK values, overall equipment effectiveness (OEE) and cycle times [22]. Today, continuous manufacturing (CM) is well established in many different industries, due to its flexibility, efficiency and high output quality [1, 25]. During the past decades, CM has also been introduced to the pharmaceutical industry to increase manufacturing effectiveness and efficiency [2, 3]. The advantages of the continuous over the traditional batch process are [3, 14–16, 26]:

Continuous Manufacturing of Pharmaceuticals, First Edition.
Edited by Peter Kleinebudde, Johannes Khinast, and Jukka Rantanen.
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- An expected increase in production efficiency by using small continuous manufacturing units;
- Reduce scale-up effort;
- Decrease of the risk of out of specification (OOS) failures of intermediates and end products.

The benefits have been recognized by regulatory bodies such as the United States Food and Drugs Administration (FDA), which is pushing for the pharmaceutical companies to embrace continuous processes developed based on Quality by Design (QbD) principles, process analytical technology (PAT) and closed-loop quality assurance [4]. Since then, expectations have been raised regarding favorable economies [9] as well as increased patient benefits, when switching from batch manufacturing to CM [10, 11].

Continuous production units have already been implemented in pharmaceutical research and development facilities, and many can now be operated at production scales. In fact, the first continuously manufactured drug product Orkambi, a cystic-fibrosis drug by Vertex, received FDA approval in 2015. Other major pharmaceutical companies (Pfizer, GSK, Novartis, Johnson and Johnson, etc.) are either close to or have already started to continuously manufacture selected products. Although decision to adapt continuous processing typically hinges on technical, regulatory and quality related concerns, balancing these concerns against economic factors, such as equipment and operational costs, is essential to support the right decisions in the early product development phases.

During the last decade of the development, different attempts have been made to compare the economic aspects between batch and continuous processes for given pharmaceutical products [5, 6]. For example, comparisons were performed between batch and continuous processing, using a specific Novartis product based on a 24/7 production plant starting from chemical synthesis [7]. Additionally, Schaber *et al*. estimated CAPEX and OPEX costs for a large-scale (2000 t/year) pharmaceutical production, which includes both primary processing and different downstream options [8]. However, these approaches typically rely on financial and operational data which are not available in the early conceptualization and decision stage. Essentially, the typical cost-effective or cost–benefit analysis is appropriate at the earliest during the detailed evaluation stage, as shown in Figure 14.1, when the equipment supplier is first involved. However, the authors believe that a standardized methodology to incorporate some key cost and economic factors at the earlier, basic evaluation stage could bring significant strategic values to the pharmaceutical companies.

We present in this chapter a fast, semi-quantitative approach to a technical–economic comparison between different process options at the early conceptualization stage. The comparison is aimed to support "go or no go" decisions in selecting the right product design and manufacturing process to progress to detailed evaluation and design/implementation.

14.2 Technical–Economic Evaluation Methodology

The key to develop early-stage technical and economic drivers for continuous pharmaceutical manufacturing is the availability of information and data. Therefore, assumptions often need to be made because some information might not yet be available. These assumptions are often product- and process-specific and may require qualitative or semi-quantitative validation. For example, it is often assumed that the quality target product profile (QTPP),

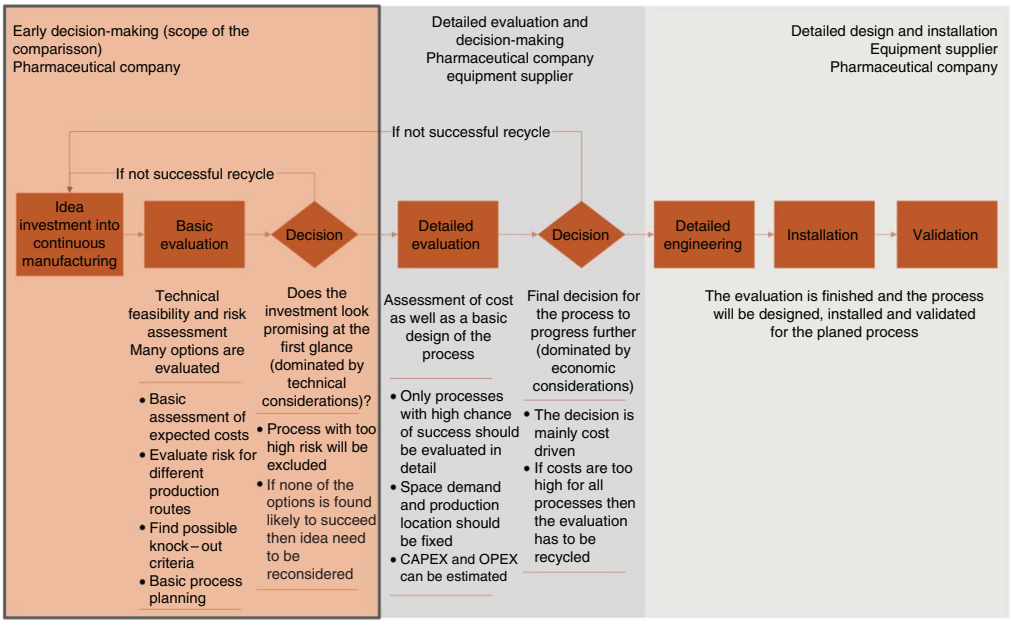

Figure 14.1 *Decision-making chain and development progress for implementation of a new process.*

such as a product's biopharmaceutical performance and regulatory requirement, can be met by the process options (batch or continuous) considered. However, the likelihood of this being indeed the case may only be assessed at this stage by potential weighted risk factors. The same applies to certain technical feasibility and performance factors. They are either weighted/scored as risks at this point or deferred to be investigated in depth through simulation or experiments later. As it is typically the case, the more data are available the more accurate and insightful the scoring becomes.

The primary aims of the technical–economic comparison were defined as follows:

- Selection of the best process from the economic and technical prospective;
- Early identification of the risk factors for implementing a new process chain;
- Assessment of technical feasibility and suitability;
- Providing a rational basis for investment decisions.

Our approach is a combination of our earlier techno-economic profiling work [12] and a modified method to evaluate the cost effectiveness of process set ups [13]. It is further applied using the problem and structuring process for technology systems and products according to VDI Guidance 2221 [14].

The work flow to carry out the comparison and subsequence revision is outlined in Figure 14.2. It starts with the definition of the system boundaries and follows a logical sequence of detailed analysis (modeling), risk assessment, cost calculation and scoring, to establishing a techno-economic profile (TEP) in the end. The TEP can then be further analysed through sensitivity and uncertainty analysis. Additionally, the equipment portfolio needs to be evaluated in a separated workflow. Therefore, a separate set of analyses has to be carried out for each process option. The analyses should consider: the relevant cost categories and factors, process modelling, evaluation of technical feasibility and calculation of the costs associated with the process and equipment.

14.2.1 Definition of the System Boundaries and Performance Targets

In order to evaluate and forecast manufacturing process efficiency and costs, special attention needs to be paid to the definition and understanding of the system boundaries. Figure 14.3 displays an example of a downstream manufacturing process for a direct compressed, coated tablet. It serves as the base line for any manufacturing efficiency evaluation. For a comparative efficiency analysis, the specific pharmaceutical manufacturing process which should be replaced by another (i.e., continuous manufacturing process) has to be evaluated. This evaluation has to consider all relevant parameters in depth. The chosen production capacity of a plant is one of the main influencing factors for the economic performance, analysis of a process and its alternative process options. The comparative efficiency analysis will also include product-specific predictions, such as the long-term production planning and supply chain forecasts. Also production constraints like the number of shifts should be evaluated for their impact on the manufacturing efficiency. When choosing the system boundaries for the TEP, system boundaries could be set to primary or secondary manufacturing only. It is also possible to narrow the boundaries further, for example, to consider only the granulation and drying step, if the subsequent processes are independent form the chosen granulation step.

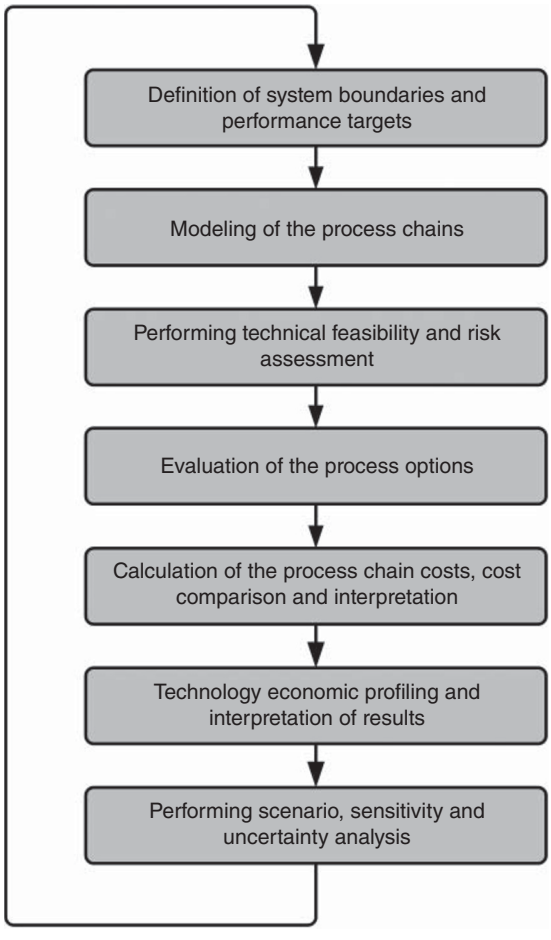

Figure 14.2 *Methodology for evaluating process chains in early stage development.*

14.2.2 Modeling of the Process Chains

After the desired capacity and system boundaries have been defined, the unit operations involved need to be specified (for the continuous process and, if needed, the default batch process). It is important to systematically include all main and auxiliary equipment needed for process integration into a processing flow sheet. For both the batch and the continuous process, all key figures, such as batch size/throughput rate, overall equipment or processing times, have to be evaluated.

For the selected process options, either standard or prototype formulations have to be developed in order to set up the mass balances between the involved equipment. Finally, the required overall throughput of the plant (batch or continuous) can be defined.

For the overall equipment effectiveness (OEE) many parameters need to be considered. The basic concept of the factors that determine the equipment effectiveness are shown in Figure 14.4 and a detailed description is given in Table 14.1.

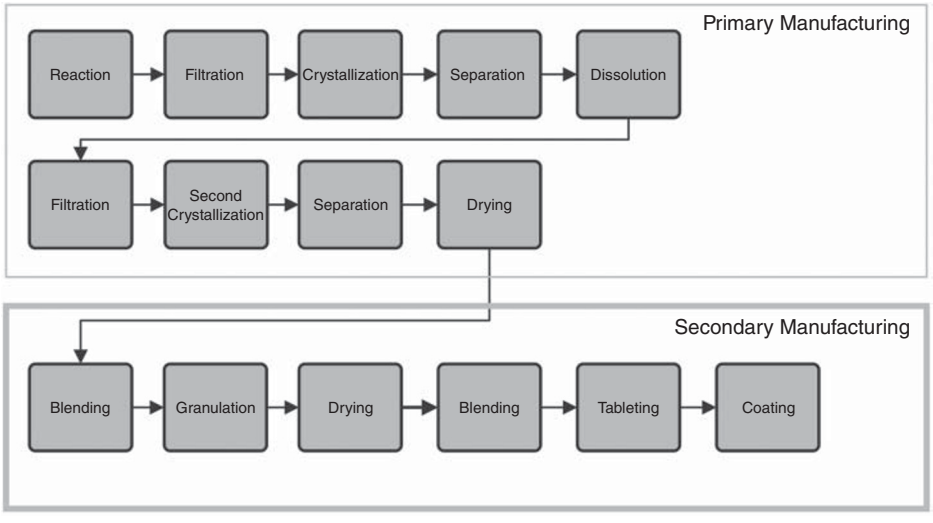

Figure 14.3 *Example of pharmaceutical process chain of primary and secondary manufacturing.*

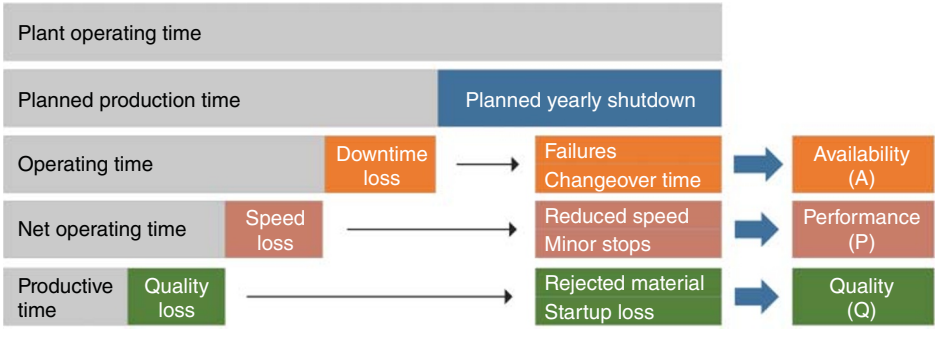

Figure 14.4 *Overview of the overall equipment effectiveness [15, 16, 22].*

14.2.3 Performing Technical Feasibility and Risk Assessment

Following the analysis and modeling of the process options (both continuous and batch), the technical feasibility and potential risks need to be assessed.

The assessment starts with a definition of the most important criteria that need to be included and reviewed to evaluate the feasibility and process risk. For pharmaceutical processes, the main categories are related to the product, to the process or to the costs (Table 14.2).

The assessment also includes the calculation of risks associated with a product or process to not achieve the predicted and desired outcomes. Such risks can also be related to the product (e.g., stability of API, change in biopharmaceutical profile), the process (e.g., blend inhomogeneity) or costs (e.g., maintenance intervals). An approximate quantification of risk is done by using criteria-specific, pre-defined risk scores to indicate potential unknowns within the suggested manufacturing process. An example of risk score definition (material

Table 14.1 *Detailed analysis to determine the OEE, based on the impacting factors*

Time	Explanation	Comment
Plant operating time	Depending on the shifts and working days the plant operating time can be calculated. The plant operating time corresponds to the working days per year. Different scenarios are possible (e.g., 24/7: on 365 days, 24 h production; 8/5: on 250 days, 8 h production)	Target scenario should be fixed for the continuous plant (24/7 or 8/5)
Planned production time	Subtracting the *planned shut down* from the *plant operating time* equals the *planned production time*. In the *planned shut down*, all events without the intention of running production (e.g., breaks, cleaning, scheduled maintenance, etc.) are included.	Planned maintenance (according maintenance plan) Cleaning (according cleaning validation)
Operating time	Availability takes into account *down time loss*, which includes equipment failures, material shortages, and changeover time.	Changeover losses (multipurpose plants) Not scheduled cleaning Tool changes (e.g various tablet sizes) Preparation time
Net operating time	Performance takes into account speed loss, factors which cause the process to operate at less than the maximum possible speed while running.	Machine wear, misfeeding and operator inefficiency
Productive time	Quality takes into account quality loss, which accounts for products made that do not meet the defined quality standards. The remaining time is called *fully productive time*.	Yield – estimated from experience with the batch process and equipment supplier information Rejects during start-up Rejects during shut down Losses

flowability) is provided in Table 14.3. It is worth noticing that due to the low fidelity of data available at the early development, the scoring system often consist of broad levels only (four in this case). While this does not provide for a granular analysis, it is often sufficient to support the early go/no go decisions.

These risk factors will be reflected in the final process evaluation and can be used as trigger for further simulation or experimental work prior to the final investment decision.

Table 14.2 *Major criteria for feasibility and risk evaluation (modified from [7])*

Product-related criteria	Biopharmaceutical performance
	Regulatory compliance and clearance
	Dosage form size, shape and presentation
	Solid state of the API
	Stability and shelf life
	Impact on pharmaceutical packaging
Process-related criteria	Number of unit operations
	Overall manufacturing time
	Product yield or efficiency
	Commercial availability of process equipment
	Footprint
	Scalability
	Robustness
Cost-related criteria	Equipment costs
	Depreciation
	Direct material costs (e.g., API and excipients)
	Utility costs (e.g., energy, water and HVAC)
	Direct labor costs

Table 14.3 *Risk scores for flowability in comparison to a given proces*

Ranking	Ranking criteria
3	Significantly better than with current product
2	Slightly better than with current product
1	Equal to current product
0	Worse than with current product

Due to the theoretical nature of the feasibility and risk assessment and the different importance of the elements, weighting factors are used to support qualification. These weighting factors describe the importance of a criterion within the process based on a 100-point scale for the total process. For example, a criterion of high importance would be given a weighting factor of 25, while a criterion of less importance will be attributed a factor of 5. Besides the weighting factors, scores are defined to attribute qualitative figures to each criterion. For example, a score of 0 means that there is no difference of an alternative process on this specific criterion (e.g., cost) while a score of 2 would reflect, for example, a 40% cost reduction and a score of –2 e.g. a 40% cost increase. The results of the feasibility and risk assessment will steer the decision towards the most favorable and efficient process alternative compared to the batch-based process.

14.2.4 Evaluation of the Process Options

The selected process options derived from the feasibility and risk assessment need to be evaluated in more detail. The evaluation of the process follows the systematic work flow as depicted in Figure 14.5. The tasks involved in each step are described in the following sections.

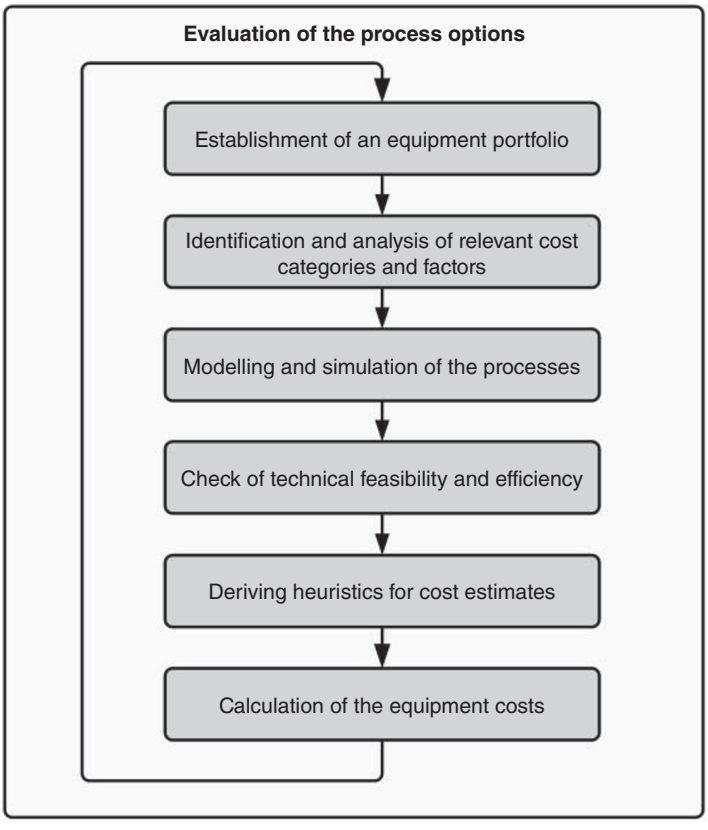

Figure 14.5 *Methodological sequence to evaluate the process option.*

14.2.4.1 Establishment of an Equipment Portfolio

The continuous process evaluation will require the integration of equipment and auxiliary equipment. The equipment portfolio is established to realize the evaluated process chain options. This will also include the relevant quality control measures, such as PAT tools, that will be applied to the process chain.

The same approach is applied to the batch-based process and the associated quality control systems. However, the requirements in terms of capacity and therefore space will vary. This should be considered and compared.

14.2.4.2 Identification and Analysis of Relevant Cost Categories and Influencing Factors

A variety of different costs contribute to the overall production cost of any pharmaceutical process. In order to establish and analyze the economic profile of different manufacturing processes the costs have been grouped in the following four categories:

- Direct material costs

- Indirect material cost
- Direct manufacturing costs
- Indirect manufacturing cost

The differentiation between direct costs and indirect costs (or overheads) was used in this approach. Direct costs are the costs that are directly assignable to a specific product or process. For example, the costs for labor or raw materials. In contrast, indirect costs or overheads are not directly attributable to a cost object but may have a significant impact on the final product costs. These costs are typically allocated to a product on the basis of shared costs of a manufacturing plant or commonly used resources like management, insurance, taxes or maintenance [17].

14.2.4.3 Modeling and Simulation of the Process

While some fixed direct or indirect costs can be estimated directly, certain operational costs, such as energy, water and air consumptions, are typically process-dependent for which predictions are difficult to make. Therefore, these costs are often approximated by simulation (e.g., flowsheet modeling) based on cost-influencing factors including:

- Formulation composition
- Preparation work
- Processability
- Process optimization
- Start up and shut down times
- Yield
- Recuperation and additional investments into equipment or engineering
- Storage and logistics
- Cost for the quality system

A schematic of the simulation work flow is shown in Figure 14.6.

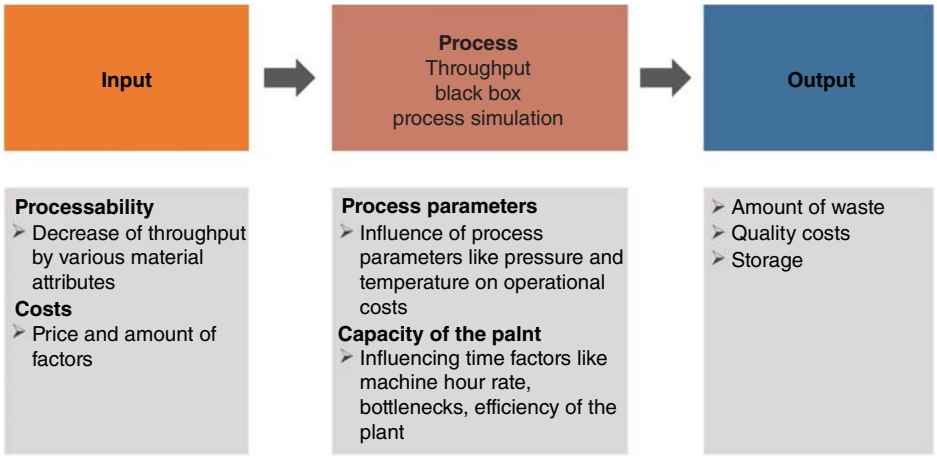

Figure 14.6 *Typical simulation work flow and cost influencing factors [13].*

14.2.4.4 Evaluation of Technical Feasibility and Efficiency

In the early phases of evaluation, the process and/or its alternative process might only exist as a concept with limited understanding and experience on its final performance. Evaluating the technical feasibility and efficiency of the conceptualized process can be derived from the prior research and the portfolio of existing technology. One of the tools used in the assessment of the technical feasibility and efficiency is process simulation (e.g., flowsheet modeling). In general, process simulation provides the means for technical feasibility and assessment of the process efficiency, including process optimization options. The final cost calculation is then initiated only for the most promising process option.

14.2.4.5 Deriving Heuristics for Cost Estimation

Approaches to evaluate processes regarding their economic variables have their origin in production-cost-theory, accounting and cost-oriented product development that led to four major approaches [5]:

- Production and cost theory
- Accounting
- Product costing with activity units
- Activity-based costing

After reviewing the different approaches to capture the economic variables in the cost estimation, and balancing the advantages and disadvantages of each approach, the product costing with activity unit model was selected. For comparison reasons between different processes (in this case between a batch and continuous process) the machine-related production overheads were allocated via the machine hour rate.

Product costing with activity units. The product costing with the activity units approach to calculate the process variable costs is starting with the definition of the variable items. These cannot be specifically allocated to a specific product in a production process. Typically, these costs cover infrastructure-related costs without considering the labor costs. The costs which are considered as production-overhead costs are listed below:

- Imputed depreciation
- Imputed interest
- Energy costs
- Maintenance and repair
- Room costs
- Operating material cost

To derive and allocate the overhead costs to the specific product for the comparison of a batch-based and continuous production process, the machine rates have to be calculated over their expected life cycle.

Calculation of the machine rates. To calculate the machine rates the machine hour rate method has been proposed. The machine hour rate is the total number of effective working hours of a machine during its effective life cycle. By dividing the investment costs of the machine or equipment by the expected number of productive hours the machine will manufacture the desired product, also called the net working time, the machine rate per hour is determined.

Heuristics used for cost calculation of the manufacturing overhead. In contrast to the machine hour rates, which are basically determined by initial investment costs and relatively predictable output rates and life time, other economic variables depend on the development of costs over the life cycle time of the process. This life cycle is normally between 10 and 20 years. Such variable costs have to be estimated or calculated based on actual costs, experience, predictions or assumptions to the best of our knowledge today. For these variables the following factors need to be considered:

- Maintenance and repair (e.g., wear of tools)
- Energy cost
- Room costs of manufacturing space
- Depreciation time
- Interest rates
- Operating material cost

The below listed calculations and assumptions have been suggested in the year 2015 by [18] as a reasonable approximation.

The costs for maintenance and repair can represent a significant cost factor for certain equipment and process units. *Maintenance and repair costs* can be expressed by the so-called maintenance factor. The maintenance factor is calculating the continuing investment costs in preventive maintenance and replacement of equipment parts in order to maintain the full functionality and efficiency of the given process. A maintenance factor is expressed as a value of ≤ 1. For example, for manufacturing machines the maintenance factor (J_{AT}) of 0.03 €/year has been calculated over a 10-year period, and for buildings and infrastructure (J_{BT}) the value has been calculated with 0.01 €/year. The maintenance factor of 0.3 means that 30% of the machine costs or its replacement cost will have to be invested into the machine over the predicted life cycle time of 10 years for the machine [18].

$$(W + R)_{MP} = 0.03\, J_{AT}\,[€/\text{year}] \tag{14.1}$$

for manufacturing plants.

$$(W + R)_{BI} = 0.01\, J_{AT}\,[€/\text{year}] \tag{14.2}$$

for buildings and infrastructure.

W are the costs for maintenance and R represents the costs for repair.

Energy costs are derived from process simulation and/or technical data sheets. The costs per kWh were typically between 0.5 and 0.15 €/kWh for pharmaceutical manufacturing in Europe in 2007 [18]. The energy consumption is multiplied by the actual energy price. As a conservative estimate suitable for a new product, we may assume that the energy

consumption between two processes is similar. In the case when converting an existing batch process with a continuous equivalent, the impact of the expected reduction in energy costs should be considered over the life cycle of the process compared.

Room cost and manufacturing space are important cost elements in pharmaceutical manufacturing due to the required GMP compliance and air treatment systems. An estimation is derived from the technical data sheet of the equipment/ layout plan which determines the required manufacturing space. The room costs for the specific manufacturing process or unit operation are calculated by multiplying the costs per m^2 GMP with the technical area space of the manufacturing plant.

Depreciation time is based on the general assumption that the life cycle of manufacturing and processing installations is about 10 years and that equipment is depreciated over this period, while for buildings and infrastructure 20 years depreciation time is being considered [18]. As a basis for the cost-accounting depreciation the replacement cost (substance conservation principle) are accounted.

Interest rates differ by country, company and time and can be included as a specific number in the case these rates are known or fixed. For a general comparison of different potential process options, the interest rates are accounted by an average cost method in the early stage of the evaluation process.

Operating material cost might also be applicable and should be part of the evaluation process. The process specific operating material cost like lubrication of the equipment, tools needed for production have to be entered into the cost equation. Operational helping cost are dependent on the runtime of the machine and usually are not.

14.2.4.6 Calculation of Equipment Costs

For a new process, the equipment costs have to be estimated in an early phase based on the theoretical concept of the future equipment. The most frequently used approach to estimate the costs of a planned manufacturing process is based on existing knowledge, past purchases and actual offers of the most prominent equipment suppliers derived from the technical feasibility and efficiency analysis. It has been demonstrated that such estimation of equipment costs in the conceptual/feasibility stage reach an accuracy of ±20% of final costs of an equipment after realization [19].

Estimation of Investment Costs for early stage product and process development it is useful to identify the total plant costs including the indirect costs. The cost estimating relationship method [19] has been applied. The basic concept of the cost estimating relationship is based on an overall cost factor multiplied by the major equipment item costs. The total plant cost estimate (C_T) is overall cost factor (h) times total cost of major equipment items (C_E).

$$C_T = h \times C_E \tag{14.3}$$

This method allows the inclusion of direct and indirect costs.

The *overall cost factor (h)* can be determined either through the delivered-equipment cost model, the installed equipment costs model, or through direct estimation based on experience and supplier information [20]. The *delivered equipment cost* includes the purchase cost of major equipment. The *installed-equipment cost* also includes in addition to the equipment cost the costs for installation and qualification. Another often-used approach to define

Table 14.4 *The Lang factors (f) for different plant operations*

Type of manufacturing	Lang factor (*f*)
Solid process plant	3.10
Solid-fluid process plant	3.63
Fluid process plant	4.74

Table 14.5 *Examples of factors for the calculation of process chain costs*

Equipment-related cost	Product-related cost	Site-related cost
Investment cost [€]	Economic life [year]	Footprint [m^2]
Depreciation [€/year]	Power consumption [kW]	Energy cost [€/kWh]
Imputed interest rate [%]	Material cost [€/kg]	Room cost [€/year]
Maintenance cost [€/year]	Throughput [kg/h]	Labor cost [€/h]
Imputed interest [€/year]	QA costs [€/kg]	Site-related overheads [€/m^2]
Operating hour [h/year]		

the overall cost factor (h) is the total installed cost (TOT) calculation proposed by Lang [24]. The TOT value is calculated from the installed equipment cost (Equip) multiplied by the Lang factor (f).

$$TOT = \text{Equip} \times f \tag{14.4}$$

The Lang factor (f) is specific for the type of manufacturing plant and is derived from experience (Table 14.4).

14.2.5 Calculation of Process Costs, Cost Comparison and Interpretation

For the interpretation of the obtained data, generated through the various estimates per unit or process, data are integrated into the related process option. The options are then compared with each other. Factors which should be considered in a comprehensive evaluation sheet are exemplified in Table 14.5.

14.2.6 Technology–Economic Profiling and Interpretation of Results

According to the methodology introduced in [12] the TEP of the previously defined process options will be evaluated through a systematic method (Figure 14.7). The results are summarized in Table 14.6. As can be seen in the table, the overall most favorable process can be identified by the highest total score. In the example shown in Table 14.6, the most favorable (or effective process) was a hot-melt granulation/extrusion process with a total process score of 69.3, compared to the reference process with a score of only 29.6.

The relative weighting factors add up to 100% per category and the absolute weighting factor adds up to 100% overall. The scoring for the individual criteria is done as follows: the individual score is the product of the ranking and the absolute weighting factor divided

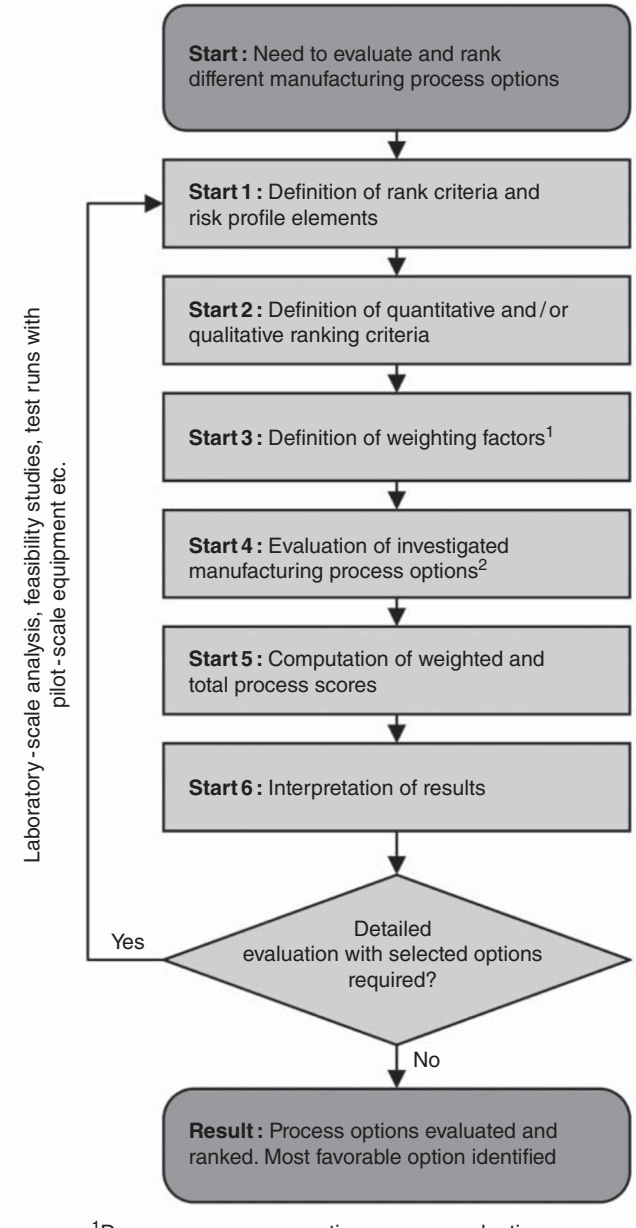

Figure 14.7 *Methodology to evaluate processes and their technical feasibility according to the cost-utility analysis [12].*

Table 14.6 *Process evaluation sheet resulting from comparative process evaluation*

		Absolute weighting factor (=100)	Relative weighting factor within category (per = 100)	Wet granulation /extrusion		Hot-melt granulation /extrusion		Dry granulation		Reference process	
				Rank	Score	Rank	Score	Rank	Score	Rank	Score
A	Costs										
1	Investment	10	100		5		10		5		0
1.1	Equipment	5	50	1	2.5	2	5	1	2.5	0	0
1.2	Building and structures	5	50	1	3	2	5	1	3	0	0
2	Operational costs	40	100		13		28		14		0
2.1	Material costs	8	20	0	0	−1	−4	−1	−4	0	0
2.2	Direct labor costs	6	15	1	3	2	6	1	3	0	0
2.3	Costs for maintenance	10	25	1	5	2	10	2	10	0	0
2.4	Utility costs	10	25	1	5	2	10	1	5	0	0
2.5	QA/QC costs	6	15	0	0	2	6	0	0	0	0
B	Qualitative process and product property ranking										
1	Product	25	100		13.3		9.2		10.0		17.5
1.1	Compatibility with existing dosage form and composition	5	20	2	3.3	1	1.7	2	3.3	3	5.0
1.2	Dosage form size and shape	7.5	30	2	5.0	1	2.5	1	2.5	3	7.5
1.3	*In vitro* profile	7.5	30	1	2.5	1	2.5	1	2.5	1	2.5

1.4	Flowability	2.5	10	3	2.5	3	2.5	2	1.7	3	2.5
1.5	Compressibility	2.5	10	0	0	0	0	0	0	0	0
2	Process	25	100		16.3		22.1		16.3		12.1
2.1	Maximum throughput of commercially available unit operations	7.5	30	3	7.5	3	7.5	2	5	1	2.5
2.2	Footprint	2.5	10	1	0.8	3	2.5	3	2.5	1	0.8
2.3	Scalability (scale-up from pre-trials to production scale)	2.5	10	2	1.7	2	1.7	3	2.5	3	2.5
2.4	Robustness (process understanding and control)	6.25	25	2	4.2	3	6.3	1	2.1	2	4.2
2.5	Cleaning, dust, health and safety	6.25	25	1	2.1	2	4.2	2	4.2	1	2.1
	Total process score				47.6		69.3		45.3		29.6
	Ranking result				2		1		3		4

by the number of the ranking levels. For example the score for the material costs of the hot-melt extrusion process (–4) arises from the ranking (–1) times the absolute weighting factor (8) divided by the number of the ranking levels (2).

Therefore, the outcome of the evaluation depends not only on the individual rankings, but also on the associated weighting factors. While the ranking can be semi-quantitative by incorporating quantitative metrics into the ranking levels (e.g., +1 and +2 equaling 20% and 40% cost reduction), the weighting factors are more often qualitative in nature. For example, as the intention of the current case study (Table 14.6) was to update an existing product and its associated process (reference), the maintenance and utility costs were key economic drivers, while the material costs were expected to be the similar. Therefore, a smaller weighting factor was assigned to the later (8 vs 10). However, the modeling of the hot-melt extrusion process has revealed additional risks in terms of raw material requirement which were reflected in a negative scoring (–1) for the material costs criterion. The weighting factor should be adjusted accordingly in a subsequent iteration of the evaluation, if the risk profile for raw material requirements reveals that stricter material requirement can become a knock-out criterion for a specific process.

14.2.7 Performing Scenario, Sensitivity and Uncertainty Analysis

For the comparison of different process options in the early stages of the process, several estimations and assumptions have entered into the analysis. Using additional analytical methods the results can further be qualified for their robustness.

Using statistical methodologies (e.g., sensitivity and uncertainty analysis) the range of input values can be analyzed regarding their level of estimation validity within the respective process item and with respect on their impact on the overall economic model. The uncertainty analysis aims to quantify the uncertainty with the economic model used, while the sensitivity analysis evaluates how much each factor is contributing to the uncertainty of the model.

As some preset estimates or assumptions might have a significant impact on the overall economics of a defined process, such critical assumptions can be evaluated through uncertainty and sensitivity analysis of different scenarios. The critical assumptions have to be determined early in the conceptual phase and process of the economic comparison. These critical assumptions are in general assumptions, such as increasing capacity by additional shifts, to increase or decrease the throughput rate or OEE.

14.3 Conclusion

Pharmaceutical drug product development is a long and costly process with high risks involved. According to the Tufts Center for the Study of Drug Development [21], the average development costs rose to USD 2.6 billion in 2014. However, the manufacturing processes of the pharmaceutical industry have not advanced as they do in other industries during the past decades [22]. During the drug product development the decisions about the formulation and the associated manufacturing process have to start as early as the end of the preclinical phase. Mitigating the risk of the pharmaceutical development and manufacturing, as well as minimizing manufacturing costs and improving supply chain security, are

important elements to be considered before final decisions on the product and process can be reached.

In order to support the rational evaluation and selection of the most efficient manufacturing process at the early, conceptual stage of drug product development, rational and reliable way to incorporate economic factors are required. Such factors are also useful for the cost–benefit or cost–effect analysis carried out at the later development phase or during the product life cycle itself. To reduce the long term manufacturing costs it can often be beneficial to consider advanced technology, such as continuous manufacturing. By using a rational method to evaluating the alternatives early on can have significant strategic values.

An economical and technical comparison methodology is especially required when introducing advanced pharmaceutical manufacturing methods, such as continuous manufacturing, closed-loop control systems and real-time release testing (RTRT). The presented methodology combines known approaches and tools to rationally evaluate and predict the technical feasibility, the potential risks, uncertainties and the economical profile in the early conceptual stage. The methodology allows the evaluation of different scenarios for a product and also for the associated process technology, taking into account different demands and needs of the pharmaceutical industry as well as the market. Using weighting factors and score-based evaluation methods coupled with a thorough risk assessment, sensitivity and uncertainty analysis, the proposed methodology provides semi-quantitative metrics between different processing options. Additionally, due to the rational approach the method may help to identify sensitive areas of an existing or alternative manufacturing process which should be investigated further so the impact on the technical–economical profile can be better understood. The evaluation of unknown impact factors of a manufacturing process can be done by using modeling and simulation to obtain missing information for decision making especially at the early stages [23]. As the proposed methodology is based on known procedures, the evaluation process can be improved iteratively as better data becomes available.

The methodology is flexible to include and evaluate additional data and risk factors that are not directly considered in this article. For example, the impact on the clinical development program or regulatory implications might be critical factors for products in an advanced stage of development. These factors can be evaluated in a similar manner as the factors included in the proposed methodology and case study.

The methodology was applied in a presented case study, which reveals three major areas that importantly affect manufacturing costs. Longer operating period and reduction of equipment time used are shown to significantly reduce the manufacturing costs, for example when moving from a single shift operation to a full time, three-shift operation mode. The initial investment costs into the process equipment and the auxiliary equipment have been found to differ substantially and can have a significant impact on the life cycle costs of the product. Finally, the product and process related risks have been carefully evaluated in regards to their potential effect on the product performance.

The method described has provided good basis to evaluate different product and process options by allowing a rational comparison and selection during the early stages of the product and process development. Due to the early stages, the available economic and technical information are often limited. However, the method can be updated as additional economic and technical data become available during the development or during the product life cycle itself.

References

[1] Nachiappan, R.M., Anantharaman, N. (2006) Evaluation of overall line effectiveness (OLE) in a continuous product line manufacturing system. *International Journal of Manufacturing Technology and Management* **17**(7), 987–1008.

[2] Plumb, K. (2005) Continuous processing in the pharmaceutical industry: Changing the mind set. *Chemical Engineering Research and Design* **83**(6), 730–738

[3] Mascia, S., Heider, P.L., et al. (2013) End-to-end manufacturing of pharmaceuticals: Intergrated synthesis, purification, and final dosage formation. *Angewandte Chemie International Edition* **52**, 12359–12363.

[4] Chatterjee S (2012) FDA perspective on continuous manufacturing. *FPAC Annual Meeting*, FPAC, Baltimore. Available at: http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/UCM341197.pdf (accessed 2 February 2016).

[5] Wallack T. (2007) Novartis to give MIT $65m to find new way to produce drugs. Focus on manufacturing. *Boston Globe*, Boston.

[6] Bell E.R. (2008) *Melt Extrusion and Continuous Manufacturing for Pharmaceutical Materials*. PhD thesis, MIT, Cambridge, Mass.

[7] Wilburn, K.R. (2010). *The Business Case for Continuous Manufacturing of Pharmaceuticals*. PhD thesis, MIT, Cambridge, Mass.

[8] Schaber, S. D., Gerogiorgakis, D. I., Ramachandran, E., et al. (2011). Economic analysis of integrated continuous and batch pharmaceutical manufacturing: a case study. *Industrial and Engineering Chemistry Research*, **50**(17), 10083–10092.

[9] Srai, J.S., Badman, C., Krumme, J., et al. (2015) Future supply chains enabled by continuous processing – opportunities and challenges. *Journal of Pharmaceutical Sciences*, **104** (3), 840–849.

[10] Götze, U., Hache, B., Schmidt, A., Weber, T. (2011) Methodik zur kostenorientierten Bewertung von Prozessketten derWerkstoffverarbeitung (Methods for evaluating the cost effectiveness of materials processing chains), *Materials Science and Engineering* **42**(7), 647–657.

[11] McKenzie, P., Kiang, S., Tom, J. et al. (2006) Can pharmaceutical process development become high tech? *AIChE Journal*, **52**(12), 3990–3994.

[12] Fraser, S., Dujmovic, D., Khinast, J.G. (2014) Comparing manufacturing process options: a techno-economic profiling method supports process development. *Pharmaceutical Technology Europe* **37**(8), 32–39.

[13] Götze, U, Zönnchen, S., Schönherr, J. (2013) Wirtschaftliche Bewertung von Prozesskettenvarianten am Beispiel von Strukturbauteilen (Economical appraisal of process chain alternatives for structure components). In: *Energetisch-wirtschaftliche Bilanzierung und Bewertung technischer Systeme – Erkenntnisse aus dem Spitzentechnologiecluster eniPROD*. Wirtschaftliche Scripten, Auerbach Available at: http://www.qucosa.de/recherche/frontdoor/?tx_slubopus4frontend[id]=10906] (accessed 2 February 2016).

[14] VDI (1933) *VDI 2221: Methodik zum Entwickeln und Konstruieren technischer Systeme und Produkte*. VDI, Berlin.

[15] Muchiri, P. and Pintelon, L. (2008) A performance measurement using overall equipment effectiveness(OEE): literature review and practical application., *International Journal of Production Research*, **46**(13), 3517–3535.

[16] Vorne (2015) *The Fast Guide to OEE™*. Presented by Vorne Industries specialists in Visual Factory and Production Monitoring Systems. Available at: http://www.vorne.com/pdf/fast-guide-to-oee.pdf (accessed 2 February 2016).

[17] AACE (2010) *Standard AACE International Recommended Practice No. 10S-90 COST ENGINEERING TERMINOLOGY TCM Framework: General Reference*, Association for the Advancement of Cost Engineering International, Boston, P. 35.

[18] Melin, T. and Rautenbach, R. (2007) Kosten, in: Melin, T. and Rautenbach, R. (eds) *Membranverfahren. Grundlagen der Modul- und Anlagenauslegung*. , Springer, Heidelberg.
[19] Blank, l:, Tarquin, A. (2013) *Engineering Economy*, 7th edn. Available at: http://de.scribd.com/doc/169018566/Engineering-Economy-7th-Edition-Solution-Manual-Blank-Tarquin#scribd (accessed 2 February 2016).
[20] Lang, H. J. (1948) *Simplified Approach to Preliminary Cost Estimates, Chemical Engineering*. Chemical Week Associates, New York.
[21] Tufts (2014) Cost Study. Available at: http://csdd.tufts.edu/news/complete_story/pr_tufts_csdd_2014_cost_study (accessed 2 February 2016).
[22] Benson, R.S. and McGabe, J.D.J. (2004) From good manufacturing practice to good manufacturing performance. *Pharmaceutical Engineering*, **24**(4), 26–34.
[23] Stocker, E., Toschkoff, G., Sacher, S., Khinast, J.G. (2014) Use of mechanistic simulations as a quantitative risk-ranking tool within the quality-by-design framework. *International Journal of Pharmaceutics*, **475**(1/2), 245–255.
[24] Lang, H.J. (1947) Simplified approach to preliminary cost estimates. *Chemical Engineering* **55**, 112-113.
[25] Rantanen J., Khinast J.G. (2015) The future of pharmaceutical manufacturing sciences, *Journal of Pharmaceutical Sciences*, **104** (11), 3612-3638.
[26] Lee S., O'Conner T. F., Yang X. et al. (2015) Modernizing pharmaceutical manufacturing: from batch to continuous production. *Journal of Pharmaceutical Innovation*, **10**(32), 191–199.

15

Drivers for a Change – Manufacturing of Future Medicines for Personalized Drug Therapies

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15.1 Introduction

The manufacturing of pharmaceuticals is often considered a traditional area of engineering and typically reluctant to implement innovative manufacturing principles. In this millennium, the tableting machine and a tableting process are still the most important unit operations in the pharmaceutical business area. There are, however, several drivers for implementing innovative and more flexible manufacturing solutions. The special need for patient-centered medicine covering paediatric, geriatric and ethnical subpopulations is increasing the pressure for a change within the whole pharmaceutical sector. The development of treatment strategies that take into account the individual variability of patients is not easily implemented with the existing level of flexibility in the pharmaceutical manufacturing area. The current state of the art in pharmaceutical product design is not directed towards products with a possibility for flexible dosing, but on the other hand, a recent development within manufacturing sciences clearly indicates that we are proceeding in the right direction. Processing principles that are by nature continuous, such as hot melt extrusion and printing, are being increasingly utilized.

Continuous Manufacturing of Pharmaceuticals, First Edition.
Edited by Peter Kleinebudde, Johannes Khinast, and Jukka Rantanen.
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One of the future elements of new enabling medicines will relate to the data mining of huge biological databases and sequencing the human genome is a rich source of information [1]. At the same time we are capable of achieving – at a reasonable cost – a picture of each individual's genomic profile and metabolic variation. New efficient data handling solutions can be utilized for turning this information into new treatment strategies, for example, in oncology where the drug product is coupled with companion diagnostics to identify patients who are most likely to benefit from a particular pharmaceutical product.

When implementing the Quality by Design (QbD) principles in practice, it is increasingly important to aim for a patient-centric drug development process instead of a purely engineering-oriented and cost-saving approach. We should not only aim for optimized production systems with real-time release testing (RTRT) but also keep a clear focus on the patient. This is highlighted in the Biopharmaceutics Risk Assessment Roadmap (BioRAM), utilizing a systems approach with a framework based on therapy-driven drug delivery scenarios [2].

All these developments create an obvious need for novel dosage forms, medical devices and related manufacturing processes, which enables flexible treatment scenarios and patient-adapted dosing. In general, this may be achieved by two different strategies: either the dose strength is adjusted by compiling multiple dose units or dosage forms with high dose strengths are divided into smaller ones. This might in some cases be difficult to realize with existing manufacturing technologies that are based on compacting a given volume of powder into a solid dosage form. Another opportunity to meet the needs of future personalized medication is the utilization of innovative, more flexible processing solutions [3]. By implementing technologies that inherently are flexible, such as active pharmaceutical ingredient (API) printing, a different production philosophy can be constructed and from the logistic point of view we have "manufacturing on demand production units." From the regulatory point of view, this increases the total count of production batches and reveals small batch sizes. Therefore, we will face increasing pressure to modify existing regulatory framework.

In this chapter, we present the most recent advancements in optimized drug delivery systems, enabling medical devices, manufacturing methods and related analytical methods for future personalized medicine approaches.

15.2 Personalized Medicine

15.2.1 Therapy Based on Individualized Needs for Different Patient Groups

Pharmacogenomics is an increasingly important research area and a crucial element in all drug discovery and development programs. This approach involves identification of special features in a given part of population and potentially spending more health care resources on one or more segments of the population. This variation can be related to several factors, for example, to the metabolising capacity of this ethnical population segment. This can be potentially related to drug development and drug products/combinations should be easily tailored for different segments of population. The existing manufacturing solutions, quality systems and supply chains do not support product variety and smaller production volumes. Continuous manufacturing-based solutions would support the development of patient-centric supply chains.

Genetic factors directing pharmacokinetics (e.g., cytochrome family; CYPs) are a well-described challenge in medication. There is potential variation in drug metabolic pathways which can affect individual responses to a given drug, and in the worst case, cause severe adverse effects. Complex drug–drug interactions can also occur, highlighting the need for including genetic information in the overall treatment plan. Naturally, gender should also be considered when defining treatment strategy. There can be also additional challenges related physical activity, lifestyle, weight and body fat percentage – all these are factors that can be increasingly monitored using mobile app-based personal monitoring.

Molecular biology gives us a possibility to identify relevant biomarkers and to link these to individual needs. Cancer is a disease that has been identified as one of the leading sources of death internationally and the number of cases is increasing with the aging population. Even though cancer can be related to accumulated genomic damage throughout life, it is becoming equally important to consider the role of inherited genetic variation. As an example, after diagnosing a patient with breast cancer, it would be important to investigate whether or not the tumor is HER2-positive in order to make a decision about administering Herceptin.

The age of a patient is an additional factor that should be addressed in this context. The special needs of an elderly population can bring several challenges [4]. Several factors are changing with age, including the altered absorption, distribution, metabolism and elimination (ADME) properties of drugs. In a same way, many cognitive functions related to medication can be a challenge, including understanding and remembering the instructions. There is also a natural reduction in visual, swallowing and motoric functions, which should be addressed with elderly patients. Innovative drug products are potentially a solution for improving the compliance and adherence of geriatric patients. In a similar way, specific challenges related to different patient groups including pediatric patients can be addressed.

15.2.2 Point of Care Diagnostics

An important element of future medication is the development of point of care (POC) diagnostics [5]. The typical POC diagnostic test is done with the patient or near the patient and leads to an expedited clinical decision [6]. This area involves with diverse analytes including proteins, nucleic acids, metabolites, drug molecules, dissolved ions and gases, human cells and microbes; additionally, there is huge variation in the sample matrices ranging from blood, saliva and urine to other bodily fluids or (semi-)solids. There are certain similarities between process analytical technologies (PAT) and POC diagnostics: inherent resistance in the professional end-user group to implement state of the art possibilities, a need for the utilization of latest innovations within analytical chemistry and a knowledge management challenge after receiving all the data. The ideal POC device can handle small sample volumes in complex biological media with a low concentration of analytical (diagnostic) target (Figure 15.1).

In-home POC testing is well-established for several diagnostic targets, for example, in the case of blood glucose testing, pregnancy and anticoagulant testing. These tests have really improved patient compliance and they are currently manufactured on a massive scale, using innovative manufacturing techniques including printing and laminating [5]. There is also a development in genetic testing allowing for, for example, identification CYP family and

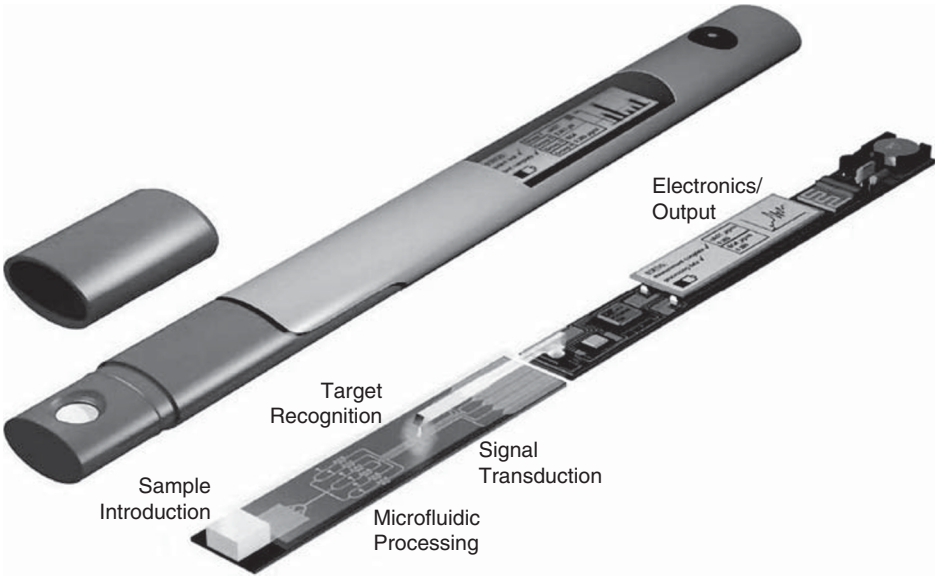

Figure 15.1 *Idealized point of care device. Reprinted with permission from [5]. Copyright (2012) American Chemical Society.*

related potential variation in pharmacokinetics, as well as medical devises following, for example, airflow in relation to pulmonary medication [6].

There is also a fast development within genomics and the price of sequencing an average human genome has decreased remarkably. We have now reached the US$ 1000 human genome, which means that the whole picture starts to get sharper: individual information even at the genome level can be combined with real-time information of the progress of disease, metabolic information and behavioural data. All this biomedical information will form a basis for precision medicine.

15.3 Flexible Dosing with Innovative Products

Flexible dosing is mandatory for personalized medicine. It is obvious that suitable drug dosage forms and – if required in combination – medical devices are needed which enable precise measuring and administration of individual drug doses. In the best case these medications are suitable for the complete patient population, ranging from newborn children to elderly patients [4, 7]. Only few medicinal products are available today which are able to serve every subpopulation and to meet the needs of all patients. Previously, individual therapy has been predominantly linked to the parenteral application of liquid drug formulations (infusions and injections) in a hospital setting. Only a few parenteral applications for individual therapy have become a reality for outpatients, for example, the treatment of diabetes by insulin dosage pens or pumps and growth hormone supplementation using child-appropriate injection devices. However, parenteral drug formulations are restricted to certain conditions and are often poorly accepted by patients due to needle phobia and inconvenient daily handling. Therefore, oral drug application is still the preferred administration route.

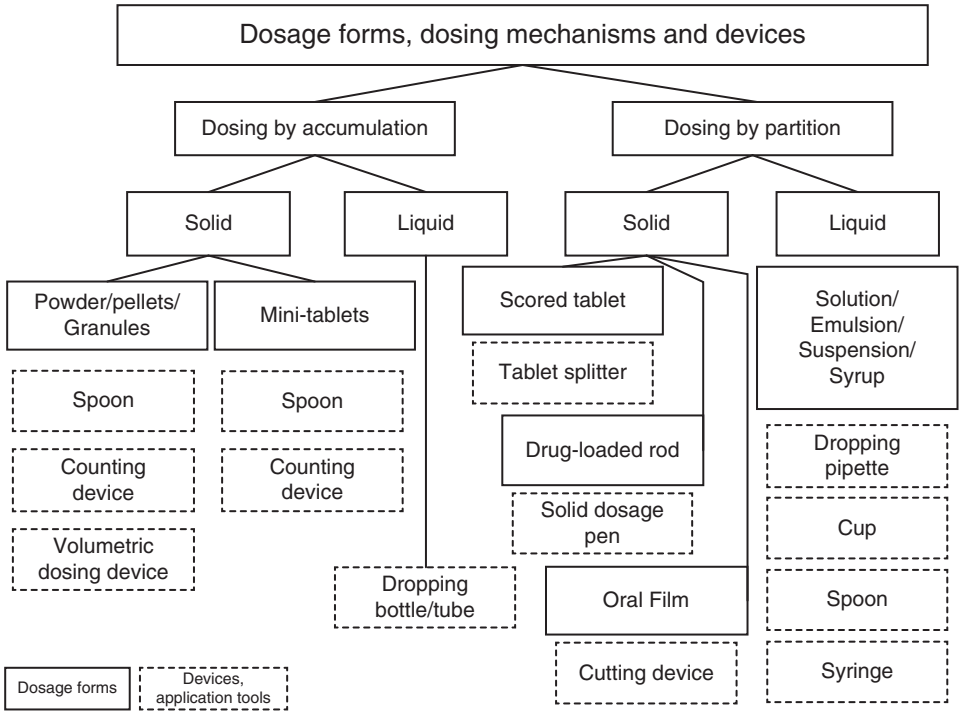

Figure 15.2 *Concepts for individual dosing using solid and liquid oral drug formulations [11] with permission from Elsevier.*

Various products have been developed that enable flexible dosing by liquid and solid oral drug formulations [8]. The strategies are based either on the accumulation of small drug carriers like drops, mini-tablets or pellets, or on partitioning a defined volume from a multi-dose container (Figure 15.2). Liquid medicines for oral drug administration are widely available as drug solutions, syrups, emulsions or suspensions. Single-dose containers for oral liquid medications like sachets or stick-packs are rarely available on the market. Most frequently, partitioning dose approaches are utilized which require measuring or counting devices. Dropper inlets or dropping tubes are a substantial part of the primary package. Medical devices which are separately delivered with the medicine comprise dosing spoons or cups, dropping pipettes and oral syringes. All concepts should enable precise dosing by the counting of drops which assemble the total dose or by withdrawing the individual dose from a multi-dose container. However, it became evident in recent studies that many devices for liquid medicines underperform in real practice, in some cases with a fatal outcome [9]. In particular dosing spoons and cups often show unprecise dosing and residues in the device which are not administered to the patient [10]. Hence, safe dose titration for the individual needs of a patient is hardly feasible.

One common strategy for flexible dosing by partition using solid drug formulations is the splitting of scored or unscored tablets into segments. However, this approach includes the disadvantage that only a limited number of dosing steps is feasible [12], and further,

imprecise dosing or drug loss may appear [13]. Tablet splitters may facilitate the splitting process, but they usually do not improve the dosing precision [14]. Improved tablet geometries like the Snap-Tab® form show a better relation between the volume of the segments and the area of the breaking notches, and hence, may improve dosing accuracy. Another interesting concept utilizes drug-free compartments for splitting whereas the drug-loaded compartments remain intact [15].

A recent innovative partitioning concept for solid formulations is the so-called solid dosage pen (SDP). It consists of an adjusting screw for dose selection, a feeder and a cutting mechanism, a sample outlet and a sealing cap (Figure 15.3). The contained drug-loaded rod is fed to an orifice where an appropriate dose is sliced from the rod by the cutting mechanism. Hence, the SDP enables full flexible dosing.

The first slices cut from the solid rod within the SDP exhibited an immediate drug release or an effervescent character [8]. Controlled drug delivery was hardly feasible, as the drug release depends on the size of the slices and the dissolution profiles from individually cut slices were not linear, that is, it made a difference whether two pieces of 1 mm was cut or one piece of 2 mm, which is not appropriate for a flexible dosing. Most recently, sustained drug release was achieved by core–coat systems continuously manufactured via co-extrusion technology [16] or by implementing multiple-unit pellet systems into the extruded rod [17]. Now, the SDP should be suitable for all drug substances, even for controlled drug delivery.

Another option for partitioning individual doses from continuously manufactured multi-dose solid preparations is the oral film strip. In the easiest setup the individual doses may be cut from a bigger film. More convenient is a rolled-up film material which is delivered by a device [18]. The device may operate electronically or the individual doses may be indicated by graduations on the film material and cut manually. The dose flexibility could potentially be further improved by printing technologies [19]. Dotted spots of the active or traces which could be regular or irregular may enable almost all therapeutic regimens which are required [20].

The accumulation concept of solid dosage forms comprises miniaturised drug carriers like powders, granules, pellets or mini-tablets. In all cases a medical device is required to select or extract a predefined volume or to choose a specific number of dosage units from the multi-dose container. The measured doses could be swallowed directly, dissolved or dispersed in a potable medium, or given with a meal. There are numerous proposed concepts with varying types of devices such as spoons and cups (see further details in a review [11]).

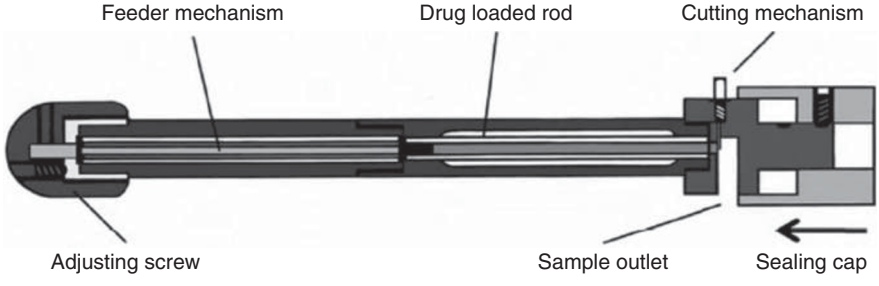

Figure 15.3 *Schematic drawing of the solid dosage pen [8] with permission from Elsevier.*

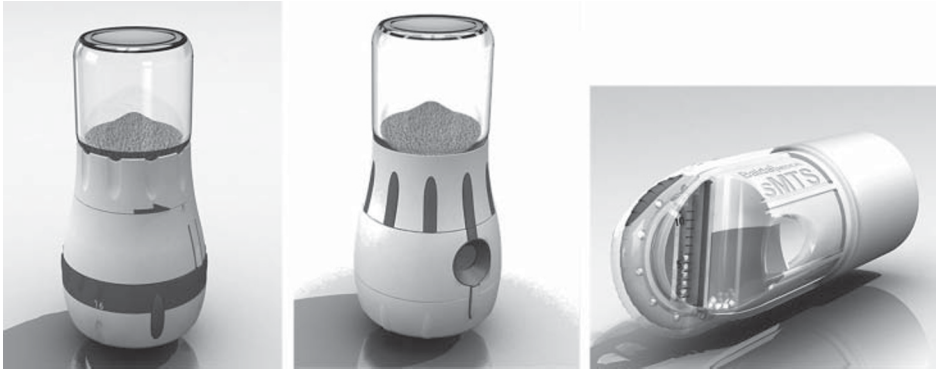

Figure 15.4 *Counting and dispensing devices from Balda Medical. Left: mechanical device (mMTS); center: electronical device (eMTS); right: "wheel mouse" (sMTS) with control tube for visual inspection.*

In another simple approach, dosing spoons with a fixed number of cavities are used to measure an adequate amount of mini-tablets enteric-coated with pancreatin (Panzytrat OK®). Mini-tablets offer the advantage that the dimensions are precisely constant which results in high content uniformity [21]. An interesting new option is the development of orodispersible mini-tablets [22], which immediately disintegrate in the oral cavity and may be in particular useful for very young children and older patient with dysphagia. Most recently advanced counting and dispensing devices for mini-tablets have been developed which accurately measure and release the pre-defined number of mini-tablets (Figure 15.4).

The selection of the appropriate concepts for flexible dosing does not only depend on the technical feasibility, but also on the cost of goods and the freedom to operate for these combination products compiled from the drug preparation and the device. High variability in dosing and simultaneously low cost of goods are most desirable and therefore classified in Class I (Figure 15.5) [11]. Class II may be appropriate for new medicinal products under patent protection and limited price binding. Class III may be still acceptable for generic products under certain precautions, whereas development of products of Class IV should be avoided as much as possible.

15.4 Future Health Care Scenario

15.4.1 Enabling Manufacturing Technologies and Materials Science

This chapter has introduced the rationale for developing more flexible pharmaceutical products based on dosing for individual needs. It is not straightforward to develop these innovative products with the existing, generally accepted manufacturing solutions; basically a paradigm shift in the field of manufacturing is needed. There is substantial development within innovative manufacturing technologies and this development has already reached some mature processing solutions.

Extrusion is an example of the widely utilised manufacturing solutions already established in several other areas of chemical engineering and innovative product design. Several

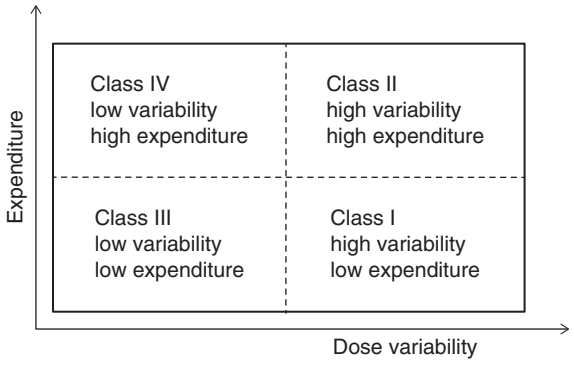

Figure 15.5 *Classes for combination products enabling flexible drug dosing [11] with permission from Elsevier.*

major products based on hot melt extrusion already exist in the pharmaceutical market and the knowledge base in the pharmaceutical field is strong. Thermoplastic processes such as hot melt extrusion open up fascinating possibilities to design innovative products – without compacting a given volume of powder but instead having more freedom to develop innovative shapes and inner structures for products, such as Egalet® technology [23] and a solid dosage pen based on a feeding drug-loaded rod [11]. Processing of polymer–active pharaceutical ingredient (API) mixtures can also be performed using electrospinning (solution- and melt-based) and wet-spinning (solvent-based approach) with a specific goal of manufacturing of 3D structured drug delivery systems [24].

Multiparticulates like mini-tablets and pellets will be dosage forms of choice in future as they have the potential for personalised dosing, as described before. Manufacturing of these systems is relatively straightforward when compared with, for example, extrusion, injection molding and 3D printing, but the more challenging part of multiparticulate products is the development of dosing device.

Orodispersible drug formulations are increasingly utilised and there are several products in the market, such as orodispersible tablets (ODTs) or films (ODFs). ODFs are an attractive option in combination with printing technologies to create advanced multi-layer coatings, stacked systems and integrated multi-compartmental medical products [20]. This type of manufacturing solution would be ideal for customised products that can be tailor-made for each patient (Figure 15.6). Products for different patient groups (e.g., pediatric and elderly) with different doses, fixed dose combinations and release behaviour can be designed with an additional possibility to optimise safety and stability.

Printing drug products is potentially an enabling manufacturing method for the preparation of customised products. Several printing methods, including inkjet printing, flexographic principle and 3D printing (additive manufacturing) of pharmaceuticals have been introduced in this book [19]. The fascinating feature of printing is that one can really start rethinking the whole pharmaceutical product concept when not more limited by the principle of compaction. The possibility to design freely the shape of a product combined with a possibility to tailor-make different inner structures and compartments (Figure 15.7) should be translated into new pharmaceutical products [25]. The pharmaceutical products can in future be designed *in silico* starting from a CAD drawing of a product and simulation of

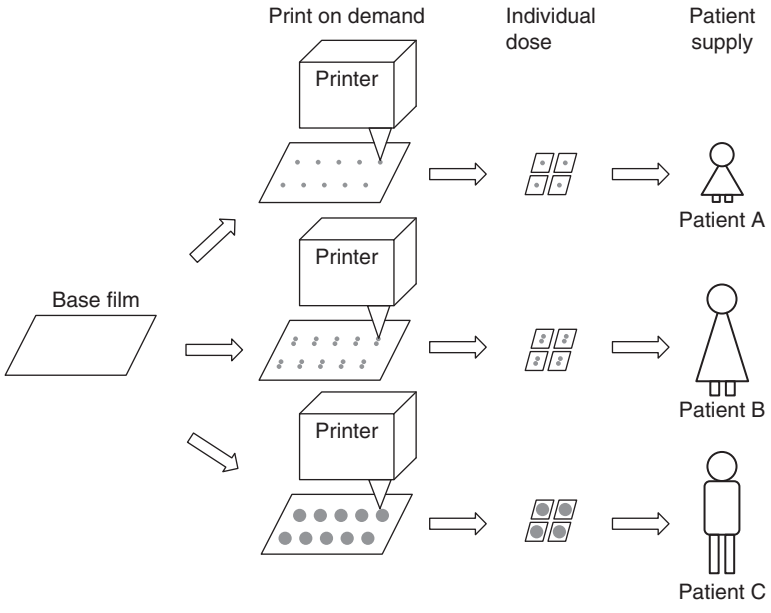

Figure 15.6 *Manufacturing on demand based on printing: inkjet printing of different drugs and drug loads. Reprinted from [20] with a permission from Elsevier.*

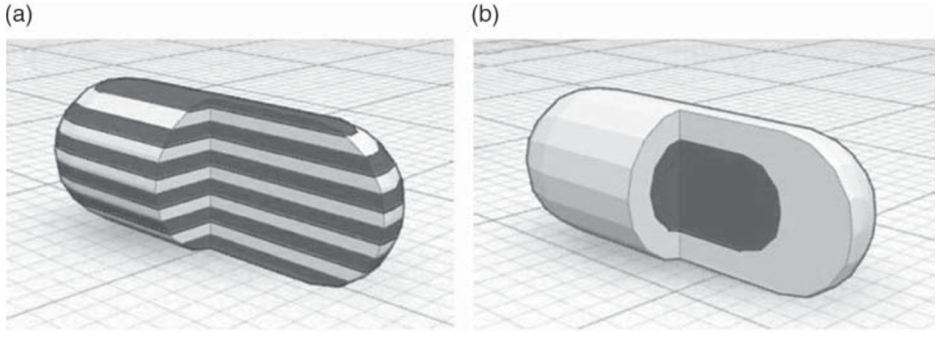

Figure 15.7 *Customised structures for 3D printed products: (a) API in layers; (b) API core inside a coat. Reprinted with permission from [25]. Copyright (2015) American Chemical Society.*

the release behaviour, followed by innovative manufacturing of a product with exactly the desired size, shape and inner structure.

Miniaturization of manufacturing processes has been introduced as an approach for more efficient production. Small-scale production systems based on microfluidics have potential for accelerating the clinical translation of nanoparticle production [26]. Nanoparticle systems are based on physicochemically complex structures and production methods are still at an immature level. Microfluidic methods offer a possibility for parallel and stackable continuous production of nanoparticles, even on the gram to kilogram scale.

When considering all these innovative manufacturing principles, we have to remember that we do not yet have the required pharmaceutically acceptable excipients [27]. Excipients for the extrusion of pharmaceuticals are more well-established than those for printing and there are already several existing products, but more work is needed with printing technologies. Thermoplastic polymers such as polylactic acid (PLA), polyvinyl alcohol (PVA), and acrylonitrile butadiene styrene (ABS) are golden standards in commercial desk-top 3D printing devices based on fused deposition modeling (FDM), and these materials are broadly available in grades that can be directly fed into a 3D printer. There is only a limited number of examples of printed dosage forms and typically these examples consist of the following processing cycle: extrusion of model polymer:API mixture, feeding extrudate to a nozzle of a 3D printer and melting/printing of the mixture into the desired shape. While adding different APIs into these polymer mixtures, the rheological characteristics of the material are changing and this affects the quality of the final 3D printed object. Current commercially available 3D printers are optimized for these ideally behaving thermoplastic polymers (PLA, PVA and ABS), and the quality of the 3D printed object can be really compromised when using polymer:API mixtures as a feed.

When considering product performance testing, we can no longer focus only on characterising the particulate properties of powders with a focus on tabletability, but more fundamental work is needed with the polymer–drug mixtures. These type of systems are well-investigated from other physicochemical points of view; the solubility and miscibility of API into polymer are critical factors related to the amorphous nature of the final product. There is a well-established scientific community focusing on using various solid state analytical methods for exploring the solubility/miscibility and amorphous nature of these systems. Equally important is a better understanding of the rheology of molten phase polymer-API mixtures in order to optimize material behaviour in thermoplastic processes, for example, extrusion, injection molding, film casting and 3D printing processes [28]. Inkjet printing of pharmaceuticals involves several formulation challenges at different levels, as displayed in Figure 15.8 [29]. The solubility of a drug compound in the solvent and the rheological properties of these mixtures need to optimized for the selected printing method (flexographic or inkjet principle). Similarly to 3D printing, the selection and characterization of substrate can be challenging and only a limited amount of generally accepted materials is available [30]. Innovation in the field of excipient development for both inkjet and 3D printing applications is crucial and more generally acceptable materials are needed to enable further development.

All these earlier mentioned manufacturing methods enable innovative product design and even totally new compartmental structures can be prepared. Products with varying dose and fixed dose combinations can be prepared and all this will be challenging, as will the analytical methods. Production for personalized needs will mean smaller batch sizes; and really fast analytical solutions are needed. The recent development of PAT tools should be utilized while coping with these challenges. Especially the development of imaging tools is crucial for fast analysis and potential real-time release testing. Optical imaging and machine vision-based solutions of multiparticulate systems (mini-tablets) can be used in supporting the counting of dosage units. In the chemical mapping area, near infra-red imaging is a technique with an obvious potential for the fast analysis of, for example, printed pharmaceutical products [30]. Identification of different compounds and quantification of the

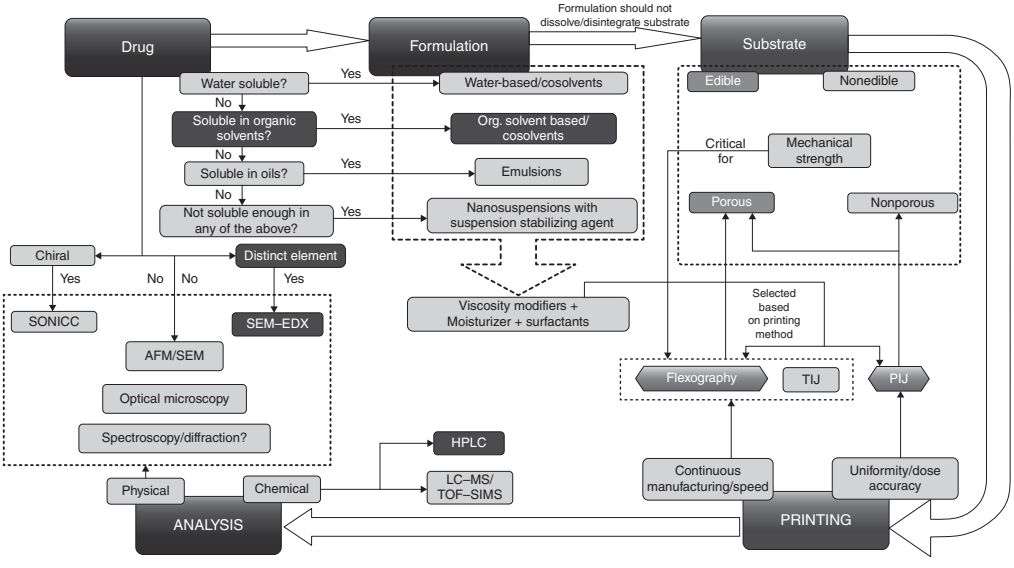

Figure 15.8 *Preformulation and characterization challenges of inkjet printable formulations. Reprinted from [29], with permission from Elsevier.*

amount of drug can be used for the quality control purposes. In the same way, Raman imaging offers a possibility to visualize the distribution of components in the dosage form, and additionally, Raman is a sensitive technique for the identification of different solid forms. An additional challenge will be the analysis of inner structures in compartmental systems where these internal structures not only contain different drug compounds and different amounts of them, but also have other functionalities, such as release control. There are several potential approaches for imaging the inner structures of solid objects, including X-ray computed microtomography, magnetic resonance imaging, terahertz imaging and optical coherence tomography [31].

Future product development should be based on a sound combination of experimental work, state of the art analytics/experimental and modeling/simulation providing a holistic view into the final product (Figure 15.9). Designing a product based on simulation, "*in silico* pharmaceutical product design", can be an ideal starting point for innovative pharmaceuticals. These simulations can include all elements of pharmaceutical product design – biopharmaceutics, processing, product and material levels. The current development of computational methods and related hardware enables simulations of more realistic systems ranging from molecular dynamics of materials in crystalline state into simulation of tablet coating process in realistic process equipment geometries using the discrete element method (DEM) to reproduce the tablet motion inside a chamber of the coating pan. 3D printing is an example of a potential game-changing process (Figure 15.7); product design starts from a CAD drawing of a product and potentially contains compartments for different drug compounds. It would be natural to simulate the release behaviour of these geometries and design the desired product functionality *in silico*. Simulations can be used as a starting point to design structured pharmaceuticals with tailor-made release characteristics [2], which can be further manufactured using innovative manufacturing principles. All simulations should be naturally supported by experimental verification using state of the art analytical possibilities.

15.4.2 The Regulatory Environment

There is a clear support from the regulatory side for innovative and more efficient manufacturing solutions, including continuous manufacturing principles (FDA guidance draft "*Advancement of Emerging Technology Applications to Modernize the Pharmaceutical Manufacturing Base Guidance for Industry*" [33]). However, several fundamental issues need careful attention [34]. The definition of a batch can also be related to the quantity produced or to the duration of a process (e.g., one working shift, one day or one week of production). Continuous processes are characterized by different start-up and shut-down procedures when compared to batch processing. Both start-up and shut-down may involve a phase where only part of the unit operations related to the whole production line are operating. The time stamp of each produced unit is really important in continuous manufacturing.

Many of the processes introduced earlier in this chapter (e.g., extrusion and printing technologies) are continuous by nature and the batch definition is not absolutely clear. Traditional in-process controls and sampling procedures need reconsideration and commonly accepted pharmacopoeial methods need modification to reflect the state of the art. Chemical

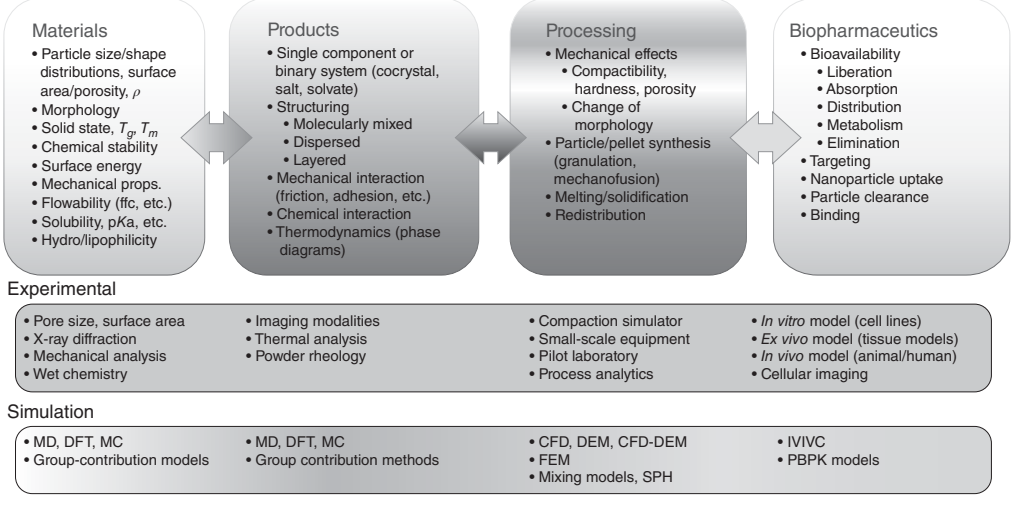

Figure 15.9 *Engineering view of pharmaceutical development. Reprinted from [32], with permission from Elsevier.*

imaging has a huge potential as an innovative analytical method for continuously operating manufacturing lines and the installation of *in-line* PAT tools can provide us with a full picture of the product quality. Increasing information from the process can potentially be challenging and some of the regulatory documents are already getting prepared for this, for example, European Pharmacopeia monograph 2.9.47: "*Demonstration of Uniformity of Dosage Units using Large Sample Sizes*." Another important point to consider is related to non-confirming materials and a plan to identify and remove these is needed. It would be attractive to implement RTRT principles into continuously operating manufacturing lines, but careful consideration of non-confirming material should be included.

There are several additional regulatory challenges related to the innovative manufacturing solutions. Some of the future ideas described involve products that do not exist as dosage forms in pharmacopeias. It is not clear what one should call a 3D printed product with different compounds in different internal compartments. These new products can be brought into easily-swallowable shape and look like a traditional tablet, but can we still call these systems "tablets", like the ones produced with compaction process? New terminology would be needed to describe precisely dosage units produced using additive manufacturing principles.

Finally, when designing increasingly individualized products, we face additional challenges related to both batch definition, batch release and retained samples. These concepts are forming a basis of pharmaceutical quality systems and while manufacturing different products for different patient populations, and potentially even for each individual patient, the batch size will be really small or just one. How to deal with today's regulatory requirement of retained samples? Quality control of and release of personalized products should be carefully considered.

15.4.3 Supply Chain

The supply chain structure of the pharmaceutical industry is another area that has remained unchanged during the past decades. In terms of quality, many companies operate at 3σ and 4σ levels concerning manufacturing right first time [35]. Several opportunities have been identified for more flexible, responsive continuous manufacturing-based end to end supply and innovation chains. There can be greater product and volume flexibility, potential for significant inventory reduction opportunities, improved quality, rapid scale-up after clinical trials and reduction in the management burden. Continuous production has the potential for changing the supply chain towards a patient-centric supply chain and many personalized medical needs can be fulfilled. The cost of scale-up after clinical trials can be substantially affected by simply producing products basically in the same processing unit, but with longer production times. Design of experiment (DoE) plans can be performed remarkably faster in a continuously operating manufacturing line in contrast with batch processing.

Manufacturing of tailor-made and personalized medicines will challenge the whole supply chain and the existing structure of the health care system (Figure 15.10). Some of the described technologies, like API printing on orodispersible films, enable the production of individual doses outside the GMP environment, for example, in a hospital or community pharmacy on prescription by the physician.

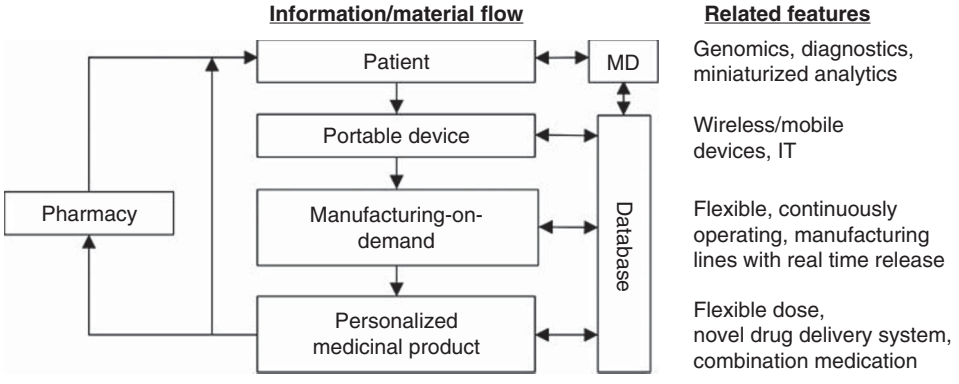

Figure 15.10 *Elements of the future healthcare system. Reprinted from [32], with permission from Elsevier.*

There are increasing possibilities not only to provide a tailor-made dose for each patient, but also to follow-up the success of treatment by point of care diagnostics and wearable technologies. The potential of app-based personal monitoring has been recognized and the use of mobile health apps is increasing. All these portable technologies and devices such as iPhone can be used as a part of the overall treatment and provide a possibility for the treatment of elderly people. This information is forming a real *big data* challenge but once we have a centralized and structured ways of handling this information, it can also be used for the manufacturing on demand type of solutions. While innovative manufacturing is becoming generally more accepted way of preparing, for example, complex dose combinations, techniques such as printing of medicines can be performed by several players in the health care system. This will challenge the existing distribution chain based on pharmacies, or the other way around: it can bring manufacturing back to the pharmacies.

The increasing use of information technology as a part of health care system has potential threads. Continuously monitoring of body functions and remote control of treatment using mobile devices is a potential cybersecurity hazard. These problems are already identified with medical devices containing functionalities based on wireless communication and Internet connectivity for software-based control of therapies and network-based transmission of patients' stored medical information [36].

References

[1] F.S. Collins and H. Varmus (2015) A new initiative on precision medicine, *New Engl. J. Med.* **372**, 793–795.

[2] A. Selen, P.A. Dickinson, A. Müllertz et al. (2014) The biopharmaceutics risk assessment roadmap for optimizing clinical drug product performance, *J. Pharm. Sci.* **103**, 3377–3397.

[3] A.T. Florence and V.H.L. Lee (2011) Commentary: Personalised medicines: More tailored drugs, more tailored delivery, *Int. J. Pharm.* **415**, 29–33.

[4] S. Stegemann, F. Ecker, M. Maio et al. (2010) Geriatric drug therapy: Neglecting the inevitable majority. *Ageing Res. Rev.* **9**, 384–398.

[5] V. Gubala, J. Harris, A. Ricco et al. (2012) Point of care diagnostics: Status and future. *Anal. Chem.* **84**, 487–515.

[6] P.K. Drain, E.P. Hyle, F. Noubary et al. (2014) Diagnostic point-of-care tests in resource-limited settings. *Lancet Infect. Dis.* **14**, 239–249.
[7] J. Breitkreutz and J. Boos (2007) Paediatric and geriatric drug delivery. *Expert Opin. Drug Deliv.* **4**, 37–45.
[8] K. Wening and J. Breitkreutz (2011) Oral drug delivery in personalized medicine: Unmet needs and novel approaches. *Int. J. Pharm.* **404**, 1–9.
[9] M. Hermanns-Clausen, W. Weinmann, V. Auwärter et al. (2009) Drug dosing error with drops: severe clinical course of codeine intoxication in twins. *Eur. J. Pediatr.* **168**, 819–824.
[10] K. Griessmann, J. Breitkreutz, M. Schubert-Zsilavecz et al. (2007) Dosing accuracy of measuring devices provided with antibiotic oral suspensions. *Paediatr. Perinat. Drug Ther.* **8**, 61–70.
[11] K. Wening and J. Breitkreutz (2010) Novel delivery device for monolithical solid oral dosage forms for personalized medicine. *Int. J. Pharm.* **395**, 174–181.
[12] E. Kayitare, C. Vervaet, J.D. Ntawukulilyayo et al. (2009) Development of fixed dose combination tablets containing zidovudine and lamivudine for paediatric applications. *Int. J. Pharm.* **370**, 41–46.
[13] E. Van Santen, D.M. Barends, H.W. Frijlink (2002) Breaking of scored tablets: A review. *Eur. J. Pharm. Biopharm.* **53**, 139–145.
[14] T.J. Cook, S. Edwards, C. Gyemah et al. (2004) Variability in tablet fragment weights when splitting unscored cyclobenzaprine 10 mg tablets. *J. Am. Pharm. Assoc.* **44**, 583–586.
[15] L. Solomon, A.S. Kaplan (2010) *Method of Administering a Partial Dose of a Segmented Pharmaceutical Tablet*, US patent 7713547B2.
[16] E.J. Laukamp, A.K. Vynckier, J. Voorspoels et al. (2015) Development of sustained and dual drug release co-extrusion formulations for individual dosing. *Eur. J. Pharm. Biopharm.* **89**, 357–364.
[17] E.J. Laukamp, K. Knop, M. Thommes et al. (2015) Micropellet-loaded rods with dose-independent sustained release properties for individual dosing via the Solid Dosage Pen. *Int. J. Pharm.*, **499**, 271–279.
[18] J.D. Allen, D. Mungall, M.E. Cobb et al. (1992) *Integrated Drug Dosage Form and Metering System*, European patent EP 000000224335B1.
[19] N. Sandler and P. Ihalainen (2017) Perspectives of printing technologies in continuous drug manufacturing, in *Continuous Manufacturing of Pharmaceuticals* (eds P. Kleinebudde, J. Khinast, J. Rantanen), John Wiley & Sons, New York.
[20] M. Preis, J. Breitkreutz, N. Sandler (2015) Perspective: Concepts of printing technologies for oral film formulations. *Int. J. Pharm.* **494**, 578–584.
[21] C. Tissen, K. Woertz, J. Breitkreutz et al. (2011) Development of mini-tablets with 1 mm and 2 mm diameter, *Int. J. Pharm.* **416**, 164–170.
[22] I. Stoltenberg and J. Breitkreutz (2011) Orally disintegrating mini-tablets (ODMTs) – A novel solid dosage form for paediatric use, *Eur. J. Pharm. Biopharm.* **78**, 462–469.
[23] D. Bar-Shalom, M. Roberts, J. Ford (2011) Extrudable technologies for controlling drug release and absorption, in *Controlled Release in Oral Drug Delivery* (eds C. Wilson and P. Crowley), Controlled Release Society/Springer, Heidelberg.
[24] S. Moulton and G. Wallace (2014) 3-dimensional (3D) fabricated polymer based drug delivery systems. *J. Contr. Rel.* **193**, 27–34.
[25] A. Goyanes, J. Wang, A. Buanz. et al. (2015) 3D printing of medicines: Engineering novel oral devices with unique design and drug release characteristics. *Mol. Pharm.* **12**, 4077–4084.
[26] P. Valencia, O. Farokhzad, R. Karnik et al. (2012) Microfluidic technologies for accelerating the clinical translation of nanoparticles. *Nature Nanotechnology* **7**: 623–629 (2012).
[27] L. Prasad and H. Smyth (2017) 3D Printing technologies for drug delivery: a review. *Drug Dev. Ind. Pharm.* (in press) doi:10.3109/03639045.2015.1120743.

[28] J. Aho, J. Boetker, S. Baldursdottir et al. (2015) Rheology as a tool for evaluation of melt processability of innovative dosage forms *Int. J. Pharm.* **494**, 623–42.
[29] D. Raijada, N. Genina, D. Fors et al. (2013) A step toward development of printable dosage forms for poorly soluble drugs. *J. Pharm. Sci.* **102**, 3694–3704.
[30] N. Genina, E.M. Janßen, A. Breitenbach et al. (2013) Evaluation of different substrates for inkjet printing of rasagiline mesylate. *Eur. J. Pharm. Biopharm.* **85**, 1075–1083.
[31] J.A. Zeitler and L.F. Gladden (2009) *In-vitro* tomography and non-destructive imaging at depth of pharmaceutical solid dosage forms. *Eur. J. Pharm. Biopharm.* **71**, 2–22.
[32] J. Rantanen and J. Khinast (2015) The future of pharmaceutical manufacturing sciences. *J. Pharm. Sci.* **104**, 3612–3638.
[33] U.S. Food and Drug Administration (2015) *Advancement of Emerging Technology Applications to Modernize the Pharmaceutical Manufacturing Base Guidance for Industry*, guidance draft. FDA, Rockville.
[34] G. Allison, Y. Gain, C. Cooney et al. (2015) Commentary: Regulatory and quality considerations for continuous manufacturing. *J. Pharm. Sci.* **104**, 803–812.
[35] J. Srai, C. Badman, M. Krumme et al. (2015) Commentary: Future supply chains enabled by continuous processing – opportunities and challenges. *J. Pharm. Sci.* **104**, 803–812.
[36] D. Kramer, M. Baker, B. Ransford et al. (2012) Security and privacy qualities of medical devices: An analysis of FDA postmarket surveillance. *PLOS One* **7**(7), e40200.

16

Perspectives of Printing Technologies in Continuous Drug Manufacturing

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16.1 Introduction

16.1.1 Printing Technologies – Enablers of Continuous Drug Manufacturing Approaches

Different types of printing methods have attracted interest as emerging technologies for fabrication of drug delivery systems (DDS). Recent examples include the use of different types of inkjet (IJ) printers [1–4] depositing drug-loaded inks to produce accurately and precisely dosed units of active pharmaceutical ingredients (APIs). Furthermore, the exploitation of flexographic printers [5, 6] and a combination of inkjet and flexographic technologies [7, 8] has been done. Different additive manufacturing technologies or three-dimensional (3D) printing approaches also play an integral role in future fabrication scenarios.

Many type of scenarios for printed dosage form exits as presented recently by Preis *et al*. [9]. The concepts include on the simplest level accurately deposited doses of drug substances and one-layer films. On the other hand, printing technologies allow the manufacture of advanced multi-layer membranes, various type of stacked systems, and integrated multi-compartment systems with bioactive components. These can comprise integrated combinations of diverse materials to form sophisticated bio-functional constructs.

Continuous Manufacturing of Pharmaceuticals, First Edition.
Edited by Peter Kleinebudde, Johannes Khinast, and Jukka Rantanen.
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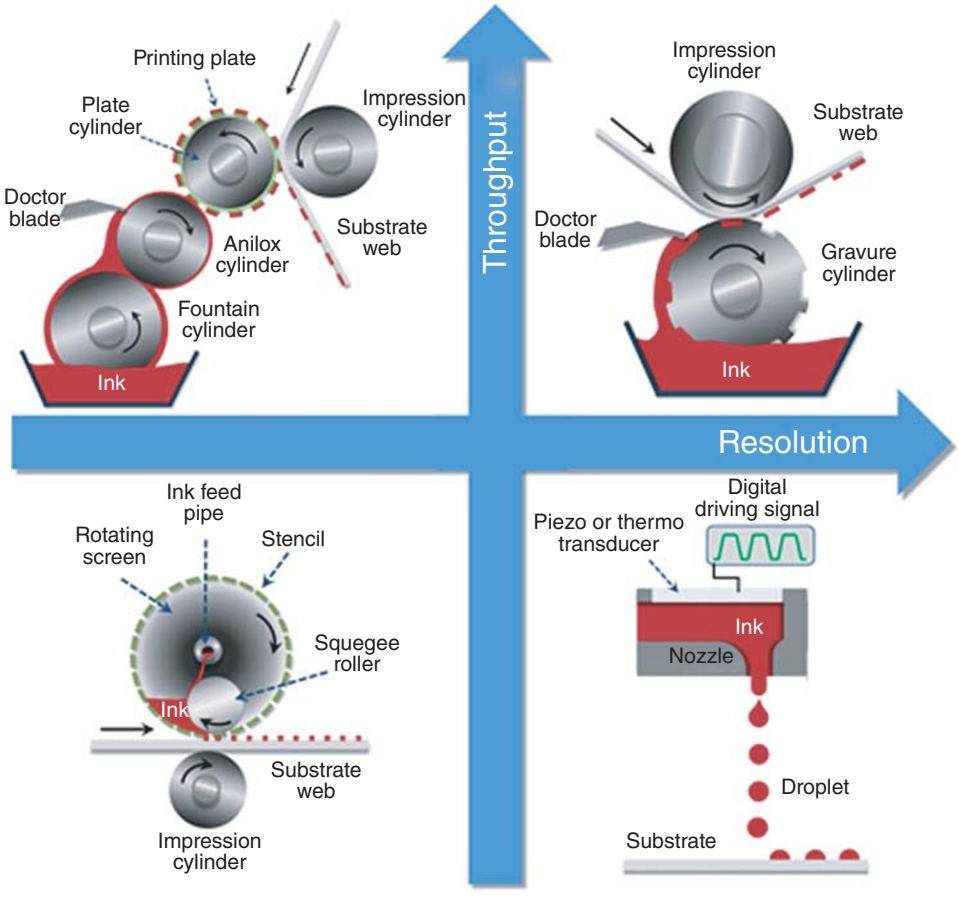

Figure 16.1 *Schematic presentation of printing technologies of potential interest for the printing of bioactive substances. The printing technologies shown are qualitatively divided according to their print resolution and throughput capabilities. Top left: flexography; top right: gravure; bottom left: screen; bottom right: inkjet.*

Moreover, computer aided design allows endless opportunities to create suitable geometries with tailored functionality, for example, through controlling the release properties of one or multiple drug substances. Figure 16.1 summarises printing technologies that are of potential interest in printing of bioactive substances [10]. The printing technologies shown are qualitatively divided according to their print resolution and throughput capabilities.

Many of the notions for using this type of technology in drug manufacturing are based on ideas for the development and fabrication of pharmaceuticals in a tailored manner to meet some of the foreseen personalization needs of treatments for patients. This optimally means more possibilities to accomplish on-demand fabrication of custom-made medications. Printing technologies are inherently continuous by nature or can be designed in that manner. Drug manufacturing by printing also allows direct integration of quality control systems and technologies to monitor the manufacturing process. This chapter discusses and

gives future perspectives of the use of printing technologies in the manufacture of drugs. The following techniques will be described:

- *Inkjet printing (drop deposition)*: Accurate amounts of liquid are deposited onto a surface or substrate in a non-contact manner in accurately defined spatial positions.
- *Flexographic printing*: Materials are transferred in a contact manner roll-to-roll manner onto a substrate forming predefined geometries.
- *Fused filament deposition*: Materials are transformed through melting and solidification to a certain predefined geometry.

16.2 Inkjet (Microdrop Generation Techniques)

16.2.1 Inkjet – Technical Description

Digital inkjet printing technology has become widely known and available to most people through household and office printers used in everyday life to produce text documents and images. Inkjet printing is an attractive non-contact technique with high precision, speed, and flexibility, and is very suitable for material deposition processes needing the precise control and defined localization of deposited material on the substrate. In addition to the important role inkjet printing plays in the graphical printing industry, it has also a wide range of emerging applications in other industrial and medical fields and has been implemented in many different designs which differ substantially in terms of technological solutions. Despite the differences in technology, the end result of all inkjet printers is the emission of ink droplets from a nozzle to create patterns of dots at a specific position on a given substrate. Primarily, ink-jet printing operates either in the continuous or the drop on demand mode. In continuous mode printers, droplets are propelled in unremitting manner, while in drop on demand printers, drops of ink are only ejected as required.

16.2.1.1 Continuous Inkjet System

Ink-jet printers in continuous mode have a high-pressure pump directing liquid ink from a reservoir through an orifice in the nozzle, which is typically 50–80 μm in diameter (Figure 16.2) [11–15]. This causes a continuous stream of cylinder-shaped jet to emerge from the nozzle with a velocity typically between 10–30 m/s. Under a regular disturbance, for example, by the vibrations of a piezoelectric crystal, the continuous jet will break into droplets at regular intervals with repeatable size and velocity. This is driven by surface tension forces acting on the cylinder-shaped jet according to Plateau–Rayleigh instability [16]. The droplet diameter is roughly twice the diameter of the orifice in the nozzle.

A charging electrode is placed close to the break-off point where droplets are forming from the continuous jet. A potential applied over this electrode induces an opposite electrical charge on the surface of the forming drop and, by varying the potential, each successive droplet can be charged as required or left uncharged (with zero potential). For charging to occur, the ink liquid must be sufficiently conductive, typically between 50 and 2000 Ω cm. The continuous droplet stream is then directed to the substrate through a fixed electric field using high-voltage deflection plates positioned closed to the substrate.

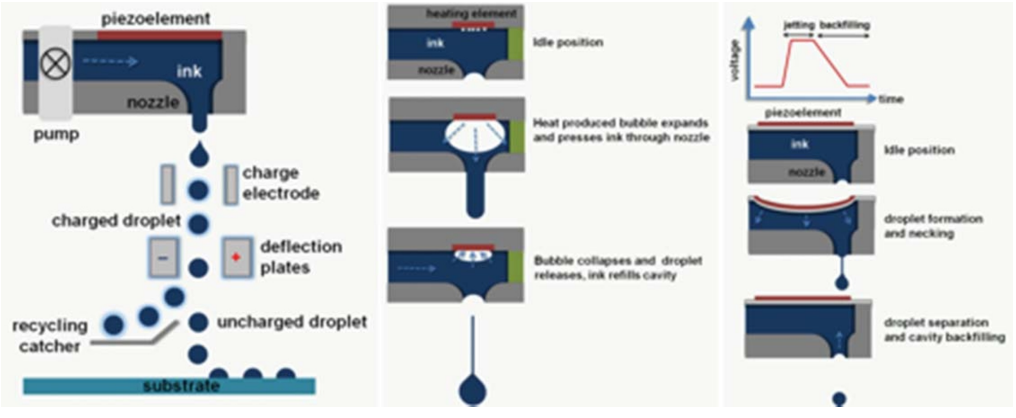

Figure 16.2 *Schematic illustrations of the operating principles of various inkjet technologies. Left: Single jet continuous inkjet system (binary mode). Middle: Drop on demand thermal inkjet system (single drop). Right: Drop on demand piezoelectric inkjet system (single drop).*

Continuous ink-jet printers are typically utilizing either a binary or multiple deflection system, both which are widely used in the industrial coding, marking, and labelling markets [13, 15]. In a binary deflection system, the uncharged droplets are allowed to travel directly onto the substrate, while the charged droplets are deflected into a catcher (gutter) for recirculation. In a multiple deflection system, drops are charged at different levels and deflected to the substrate by the electric field in proportion to the charge they carry (charge–mass ratio). The uncharged drops are collected into a catcher for reconditioning and reuse. A printed pattern is formed by controlling the time and level of droplet charging whilst moving the substrate relative to the droplet stream and the electric field.

Continuous inkjet systems offer high-throughput dispensing with printing speeds up to 200 m/s (i.e., as many meters of substrate per second as can be fed through the inkjet). In addition, the method is able to print volatile liquids due to the continuous nature of droplet formation which prevents nozzle dry-out. However, continuous inkjet systems tend to be more complex than other inkjet technologies, as they require separated methods for drop formation and selection as well as for liquid recovery and control. In addition, the achieved printing resolution is lower (typically drop spacing > 30 μm) compared to drop on demand printers.

16.2.1.2 Drop on Demand Inkjet System

The majority of ink-jet printers on the market today are based on drop on demand systems. In the drop on demand system, the ink is maintained at ambient pressure and a transducer is used to create a droplet only when needed. In drop on demand systems, the volume of the expelled droplet is typically in the range 1–100 pL and the impact velocity in the range 5–8 m/s [15, 17]. The nominal diameter of expelled droplet (d_d) is approximately equal to the diameter of the orifice in the nozzle (d_n) and can be expressed as $d_d \approx 12.4\, V^{1/3}$, where V is the volume of droplet [15]. Four different main principles exist for the ejection of droplets from a drop on demand printhead: piezoelectric, thermal, electrostatic, and acoustic ([14, 15]. Out of these four principles, drop on demand piezoelectric and thermal printheads are most commonly utilized in commercial products and their operating principles are described below.

16.2.1.3 Thermal Inkjet Printer

A thermal inkjet (TIJ) printer comprises a reservoir of liquid to be jetted and a printhead consisting of a number of small channels filled with ink from the reservoir [13–15]. Every channel is equipped with a heat transducer in the form of a thin film resistor (Figure 16.2). TIJ printers typically use print cartridges with a series of tiny electrically heated chambers constructed by photolithography behind each nozzle. The orifice in a drop on demand TIJ printhead is usually located either on top of (roof-shooter configuration) or beside (side-shooter configuration) the heater. When a current pulse of less than a few microseconds is passed through the resistor, its temperature rapidly rises and heat is transferred from the surface of the heater to the ink. The ink becomes superheated to the critical temperature for bubble nucleation. For water-based inks, the critical bubble nucleation temperature is around 300 °C [13]. However, only a very thin layer of ink next to the heater is actually heated and vaporised, and temperature change in the bulk of the ink is only a few degrees Celsius. The rapid superheating and vaporization causes the formation and rapid expansion

of vapour bubbles which produce fluid displacement and sufficient energy needed for an ejection of the ink droplet from the nozzle. Once the heating is switched off and all the heat energy stored in the ink is exhausted, the bubbles quickly collapse on the surface of the heater. The whole process is very fast and the bubble formation–collapse cycle takes place typically within 20 μs [13, 15]. Simultaneously with the bubble collapse, the ink droplet breaks off and travels toward the substrate. The channel is then refilled by ink flow from the reservoir. Depending on the channel geometry and the ink's physical properties, the ink refill time can take between 80 and 200 μs [13]. The whole droplet formation process is repeated in manner determined by current pulses creating the droplets as required (droplet on demand). The main advantage of the TIJ technique is the simplicity of fabrication of the heating element and thus printhead architecture, making it suitable for large quantity manufacture. However, the limit of solvent types which can be used and the careful selection of ink ingredients which do not thermally decompose and deposit on the surface of the heating element could be seen as a hindrance in some respects.

16.2.1.4 Piezoelectric Inkjet Printer

A piezoelectric inkjet printer comprises a reservoir of liquid to be jetted and a printhead consisting of a connection to an ink supply, a pressure chamber, a connecting channel to the nozzle, and the nozzle itself [13, 15, 18]. The wall of the pump chamber is partly covered with a small piezoelectric transducer element and the ejection of droplets with a precisely defined volume and speed is provided by action of the piezoelectric element (Figure 16.2). The piezoelectric element (made of piezoceramic material) changes shape or size under the applied voltage. Deformation of the piezoceramic material causes an ink volume change in the pressure chamber, generating a pressure wave in the ink fluid that propagates towards the nozzle. The acoustic pressure wave has to overcome both the viscous pressure loss in the nozzle (typically 0.5–1.0 atm; 50–101 kPa) and the surface tension force from the ink meniscus (pressure rise $<$ 0.1 atm; 10.1 kPa) before a droplet of ink can begin to form at the nozzle. In addition, sufficient pressure ($\sim$0.5 atm; 50 kPa) has to be generated to eject the droplet from the nozzle towards the substrate. The whole drop formation process takes several tens of microseconds. When the element returns to its starting position, the liquid meniscus retracts and the channel is refilled with ink from the ink reservoir. Refilling is controlled by surface tension and inertia-related phenomena in the nozzle.

The droplet formation process is controlled by the diameter of the orifice in the nozzle (d_n), the maximum velocity (v_{max}) in the nozzle generated by the actuation of the piezoelectric element and the frequency (ω_0) of the fluid motion in the nozzle that depends on the acoustic characteristics of the pump design, the waveform shape of the pulse (positive or negative), and the viscosity of the ink [15, 18]. Above a certain threshold v_{max} value, eventually enough momentum begins to build up for the droplet to escape from the nozzle. At first, the droplet is connected with the fluid inside the nozzle by an extending filament of fluid. Ultimately, surface tension forces lead to the rupture of the filament, and the remnants of the filament attached to the droplet merge with the main droplet. Slightly above the threshold value, slow-traveling droplets are created and following condition holds true: $2v_{max}/\omega_0 d_n \approx 1$ [15, 18]. For velocities far above the threshold value, a high-speed stream is jetted that breaks up into a number of small droplets.

In general, the deformation of a piezoelectric driver is on the submicron scale and the physical size of a piezoelectric driver is often much larger than the nozzle orifice to have large enough ink volume displacement for drop formation [13]. Depending on the deformation mode of piezoceramic material, the piezoelectric inkjet technology can be further classified into four main types: squeeze, bend, push, and shear [15, 18]. A squeeze-mode inkjet can be designed with a thin tube of piezoceramic surrounding a glass nozzle or with a piezoceramic tube cast in plastic that encloses the ink channel. In a typical bend-mode design, the piezoceramic elements are bonded to a thin, semi-rigid membrane that vibrates to transmit sound waves (diaphragm) forming an array of bilaminar electromechanical transducers used to eject the ink droplets. In a push-mode architecture, expanding piezoceramic rods push against the ink to eject the droplets. In both the bend- and push-mode architectures, the electric field generated between the electrodes is in parallel with the polarization of the piezoelement. In shear-mode design, the shear-induced deformation of the piezoelements against the ink fluid expels the droplets and the piezodriver becomes an active wall in the ink chamber. In a shear-mode printhead, the electric field is designed to be perpendicular to the polarization of the piezodriver.

16.2.2 Ink Development and Printability

The choice of printhead technology restricts the range of which types of inks can be printed. With TIJ technology, the drop ejection mechanism requires the ink fluid to have a high vapor pressure and low boiling point, and consequently aqueous-based inks (solutions, dispersion, and microemulsions) are exclusively used [13]. With continuous inkjet technology, nonaqueous-based ink (oils, solvents) and UV-curable inks are mainly used [13]. The unique capability of piezoelectric inkjet technology lies within its drop generation process which offers the ability to print a wide range of different fluid formulations and materials not possible with continuous inkjet and thermal drop on demand inkjet systems. In addition to aqueous, nonaqueous-based, and UV-curable inks, also solid inks like wax can be printed with piezo-based inkjets [13].

In the ink development, two major parameters should be considered: viscosity and surface tension. The operational window in terms of rheological properties depends on the selected printing method. Inkjet printers will normally function over a viscosity range from 2 to 20 mPa s and surface tension range from 20 to 50 mN/m [15]. The increase in viscosity will decrease the speed and accuracy of the expelled drop and the printing will fail at high viscosities and high drop rates if the ink cannot flow into the liquid chamber rapidly enough to refill it between jettings. On the other hand, surface tension affects the tendency of the ink column to wick out of the nozzle and to form a drop (piezoelectric printing) or a bubble (thermal printing).

A group of dimensionless numbers and their relationships can be used to define a set of boundary conditions for the inkjet printability (drop generation, flight, and impact) of the fluid under normal atmospheric conditions at standard temperature and pressure [15]. The Weber number (We) describes the ratio between inertia and surface tension which is important in the early stages of drop generation: $\mathrm{We} = \rho d v^2/\gamma$, where ρ is the density of the fluid, d is the diameter of the orifice of the nozzle, v is the velocity of the fluid, and γ is the surface tension of the fluid [15]. The Reynolds number (Re) presents the ratio of inertial

and viscous forces in a moving liquid. The ratio is important in the middle and latter stages of drop formation where the interplay with the viscoelasticity of the ligament is critical: $\mathrm{Re} = \rho d v/\eta$, where η is the viscosity of the fluid [15, 19]. The Ohnesorge number (Oh) removes the velocity dependence by combining We and Re: $\mathrm{Oh} = \mathrm{We}^{1/2}/\mathrm{Re} = \eta/(\gamma\rho d)^{1/2}$ [15, 20]. The inverse of Oh is sometimes used with the symbol of Z ($\mathrm{Z} = 1/\mathrm{Oh}$) [15]. The Oh number predicts the ink fluid to be printable with drop on demand inkjets when $0.1 < \mathrm{Oh} < 1$ (or $10 > \mathrm{Z} > 1$) [15, 21]. Others have suggested that the Z value in the range 4–14 could be more appropriate for reliable printability [22]. When $\mathrm{Oh} > 1$, the viscous dissipation within the fluid prevents droplet formation, and when $\mathrm{Oh} < 0.1$, the balance between surface tension and viscosity results in the jet of fluid breaking into a series of satellite droplets. However, in practice, systems in which Oh is much less than 0.1 are printable so long as the satellites merge with the main droplet [15]. The droplet volume has been shown to increase with increasing Oh number [15, 23]. In addition to the boundary conditions predicted by the Oh number, the relationships between the We, Re, and Oh numbers can be used to predict other factors affecting the drop formation and printability of the fluid. For example, the boundary condition $\mathrm{Re} > 2/\mathrm{Oh}$ must be fulfilled for the fluid to have sufficient kinetic energy for drop formation [15, 24]. On the other hand, the boundary condition $\mathrm{OhRe}^{1.25} < 50$ must be fulfilled to avoid splashing of the droplet on the impact with the substrate [15, 25]. The maximum extent of droplet spreading on nonporous and nonwetting substrate has been shown strongly correlated with $\mathrm{We}^{0.25}$ for the fluids with low We number [15, 26]. Aerodynamic drag on the droplet in flight can reduce significantly the velocity of the droplet before impact and also allow random fluctuations in the surrounding atmosphere that could deflect a drop away from the desired trajectory. It has been showed that the critical value of Re will vary from 19.5 for a liquid of viscosity 1 mPa s to 0.48 for a liquid of viscosity 40 mPa s [15, 27].

Other factors related to the properties of additives in ink fluid should be also considered when designing ink formulations and predicting their printability. Surface tension of the ink fluid can be adjusted by the addition of surfactants. However, the actual surface tension of the fluid may change because of the sudden enlargement of the free surface during droplet formation [28–30]. A depletion of the local surfactant concentration at the surface occurs which has to be replenished by diffusion from the bulk. For water-based ink, this means that the surface tension during droplet formation is generally higher than that measured by static methods. The particle size or radius (r) in the ink dispersions containing nanoparticles has to be considered, as according to Stoke's law, the settling velocity of the particle in the fluid increases as r^2 [31]. This limits the size of the nanoparticle which can be used in the ink dispersion and uphold the long-term stability in printing. In addition, the diameter of the orifice of the nozzle is another limiting factor for the particle size which can be printed and it is typically recommended to use particles with size up to 0.01 of the diameter of the orifice. Finally, the relative high shear rates in extensional flow (typically between 10^4 to 10^6 s^{-1}) could result in a breakage of thin high molecular weight species with coiled structures [32, 33] and the jetting behavior of linear polymeric materials in piezoelectric inkjet systems has shown to be dependent on the molecular weight (M) and concentration (c) of the polymer. The linear polymer is shown to be printable if M (in kilodalton) $\times$ c (in wt%) < 100, which limits the use higher molecular weight polymers only in diluted solution (<1 wt%).

16.2.3 Pharmaceutical Applications of Inkjet Printing

The use of printing technologies in the fabrication of drug delivery systems is a relatively novel idea, which has increasingly been studied and explored during the last few decades. Basically all examples in this paragraph are extendable easily to the continuous type of manufacturing. The idea of using inkjet printing in drug fabrication derives from the possibility to use ink jetting to accurately deposit small amounts of liquid in digitally predesigned patterns. The well-defined shape and composition of these drops, coupled with their small size, low mass, and ability to be ejected with precision, are the enabling features for a variety of scientific and industrial applications. From a pharmaceutical perspective, the deposition of a desired ratio of APIs and excipients into or into a substrate surface can be achieved in a highly precise and controlled manner. This optimally permits the manufacture of single or multi-drug dosage forms in a continuous manner. Many research groups have described the application of inkjet printing or droplet deposition technologies or combinations of these types of techniques to produce drug delivery systems. The majority of the reported studies have focused on prototypes or proof of concept studies regarding solid oral dosage form fabrication, partly most likely due to the fact that the oral administration route is the most commonly used and convenient from a patient perspective. The use of and research into inkjet technologies in drug delivery system development have been recently reviewed by Palo *et al*. [8] and in biomolecules by Ihalainen *et al*. [34]. Here we introduce a number of these studies.

Tarcha *et al*. [35] described the use of ink-jet technology for coating and loading of drug-eluting stents by a piezoelectric inkjet printer. They studied how the jet stream of a drug solution can be directed to exact positions on the device surface. The jetting was performed using an *off-axis jetting*. In the setup the stent was mounted on a rotating spindle and the positioning of the jet stream was tangent to the cylindrical surface. It was possible to create an even coating of fenofibrate and a rapamycin derivative with high jetting efficacy and with no detectable drug decomposition.

Meléndez *et al*. [1] reported one of the first studies of deposition of APIs, namely prednisolone, by TIJ printing. Prednisolone, being a poorly soluble drug, the printing solution was formulated by dissolving the drug in a ethanol–water–glycerol (80/17/3%v/v) solvent mixture. The printing was performed on a non-porous PTFE-coated fiberglass film as the substrate. After 60 deposited layers the therapeutic dose (8 mg) was achieved. The authors showed that the printed API was in crystalline form after the printing and no chemical degradation had occurred. When using TIJ printing the resistive element may momentarily reach up to temperatures of 300 °C. It was estimated that only about < 0.5% of the drug solution experiences the elevated temperature when a vapor bubble is created, quickly expands, and consequently collapses (between 3–10 μs) [1].

Sandler *et al*. [3] introduced the printing of various API solutions on porous substrates. The aim was to study the potential of the substrates to incorporate the APIs into the structure and serve as a matrix to carry the drug. In this proof of concept study they used a piezoelectric inkjet printer to deposit three classical drugs (theophylline, acetaminophen, and caffeine) using three types of substrates [uncoated paper, pigment coated paper, and polyethylene terephthalate (PET) films]) as substrates. The crystallization behavior was studied upon printing and it was found that the absorption and penetration of APIs into the

porous papers resulted in differences in crystallization of the compounds when comparing behavior on the PET film.

Scoutaris *et al*. [36] described and reported the use of PIJ approach in fabrication of solid dispersion of felodipine. Their intention was to demonstrate the increasing dissolution rate of a the drug by an API and polymer (PVP) formulated ink. The mixture was deposited on coated cover slips of glass with the aim to produce micron-sized particles. An amorphous end product was made from a single droplet via a quick evaporation of the solvent upon jetting. Nonetheless the authors showed that continued spraying (for > 1 min) induced crystallization of the API.

Genina *et al*. [4] studied the effect of printing parameters on the solid state properties of printed drugs. The effect of printing parameters namely, the drop spacing and the physical dimensions of the printed area and the effect of different substrates was studied. Caffeine and loperamide hydrochloride were used as experimental drugs with three different substrates (edible sugar-based icing sheets, films of hydroxyl-propyl cellulose films, and PET). They concluded that different interactions with the substrate component and variability in penetration of the drug substances into the porous carrier structures altered the crystallization properties of the APIs. Scoutaris *et al*. [36] produced a solid dispersion to increase the dissolution rate of a drug using a piezoelectric inkjet printer. A model drug, namely felodipine, and PVP as a polymer were dissolved in a solvent and the mixture was deposited, to form micron-sized particles on glass cover slips which had been coated with a perfluorocarbon liquid. They demonstrated the formation of an amorphous product through quick evaporation of the solvent, but longer spraying times (>1 min) caused crystallization of the deposited systems.

Buanz *et al*. [2] utilised a TIJ printer to produce oral films of personalized doses containing salbutamol sulfate as the active ingredient. They deposited the drug on two different substrates (edible potato starch sheets and acetate films) and investigated the effects of the viscosity and surface tension of the printing liquid and the deposition efficacy of the printer. It was found that an increasing number of printed layers led to a nonlinear increase in the printed amount of drug on the carrier substrates. The authors concluded that this was due to erosion of the printed layers due to a shearing feeding tray caused when feeding the substrates consecutive times though the printer.

A similar manufacturing principle, that is, the use of an off the shelf TIJ printer was used by Genina *et al*. [4] to fabricate personalized doses of rasagiline mesylate. Three different carrier substrates were used. An escalating dose of deposited API was obtained by printing new layers by circulating the substrate in the printer. The increasing number of printed layers did not show linearity, but indicated a relatively high standard deviation per sample area. This could at least partly be explained by the modest absorption properties of the carrier substrates used. This lead to smearing of ink formulations when the substrates were passed under the print head, caused by shear forces between substrate and the printer feeding mechanism.

The dispensing of poorly water-soluble drugs using inkjet printing was investigated by Pardeike *et al*. [37]. They formulated a nanosuspension containing folic acid. The particle size and particle size distribution is a critical consideration for inks in suspension form, as the print head nozzle's opening diameter is typically in the micron range and therefore allows continuous printing of the particulate systems in the nanometer scale. The authors used an inkjet-based microdosing dispenser head with an aperture size of 100 μm which

allowed continuous printing of the suspension formulation with a mean particle size of 420 nm. Raijada *et al*. [6] formulated printable inks with a drug that possessed poor aqueous solubility to test the potential of a printing approach to increase the dissolution rate and thus potentially the bioavailability of a poorly soluble drug substance. A non-aqueous solvent solution (PEG 400/ethanol) for dissolving piroxicam was used and printing was performed using a piezoelectric inkjet printer. The substrate material was an edible commercially available icing sheet.

A concept of utilising a piezoelectric inkjet printer to fabricate drug-loaded polymer microparticles with distinct geometries was reported by Lee *et al*. [38]. They formulated solutions from paclitaxel and poly(lactic-co-glycolic acid) (PLGA), using N,N-dimethylacetamide as solvent. Micron-sized patterns with different geometries (circles, grids, honeycombs, and rings) were printed on glass slides. The manufacture of microparticles using inkjet was a good option and could offer the possibility to create a platform technology for developing drug delivery carriers designed with variability in their complexity features and leading to desirable release profiles.

Yeo and Park [39] created a dual microdispenser system containing two inkjet nozzles that separately jetted an aqueous and a polymer (PLGA) solution. Positioning of the nozzle was made in a way that allowed the droplets directed from two nozzles to collide with each other and cause a spontaneous interfacial phase separation. This subsequently caused the formation of a polymer film around the aqueous core to successfully create microcapsules for the delivery of therapeutic proteins.

16.3 Flexographic Printing

16.3.1 Flexography – Technique Description

Five major printing processes exist today that entail the contact transfer of a pattern: relief, intaglio, lithography, screen, and electrophotography [40, 41]. Relief printing comprises letterpress printing, flexographic printing, and other techniques of transferring an image from a raised surface. Flexographic printing is a form of printing that uses flexible rubber relief plates and fast-drying inks to print on a variety of substrates commonly used in package printing, including paper, plastic and metal foils, and acetate film [41]. Flexographic printing offers reel to reel printing with the larger flexographic printing presses running at speeds up 800–1000 m/min. The printing speed varies greatly depending on type of press and material being printed. The typical speed of a flexographic printing press is clearly higher than inkjet printing but rather lower than some of the other truly high-volume printing methods, such as gravure and offset printing. In its most basic form, the flexographic printing unit consists of three parts: inking unit, plate cylinder, and impression cylinder (Figure 16.3).

Flexographic ink is stored in an ink tray (fountain). The ink can be solvent- or water-based, or UV-curable and dries mainly by the evaporation of the vehicle. The viscosity of the ink is usually between 50 and 500 mPa s and the surface tension between 25 and 45 mN/m. The ink feeding is controlled by the inking units. The inking unit can be either of a rubber-covered fountain roller (cylinder) or a doctor blade system. The fountain roller transfers ink from the ink tray to a chrome- or ceramic-covered anilox (metering) roller whose surface contains small, engraved discrete dots (cells) of uniform size and depth with a typical density of 80–1000 cells/in (30–400 cells/cm).

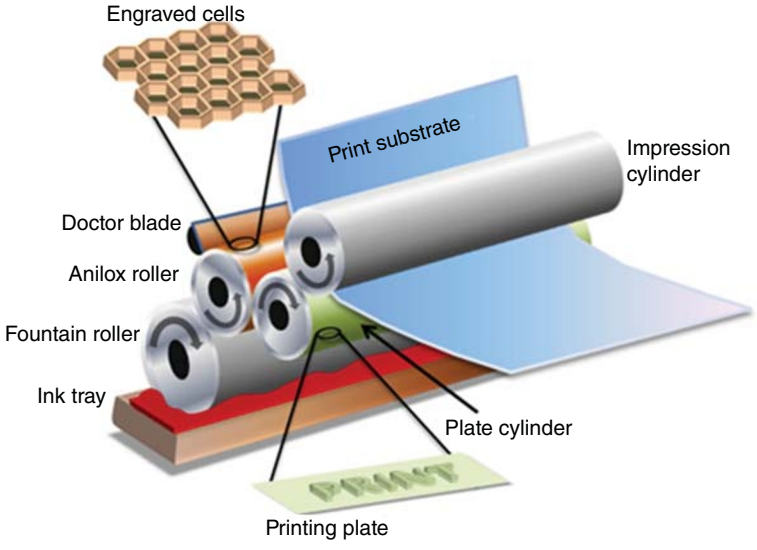

Figure 16.3 *A schematic illustration of a flexographic printing unit.*

The shape and volume of the cells are chosen depending on the anilox surface (chrome or ceramic), the doctoring system, the press capabilities, the printing substrate, and the type of ink [42, 43]. The laser-engraved ceramic covering offers tougher and more long-wearing rollers with greatly improved ink-release characteristics compared with conventional, mechanically engraved chrome coverings [42, 44, 45]. The doctor blade ensures that the cells are filled with the appropriate amount of ink. The cells are usually arranged in a hexagonal or diamond grid pattern and the number of cells and their size regulate the volume of ink transferred. The wet film thickness is typically around 0.5–8.0 μm and depends on the speed of the press, the transfer characteristics of the ink, and the nature of the substrate surface [42, 46]. The pressure between the fountain roller and the anilox roller is set so that the excess ink pools up at the top of the nip between the two rollers. In addition, the fountain roller typically turns at a slower rate than the anilox roller and the difference in revolution speed of the two rollers causes a wiping effect on the anilox roller and eliminates a problem in flexography called mechanical pinholing. Mechanical pinholing refers to the condition in which ink is not replenished uniformly across the surface of the anilox roller and the texture of the roller is transferred to the substrate. The quality of anilox roller is a crucial factor in achieving good quality flexo printing.

The inked anilox roller is adjacent to the plate cylinder, usually made of steel. A flexographic printing plate (cliché) containing raised (relief) patterns to be printed is secured to the plate cylinder with two-sided self-adhesive material or by other means, such as plate clamps. These low-cost flexible printing plates are typically made of molded rubber or photopolymer materials with a thickness of up to a few millimeters. Printing plates can be created with analog and digital platemaking processes. The hardness of the printing plate has a pronounced effect on the printing characteristics and the flexibility of the printing plate enables good printing quality, even on rough substrates. The relief pattern of the plate

is inked when in contact with an ink-covered anilox roller and the ink is transferred to the substrate passing between the plate cylinder and the smooth, steel impression cylinder. The impression cylinder applies relative low pressure (<200 N) to the plate cylinder and the printed pattern (image) is transferred to the substrate. Although the anilox roller contains engraved discrete dots (cells), a continuous print pattern can be obtained by a careful tuning of the print pressure, the physicochemical properties of the ink (viscosity, surface tension, and evaporation rate), and the substrate (surface energy, roughness, and porosity). Achievable printing resolution for typical flexo printing is around 30–75 μm. The printing resolution is limited by the possible distortion of patterns on the flexible plate during printing. Another common problem affecting the printing resolution is the formation of halo-like shapes around the edges of the printed pattern due to the squeezing of ink when the printing plate is pressed against the substrate.

16.3.2 Pharmaceutical Applications of Flexographic Printing

The use of flexographic printing has been successfully demonstrated in the fabrication of drug delivery systems as a single-step method [6, 8, 47] or as a part of a multi-step process combined with inkjet printing [48]. The combination of inkjet and flexography printing showns promise, as reported by [48]. The proposed continuous type of approach is illustrated in Figure 16.4. Tailored controlled release oral dosage forms of water-soluble model APIs were produced by deposition of an aqueous solution of propranolol hydrochloride or riboflavin sodium phosphate on three different types of substrates by piezoelectric inkjet printing.

Besides uses in graphical printing, flexographic printing has been used in printed electronics to fabricate conducting structures and electrical components from metal, carbon and

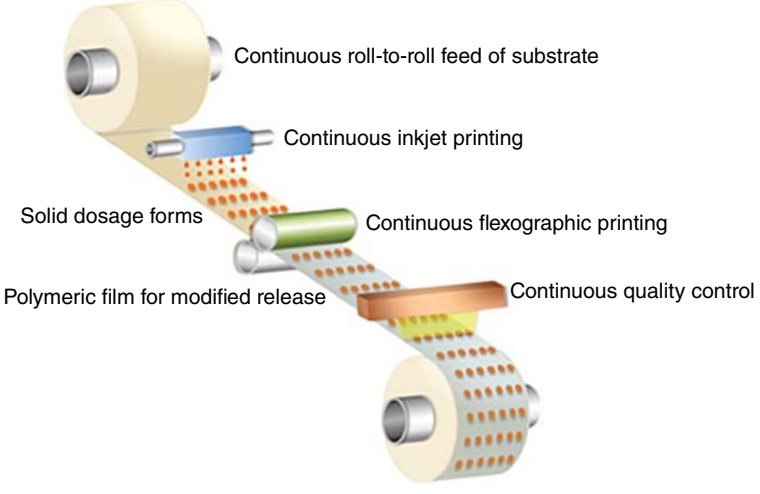

Figure 16.4 *A proposed approach for a continuous manufacturing line combining inkjet deposition of the active substance and flexographic deposition of a functional film coating on top of the active substance.*

conductive polymer-based inks [49]. However, only a few examples exist about the usage of flexographic printing in biological applications, most concerning paper-based diagnostics and microfluidic devices [50–52]. For example, Phillips *et al*. showed that pattern arrays of antibodies can be successfully transferred onto flexible plastic films and the proteins retain their activity [52]. The optimized ink was formulated using 2.5% mass concentration of high molecular weight poly(vinyl alcohol), carbonate buffer, and 0.25% mass concentration of antibody. A wider operational window in terms of rheological properties in flexographic printing, compared to inkjet printing, enables the dispensing of higher molecular weight species with higher concentrations (Figure 16.4). This might offer better possibilities of preparing biopolymer hydrogel matrices, e.g. for tissue engineering, drug delivery, and other applications. Examples of successful use of flexography in fabrication of drug delivery systems have been demonstrated, for example, by Genina *et al*. [48] and Janssen *et al*. [47].

The controlled drug release was achieved by the deposition of multiple layers of ethyl cellulose, a water-insoluble polymer, which was deposited on the top of the printed dosage forms by flexographic printing. Prototype dosage forms with different number of release-controlling polymer layers were fabricated with the aim to show the perspectives that this type of setup can bring to tailoring drug products, for instance to control the drug release kinetics or to personalise taste masking by applying different tastes in a tailored manner. It was shown that the drug release rate decreased with an increased thickness of ethyl cellulose layer as expected. Additionally, flexographic printing was utilized to make orodispersible films containing anti-Parkinsons and erectile dysfunction drugs [47]. Carrier films were first prepared by solvent casting. Then the rasagiline mesylate solution and the tadalafil-containing suspension were printed to create fast dissolving therapeutic oral films.

Palo *et al*. [8] recently investigated the possible use of flexographic printing for the deposition of nanosuspensions into solid dosage forms, that is, by aiming to stabilize nanosuspensions in a carrier substrate matrix without compromising drug release and the dissolution properties of a nanoparticulate suspension. First, aqueous nanosuspensions of indomethacin (IND) and itraconazole (ITR) with a stabilizer agent were ball-milled and the nanosuspensions were printed with a table-top flexographic printer on different types of edible substrate. A predesigned relief printing plate that comprised small rectangular areas aligned along the printing pattern was used to transfer the ink suspension onto the carrier substrate. To assure the homogeneity of the nanosuspensions, the ink suspension was continuously stirred for 15 min before printing took place. Of all the prepared formulations, 10 layers of the nanosuspensions were printed onto sample areas of 0.5 cm^2. It was shown that flexographic printing can be considered a viable fabrication method for solid nanoparticulate systems to allow an enhanced dissolution behavior of poorly soluble drugs.

16.4 Formulation Approaches for Inkjet and Flexography

Modifiers such as hydroxypropyl cellulose [47] or ethyl cellulose [48] have been added to flexographically printable formulations in order to achieve the required viscosity values and for specific functionality. Inkjet printing is more complex because multiple factors affect the droplet formation and accurate deposition of ink on the substrate.

Solvent mixtures of drug solutions containing, for instance water, ethanol, or DMSO are characterized by very low viscosities and consequently would require viscosity modifiers,

for example, propylene glycol [3, 4, 7, 48] or glycerol [1, 2]. As examples of excipients, propylene glycol and glycerol have manifold functions in inkjet formulations. Apart from viscosity adjustment, they also can be used to prevent nozzle clogging during the printing process. Nozzle clogging is a usual problematic area encountered during continuous printing. It is often caused by crystallization of the drug substance at the nozzle opening caused by evaporation of the solvent. The solution to this problem is twofold: (i) addition of a solvent having a higher evaporation point, (ii) addition of a humectant (e.g., PG or glycerol) or a low molecular weight PEG. These solutions will decrease the evaporation rate of the solvent, thus preventing the clogging problem.

An important aspect to consider when working with the formulation of printable liquids (ink) is the desired amount of drug in the final printed product (i.e., the drug dose). Naturally, the concentration of the drug in the printable liquid should be sufficient to achieve a desirable dose on a certain surface area. This is not always simple to achieve when working with poorly water-soluble APIs. This has been discussed and studied, and one approach is the use of non-aqueous solvents [1, 6, 47, 48, 53]. The use of non-aqueous solvents in the printing of low water-soluble drugs has been shown to be advantageous as the solubility of the drug can be increased.

One approach for poorly water-soluble drugs is to formulate printable suspensions with a high solid content. A few studies have described the printing of drug-containing suspensions, for example, Janssen *et al*. [47] used an aqueous suspension of tadalafil when exploring flexographic printing as a method of manufacture. The particle size in their suspensions was approximately 50 μm. These kinds of suspensions can be printed using flexography and not inkjet printers, where the limiting factor is the diameter of the printhead nozzle opening. For inkjet printing only nanosized particles are possible in the inks in order to avoid nozzle clogging in continuously operational mode [37]. Nanosuspensions have been used and there can be several advantages from using these in processing and manufacturing poorly soluble drugs. The printing of nanosuspensions also offers potential for increasing the stability of the formulations and obviously the dissolution rate of the API [37]. Furthermore, when the drug is deposited as a suspension containing nanocrystals, changes in solid state properties and challenges with recrystallization can be overcome.

Multilayer printing can be used to achieve a higher amount of drug per area in the printed systems. The formulation can be deposited onto the substrate surface layer by layer and this allows easy dose adjustment by controlling the number of the layers [1, 2, 6]. A challenge is that potential smearing of the printed drug arises upon repeated passing under the print head due to shear forces between the substrate and print head, but this highly depends on the technical setup and can be easily avoided. Smearing can also be prevented by the use of highly absorptive substrates, which means that the ink is then incorporated within a porous structure and thus protected.

16.5 Process Control and Process Analytical Technology for Continuous Printing Applications

There has been a growing interest in studying the fabrication of flexible pharmaceutical dosage forms in the past few years. The promising advancements in printing technologies support dose personalization development in this field and can contribute to attractive options for continuous manufacturing. Reliable and robust methods for the quality control of created formulations are needed if printing becomes a viable option in point of care

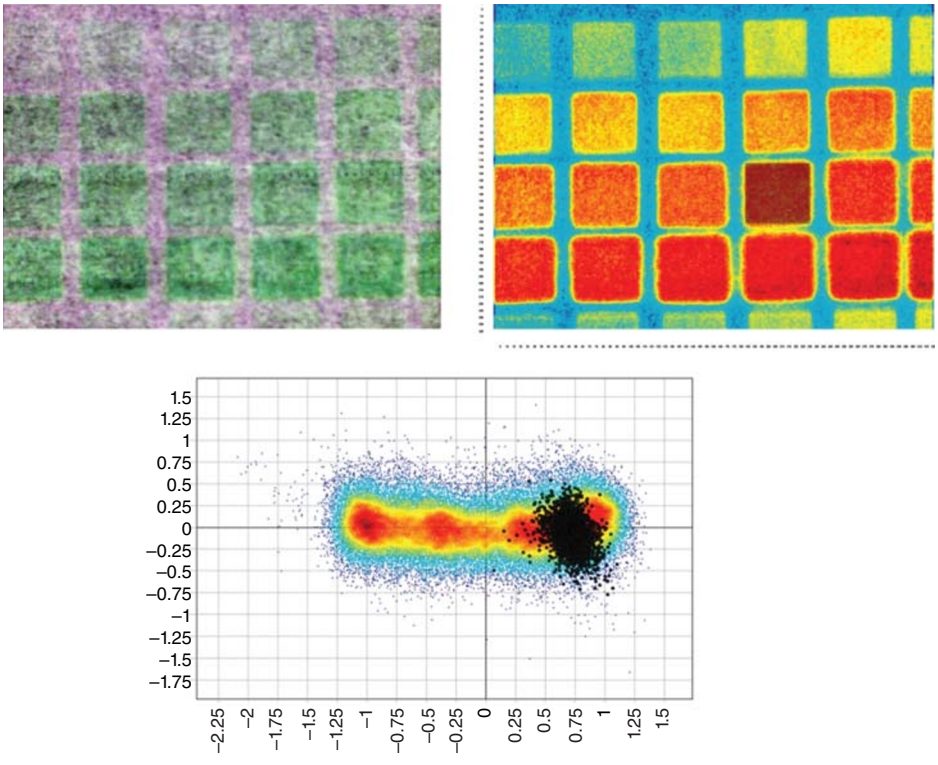

Figure 16.5 *A theophylline formulation printed on the paper substrate. Upper Left: Pseudo colored image of the original set of samples (concentration of the drug is increasing in each printed area from left to right). Upper Right: PCA contour 2D plot of the original image with a marked square of selected pixels of interest. Lower: 2D score plot showing clustering of similar pixels, contribution of each PC and the corresponding data swarm of the chosen area of interest.*

applications. As for other continuous manufacturing (CM) techniques, process control is an essential element in the implementation of printing technologies in CM. As Chapter 2 is devoted exclusively to process control in the pharmaceutical industry we will not discuss many details here as the principles are the same. Different spectroscopic techniques offer various possibilities in process monitoring and are covered in other chapters in this book. One example of a process analytical tool for printing that has shown promise is near infrared hyperspectral imaging. Vakili *et al*. [54] showed how this technique can be implemented in data visualization and on-line content uniformity measurement of inkjet printed samples. An illustration of this is shown in Figure 16.5. Optimally this kind of system can be integrated into printers and continuous printing lines, providing quality control, feed-back, and feed-forward solutions.

16.6 From Laboratory-scale Printing Towards an Industrial Scale

Most application examples in this chapter deal with desktop flexography and research-scale inkjet models that are available for drug delivery system prototype fabrication for accurate

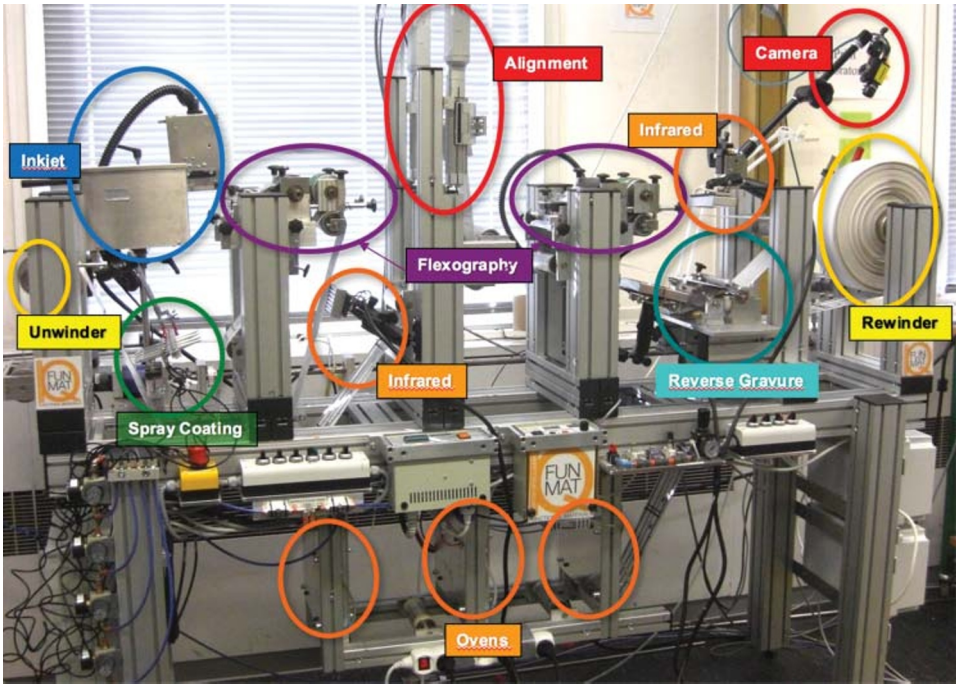

Figure 16.6 *The functional materials (FunMat) printer at Åbo Akademi University. This is used as a laboratory-scale modular prototype printer that can be operated in a continuous manner and can be used sequentially in up to six different printing units (gravure, flexo, coating, ink-jet, lamination).*

dosing, multi-dosing, and material deposition in general. Due to the varying nature of inks and the complexity in the structures to be produced, single printing methods cannot meet all the needs required in fabricating complex multilayer and composite (multi-component) structures. The type of solvent, viscosity, surface tension, and particle size of the material to be printed influence the choice of the most suitable method. Furthermore, the device configuration, alignment accuracy, and minimum feature size need to be considered when choosing the printing technique. This means that activities are needed to formulate the optimal inks and to select the best for purpose devices. As an example, at Åbo Akademi University a continuous roll to roll manufacturing technique has been developed for testing and prototyping purposes. The custom-built, modular roll to roll printer (Figure 16.6) can used sequentially in up to six different printing units (gravure, flexo, coating, ink-jet, lamination) combined with online sintering/drying/curing. The printing parameters can be analyzed *in situ* since the web speed can be controlled from 0.1 up to 20 m/min. This modular system serves as an example of a sophisticated continuous manufacturing line employing different printing technologies.

16.7 Three-dimensional Printing/Additive Manufacturing

Three-dimensional (3D) printing means typically the direct, layer by layer fabrication of any given part from digital information based on computer-aided design (CAD) without any

part-specific tooling [55]. A variety of 3D printing technologies have evolved over the past few decades that have shaped the idea of the direct printing of parts for several applications. 3D printing or additive manufacturing (AM) is defined as the activity to make 3D objects. In 3D printing successive layers of material are placed on top of each other and the pieces that are generated can be of practically any size, shape, or geometry. Various AM technologies have been used and exist, including sintering, melting, stereolithography, fused deposition modeling (FDM), or fused filament fabrication (FFF). Similarly, the inkjet technologies discussed previously in this chapter can be regarded as 3D technologies, in that 3D objects are formed by multiple layering of the ink and this is very often the case. In this section we basically only focus on FFF and FDM.

The introduction of 3D printing technology as a new manufacturing process has been called the new industrial revolution or the third industrial revolution. While the first and second industrial revolutions were grounded on the ability to manufacture more products faster and with reduced costs, the advent of the third industrial revolution conveys a new dimension with new technologies, manufacturing processes, materials, and mass customisation concepts. 3D printing (also termed AM, rapid prototyping, solid freeform fabrication, and digital fabrication) is expected to transform logistics chains, including the warehousing of spare parts and the location of production sites, because production can be accomplished based on any need, any place, for any item.

The 3D printing technology has been paralleled with mass customization processes and production techniques similar to injection moulding. A common feature between 3D printing and mass customization is that custom products can be economically built in small quantities, but the process and the logistic requirements are simpler in the 3D printing scenarios. In comparison with injection moulding, 3D printing can be a more cost-effective and faster technique, when the production quantities are small [55]. Table 16.1 presents the characteristic features of 3D manufacturing.

16.7.1 From Prototyping to Large-scale Manufacturing

3D printing technology has been applied for small production volumes, typically prototyping, customization, or when a product has a complex design, which can be difficult to manufacture with traditional techniques [55]. In current media (magazines and webpages) there are numerous reports of applications using different 3D printing techniques in various fields and a coverage of improvements in technology. For example on the 3D Printing Industry's website, which is a global media company, there are reports of 3D printed fashion items, for example, clothes, shoes, eyewear, and jewellery, applications in aerospace, transport, agriculture, art, and sculpture [56]. Moreover, reports of several 3D printing house projects exist. Researchers at the University of Southern California worked with scaling up the 3D house printing with a technique called contour crafting. Their purpose was to develop an enormous 3D printer which is capable of building a one-piece house. In chemistry a 3D printing technique has been studied and reported by Symes *et al*. [57], a chemical reaction was initiated by printing the reagents directly as the reaction ware was printed. Recent advances in the field have contributed to many variations of these FFF systems and different types of solutions. Numerous internet-based web sites exist which give a lot of update information on the developments, for example,

Table 16.1 *Characteristics of 3D manufacturing (modified from Berman [55])*

Advantages of 3D Printing in Comparison to Other Technologies

- Can economically build custom products in small quantities as if mass production were used.
  Sources of cost effectiveness include:
  - No need for costly tools, moulds, or punches
  - No scrap, milling, or sanding requirements
  - Automated manufacturing
  - Use of readily available supplies
  - Ability to recycle waste material
  - Minimal inventory risk as there is no unsold finished goods inventory
  - Improved working capital management as goods are paid for before being manufactured
- Ability to easily share designs and outsource manufacturing
- Speed and ease of designing and modifying products

Current Limitations of 3D Printing

- Higher costs for large production runs relative to injection moulding and other technologies
- Reduced choice for materials, colors, and surface finishes
- Lower precision relative to other technologies
- Limited strength, resistance to heat and moisture, and color stability

the website https://the3d.com/how-it-works/3d-printing-process gives a good overview of the different techniques and applications in areas not presented in this chapter.

16.7.2 Fused Deposition Modeling or Fused Filament Fabrication

The FDM process invented by Stratasys, is an extrusion-based process. Since the patent has expired for this process, several similar extrusion-based constructions have entered the market, called FFF [58]. Therefore, numerous extrusion-based printers are on the market that use the FDM or FFF principle [58] and the number is increasing rapidly. The main components in these printers are usually: (i) material feedstock supply, (ii) material loading system, (iii) liquefier, (iv) print head, and (v) building plate. The printers that exist may consist of single extruder or multi-extruder setups. 3D printing with FDM techniques is a interplay of several process variables and these are summarized in the literature by Agarwala *et al*. [59].

The FFF/FDM 3D printing process starts by loading the filament through a heating block. The melted polymer is then extruded through a nozzle and bonded to previous layers as it solidifies. When a layer is complete, the build plate is lowered and the process is repeated [58]. An illustration of the process is presented in Figure 16.7. The FDM process uses material for two different purposes: (i) to build the object and (ii) to support overhangs in the model. The printers can consist of a single extruder system or multi-extruder systems. Printing with the FDM technique is a complex interplay of many process variables, which are summarized by Agarwala *et al*. [59] and in Table 16.2.

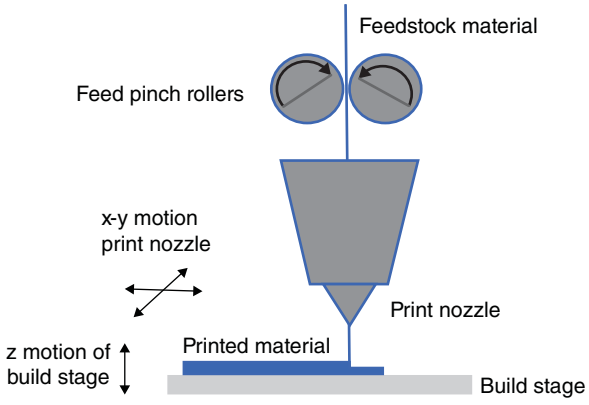

Figure 16.7 *Diagram of a typical FDM/FFF extruder (modified from [58]).*

Table 16.2 *FDM, FDMet, and FDC process variables (modified from Agarwala* et al. *[59])*

Operation-specific	Machine-specific	Materials-specific	Geometry-specific
Slice thickness		Polymer characteristics	
Road width	Nozzle diameter	Viscosity	
Head speed	Filament load rate	Stiffness (column strength)	Fill vector length
Extrusion temperature	Roller speed	Flexibility	Support structure
Envelope temperature	Flow rate	Thermal conductivity	
Fill pattern	Filament diameter		

16.7.3 Feedstock Material for FDM Printing

With the advances of FFF printing almost any type of material can be extruded and shaped using single or multiple nozzle printers. The initial feedstock material for a FDM process was commonly acrylonitrile butadiene styrene (ABS). Later, other materials were introduced involving polycarbonate (PC), polyetherimide (PEI), polyphenylsulfone (PPSF), polyamides (Nylon), polylactic acid (PLA), high-impact polystyrene (HIPS), high-density polyethylene (HDPE), and polycaprolactone (PCL). These original feedstock materials used in FFF additive manufacturing processes are pure polymers, but printing has also been performed by using polymers with incorporated metallic or ceramic particles [59, 68]. The variety and flexibility of the use of different materials has changed lately, paving the way to versatile possibilities and solutions in drug manufacture.

The drawbacks of the FDM process are limitations caused by the use of filaments. The material for the FDM technique has to be in form of a filament with a diameter of 1.75–3.0 mm. The raw polymers are usually in a form of a powder or pellets. In order to 3D print, the polymers have to be modified into the form of filaments by a hot melt extrusion (HME) technique. This leads to an additional step in the manufacturing process of 3D structures.

The properties of the rollers of the feeding system and the liquefier are optimized for each material. Therefore, the possibility of using materials other than the original feedstock for

the printer is limited. The roller's size and surface play an important role in the process of filament loading. They have to create enough friction to load the material into the liquefier [59]. The filament loading system is sensitive to variations in filament diameter. The use of a filament with a size outside the specified limits can affect the quality of the printed part, or even cause a complete stop of the extrusion process. Therefore, new variants of the 3D printing FDM process are being studied and developed.

One variant of the FDM process is called stick deposition moulding (SDM) and is utilized by a printer called "fabbster," manufactured by Sintermask GmbH. The feedstock is in the form of a 3×3 mm toothed stick, instead of a round filament, which decreases the problems of slipping and uneven flow during loading and printing [60].

Bellini *et al*. [61] developed a system called mini extruder deposition (MED) with a mini-extruder mounted on a high-precision positioning system for the extrusion of blends of polymers and ceramics. The mini-extruder uses granulated material as the feedstock. A research group at Drexel University developed a variant called precision extruding deposition (PED) for the manufacture of PCL/HA scaffolds [62]. With the pressure of rotating screws the material is forced down the chamber and extruded through the nozzle. Khaled *et al*. [63] used an extrusion printer to manufacture tablets from a drug-loaded paste, which was loaded into a syringe. Recently, Sculptify organized a kick-starter campaign to raise money for the manufacture of the first commercially available melt extrusion printer, which uses pellets as feedstock instead of filaments [64]. The printing technique is called fused layer extrusion (FLEX). The new techniques have their limitations and problems, many of them the same as in the original FDM process, except for the filament-specific ones. Bellini *et al*. [61] reported that the size of the granulated material, and variations of it, had a strong influence on the melt flow. Even in the new techniques the liquefier length and nozzle angle has to be optimized for each material.

The use of polymer pellets as a feedstock material has been already utilized in a printer where the layers are built up from small droplets instead of rods as in the case of the FDM technique. This technique is commercially available by Arburg GmbH. In this technique the pellets are melted and subsequently printed with a stationary nozzle by using piezo technology. When the filament acts as a piston to extrude the melt in the FDM technique, this printer utilizes piezo technology in the printing. This type of technology may decrease some of the limitations that the filament and liquefier properties entail, such as inappropriate column strength and melt flow behavior of the polymer. The building component can move along five axes, offering the ability to print more complex geometries. There is no original feedstock material for this printer, the manufacturer states that all the plastics used in injection moulding can be used in this printer. However, the limitations induced by the piezoelectric technique have to be taken into account by selecting the feedstock material.

Overall, developments in this field are rapidly taking place and alternative technologies are entering the market, providing flexibility in different materials, material feeding, use of multiple materials, and multi-nozzle systems.

16.7.4 3D Printing Techniques used in the Biomedical and Pharmaceutical Area

Several 3D printing techniques were presented after the first commercial system, stereolithography, was introduced in 1988 by 3D Systems Inc. The 3D printing techniques

[or solid freeform fabrication (SFF) technologies as they also are named] all have common features:

1. They create an object from a 3D model, obtained from CAD, computerized tomography, or magnetic resonance imaging scan data.
2. The model is transferred to the printer software as a file and is then printed in a layer by layer manner.

In this section, the focus is on the FDM/FFF technique. The use of other techniques in pharmaceutical and biomedical applications will only be briefly mentioned. Besides of the presented techniques, there are other 3D printing techniques used in different applications reported in the literature. In the biomedical area several researchers has used FDM in the manufacture of scaffolds with different porosities [65]. Goyanes *et al*. [69] used the FDM technique in the fabrication of tablets from a drug-loaded filament. The filament was loaded with the model drug by swelling the polymer in a liquid containing the drug. Medical devices with anti-biofilm properties was fabricated with the FDM technique by Sandler *et al*. [70] from drug-loaded filaments manufactured by HME. Biocompatible materials that have been used in this technique are PLA, polymethylmethacrylate, the original FDM feedstock material PCL [65, 66], and ethylvinyl acetate (EVA). PCL and EVA were demonstrated in the fabrication of T-frame intra-uterine devices (IUSs) [66, 67].

The 3D printing field is an emerging field and many new 3D technologies have entered and are entering the market. There is no doubt these developments will bring more versatile and suitable solutions for the 3D printing of pharmaceuticals and medical devices and also pave the way for new types of manufacturing scenarios for the pharmaceutical sector.

References

[1] Meléndez, P.A., Kane, K.M., Ashvar, C.S., Albrecht, M., Smith, P.A. (2008) Thermal inkjet application in the preparation of oral dosage forms: Dispensing of prednisolone solutions and polymorphic characterization by solid-state spectroscopic techniques. *J. Pharm. Sci.*, **97**(7):2619–2636.

[2] Buanz AB, Saunders MH, Basit AW, Gaisford S. (2011) Preparation of personalized dose salbutamol sulphate oral films with thermal ink-jet printing. *Pharm. Res.* **28**(10):2386–2392

[3] Sandler N., Määttänen A, Ihalainen P, Kronberg L, Meierjohann A, Viitala T, Peltonen J. (2011) Inkjet printing of drug substances and use of porous substrates – Towards individualized dosing. *J. Pharm. Sci.*, **100**(8):3386–3395

[4] Genina, N., Janssen, E.M., Breitenbach, A., Breitkreutz, J., Sandler, N. (2013a) Evaluation of different substrates for inkjet printing of rasagiline mesylate. *Eur. J. Pharm. Biopharm.* **85**(3):1075–1083.

[5] Janssen, E.M., Schliephacke, R., Breitenbach, A., Breitkreutz, J. (2013) Drug-printing byflexographic printing technology – a new manufacturing process for orodispersible films. *Int. J. Pharm.* **441**:818–825.

[6] Raijada D, Genina N, Fors D, et al. (2013) A step toward development of printable dosage forms for poorly soluble drugs. *J. Pharm. Sci.* **102**(10):3694–704

[7] Genina N., Fors D., Palo M., Peltonen J., Sandler N. (2013b) Behavior of printable formulations of loperamide and caffeine on different substrates – Effect of print density in inkjet printing. *Int. J. Pharm.* **453**(2):488–497.

[8] Palo, M., Kolakovic, R., Laaksonen, T., Määttänen, A., Genina, N Salonen, J. Peltonen, J., Sandler, N. (2015) Fabrication of drug-loaded edible carrier substrates from nanosuspensions by flexographic printing. *Int. J. Pharm.* **72**(5):340–347
[9] Preis M, Breitkreutz J, Sandler N. Perspective (2015) Concepts of printing technologies for oral film formulations. *Int. J. Pharm.* **72**(5):348–354
[10] Ihalainen P, Määttänen A, Sandler N. (2015) Printing technologies for biomolecule and cell-based applications. *Int. J. Pharm.* **72**(5):355–359.
[11] Hoath, S.D., Hutchings, I.M., Martin, G.D., Tuladhar, T.R., Mackley, M.R., Vadillo, D. (2009) Links between ink rheology, drop-on-demand jet formation, and printability. *J. Imaging Sci. Technol.* **53**(4), 041208.
[12] R. G. Sweet (1965) High frequency recording with electrostatically deflected ink-jets, *Rev. Sci. Instrum.* **36**, 131.
[13] Hue P. L. (1998) Progress and trends in ink-jet printing technology, *J. Imaging Sci. Technol.* **42**:49–62.
[14] Cameron, N.L. (2006) Ink-jet printing, in *Coatings Technology Handbook*, 3rd edn (ed. A.A. Tracon), CRC Press, Boca Raton, pp. 25/1–25/4.
[15] Hutchings, I.M., Martin G.D. (2012) *Inkjet Technology for Digital Fabrication*, 1st edn, John Wiley & Sons, Ltd, Chichester.
[16] Rayleigh F. (1878) On the instability of jets, *Proc. Lond. Math. Soc.* **10**(4):4–13.
[17] Dijksmanm J.F. (1984) Hydrodynamics of small tubular pumps, *J. Fluid Mech.*, **193**:173–191.
[18] Wijshoff, H. (2011) The dynamics of the piezo inkjet printhead operation, *Phys. Rep.* **491**:77–177.
[19] Stokes, G. (1851) On the effect of the internal friction of fluids on the motion of pendulums. *Trans. Camb. Phil. Soc.* **9**:8–106.
[20] Ohnesorge, W. (1936) Formation of drops by nozzles and the breakup of liquid jets. *J. Appl. Math. Mech.* **16**:355–358.
[21] Fromm. J.E. (1984) Numerical calculations of the fluid dynamics of drop-on-demand jets, *IBM J. Res. Dev.* **28**(3):322–333.
[22] Jang, D., Kim, D., Moon, J. (2009) Influence of fluid physical properties on ink-jet printability. *Langmuir* **25**(5):2629–2635.
[23] Dijksman, J.F. Duineveld, P.C. Hack, M.J.J. et al. (2007) Precision ink jet printing of polymer light emitting displays. *J. Mat. Chem.* **17**(6):511–522.
[24] Mckinley, G.R., Renardy, M. (2011) Wolfgang von Ohnesorge, *Phys. Fluids*, **23**, 127101.
[25] Derby, B. (2010) Inkjet printing of functional and structural materials: fluid property, requirements, feature stability, and resolution. *Annu. Rev. Mat. Res.* **40**:395–414.
[26] Clanet, C., Beguin, C., Richard, D, Quere, D. (2004) Maximal deformation of an impacting drop. *J. Fluid Mech.* **517**:199–208.
[27] Stringer J., Derby B. (2009) Limits to feature size and resolution in inkjet printing. *J. Eur. Cer. Soc.* **29**(5):913–918.
[28] Stückrad, B. Hiler, W.J., Kowalewski, T.A. (1993) Measurement of dynamic surface tension by oscillating droplet method. *Exp Fluids*, **15**:332–340.
[29] Grigorieva, O.V., Kovalchuk, N.M., Grigoriev, D.O., Vollhardt, D. (2004) Spontaneous non-linear surface tension oscillations in presence of a spread surfactant monolayer at the air/water interface. *Colloids Surf. A: Physicochem. Eng. Asp.* **250**:141–151.
[30] Grigorieva, O.V., Grigoriev, D.O., Kovalchuk, N.M., Vollhardt, D. (2005) Auto-oscillation of surface tension: heptanol in water and water/ethanol systems. *Colloids Surf. A: Physicochem. Eng. Asp.* **256**:61–68.
[31] Lamb, H. (1994) *Hydrodynamics*, 6th edn, Cambridge University Press, Cambridge.
[32] Ferguson, J., Hudson, N.E., Warren, B.C.H., Tomatarian, A. (1987) Phase changes during elongational flow of polymer solutions. *Nature* **325**:234–236.

[33] Odell, J.A., Muller, A.J., Narh, K.A., Keller, A. (1990) Degradation of polymer solutions in extensional flows. *Macromolecules* **23**:3092–3103.
[34] Ihalainen P, Määttänen A, and Sandler N. (2015) Printing technologies for biomolecule and cell-based applications. *Intl J. Pharm.* **494**(2), 585–592
[35] Tarcha P.J., Verlee D., Hui H..W., et al. (2007) The application of ink-jet technology for the coating and loading of drug-eluting stents. *Ann. Biomed. Eng.* **35**(10):1791–1799.
[36] Scoutaris, N., Alexander, M.R., Gellert, P.R., Roberts, C.J. (2011) Inkjet printing as a novel medicine formulation technique. *J. Cont. Rel.* **156**(2):179–185.
[37] Pardeike J., Strohmeier D.M., Schrodl N., et al. (2011) Nanosuspensions as advancedprinting ink for accurate dosing of poorly soluble drugs in personalized medicines. *Int. J. Pharm.* **420**(1):93–100.
[38] Lee, B.K., Yun, Y.H., Choi, J.S., Choi, Y.C., Kim, J.D., Cho, Y.W. (2012) Fabrication of drug-loaded polymer microparticles with arbitrary geometries using a piezoelectric inkjet printing system. *Int. J. Pharm.* **427**(2):305–310
[39] Yeo, Y., Park, K. (2004) A new microencapsulation method using an ultrasonic atomizer based on interfacial solvent exchange, *J. Cont. Rel.* **100**:379–388
[40] Adams, J.M., Faux D.D., Rieber, J.J. (1996) *Printing Technology*, 4th edn, Delmar Publisher, Albany.
[41] Kipphan H. (2001) *Handbook of Print Media*. Springer, Heidelberg.
[42] Cusdin, G. (1999) *Flexography: Principles and Practices*, vol. **1**, 5th edn. Foundation of Flexograpic Technical Association, Ronkonkoma, pp. 1–35.
[43] Chalmers, I.R. (1997) Flexographic printability of packaging grade papers, *Appita J.* **1997** 335–341.
[44] Thompson, R.C. (2001) The effect of new inks and coatings on print quality, *Surf. Coat. Int.* **2001**:24–28.
[45] Leach, R.H. and Pierce, R.J. (1993) *The Printing Ink Manual*, 5th edn, Blueprint, London.
[46] Bisset, D.E., Goodacre, C., Idle, A., Leach, R.H. and Williams, C.H. (1979) *The Printing Ink Manual*, Northwood Books, London.
[47] Janssen, E.M., Schliephacke, R., Breitenbach, A., Breitkreutz, J. (2013) Drug-printing byflexographic printing technology – a new manufacturing process for orodispersible films. *Int. J. Pharm.* **441**:818–825.
[48] Genina, N., Fors, D., Vakili, H., Ihalainen, P., Pohjala, L., Ehlers, H., Kassamakov, I., Haeggström, E., Vuorela, P., Peltonen, J., Sandler, N. (2012) Tailoring controlled-releaseoral dosage forms by combining inkjet and flexographic printing techniques. *Eur. J. Pharm. Sci.* **47**:615–623.
[49] Tobjörk, D., Österbacka, R. (2011) Paper electronics. *Adv. Mater.* **23**:1935–1961.
[50] Juvonen, H., Määttänen, A., Laurén, P., Ihalainen, P., Urtti, A., Yliperttula, M., Peltonen,J. (2013) Biocompatibility of printed paper-based arrays for 2-D cell cultures. *Acta Biomater.* **9**:6704–6710.
[51] Olkkonen, J., Lehtinen, K., Erho, T. (2010) Flexographically printed fluidic structures in paper. *Anal. Chem.* **82**:10246–10250.
[52] Phillips, C.O., Govindarajan, S., Hamblyn, S.M., Conlan, R.S., Gethin, D.T., Claypole, T.C. (2012) Patterning of antibodies using flexographic printing. *Langmuir ACS J. Surf. Colloids* **28**:9878–9884.
[53] Scoutaris, N., Hook, A. L., Gellert, P. R., Roberts, C. J., Alexander, M. R., & Scurr, D. J. (2012) ToF-SIMS analysis of chemical heterogenities in inkjet micro-array printed drug/polymer formulations. *J. Mat. Sci.: Mat. Med.* **23**(2):385–391.
[54] Vakili, H., Kolakovic, R., Genina, N., Marmion, M., Salo, H., Ihalainen, P., Peltonen, J. Sandler, N. (2014) Hyperspectral imaging in quality control of inkjet printed personalised dosage forms. *Int. J. Pharm.* **10**:483(1/2):244–249.
[55] Berman, B. (2012) 3-D printing: The new industrial revolution. *Bus. Horizons* **55**:155–162.

[56] 3D Printing Industry (2014) *Home Website*. Available at: https://the3d.com/how-it-works/3d-printing-process (accessed 12 January 2016).
[57] Symes M D, Kitson P J, Yan J, Richmond C J, Cooper G J T, Bowman R W, Vilbrandt T and Croni L. (2012) Integrated 3D-printed reactionware for chemical synthesis and analysis. *Nat. Chem.* **4**:349–354.
[58] Turner, B.N., Strong, R., Gold, S.A. (2014) A review of melt extrusion additive manufacturing processes: I. Process design and modeling. *Rapid Prototyp. J.* **20**, 192–204.
[59] Agarwala, M., Jamalabad, V., Langrana, N., Safari, A., Whalen, P. and Danforth, S. (1996) Structural quality of parts processed by fused deposition *Rapid Prototyping J.* **2**:4–19
[60] Creative Tools (2014) *CT Website*. Available at: http://www.creativetools.se/3d-skrivare-info (accessed on December 16, 2014).
[61] Bellini, A., Shor, L., Güceri, S. (2005) New developments in fused deposition modeling of ceramics. *Rapid Prototyping J.* **11**:214–220.
[62] Shor, L., Gordon, J., An, Y., Guceri, S., Sun, W. (2009) Precision extruding deposition of polycaprolactone and composite polycaprolactone/hydroxyapatite scaffolds for tissue engineering. *Journal of Manufacturing Science and Engineering*, **130**(2), 73–74.
[63] Khaled, S.A., Burley, J.C., Alexander, M.R., Roberts, C.J. (2014) Desktop 3D printing of controlled release pharmaceutical bilayer tablets. *Int. J. Pharm.* **461**:105–111.
[64] Sculptify, D. (2014) *The Next Step in 3D Printing*. Available at: http://sculptify.com/ (accessed December 16, 2014).
[65] Hutmacher, D.W., Schantz, J.T., Lam, C.X.F., Tan, K.C., Lim, T.C. (2007) State of the art and future directions of scaffold-based bone engineering from a biomaterials perspective. *J. Tissue Eng. Regen.* **1**:245–260.
[66] Holländer J, Genina N, Jukarainen H, Khajeheian M., Rosling A.; Mäkilä E, Sandler N. (2016) 3D printed PCL-based implantable prototypes of medical devices for controlled drug delivery. *J Pharm Sci*. doi: 10.1016/j.xphs.2015.12.012.
[67] Genina N, Holländer J, Jukarainen H, Mäkilä E, Salonen J, Sandler N. (2015) Ethylene vinyl acetate (EVA) as a new drug carrier for 3D printed medical drug delivery devices *Eur J Pharm Sci.* doi: 10.1016/j.ejps.
[68] Venkataraman, N., S. Rangarajan, M.J. Matthewson, B. Harper, A. Safari, S.C. Danforth, G. Wu, N. Langrana, S. Guceri, A. Yardimci, (2000) Feedstock material property – process relationships in fused deposition of ceramics (FDC), *Rapid Prototyp. J.* **6**(4):244–253.
[69] Goyanes, A., Buanz. A.B.M., Basit, A.W., Gaisford, S. (2014) Fused-filament 3D printing (3DP) for fabrication of tablets. *Int. J. Pharm.* **476**, 88–92.
[70] Sandler N, Salmela I, Fallarero A, Rosling A, Khajeheian M, Kolakovic R, Genina N, Nyman J and Vuorela P. (2014) Towards fabrication of 3D printed medical devices to prevent biofilm formation. *Int. J. Pharm.* **459**:62–64.

17

Development of Liquid Dispensing Technology for the Manufacture of Low Dose Drug Products

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17.1 Introduction

Oral dosing of drug products remains the preferred route of administration for patients, even for low dose drugs. There were over 4000 low dose (<5 mg) products on the market in the United States in 2014 [1]. Of these, about 60% were oral products and about 50% were standard tablets designed to be swallowed.

In a book on the subject of *Formulation and Analytical Development for Low-Dose Oral Drug Products* [2], Jack Zheng lists the main challenges in developing low dose drugs as follows:

- Low potency (i.e. drug content below specification) due to manufacturing loss,
- Difficulty achieving content uniformity due to low drug concentration,
- Instability due to the huge ratio of excipients to drug substance (which increases the likelihood of incompatibility),
- Chemical instability due to a micronized drug having greater surface exposure to excipients, moisture and manufacturing equipment,.

Continuous Manufacturing of Pharmaceuticals, First Edition.
Edited by Peter Kleinebudde, Johannes Khinast, and Jukka Rantanen.
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- Instability due to physical transformation to a less stable solid form (i.e. polymorphic form) during manufacture or long-term storage.

The two major concerns are low potency and non-uniformity of the drug product. Zheng [2] claims that low potency due to active pharmaceutical ingredient (API) manufacturing loss is the most common issue. It is related to the physical properties of the API and the powder handling processes commonly utilised in conventional manufacturing unit operations, for example blending, roller compaction, wet granulation and tablet compression. Possible causes are API adherence to the surfaces of manufacturing equipment (steel, plastic tubing, filter socks etc.) and elutriation segregation of API from excipients. Non-uniformity is often attributed to the inability to blend the API and excipients effectively, affording variable drug product content and possibly outliers [2].

Conventional low dose tablet manufacturing processes typically involve dry blending of micronized API with bulking excipients (i.e. levothyroxine tablets) or granulation with an API solution in a high-shear wet granulation process. Both of these processes rely upon homogeneously blending a small quantity of API (i.e. 25 μg) into a large amount of bulking agents to achieve a tablet weight that can be processed by the tablet press (>100 mg). Achieving an acceptable content uniformity and dose accuracy with conventional processes can be difficult if not formulated effectively. The pharmaceutical industry and regulators have struggled for years with content uniformity and dose accuracy for levothyroxine, one of the most successful and commonly used products in history. The MHRA [3] prepared a white paper discussing the challenges with levothyroxine products over the years.

GSK staff decided to adapt the fluid dispensing technology used to deposit adhesives and solder onto circuit boards and other substrates, and called it liquid dispensing technology (LDT). LDT is a novel, continuous tablet manufacturing process that accurately deposits the full API dose, in liquid form, onto a conventional tablet. In this way the API is located directly on the tablet surface and not distributed throughout the tablet matrix. Advanced process analytical technologies (PAT) measure the amount of API deposited on every individual tablet manufactured, creating a new quality paradigm that facilitates true real time verification of API content per tablet.

Figure 17.1 shows a schematic of the developed LDT process.

LDT doses the API in the form of a homogeneous solution directly onto the surface of the carrier tablet; there are no blending steps to achieve the desired content uniformity. As demonstrated above, as long as the dosing volume is within the 4 μL to 25 μL dosing range, the content uniformity is driven by the accuracy of the dispensing process. The delivered dose, whether 1 μg or 1000 μg, is irrelevant; the content uniformity is not driven by the API content, as in conventional processes, but is achieved by the dispenser accuracy to deliver the target volume.

17.2 Background

In 2003, GlaxoSmithKline (GSK) had a number of highly-potent compounds in pre-clinical and early-stage development (Phase I) that had oral doses in single or tens of micrograms. GSK employs a five-band occupational health category (OHC) ranking system where OHC5 has the highest health hazard potential and requires appropriate controls to limit occupational exposure. In the case of OHC5, the occupational exposure limit (OEL) is

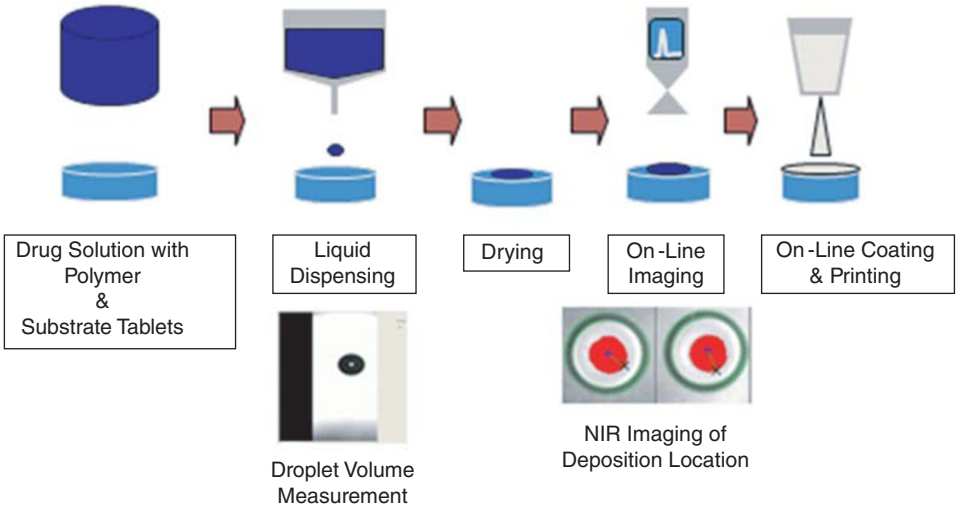


Figure 17.1 *Overview of the LDT process for the manufacture of low-dose and potent API.*

$\leq 1\ \mu g/m^3$ on an 8-h time weighted average (TWA). Due to their high potency, all of these compounds are OHC5.

At this time, GSK research and development (R+D) had one pilot scale manufacturing suite for the conventional processing of high-potency tablets with a maximum scale of 5 kg, sufficient only for Phase I clinical trials manufacturing (CTM). The pilot scale equipment had limited engineering controls and operators were required to perform all operations while wearing powered air purifying respirators (PAPR) and full-body containment suits. For some compounds, early clinical results were positive and planning for Phase II CTM had begun. GSK assessed building a new facility for Phase II CTM, utilizing conventional tablet manufacturing with high-containment capabilities, sufficient for OHC5 compounds. The cost of a new facility was in the tens of millions of pounds and had a lead time of at least two years. When contract manufacturing organizations (CMOs) were assessed, development and commercialization costs were high. With a deep portfolio of high-potency products, development of an in-house mid to late stage CTM to commercial launch manufacturing capability was deemed the most desirable alternative.

GSK R+D had a Strategic Technologies Group whose mission was to develop alternative drug delivery approaches and novel manufacturing technologies required to produce these drug products. A small team was formed to evaluate alternatives to conventional high-potency tablet manufacturing. Coincidental to this team forming, two regulatory initiatives had begun: in September 2004 the FDA published *Pharmaceutical GMPs for the 21st Century – A Risk-Based Approach* [4] and the FDA had begun assessing the need to process potent compounds in dedicated or segregated facilities, similar to the approach used for penicillin manufacture [5].

The FDA's twenty-first century initiative challenged the pharmaceutical industry to consider science-based approaches to improve manufacturing processes, to increase product quality (quality by design; QbD), to utilize modern process measuring technologies (PAT),

and importantly, to adopt a risk-based approach toward innovation in the pharmaceutical industry as opposed to the fixed recipe and fixed process parameters previously adopted [4]. When advances in pharmaceutical manufacturing technologies over, say 50 years, are compared against other industries (e.g. aviation, automotive, telecommunications, computers), the pharmaceutical industry had not had a step change in quality and performance similar to that experienced in other industries.

There are at least two other technologies that use liquid deposition to produce pharmaceutical products that are unrelated to LDT. The first is 3D printing [6] and the second is ink jet printing [7]. In 3D printing, a liquid formulation of API-polymeric binder is deposited onto a loose powder bed in many passes to build up into a 3D tablet where the API is distributed throughout the tablet matrix. In ink jet printing, printheads have been adapted from the photocopier industry to jet API containing fluids instead of ink. While there are several printhead designs (piezoelectric, acoustical, thermal) they generally involve generating many pico- to nanoliter droplets to build up a sufficient volume to produce a drug dose, often on an edible film.

GSK's LDT differs from 3D printing and ink jet technologies in two significant ways: (i) the drug dose is contained in a single deposited droplet 4–25 μL in volume, (ii) an imaging system measures the droplet volume and determines if the volume of each droplet is within process limits.

17.3 Goals for the LDT Program

Several conventional high-potency manufacturing approaches were evaluated but they were all dependent upon high-containment enclosures and had high-facility costs to build and maintain. Large volumes of waste water from the equipment cleaning processes required on- or off-site treatment, often by incineration. While wet-granulation approaches utilizing API addition as a solution or slurry can reduce exposure to API dust for that process, granulation often requires transfer to fluid-bed driers, followed by milling and then external blending prior to tablet compression or capsule filling. All of these processes require expensive high-containment equipment and/or personal protective equipment (PPE) to prevent exposure. Importantly, the use of conventional manufacturing approaches was still not amenable to the aspirations of the twenty-first century initiative.

Soft-gel manufacturing maintains the API in the liquid form and has been successfully used to manufacture highly potent compounds (e.g. vitamin D analogs). However, GSK did not have soft-gel manufacturing capacity, and having decided not to invest in soft-gel capacity, was required to develop and commercialize products at CMOs.

The team embraced the PAT and QbD tenets of the twenty-first century initiative while also addressing the challenges of manufacturing OHC5 oral dosage forms in a cost-effective process that protects operators and the environment from exposure. While taking a "white board" approach where all options were open for discussion, the team adopted the following program goals:

1. The manufacturing process must be robust and utilize PAT to ensure product quality throughout the process.
2. The process should support respirator-free manufacture of OHC5 compounds but without the expense and complexity of high-containment enclosures.

3. The manufacturing process should preferably be scale-independent from development and Phase I to commercial launch and support commercial volumes for a major oral products.
4. The process should preferably be a continuous manufacturing process in a multi-use facility.
5. The dosage form must have the desired in-vivo performance required to treat patients and have an acceptable shelf life to support commercialization.
6. The process should support Real-Time Release of drug product.

The fundamental premise that the API should be utilized in liquid form was adopted based upon the reduced occupation exposure potential of handling the API in liquid form, eliminating the potential to dust generation. Exposure to API containing dust is the primary source of occupational respiratory exposure in conventional tablet or powder fill capsule manufacture.

In 2012, GSK Barnard Castle was awarded the top prize at the Institute of Chemical Engineers for Health and Safety and highly commended for Energy, Innovative Product, and Water categories for their LDT technology [8].

The body of this chapter will address how GSK attained these goals in the LDT development program and attempted to meet the aspirations of the twenty-first century initiative.

17.4 Overview of LDT

Liquid dispensing technology is a continuous manufacturing process that produces immediate release tablets with a dose range of 1 μg to 5 mg. Tablets are manufactured by dispensing 4–25 μL of a liquid formulation, containing the API, onto the surface of a bi-concave carrier tablet (Figures 17.2 and 17.3).

17.4.1 Formulation Overview

The carrier tablet can be a conventional direct compression tablet with the usual excipients (i.e. microcrystalline cellulose, corn starch or lactose). The carrier tablet is often pre-coated with an aqueous film coat or may be uncoated before being dosed with the dosing solution. The concave feature allows the dosing solution to remain confined to the tablet and prevents

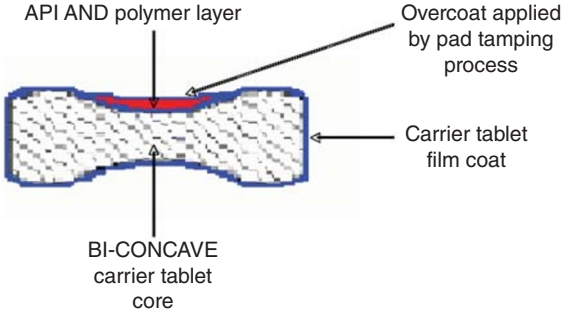


Figure 17.2 *Bi-concave carrier tablet substrate,*

Figure 17.3 *Photograph of an LDT tablet showing the deposited, dry film.*

the dose from running off the tablet and onto the holding fixture or transport element (TE). The bi-concave shape allows the tablet to be automatically placed onto the holding fixture without regard to an up or down orientation.

The dosing solution contains the API, a polymer and any additional excipients dissolved in a solvent (typically an organic solvent like ethanol, methanol or tetrahydrofuran, but others are possible). The dose quantity of the dissolved API is determined by its solubility in the solvent and the desired volume to be deposited. The dose limitation of LDT is often driven by the solubility of the API in the solvent, (i.e. if a 1 mg dose is required and the dosing volume is 10 μL, the required concentration would be 100 mg/mL).

A polymer in the dosing solution serves several purposes:

1. The polymer provides viscosity and surface tension improvements to allow dispensed fluid to form a primary droplet.
2. After the solvent evaporation, the polymer entraps the API into a film that is adherent onto the tablet surface.
3. The polymer film with entrapped API prevents release of API as dust, an important feature for safe handling of tablets after manufacture.

In the case of some compounds, the LDT formulation approached allowed the compound to be used in clinical trials where conventional formulation approaches had failed. Conventional formulations rely upon the homogeneous distribution of the API in tablet excipients. In the case of conventional low dose tablets, a very small amount of API (i.e. 25 μg) is distributed in the larger bulk of the tablet. The API has a very intimate contact with the excipients, and often, there is a greater potential for instability for such low dose compounds. In contrast, using the LDT approach the API is only in contact with the polymer and the tablet surface, minimizing contact with the excipients. Stabilizers, such as antioxidants, can also be added to the dosing solution to provide stabilization while the API is in solution or when the API is in the dried deposition. For several unstable compounds, the LDT approach enabled the compound to enter clinical trials.

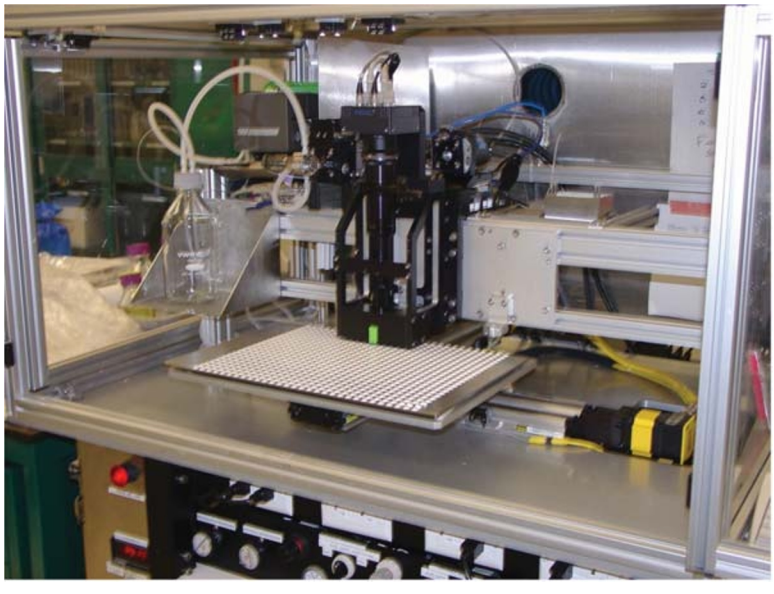


Figure 17.4 *Laboratory LDT machine.*

17.4.2 LDT Platforms

Four LDT machines have been built for specific purposes:

1. Laboratory machine used for formulation and hardware development activities (Figure 17.4).
2. GMP pilot machine used to produce clinical trial supplies at a rate of 20 000 tablets/h. Batch sizes range from a few thousand to 35 000 tablets (Figure 17.5).
3. Commercial scale machine is designed for continuous operation at up to 80 000 tablets/h with an output of about 2 million tablets/day when run continuously (Figure 17.6).
4. Commercial simulator machine was designed to simulate the liquid dispensing, motion and imaging operations of the commercial machine but in a laboratory setting. Formulations and processing parameters can be developed in the laboratory setting facilitating technology transfer of a product to the commercial scale (Figure 17.7).

LDT has been used to produce tablets for clinical trials for several GSK compounds in development up to Phase IIb. To date, a compound using the LDT approach has not progressed into Phase III; clinical development was terminated when some of the compounds failed to show sufficient efficacy in Phase II clinical trials. LDT formulations have been successfully developed for over 15 compounds.

LDT technology was developed entirely within GSK and GSK holds all patent rights to the technology in the United States [9–11], Europe [12, 13] and Japan. All countries with granted or pending patents are searchable under US20060000470 [14].

Figure 17.5 *GMP pilot LDT machine.*

Figure 17.6 *Commercial scale LDT machine.*

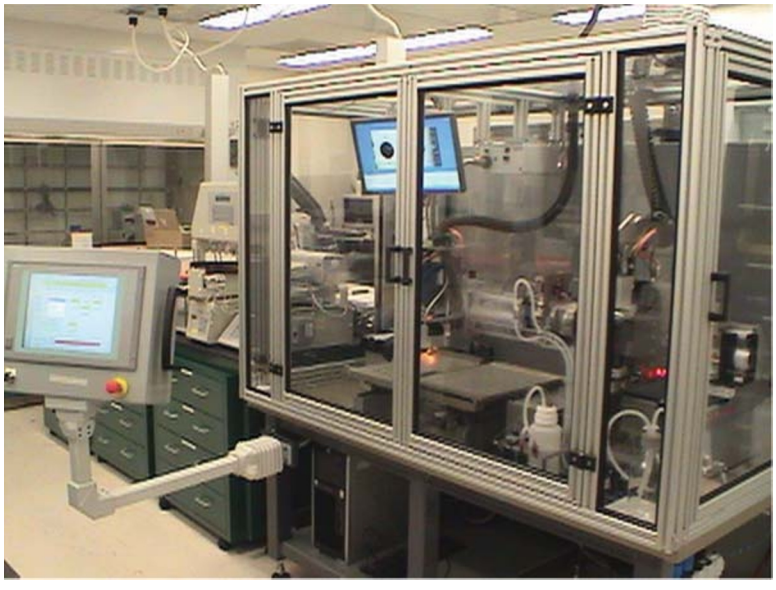


Figure 17.7 *Laboratory simulator of commercial LDT machine.*

17.5 LDT Machine Design Details

17.5.1 Commercial Line Operation

The LTD commercial machine is designed for continuous operation, typically with two operators. Accurate motion systems move TEs in a linear manner through the various processing cells on the machine (Figure 17.8).

An RFID tag on each TE allows the control system to track the progress of the TE through each of the processing cells. At the beginning of the process inert carrier tablets are loaded

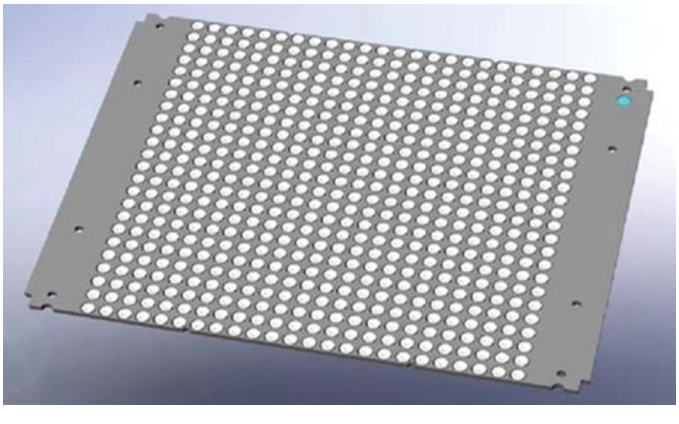


Figure 17.8 *Transport element with RFID tag.*

onto the empty TEs by a tablet feeding system that automatically places tablets in fixed, *x–y* positions on the TEs. As TEs pass through the system, tablet specific process data is collected for every tablet based upon its RFID tag number and *x–y* location, facilitating assignment of the pass–fail status of each tablet. Passed tablets are automatically separated from failed tablets by an automated vacuum culling system at the end of the machine. Empty TEs are moved to the front of the machine to be reloaded with new tablets, making machine operation continuous. The conversion time from loading of the inert tablet to removal of the dosed and inspected tablet is about 30 min. If all four dispensers are operating, the throughput is approximately 80 000 tablets/h (2 million tablets/day).

17.5.2 Liquid Dispensing Cell

LDT utilizes a positive displacement, reciprocating, ceramic piston/cylinder dispenser that produces droplets of 4–25 μL. The dispenser operates at an average rate of 6 dispenses/s with high precision and repeatability. The GMP pilot machine used to produce clinical trial materials has one dispenser while the commercial machine has up to four dispensers of the same design and capability, providing scale independence for the key function of liquid dispensing.

The dosing solution is prepared on a weight/weight (w/w) basis as this is a very accurate way to compound the liquid to a target concentration (i.e. 100 mg API/g of final solution). The density of the dosing solution is also measured by weighing a known volume of the dosing solution. The volume of the target weight, required to deliver the desired API dose to the tablet, can be calculated and this serves as the critical process parameter (CPP) for the imaging system. That is, if a 10 mg drop of liquid with a density of 0.84 g/mL is required, the target drop volume will be 11.9 μL. The calculation is:

$$\frac{10\ \text{mg}}{(0.84\ \text{g/mL} \times 1000\ \text{mg/g} \times 1\ \text{mL})/1000\ \mu\text{L}} = 11.9\ \mu\text{L}$$

Associated with each dispenser is an imaging system to capture the volume of every dispensed droplet in-flight (Figure 17.9).

The imaging system captures an image of the droplet in-flight, calculates the drop volume and compares the drop volume against control limits to determine if the correct volume was

Figure 17.9 *In-flight droplet image.*

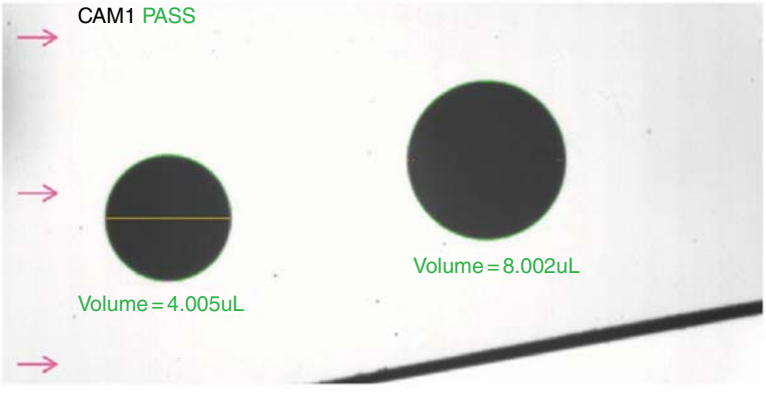


Figure 17.10 *In-flight droplet calibration check reticule.*

dispensed. Calibration of the imaging system is verified at the beginning of each processing run by imaging a National Institute of Standards and Technology (NIST) traceable reticule (Figure 17.10) with circles of known diameters that correlate with the theoretical spherical volumes, bracketing the target drop volume for the batch. A calibration curve is established by the control system and the volume of every imaged droplet dispensed is determined and recorded for the associated tablet on the transport element array.

The volume of the dispensed droplet can be adjusted by the operator through the human machine interface (HMI) by making changes to the piston stroke position for the positive displacement ceramic piston/cylinder in the dispenser. Very fine adjustments can be made to the drop volume and the reproducibility of the dispenser can be as good as <0.5% RSD across the drop volume range. Also, during setup for the run the dispensing system automatically measures the weight of several drops, dispensed into a tared container on an analytical balance in the system. The operator makes adjustments to the dispense volume until the target dispense weight is obtained and the associated drop volume is confirmed by the imaging system.

In the example (Figure 17.11), the performance of two dispensers from the commercial machine is plotted for a 6 h, 3 min production period. The *y*-axis graphs the dispense volume in μL (target was 6.9 μL). The upper and lower control limit volumes were +3% and –3% respectively (~7.11 and 6.69 μL). In terms of the dispensed dose, where the density of the Naproxen 20 mg/g liquid was 0.9 g/mL, the target dose of Naproxen was 153.3 μg (limits: 157.6 to 148.4 μg). In the plot of the 6 h run, after some operator adjustments to obtain a better drop volume for one of the dispensers at the beginning of the run, the drop volumes remained very stable throughout the rest of the run; the overall %RSD for the run was 0.267%. The approximate number of tablets processed was 261 000.

The process capability statistical analysis of the 6-h dispensing run shows a capability index (PPK) value of 3.22, well above the PPK value of 1.5 generally considered to represent a highly capable process. The corresponding σ level was 9.66, also well above the $\sigma = 6$ considered as the aspired process capability for pharmaceutical manufacturing (Figure 17.12).

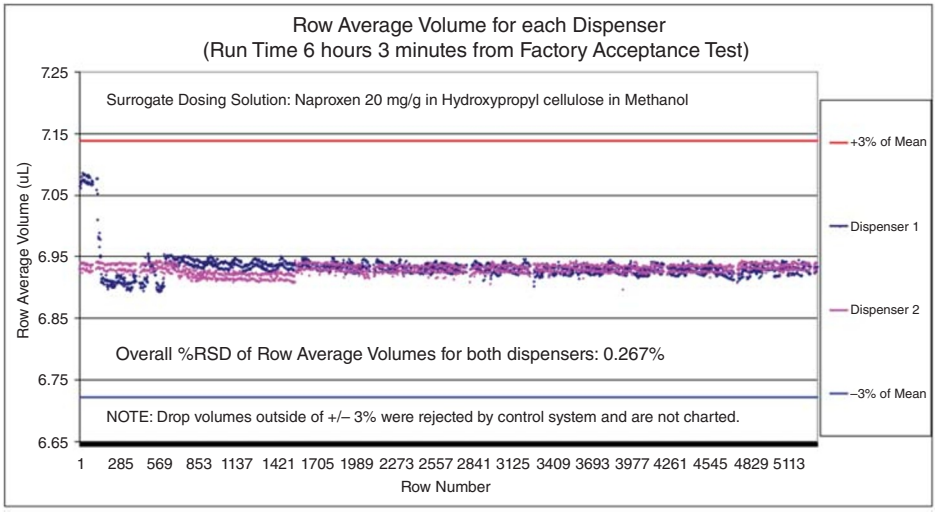


Figure 17.11 *Two dispenser reproducibility from the commercial machine.*

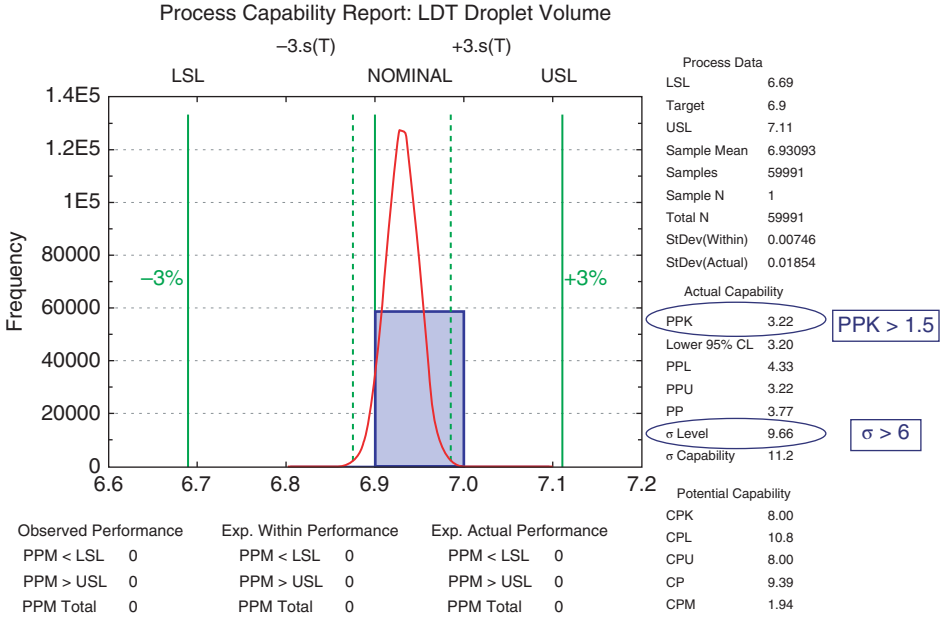


Figure 17.12 *Two dispenser process capability from the commercial machine.*

The LDT manufacturing process outlined above is very amenable to producing tablets with microgram doses that are very difficult to manufacture using conventional manufacturing approaches (i.e. wet-granulation and tablet compression). The dosing solution is a solution therefore the API concentration is homogeneous. The API concentration

Table 17.1 *Clinical campaign release testing results*

Target dose (μg)	10	10	20	20	40	50	80	150
Quantity Manufactured	11 454	4264	4241	11 483	16 466	4246	35 578	35 642
% Yield	99.4%	98.7%	98.2%	99.7%	99.4%	98.3%	98.8%	99.0%
Minimum (μg)	10.1	10.0	20.2	20.0	40.4	50.8	81.5	151.2
Maximum (μg)	10.3	10.1	20.5	20.2	40.7	51.3	81.9	153.8
Average ($N = 10$, μg)	10.2	10.0	20.3	20.1	40.5	51.1	81.6	152.5
% Label claim	102.0	100.0	101.5	100.5	101.3	102.2	102.0	101.7
%RSD	0.5	0.5	0.5	0.4	0.3	0.3	0.2	0.5

is established very accurately as the solution is compounded on a weight/weight basis. As can be seen in the discussion above, the target dosing weight/volume can be dialed-in very precisely. Once the target dosing volume is established, the positive displacement dispenser has a very high repeatability and stability over long periods.

Table 17.1 references actual analytical release data from a clinical manufacturing campaign of eight batches produced on the R+D pilot machine.

For tablet doses of 10–150 μg, dosing accuracy ranged from 100.0% to 102.2% of target dose and content uniformity ranged from 0.2 to 0.5% RSD. The efficiency of the dosing process was high with the percentage of "Passed" tablets in the batch run ranging from 98.29 to 99.68%, based upon the droplet volume imaging results. This level of dosing accuracy and content uniformity for low content tablets would be difficult to achieve using conventional tablet manufacturing processes.

17.5.3 Solvent Evaporation

A heating zone is used to evaporate the organic solvent from the tablets, leaving an adherent film on the tablet. A combination of heated air (30–60 °C) and convection flow is effective in evaporating the solvent to acceptable levels in less than 15 min. Residual solvent levels are tested against a release specification for clinical trial batches but routine residual solvent testing for commercial product is not expected. The commercial scale evaporation process will be qualified during QbD trials to ensure residual solvent levels are below specification.

17.5.4 Inspection Systems on the Commercial Machine for Critical Quality Attributes

In addition to the volume measurement inspection system, the LDT commercial machine has a significant array of imaging systems that inspect each tablet multiple times during processing for various critical quality attributes (CQAs). Each imaging system, discussed below, is verified at the time of machine startup by imaging NIST calibrated targets that confirm lighting levels, clarity of the image (i.e. focus), and in the case of color cameras, color accuracy. If an issue is detected, an alarm is raised by the control system; the machine cannot begin a production run until all imaging systems have passed their respective verifications.

17.5.4.1 Inert Carrier Tablet Inspection

The cosmetic appearance of tablets is tested several times during the process. At the beginning of the process, when carrier tablets are loaded onto transport elements, tablets are inspected for cracks, chips or blemishes (Figure 17.13). If an issue is detected, a pick and place unit removes the defective tablet and replaces it with a defect-free tablet.

17.5.4.2 Wet Dose Imaging

After the droplet is dispensed, a laser light source illuminates every wet dosed tablet, it is imaged to verify that it was fully deposited onto the tablet and an alarm is raised if the wet dose is found to be out of position (Figure 17.14).

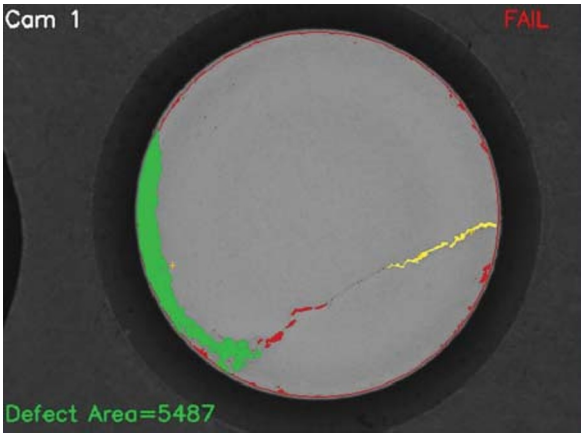


Figure 17.13 *Inert carrier tablet incoming quality inspection.*

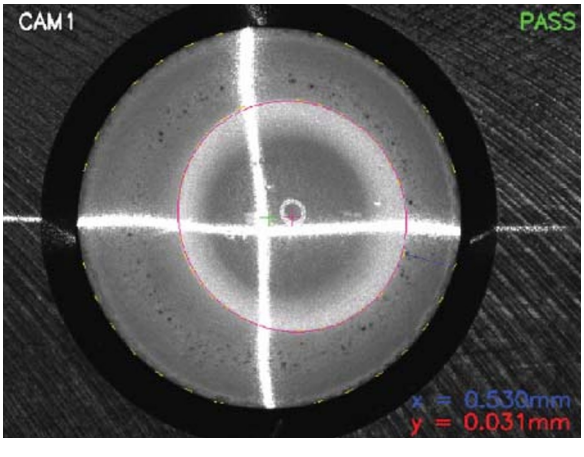


Figure 17.14 *Wet dose verification.*

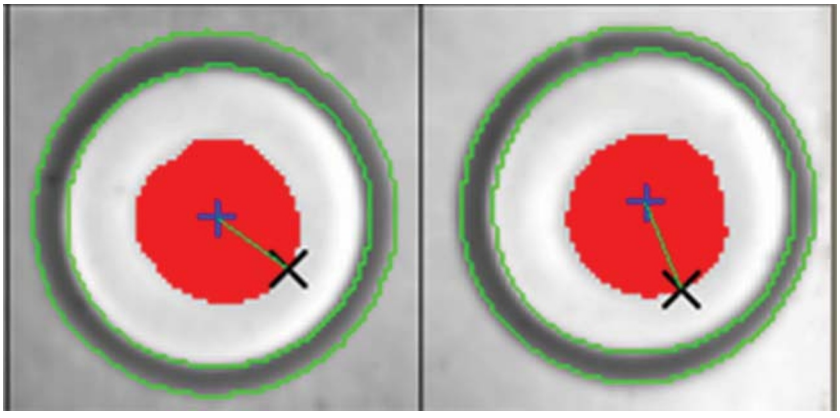


Figure 17.15 *Dry dose NIR imaging.*

17.5.4.3 Dry Dose Confirmation by Near Infrared Imaging

To confirm that the droplet, imaged in flight, was correctly positioned on the tablet after solvent evaporation, a camera images every tablet to determine that the droplet was deposited on the central portion of the tablet. If a portion of the dried droplet is too close or over the edge of the tablet, the tablet is failed. The imaging system can detect differences between the near infrared light reflectance off the carrier tablet and off the dried deposition to produce a contrast image that can be processed (Figure 17.15).

At the end of the machine, tablets are inspected a final time for quality of pad printed lettering, discussed below, and for smudges or defects. As before, if defects are detected, the tablet is removed to waste by the culling station.

Vision systems are used in the culling station to verify that only tablets with a "Passed" status in the control system are transferred to a temporary tablets holding nest. If only "Passed" tablets are verified to be in the nest, the nest is dumped into the Passed bulk tablet container. If a rogue "Failed" tablet is detected in the "Passed" nest, all tablets are dumped to waste to prevent any "Failed" tablets from being transferred into the "Passed tablet" bulk container. A similar verification nest is used to verify the "Failed" tablets are removed and sent to waste.

A final vision inspection is made on the TE to determine that no tablets remain on the TE after culling and that the TE is clean and suitable to be transfer to the beginning of the machine and reloaded with new inert carrier tablets. If a tablet still remains on the TE or it is soiled, the system automatically sets the TE in a rack for removal from the machine for cleaning.

17.5.5 Pad Printing Cell

During the development of the LDT technology, it was recognized that some APIs are inherently colored. As the entire API dose is on the surface of the tablet a dried deposition that was a different color than the carrier tablet could be viewed as a defect or blemish and not have an acceptable commercial image. A pad printing process was developed to place

Figure 17.16 *Pad printed marking of LDT tablets.*

a coating material, matching the color of the carrier tablet over the deposition, hiding the color.

In the pad printing process, used extensively to print decorative markings on many common products (i.e. coffee cup markings), a pattern is etched into a flat, polished plate, typically tens of microns deep. In the case of LDT, that pattern is a circle slightly smaller than the diameter of the tablet. A reservoir is filled with the coating suspension, and it is inverted over the pattern and the suspension is held in place by downward pressure on a precisely machined doctoring ring. When the reservoir is moved away from the pattern array, the doctoring ring removes the suspension from the metal around the etched circle but leaves a thin layer of suspension in the etched circle. After a few seconds of air exposure that dries the coating material, creating a tacky surface, a precisely positioned silicone pad touches the coating and removes that material from the etched pattern. The coating suspension on the pad then air dries to give the exposed spot a tacky surface. The pad then moves to the tablet, touches the tablet transferring the tacky coating to the tablet. The silicone pad can pad coat 144 tablets with each cycle.

An additional pad printing station is used to print text for marking onto the tablet, typically using a black ink suitable for printing of tablets. See Figure 17.16 for an example of marked tablets from the commercial machine.

In an additional approach to hide the coloration of the API, the liquid formulation is dosed onto an uncoated inert carrier tablets. After the deposition is dried, the tablets can be aqueous filmed coated in a conventional pan coater. The deposition is stable on the tablet surface and the coating process does not affect the drug content or the physical stability of the deposition.

17.6 Scale-independence of the LDT Technology

The composition of the LDT formulation is often established in pre-clinical development based upon the stability of the API when screened against the polymers, solvents, additives

Table 17.2 *Differences between the pilot scale and commercial scale machines*

Unit operation	Pilot machine	Commercial machine
Tablet loading	Manual	Automated
Incoming tablet inspection	Visual inspection	Machine vision
Replacement of defective tablets	Manual	Automated
Dispensers	One	Two or four (selectable)
Pad printing/marking	None	Automated
Final tablet inspection	Visual inspection	Machine vision
Culling of passed/failed tablets	Manual	Automated

and coating materials used on the carrier tablet. In later development, the quantitative composition of the formulation may change to improve dispensing performance, but the qualitative composition will likely not be changed. Additionally, a common inert carrier tablet formulation is usually sufficient for immediate release tablet performance.

The liquid dispenser used in the laboratory system, used for formulation and process development, uses the same positive displacement dispensing approach and the same droplet imaging approach that is used in the pilot scale and commercial scale machines. The dispensers on the pilot and commercial machines, having the same design, also operate at the same average dispense speed of 6 dispenses/s, which makes the dispensing process scale-independent.

The pilot and commercial machines do differ in a number of ways (Table 17.2) as the pilot scale is used to produce smaller numbers of tablets in a batch mode while the commercial machine was designed to produce commercial image tablets in a continuous manufacturing process.

17.7 Real-time Release Potential

The LDT drug product employs a relatively simple, immediate release tablet approach for low dose products. For most compounds in the LDT program, the small quantity of API is soluble in relatively small volumes of biologically relevant dissolution media. The carrier tablet usually disintegrates in less than one minute releasing the API-polymer deposition which also dissolves in the media very rapidly. The API is in such a low quantity and has sufficiently high solubility that drug release often occurs at the same time as tablet disintegration.

The International Conference on Harmonization (ICH) guideline, ICH Q6A [15], allows for the justification for product release based upon a disintegration specification rather than dissolution. For compounds where the API is either highly soluble and/or in low quantity, dissolution testing is irrelevant, the compound is fully dissolved in the media within minutes. For most compounds in the LDT program, an ICH 6A approach could be pursued to justify not using dissolution as a release specification.

Conventional tablet manufacturing processes typically obtain an acceptable quality limit (AQL) sample of the batch based upon the batch size and from this sample 10 individual tablets are analyzed for drug content and content uniformity. While these are standard,

compendial approaches, the reliance on testing of such a small sample of tablets from a small AQL sample of what could be a batch of millions of tablets is the old thinking that FDA was attempting to have pharmaceutical manufacturers move away from with PAT and real-time release approaches advocated in the twenty-first century GMP pharmaceutical manufacturing initiative.

In contrast, using the LDT manufacturing process, a strong case can be made that release testing for drug content and content uniformity is unnecessary. The drug content of *every* tablet is determined, if any tablets are out of specification for drug content, the control system "Fails" them and they are removed to waste. Content uniformity is achieved by default; if all tablets are within specification the "batch" would meet compendial content uniformity.

Table 17.3 includes other testing that would be expected to be included in a product release specification. For compounds that are low dose, highly soluble and amenable to the LDT manufacturing approach, true real-time release is a viable possibility.

In January 2011, the FDA issued *Guidance for Industry, Process Validation: General Principles and Practice* [16] that addressed continued process verification. The historical manufacturing process qualification approach employed "validating" a manufacturing process by running three at-scale batches to demonstrate process robustness. However, manufacturing process inputs or conditions may drift over time or not have been well understood and the process may not remain in a validated state. By advocating continued process verification, the FDA was acknowledging that the previous validation approach did not ensure processes remain validated. Continued process verification monitors batch data over multiple batches and longer time periods to detect trends that may indicate the process is drifting out of its desired design state. The LDT process facilitates continued process verification as the control system archives a large amount of process data in a searchable database. The database access and analysis tools allow data from multiple batches to be analyzed by statistical methods to look for process drift over time. It is possible that conventional tablet manufacture process may undergo a similar data treatment with considerable statistical support however the LDT data archive architecture was designed to facilitate continued process verification by first intent.

Batch manufacturing has been the standard approach for manufacture of tablets for decades. However, the FDA *Code of Federal Regulations21 CFR 210.3* [17] also has a definition for a "lot/batch" in terms of a continuous process as "... a specific identified amount produced in a unit of time or quantity in a manner that assures it's having uniform character and quality within specified limits." On the commercial machine, the documentation used for product release is time (or quantity) based. Documentation to support batch release for commercial use involves a number of summary reports generated by the control system (Figure 17.17).

Product is segregated and quarantined during the manufacturing run by units of time. Several reports are generated for a block of time (i.e. 8 h) for quality assurance to review the process data for the batch. A list of the tablet failure categories and the quantity of tablets failed is reviewed for trends. A statistical report is generated that reviews the process capability and any other factors that reflect on the quality of the product or robustness of the process.

Table 17.3 *Critical quality attributes (CQAs) and control strategy*

CQA	Included in specification?	Process measure	Rationale for control strategy
Appearance	Yes	100% inspection vision system of input carrier tablets and final printed tablets	Provides automated inspection for defined defects.
		Operator will also visually examine samples at defined points throughout manufacture	Provides manual inspection for overall general appearance.
Identity	Yes	Identity of API confirmed spectroscopically prior to compounding of dosing solution API in dosing solution confirmed by at-line analysis of using Raman spectroscopy	Provides definitive confirmation of API identity via at-line drug-specific spectroscopic methods.
Drug content	Yes	Determined at-line/on-line via: • UV analysis of API concentration in dosing solution • Monitoring of droplet size/volume	UV provides initial and continuous monitoring of API concentration.
		Optional, off-line analysis: • HPLC analysis of API concentration in dosing solution	Concentration and volume determinations provide drug content value for each tablet
Content uniformity	Yes	Determined *on-line* via: • Monitoring of droplet size/volume	Provides continuous automated monitoring. Content uniformity is directly related to precision and reproducibility of dosing
Drug-related impurities	Yes No routine testing planned	Determined by HPLC during development	Demonstrate via development studies: – Synthetic impurities controlled at release of drug substance – No impurities formed during LDT manufacturing process – API and drug product are stable

(*continued*)

Table 17.3 *(Continued)*

CQA	Included in specification?	Process measure	Rationale for control strategy
Residual solvents	Yes No routine testing planned	Determined by GC analysis during development	Demonstrate via development studies: – LDT manufacturing process is well controlled and any residual solvent (methanol) is well within ICH 3 limits
Dissolution	No If conditions allow ICH 6A to apply	If drug product performance complies with ICH 6A, dissolution testing may be waived	Since drug substance resides on surface of tablet and is not dispersed in tablet matrix, intent is to demonstrate that: – Rate of dissolution of drug substance is independent of disintegration of carrier tablet
Microbial limit tests	Yes No routine testing planned	Complies with compendial requirements	– Microbial content of carrier tablets and raw materials is controlled – Manufacturing environment is controlled – Microbial quality is assured for life of product through stability studies

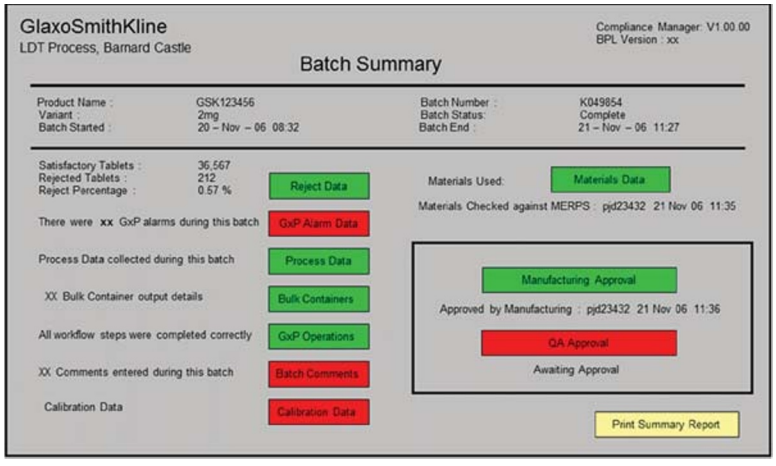
17.8 Occupational Health, Environmental and Cleaning Considerations

17.8.1 Occupational Health

As noted above, the LDT process is run in a conventional pharmaceutical manufacturing space, without enclosing the LDT machine in expensive high-containment enclosures, commonly employed for conventional tablet compression of high-potency products (i.e. OHC4/5). For clarification, high-potency APIs, in powdered form are still hazardous and must be handled within suitable high-containment gloveboxes. APIs are weighed in a glovebox and transferred into a tared vessel used to contain the final dosing solution. Once the polymer and any other excipients are added to the vessel, the solvent is added to final weight and the contents are mixed until fully dissolved. Once the API is dissolved and in the sealed vessel, it is removed from the glovebox. When the API is in the liquid form, the exposure potential is greatly reduced. When the dosing solution is loaded on the LDT machine and all connections to the dispenser have been made, the system is ready to prime and begin setup for the batch.

GSK has performed extensive occupational health (OH) air monitoring to detect respirable aerosolized API powder or droplets during the solution compounding, the transfer

(a)



(b)

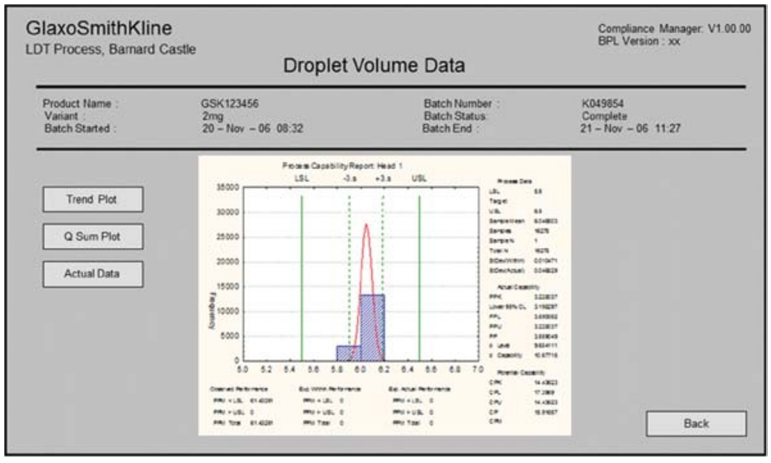


Figure 17.17 *Three examples (a, b, c) of commercial batch release screens.*

and attachment to the LDT machine, set-up and machine operation. GSK has processed many APIs in the LDT process that have had OELs between 0.1and 10 μg/m^3 on an 8-h TWA. With the rare exception, the API is non-detectable in OH samples and when the API was detected it was well below the OEL limit. Based upon the body of OH testing, the operation of the LDT machine is performed in a respirator-free manner. Double gloves are utilized to prevent dermal exposure to the dosing solution. Of note, on the R+D pilot and commercial machines, guarding is in place to prevent physical injury. The machines are open to the room and the guarding is not regarded as a high-containment enclosure.

Once the tablets have been processed and the liquid deposition dried onto the tablet, the tablets can be handled by operators in open operations. OH monitoring has been performed on packaging operations using released LDT tablets and there was no API detected

(c)

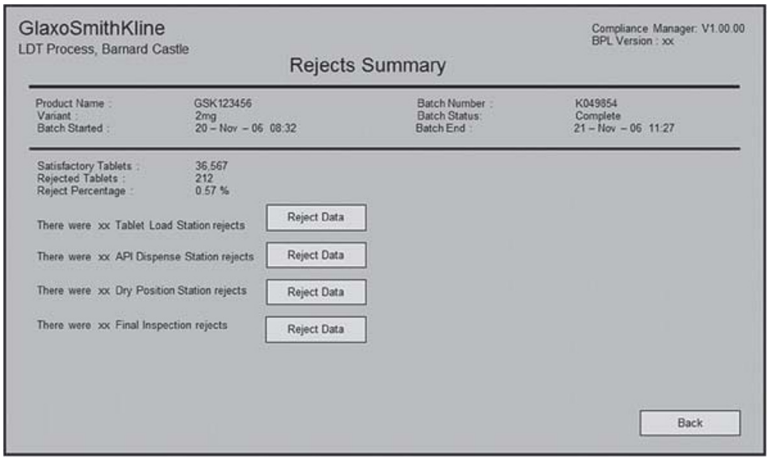


Figure 17.17 *(Continued)*

during sampling. No special packaging facilities and respirators are required for packaging OHC4/5 LDT tablets.

17.8.2 Environmental Controls/Cleaning

Equipment used for high-potency conventional tablet manufacturing often needs to facilitate wash in place features that are labor-intensive where operators clean the equipment within the high-containment enclosures to prevent exposure to powder. Some equipment is clean in place (CIP) where cleaning solutions are sprayed into the enclosed equipment. These processes often generate hundreds of liters of waste water that, for high-potency APIs, needs to be collected for subsequent disposal. Disposal often requires hauling of the water to specialized waste treatment facilities where the water is incinerated. High-containment enclosures typically have double-HEPA filtration of all process air and conditioned facility air is usually single-pass and is not recirculated. Disposable HEPA filters contaminated with OHC4/5 powders must also be handled as hazardous waste. All of these factors add considerable expense to the operation of conventional high-potency manufacturing facilities. Should the facility also be considered a multi-use facility where more than one high-potency API is processed in the same facility or equipment train, a risk-based approach must be adopted to show that cross-over contamination is minimized [5]. There is a considerable expense for product change over (i.e. new HEPA filters, dedicated vessels) and cleaning qualification expenses can be considerable.

LDT, in contrast, does not have the environmental/cleaning constraints identified above. In R+D, where the dosing solution volume is usually less than 500 mL, the reservoirs used are glass or plastic and are discarded after use. The tubing used to connect the reservoir to the dispenser and the dispense nozzle is likewise used once then discarded. The only wetted product contact part that requires cleaning is the stainless steel holder for the ceramic piston/cylinder. This assembly costs <£ 1000, is dedicated to a single API and is reused

Figure 17.18 *Stainless steel holder and piston/cylinder assembly.*

after cleaning. The entire assembly is small enough to fit in a coffee cup (Figure 17.18) and requires a trivial amount of solvent or water to clean. The transport elements are not exposed to the API to any great degree as the droplets are confined to the tablet. Cleaning of these plates can be performed in standard parts washers.

The commercial LDT machine has a similar cleaning approach. While the dosing solution reservoirs may be of stainless steel construction and larger (i.e., 20 L) they can be product dedicated. Cleaning of these portable vessels can occur in standard CIP stations and volume of waste water generated is much smaller, compared to the waste water generated by clean conventional tableting equipment. Fully disposable bag reservoirs with associated tubing for connection to the dispensers are possible, avoiding the cleaning of reservoirs altogether. As above, up to four wetted stainless steel and product dedicated piston/cylinder assemblies would require cleaning.

The utility requirements for the LDT process are far less than for a conventional manufacturing facility. Significantly less high-purity water would be required for cleaning. Air in the manufacturing facility could be recirculated and would not have the significant expense required for conditioned, single pass air. At most times, two operators are required to operate the LDT machine, a larger number of operators is required for all of the unit operations in a conventional facility. LDT does produce solvent during the evaporation process and this is exhausted to the environment. However, daily output of ethanol or methanol is up to 20 L/day and is well within emissions normally permitted for industrial processes.

In summary, LDT provides an efficient, respirator-free manufacturing process for highly potent compounds. The waste treatment and facility operating costs are significant less for the LDT process, when compared to conventional high-potency tablet manufacturing.

17.9 Conclusion

LDT tablet manufacturing equipment and continuous manufacturing process were designed to safely manufacture low dose tablets with an unprecedented level of process control. Unlike conventional tablet manufacturing processes where there is higher dose variability,

especially with very low dose tablets, the LDT process provides tablets with excellent content uniformity and the on-line droplet imaging system determines the drug content of each individual tablet. The control system allows out of specification tablets to be removed from the batch. The 100% dose confirmation approach and the dosage form design facilitate real-time release of tablets. In addition, the process allows operators to safely manufacture high potency, OHC4/5 tablets in a respirator-free process.

Acknowledgments

The authors would like to acknowledge the significant contributions of the following GSK scientists and engineers who have were part of the LDT success: Fritz Fiesser, Yu Li, Rob Smith, Nigel Wood, Peter Heaton, James McHugh, Robert Finn and Robert Glinecke.

References

[1] FDA (2014) *Drugs@FDA Database*. Available at: http://www.fda.gov/Drugs/InformationOnDrugs/ucm135821.htm (accessed 13 August 2014).

[2] Zheng, J. Y. (ed) (2009) *Formulation and Analytical Development for Low-Dose Oral Drug Products*, John Wiley & Sons, Inc., New York

[3] MHRA (2013) *Levothyroxine Tablet Products: A Review of Clinical and Quality Considerations*. Available at: http://webarchive.nationalarchives.gov.uk/20141205150130/http://www.mhra.gov.uk/home/groups/pl-p/documents/drugsafetymessage/con222566.pdf (accessed 28 January 2015).

[4] FDA (2004) *Pharmaceutical cGMPs for the 21st Century – A Risk-Based Approach* Available at: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/Manufacturing/QuestionsandAnswersonCurrentGoodManufacturingPracticescGMPforDrugs/ucm137175.htm (accessed 28 January 2015).

[5] Van Arnum, P. (2010) Risk Mitigation in High-Potency Manufacturing, *Pharmaceutical Technology*, **34** (10), 52–58.

[6] Ursan, I., Chiu, L. and Pierce, A., (2013) Three-dimensional drug printing: A structured review, *Journal of the American Pharmacists Association*, **53**, 136–144.

[7] Daley, R., Harrington, T. et al. (2014) Ink-jet printing for pharmaceuticals – A review of research and manufacturing, *International Journal of Pharmaceutics*, **494** (2), 554–567.

[8] IChemE (2012) *GlaxoSmithKline Wins Top Prize at IChemE Awards*. Available at: http://www.icheme.org/media_centre/news/2012/glaxosmithkline%20wins%20top%20prize%20at%20icheme%20awards.aspx#.VLMpGCvF-AU (accessed 28 January 2015).

[9] Clarke, A.J., Doughty, D.G., Fiesser, F.H. et al. (2012) *Apparatus for Producing a Pharmaceutical Product*. US Patent US8252234 B2, filed 9 June 2005, granted 28 August 2012.

[10] Clarke, A.J., Doughty, D.G., Fiesser, F.H. et al. (2012) *Apparatus and Method for Producing a Pharmaceutical Product*. US Patent US8122849 B2, filed 9 June 2005, granted 24 January 2012.

[11] Clarke, A.J., Doughty, D.G., Fiesser, F.H. (2012) *Apparatus and Method for Producing or Processing a Product or Sample*. US Patent US8101244 B2, filed 9 June 2005, granted 28 February 2012.

[12] Clarke, A.J., Doughty, D.G., Fiesser, F.H. et al. (2013) *Apparatus for Pharmaceutical Production*. European Patent EP1773708 B1, filed 9 June 2005, granted 12 June 2013.

[13] Clarke, A.J., Doughty, D.G., Fiesser, F.H. et al. (2013) *Apparatus for Pharmaceutical Production*. European Patent EP2638891 B1, filed 9 June 2005, granted 18 September 2013.

[14] Various authors (2005) *Apparatus and Method for Producing a Pharmaceutical Product, and Similar Titles*. US Patent US20060000470 A1, filed 9 June 2005. Available at: http://worldwide.espacenet.com/publicationDetails/inpadocPatentFamily?CC=US&NR=2006000470A1&KC=A1&FT=D&ND=3&date=20060105&DB=worldwide.espacenet.com&locale=en_EP (accessed 28 January 2015).

[15] International Conference on Harmonization (1999) *Guideline Q6A, Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products, Chemical Substances, Decision Tree #7*. Available at: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q6A/Step4/Q6Astep4.pdf (accessed 28 January 2015).

[16] FDA (2011) *Guidance for Industry, Process Validation: General Principles and Practice*. Available at: http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm070336.pdf (accessed 28 January 2015).

[17] FDA (2014) Code of Federal Regulations (21 CFR 210.3, Definitions) Available at: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?cfrpart=210&showfr=1 (accessed 28 January 2015).

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Continuous Manufacturing of Pharmaceuticals, First Edition.
Edited by Peter Kleinebudde, Johannes Khinast, and Jukka Rantanen.

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