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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).

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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.

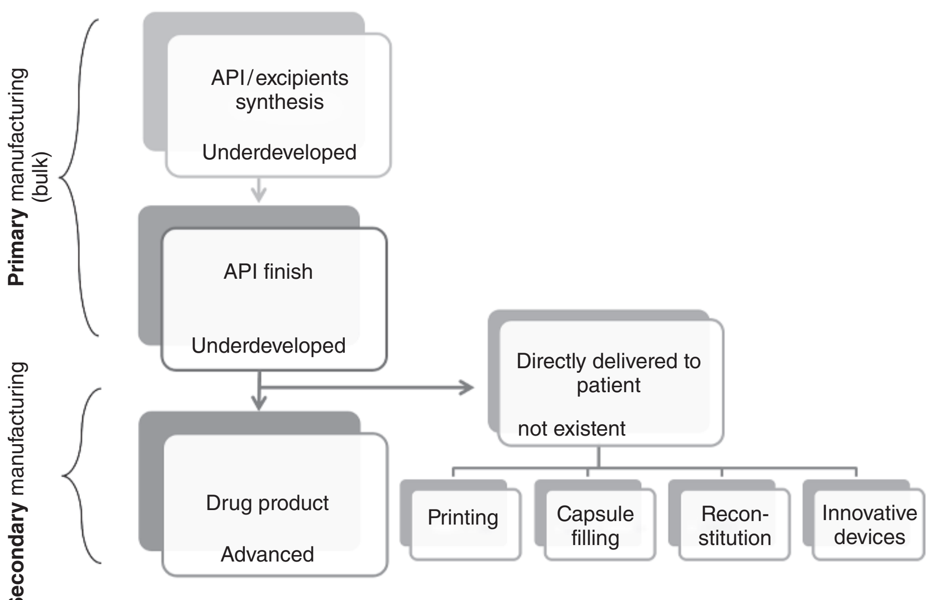

Figure 1.1 General overview of a CM process chain.

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

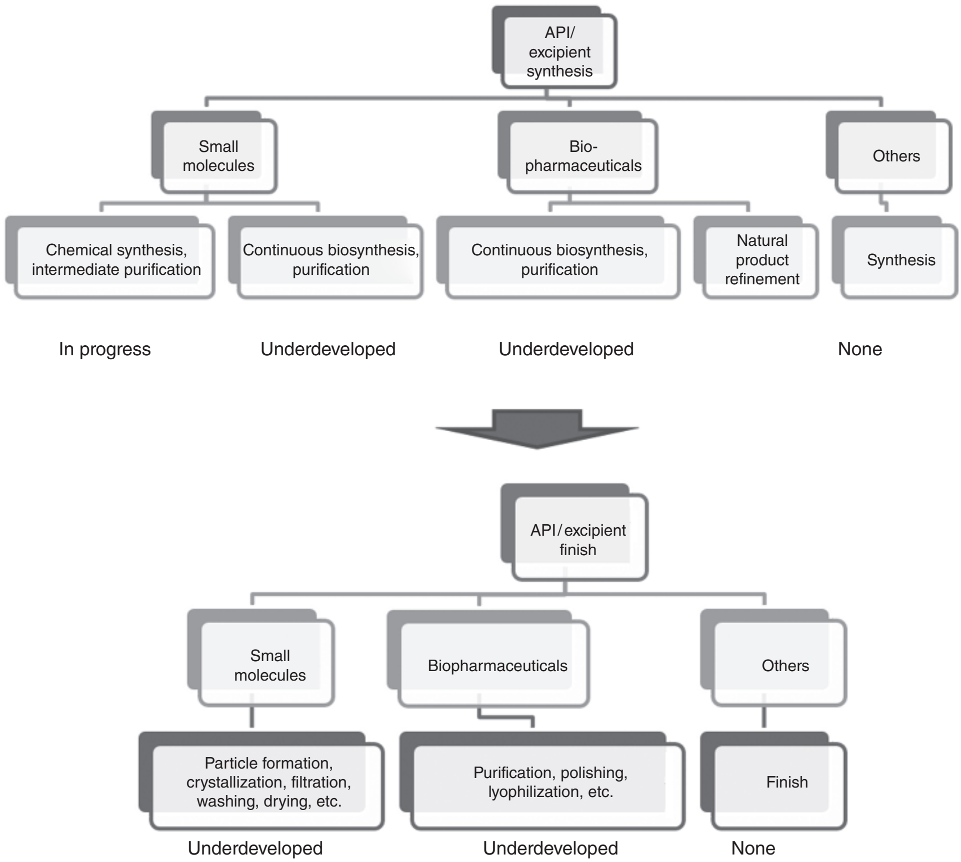

Figure 1.2 *Overview of continuous primary pharmaceutical manufacturing.*

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.

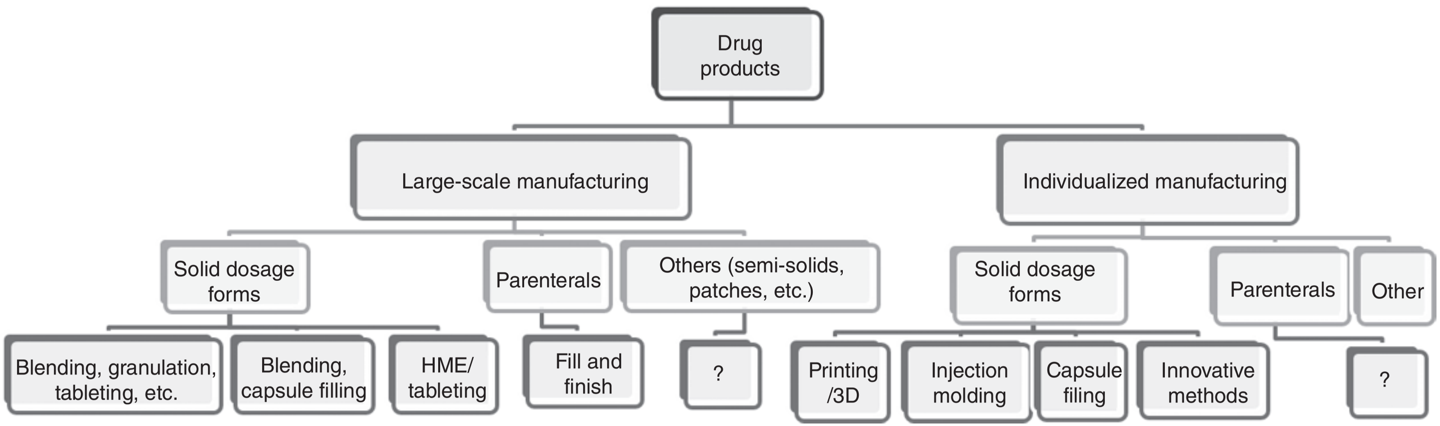

Figure 1.3 Overview of continuous secondary pharmaceutical manufacturing.

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).

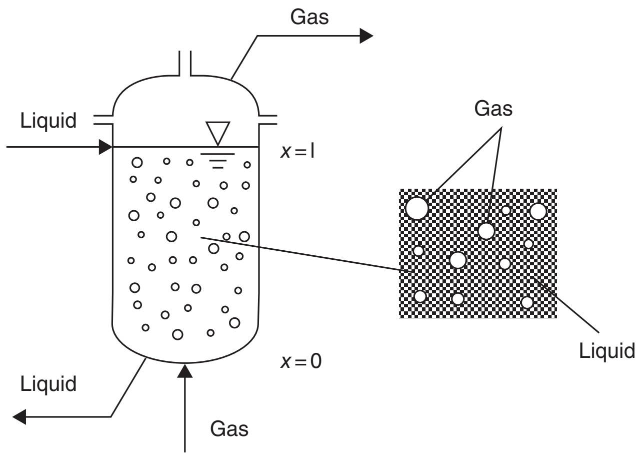

Figure 1.4 Schematic of a system with continuous phase contact.

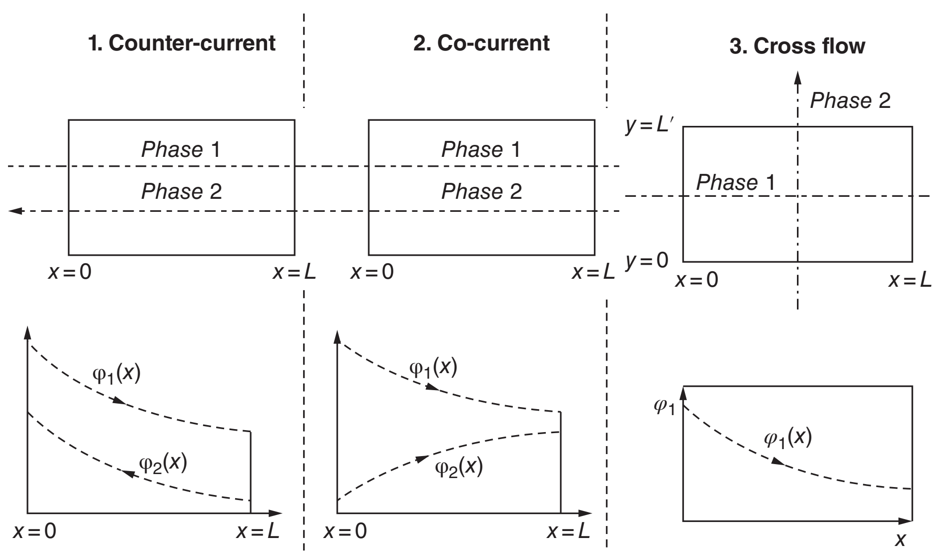

Figure 1.5 The three principal flow modes.

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.

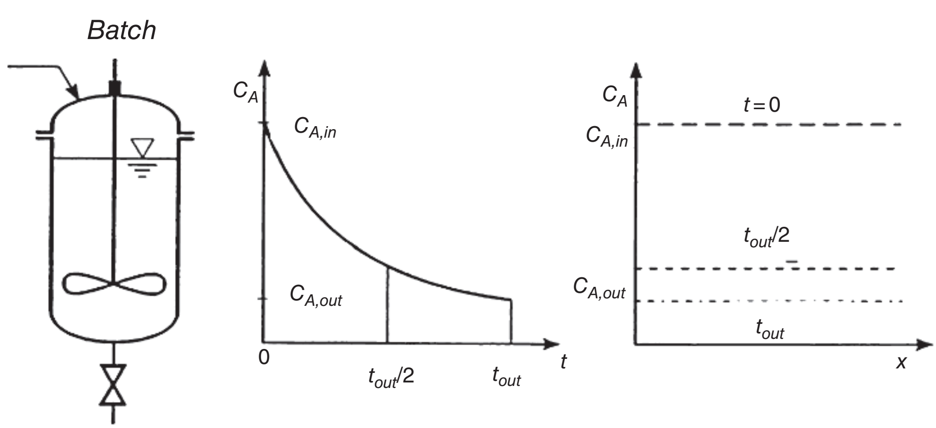

Figure 1.6 *Batch reactor and the associated temporal and spatial gradients.*

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:

Accumulation = $\text{Transport}_{\text{IN}}$ – $\text{Transport}_{\text{OUT}}$ + 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:

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

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.

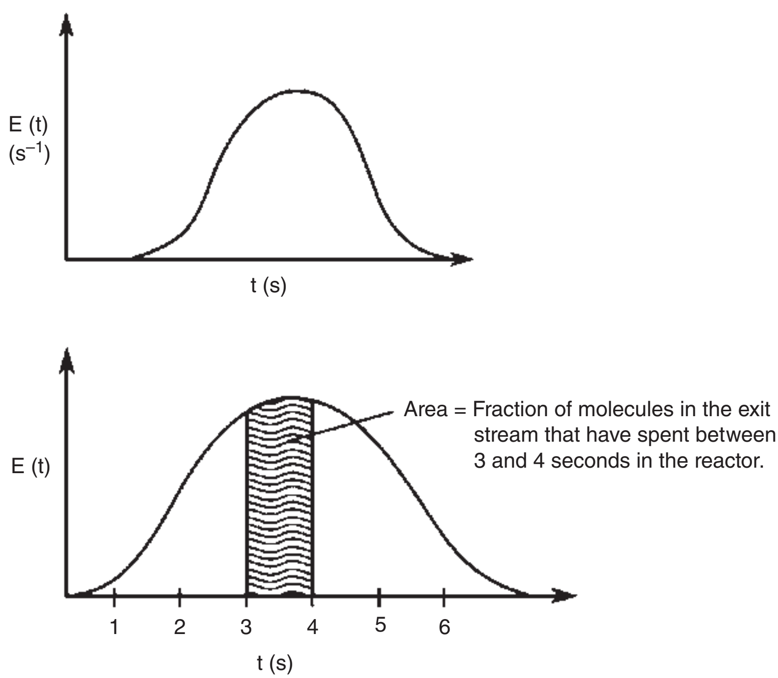

Figure 1.7 Schematic of residence time distribution.

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.

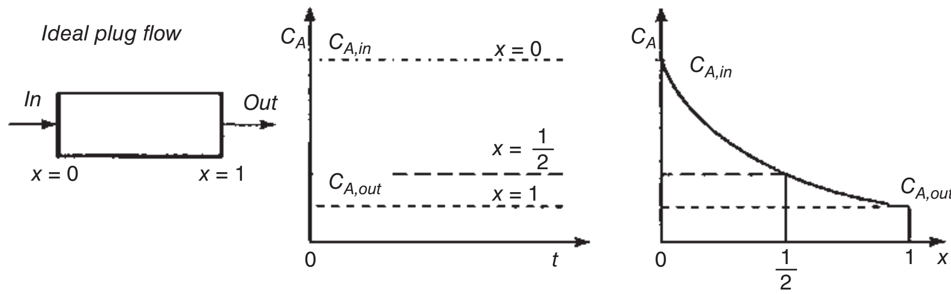

Figure 1.8 Schematic of a plug-flow reactor and temporal and spatial profile.

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).

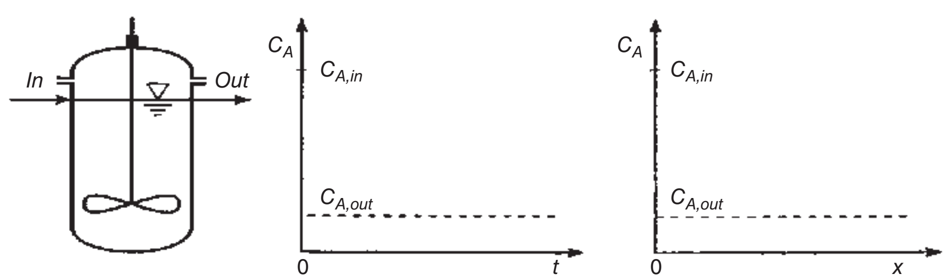

Figure 1.9 Schematic of a ideally mixed reactor (left). Corresponding temporal and spatial profiles (right).

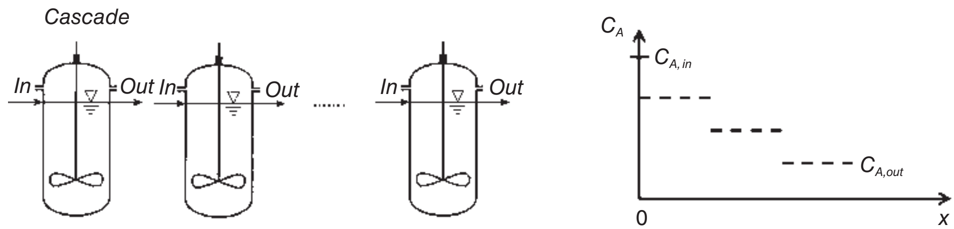

Figure 1.10 *Schematic of a cascade of CSTRs and spatial profile.*

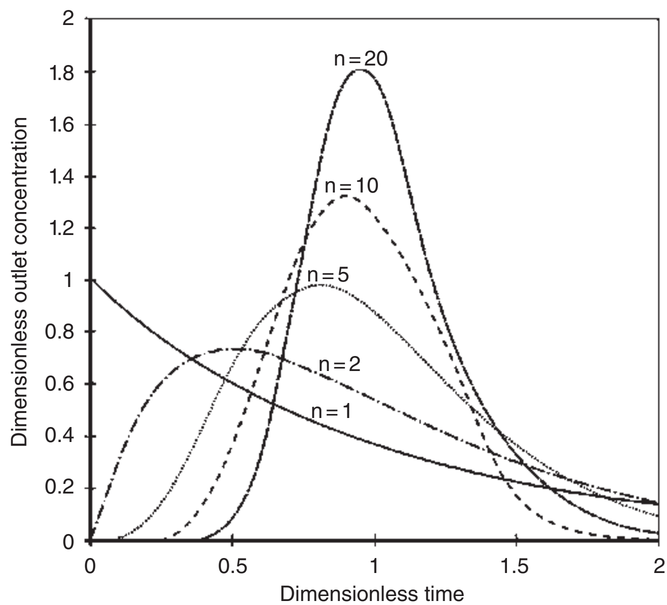

Figure 1.11 *RTD for various numbers of CSTRs.*

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

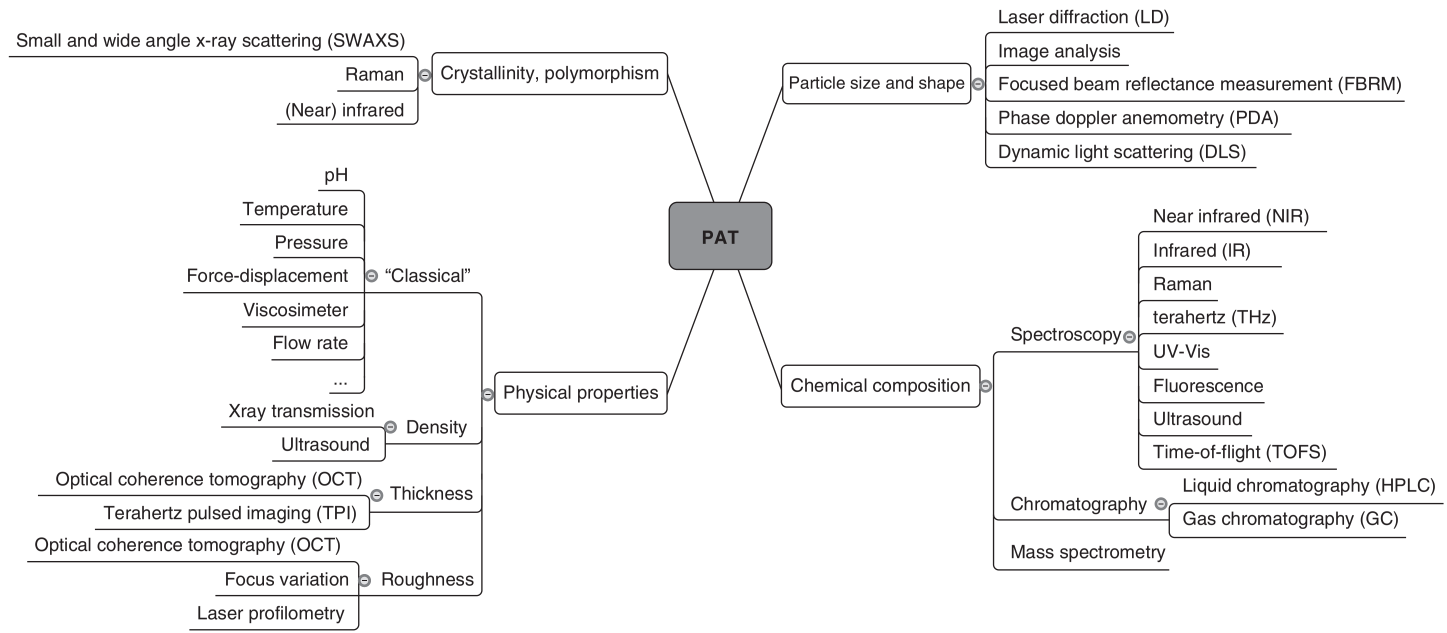

Figure 1.12 *Schematic overview of typical sequence, from multivariate raw data (e.g., spectra, images) to product quality parameters (e.g., API concentration, coating thickness of pellets or tablets).*

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− ε_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

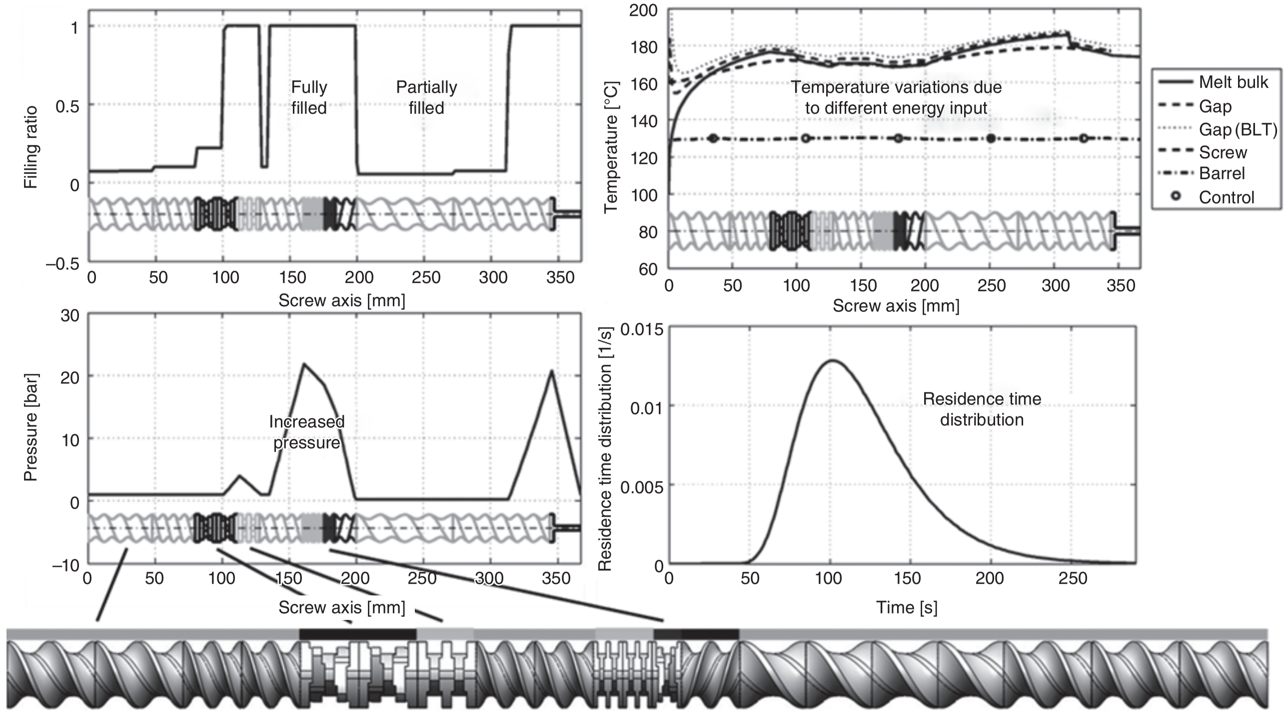

Figure 1.13 Model simulation of an extruder with filling ratio, temperature, pressure and RTD [29].

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.

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