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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.

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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.

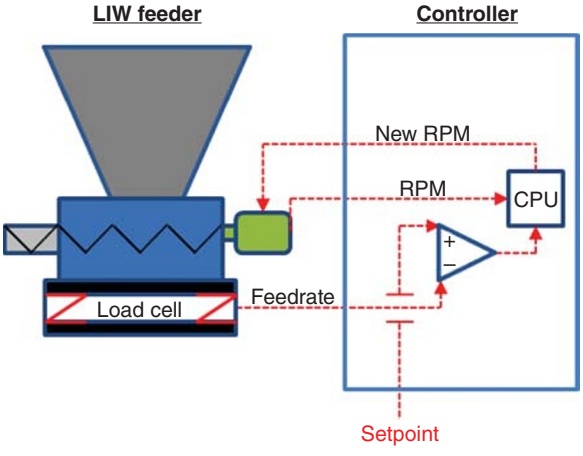

Figure 12.1 *Diagram of the main components of a loss in weight feeder. A volumetric feeder is mounted on a load cell with a feedback controller monitoring and controlling the feed rate.*

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

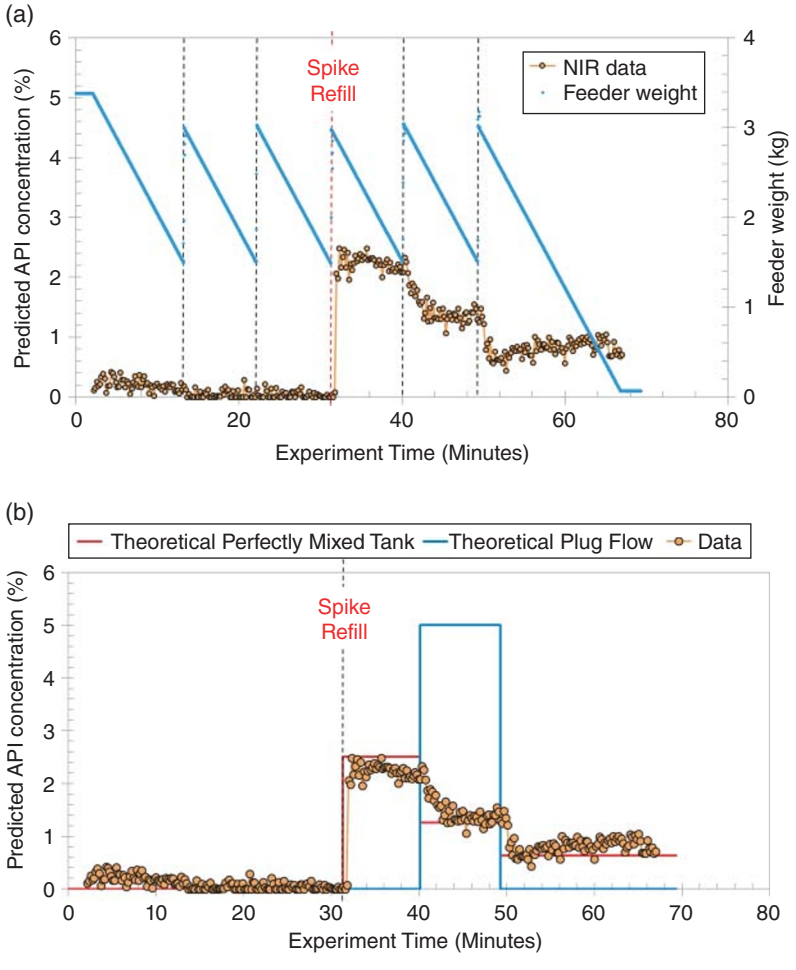

Figure 12.2 *(a) RTD response of a K-Tron KT-20 feeder to a pulse of tracer material (acetaminophen). The solid lines show the weight of the material in the feed hopper as a function time. The spikes indicate hopper refills. (b) Fit of the data to standard CSTR and PFR models. It can be observed that 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.

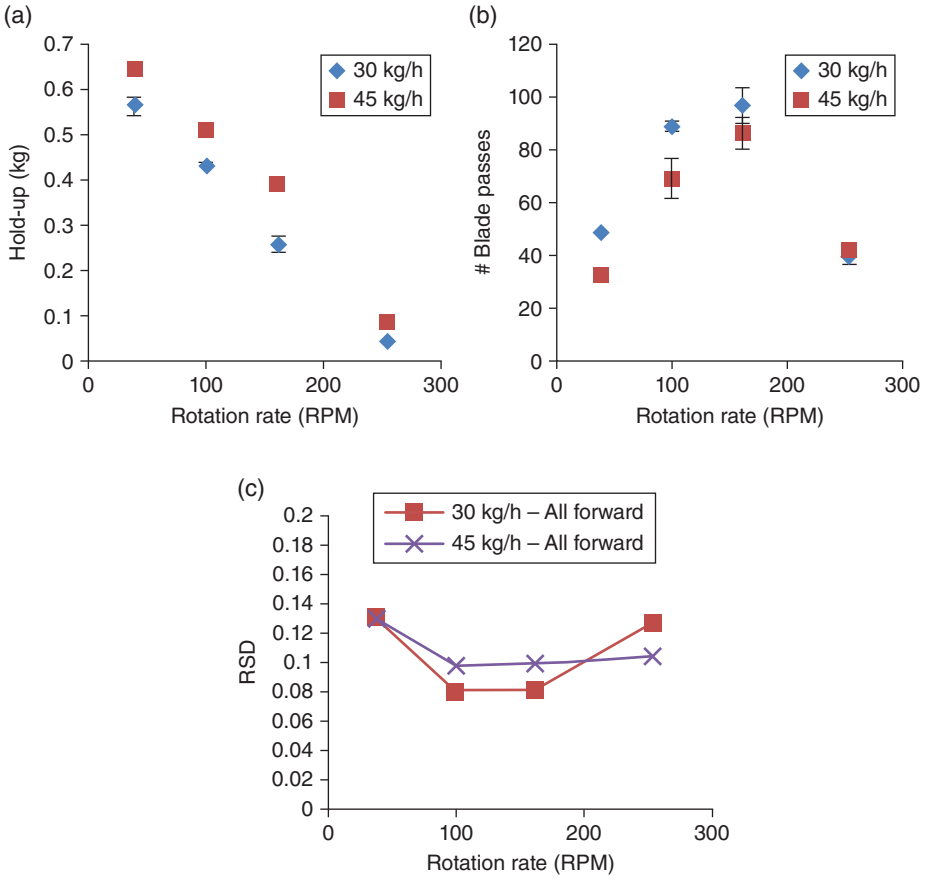

Figure 12.3 *Effect of impeller speed on (a) mass-holdup, (b) number of blade passes, and (c) relative standard deviation of the active concentration in the outlet stream for an all forward blade configuration.*

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.

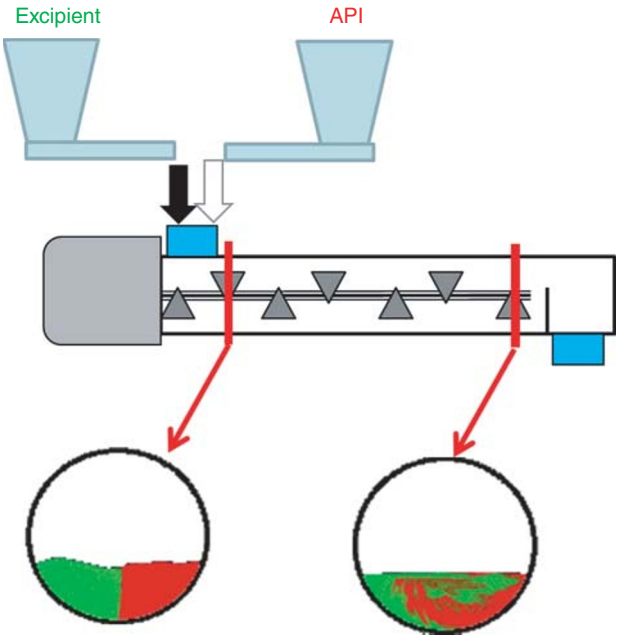

Figure 12.4 *Illustration of radial mixing phenomenon in a continuous tubular blender along the blender length. Each radial cross-section in the blender exhibits the same arrangement of components over time but subsequent cross-sections do not.*

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

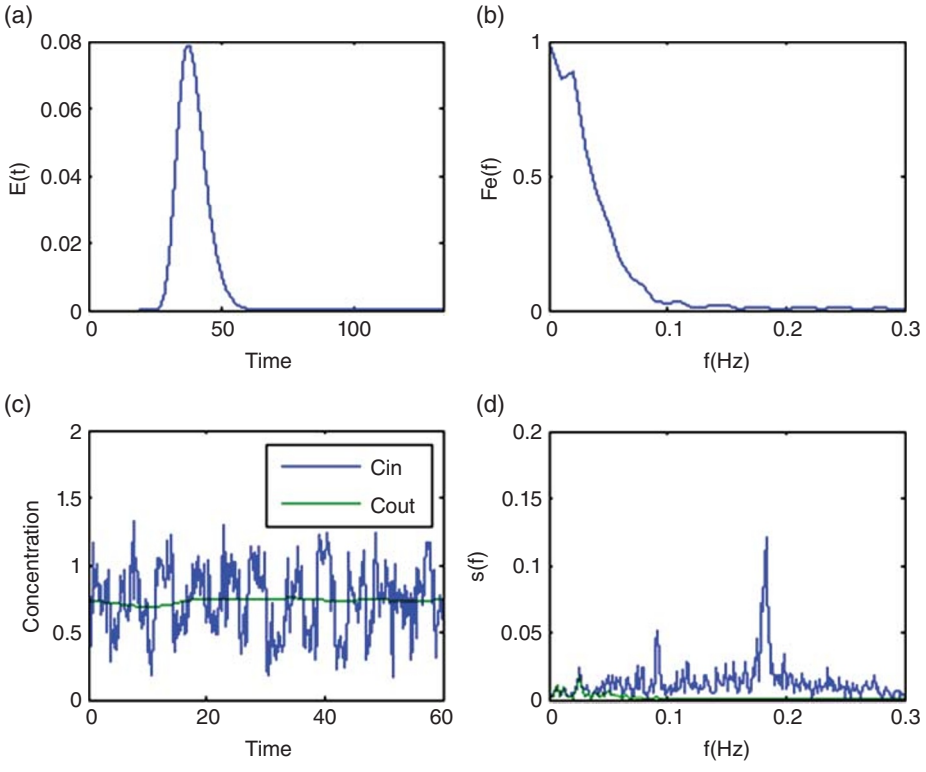

Figure 12.5 *Noise analysis of KT-20; worst case noise coupled with worst case RTD for filtering noise. (a) Normalized RTD of the blender. (b) Filtering ability of the blender. (c) Concentration in versus predicted concentration out after axial mixing in blender. (d) Noise spectrum of the raw feeder (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

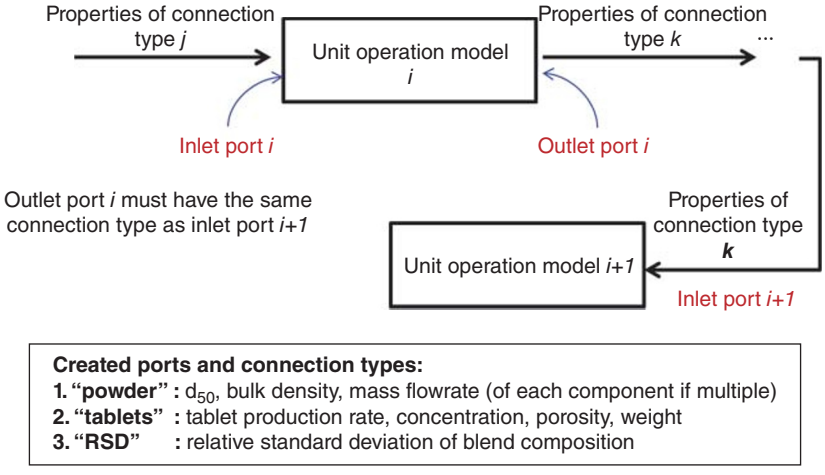

Figure 12.6 *Model integration for a multi-unit operation process. Each block represents an individual unit operation model connected to a subsequent model using an information transfer port and an information connection. Both the port and connection type transfer specific information between units, 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.

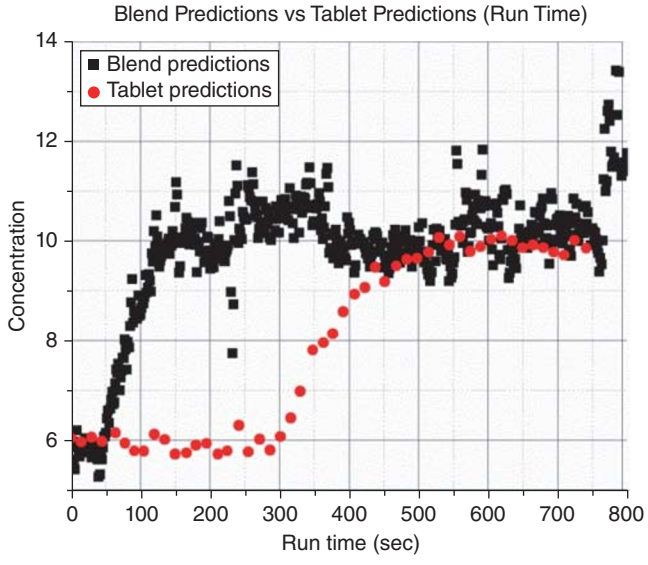

Figure 12.7 *At time 0, feed ratio was changed from 6% APAP to 10% APAP. The series of squares is the in-process spectra of the material post the blender. The series of circles represents NIR measurements on tablets sampled at the exit. It takes about 9 min after the perturbation having exited the blender 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

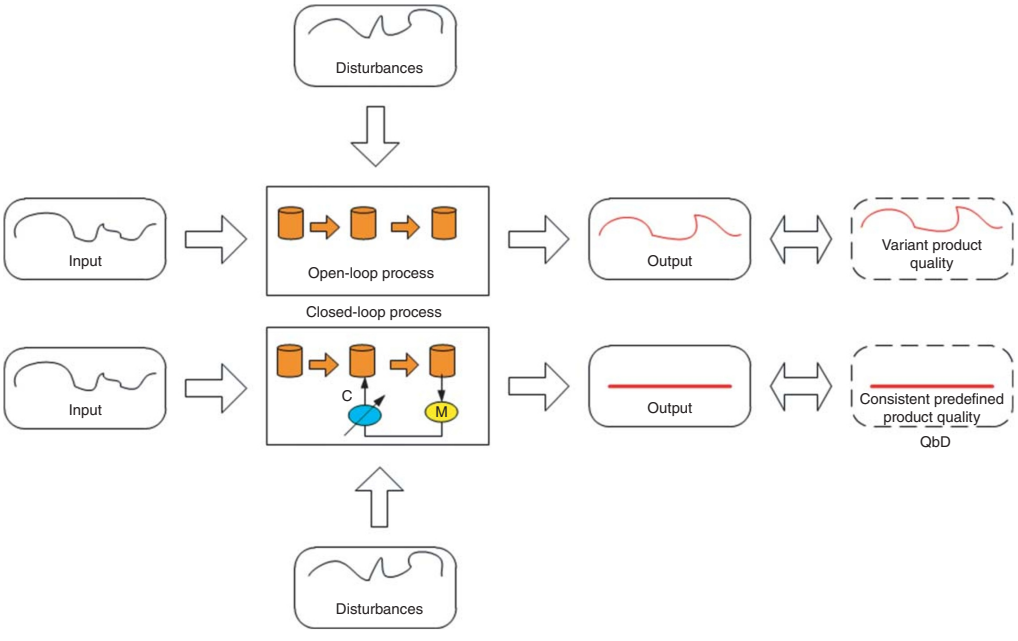

Figure 12.8 *Illustration of closed-loop and open-loop operation (adapted from [50]).*

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.

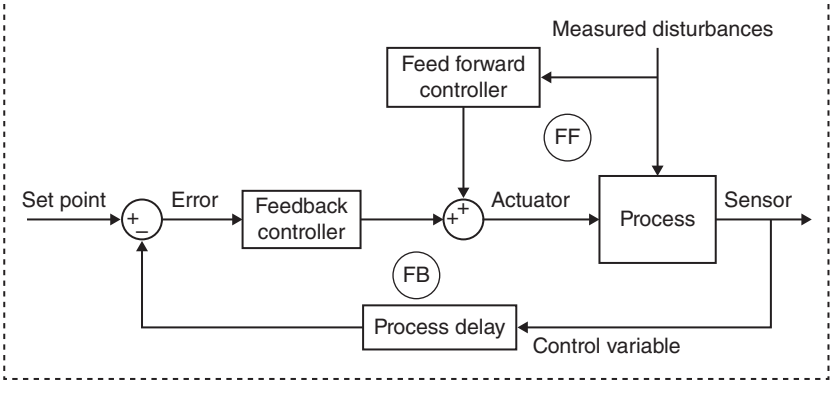

Figure 12.9 *Combined feedforward/feedback control.*

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

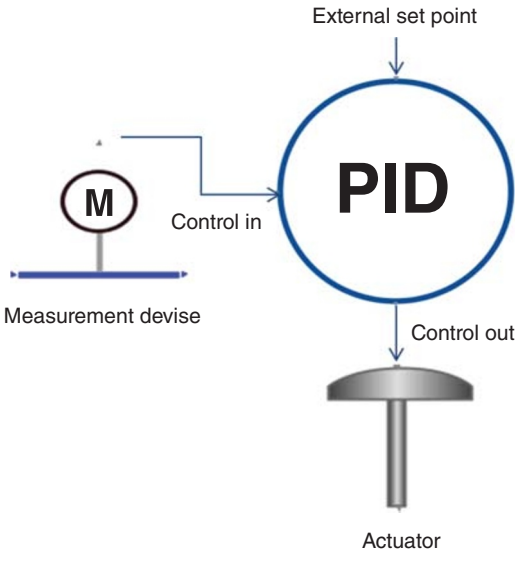

Figure 12.10 *Integration of a control loop with the process model.*

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

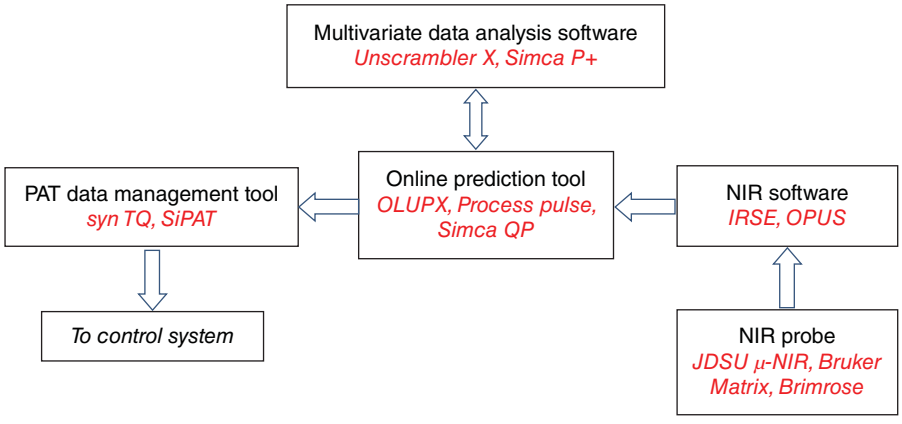

Figure 12.11 *Flow of communication from a sensor to the data management tool. Examples of each tool from different vendors are also given.*

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.

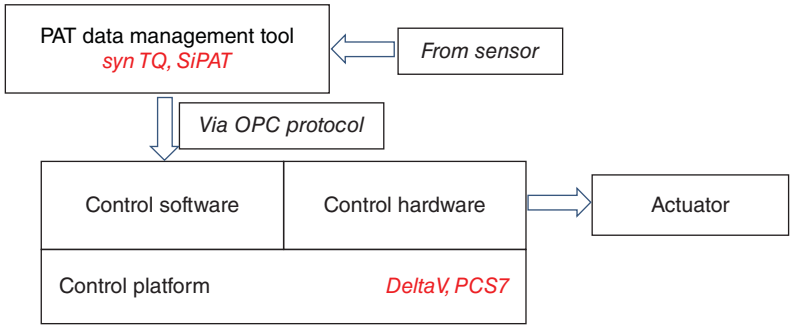

Figure 12.12 *Flow of communication from the PAT data management tool to the actuator.*

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

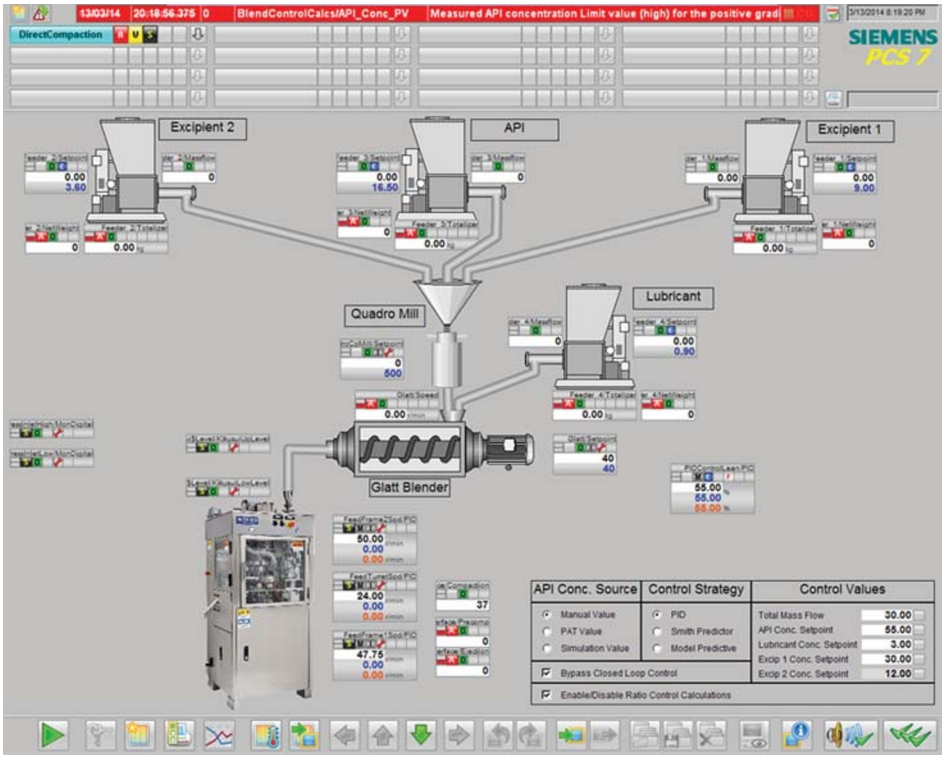

Figure 12.13 *Plant operating and control user interface.*

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.

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