



GOOD PRACTICE GUIDE:

Continuous Manufacturing of Oral Solid Dosage Forms

Equipment Requirements for
Integrated Continuous
Manufacturing

Automated Control
System

Material Handling

Loss-In-Weight
Feeding/Blending

Granulation,
Compression,
Coating

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Continuous Manufacturing of Oral Solid Dosage Forms

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Preface

The pharmaceutical industry has begun to embrace Continuous Manufacturing (CM) technologies to develop and commercialize both new and legacy products. While there continues to be significant production executed routinely and acceptably under the traditional batch paradigm, the application of continuous manufacturing principles and equipment to pharmaceutical processing can lead to decreased costs and time in development as well as robust assurance of final product quality for manufacturers.

This Good Practice Guide reviews the major drug product unit operations typically employed in continuous manufacturing and aims to establish a set of minimum equipment requirements for each type of system to function as part of an integrated process train. Although most of the unit operations discussed are already well-understood and utilized in batch manufacturing (the notable exceptions being loss-in-weight feeding and continuous blending), the physical and automation requirements for all equipment to work in concert as part of a successful continuous manufacturing platform need to be carefully considered. This Guide can be utilized as a companion reference to the *ISPE Baseline® Guide: Volume 2 – Oral Solid Dosage Forms (Third Edition)* [1] by pharmaceutical companies looking to deploy new continuous manufacturing technology, as well as by vendors and end-users focused on designing the next generation of continuous manufacturing systems.

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1 Introduction

Starting in the mid-2000s, the pharmaceutical industry began to apply the principles of continuous processing to the manufacture of Oral Solid Dosage (OSD) medicines. While the industry initially focused on establishing the technical capabilities of continuous manufacturing systems, it has now advanced to the commercial manufacture of multiple drug products with distribution approved in the US, Europe, and other countries around the globe.

The consensus among experienced practitioners is that the continuous approach has numerous benefits. It is often more robust than its batch counterpart, it is designed for reduced variability, and it can achieve improved product quality through better blend uniformity. These features can be especially beneficial in the case of drugs with a narrow therapeutic index. In addition, continuous manufacturing offers potential safety benefits such as lower exposure risk for operating personnel.

Moreover, the same attributes of continuous manufacturing that make it technically favorable have long been predicted to make it economically advantageous [2]. This leaves the industry in a non-ideal state, where few people question the merits of the approach but many challenges to widespread adoption remain.

The following four conditions are recognized as fundamental business challenges for continuous manufacturing:

- CM lines are capital intensive, often costing US\$10–30 million (€9–27 million).
- CM lines involve complex automation that require significant validation effort in addition to the validation of the physical equipment comprising the various unit operations.
- CM lines are capable of producing large scale quantities (0.5–3 billion units per year), but the average product volume of new drugs in development is in the low 100s of millions of units, which does not require high-throughput plants.
- Fully integrated CM lines require different operator skill sets than are currently available, typically including higher levels of automation and process understanding.

While some organizations may have a small number of very high volume products for which a dedicated continuous line could be built, most companies are discovering that in order to justify the cost of the technology, continuous manufacturing lines need to be multi-product capable and rapidly deployable. Given the wide range of variability of pharmaceutical product profiles (e.g., dose, weight, volume, number of components, raw material handling needs), a line with a fixed design is highly likely to be incompatible or suboptimal for the breadth of products in an organization's portfolio. If the line cannot sustain a high rate of utilization, the positive economic benefits of continuous manufacturing may not be realized. The technical skills required to design and deploy a customized flexible build are also a challenge for many pharmaceutical companies above the investment in the machinery itself. Therefore, the time investment before a return on investment is achieved also becomes a limiting factor.

It is evident that for continuous manufacturing to achieve its full potential, a different approach to process engineering, system design, and operation is imperative without compromising the robustness required for manufacturing in a Good Manufacturing Practice (GMP) environment. As more companies integrate continuous manufacturing into their development and commercial operations, there will inevitably be an increased demand for more flexible, modular, and robust systems that can accommodate a wider range of products and production control strategies. This Guide provides a valuable resource for new and existing companies as they design and integrate continuous processing equipment into their operations, highlighting best practices and opportunities for enhancement to both vendors and end-users already engaged in developing continuous manufacturing lines of the future.

1.1 Rationale and Purpose

In 2017, the ISPE OSD Community of Practice [3] formed a working team to advance the use of continuous manufacturing in the pharmaceutical industry and increase the long-term efficiency and affordability of the manufacture of OSD products. Members of the team included end user pharmaceutical companies, equipment vendors, and academics with expertise in continuous processes and automation. This group conducted a broad survey of the pharmaceutical industry with respect to its adoption of continuous manufacturing, in order to highlight best practices and identify opportunities for improvements in the technology. Individual sub-teams were created that focused on specific drug product unit operations, and a separate team focused on the automation and measurement system aspects of continuous lines. The collective output from these teams formed the raw material for this Guide.

The Guide was produced with the following objectives:

- To establish a set of minimum equipment requirements for various pharmaceutical unit operations to be integrated as components of a continuous line, including design considerations for the required automated controls
- To identify opportunities for future harmonization and flexible integration of both physical equipment and control software
- To identify areas where currently available equipment can be enhanced to meet the needs of the industry as the next generation of continuous manufacturing platforms are developed.

It is intended to serve as a comprehensive reference for pharmaceutical companies, regulators, and vendors as this emerging technology continues to develop.

This Guide serves as a companion document to the *ISPE Baseline® Guide: Volume 2 – Oral Solid Dosage Forms (Third Edition)* [1].

1.2 Scope

The Guide considers the production of OSD forms via continuous manufacturing processes and equipment. The major unit operations in tablet manufacturing are reviewed in separate sections, including information covering the internal feedback controls required to run each unit operation as a stand-alone system. Chapter 7 covers the automation control systems typically deployed to run fully integrated continuous lines, as well as Process Analytical Technology (PAT) measurement systems used to provide feedback on the process or materials.

Information contained in this Guide is neither a set of standards nor is it a commissioning/qualification/regulatory design guide. It is not intended to supersede governing laws or regulations that apply to the manufacture of pharmaceutical materials, nor is it intended to invalidate any existing facilities that may not align with the guidelines presented. The use of this document for new continuous manufacturing installations or renovations of current systems is at the discretion of the facility owner or operator, and is subject to the current codes and standards of governing regulatory bodies and local GMP and Good Engineering Practice (GEP).

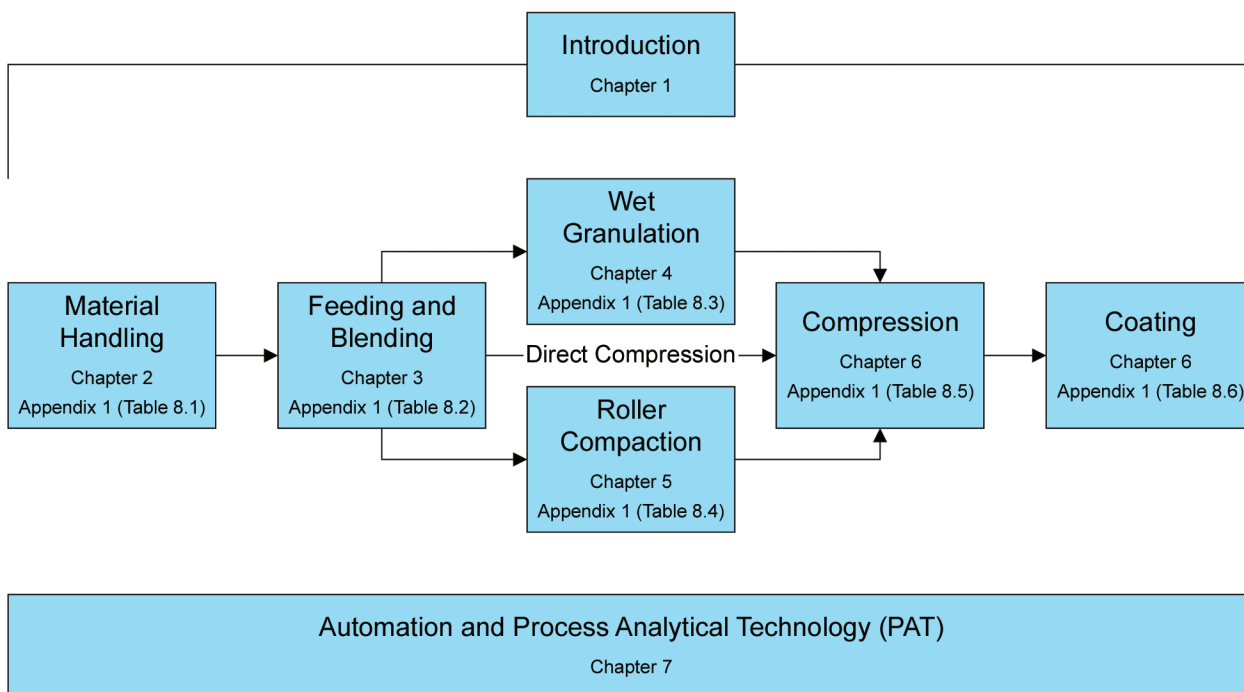
The Guide is not intended to address safety or facility-level issues related to the manufacture of pharmaceutical products.

1.3 Structure of this Guide

The structure of the Guide is shown in Figure 1.1. Chapters 2 to 6 cover the various unit operations and are presented in the same order those systems are commonly connected in actual continuous manufacturing lines. Chapter 7 covers automation and PAT. It is located after the chapters dealing with the physical equipment as that information is generally relevant for all process trains.

In Appendix 1, tables are presented listing the various equipment attributes for each type of system, along with information on the criticality of those attributes for the system to function well in a continuous manufacturing operation.

Figure 1.1: Structure of Guide Chapters



2 Material Handling

2.1 Introduction

This chapter reviews the relevant considerations for design and implementation of material handling as part of a continuous manufacturing platform. In continuous manufacturing, the primary focus of material handling is long-term and stable performance in providing material into the process line, without introducing process risk and without material losses.

Material handling equipment types and attributes are discussed in this chapter. These topics include storage conditions, storage container types, storage container features, mechanical flow aids, milling and screening, sampling and monitoring, pneumatic conveying, interfaces between unit operations, cleaning, and other considerations such as robustness, containment, changeover, and flexibility. Minimum requirements (as derived from basic process descriptions and appropriate performance indicators), operational aspects (such as safety or product changeover requirements), and opportunities for enhancement (related to cleanability, assembly and disassembly, control of dust explosion risks, etc.) are provided. This information should be referenced in relation to the full process line and the desired control strategy.

Table 8.1 provides additional information on the unit operation equipment attributes.

2.1.1 Background

A continuous process is characterized by a simultaneous flow of raw materials into and product out of the process [4]. Regardless of the continuous or batchwise (discontinuous) nature of individual unit operations, the integration of the operations allows for overarching automation systems to monitor and control the process within a set of defined limits to ensure quality of the product, which is a clear benefit of continuous manufacturing. When continuous manufacturing is applied to make a product, this integration is typically achieved by linking multiple continuous processes together. In cases where the transit of raw materials is discrete, the size and timing of the batch allow for a continuous process with the use of an intermediate hopper. For powders, however, every raw material may behave differently due to their physical properties and their ability to retain some history of their earlier processing conditions. This results in continuous processing equipment designed to actively drive the flow of powders (e.g., mechanical flow aids), rather than passively guiding the flow (e.g., such as gravity discharge from a hopper).

The front end of every continuous manufacturing process must start with the supply of raw materials, the active metering of these and in-process materials, and the mixing of the incoming streams. In these operations, gravity flow and other bulk handling concepts are of interest. In addition, it is often necessary to have a mixture of batch and continuous operations to achieve the required fine level of control. Material handling equipment is usually designed as a batch process to allow precise accountability of the material. Once the material enters the manufacturing line, it is then metered into a continuous blender by the use of Loss-in-Weight (LIW) feeders.

Figure 2.1 is a generic image of the front end of a continuous manufacturing line and shows:

1. Material handling (blue) to the LIW feeders:
 - a. By gravity via bins, drums, or bag systems, or
 - b. Through vacuum transfer
2. Conveying of each material by the LIW feeders (yellow) into collection chute (green) for transfer to the continuous blender
3. Continuous blending (purple) by:
 - a. Vertical blender, or
 - b. Horizontal blender

Figure 2.1: Generic Front End of a Continuous Manufacturing Line

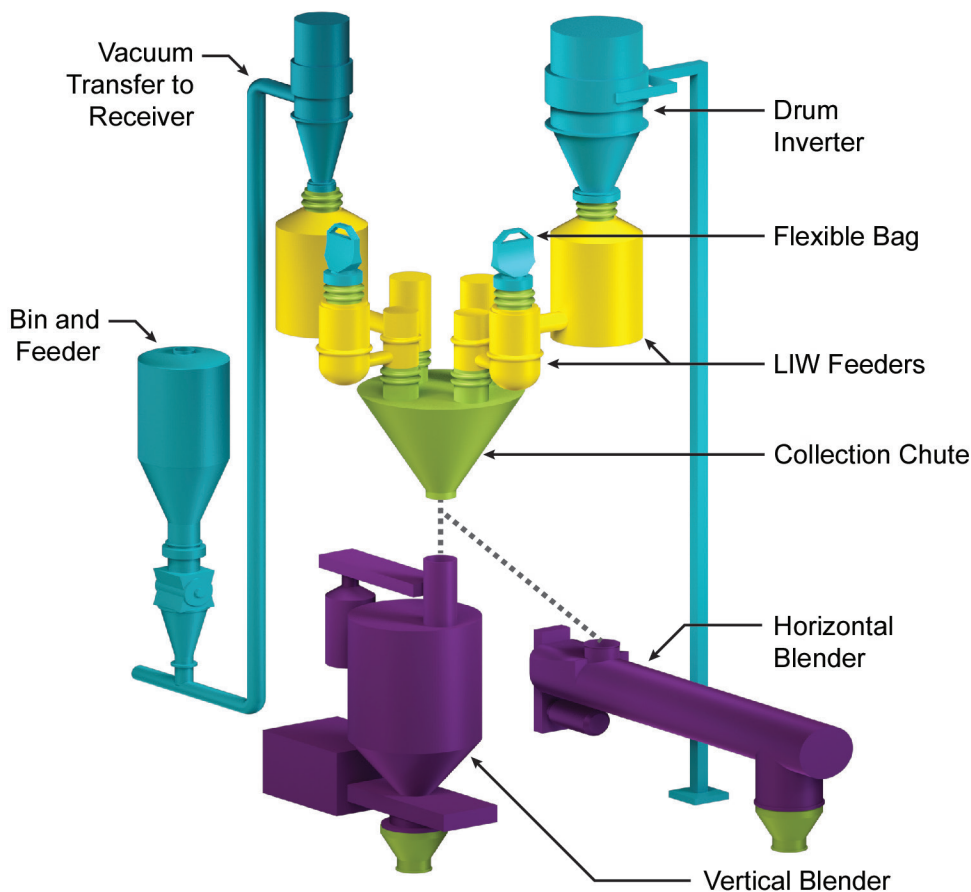


Figure Note: Material handling (blue), feeding (yellow), transfer points (green), and blending options (purple).

2.1.2 Powder Characteristics

The focus of this chapter is on the handling of powders to a number of continuous manufacturing unit operations. The characteristics of the powders passing these operations will have an influence on performance and can be used to select some of the features involved. Basic classifications to describe powders relative to their handling characteristics are as follows:

- **Cohesive:** Powders that are cohesive have high interparticle contact forces that accumulate as a bed strength. Cohesion can result in a resistance to gravity flow and in shearing, as well as clumping or agglomerating during feeding. Potential behaviors associated with cohesive powders include arching over hopper outlets, narrow flow channels and ratholing, high shear resistance to agitation, and non-uniform dispersion when mixed with other powders. At the extreme of cohesion is caking, which can occur due to handling conditions such as high humidity or temperature, and can result in the forming of hard lumps that do not easily revert to their primary powder particles.
- **Frictional:** Powders that have a high coefficient of sliding friction against surfaces can also be resistive to flow. This effect is dependent on the surface in contact with the powder (composition and finish). Potential behaviors associated with highly frictional powders include a resistance to sliding on a chute surface, funnel flow discharge and the potential for ratholing (if the powder is cohesive), buildup on a surface, or a lack of release after some time in contact (adhesion).
- **Segregating:** Powders that are free flowing and have a range of particle size, can be prone to segregation by several different mechanisms. This is particularly a risk for continuous manufacturing processes where a pre-blend that varies in composition is handled. The potential for segregation is further based on the manner in which the powder is handled, with a primary risk from forces applied during transfers when interparticle motion occurs.
- **Aeratable:** Two-phase (air:solid) flow behaviors can result with fine particle size powders below a general threshold of 100 µm. These behaviors can include air retention in powder beds, resulting in problems such as flushing through feed equipment and long settling times needed to fit intended masses into fixed volume containers. Further, two-phase flow issues can occur once powder beds settle, resulting in limited discharge rates through processing equipment, or secondary problems with packing or gravimetric feed uniformity.
- **Dust forming:** Also related to particle size, materials that have a fraction of very fine particles can result in dusting if air currents are present. This can in turn have a number of consequences, including segregation or hazard exposure if the dust is an Active Pharmaceutical Ingredient (API) as well as a risk of explosion if the dust is prone to such issues.
- **Compressible:** The bulk density of a given powder varies as a function of the consolidating pressure applied to it, in addition to the state of aeration of the powder. Powders that are highly compressible can exhibit variations in mass stored or being fed over time, depending on factors such as head pressure (weight of material above) or applied energy (vibration or shearing).
- **Static-Sensitive:** Some powders can become electrically charged due to frictional contact (triboelectric effect) and, when they are resistive to relaxation of that charge, the result can be cohesion or sticking to surfaces. In addition to these flow concerns, the release of this energy can result in a spark and a risk of a dust explosion if other conditions are present.

2.1.3 System Design Considerations

In continuous manufacturing, material handling systems are deployed as connection points, i.e., a means to deliver material from one process to another while ensuring other goals such as containment are met. When operating effectively, material handling systems primarily support the objectives of the processes around them and are rarely the focus of Critical Process Parameters (CPPs). However, problems can and often do occur with material handling systems, in terms of their ability to efficiently achieve reliable powder flow.

As a result, features of a material handling system should be carefully evaluated during the design stage, whether at the development and initial deployment of equipment or as part of the consideration for a material change with an existing system. The material itself has an important role, as the resulting behavior of a system is fundamentally an interaction between the material and the equipment features. A cohesive and aeratable material will require different system features than material that is more free flowing and settles quickly [5]. A basis for design should be established before manufacturing is attempted (i.e., off-line performance testing of a particular system with the material and/or flow property testing of the material) [6]. The focus of material handling in a continuous manufacturing process is primarily on raw ingredients, since these are the materials that are handled in bulk prior to feeding and blending; however, there are some areas where accumulation and handling of blended powder could also occur.

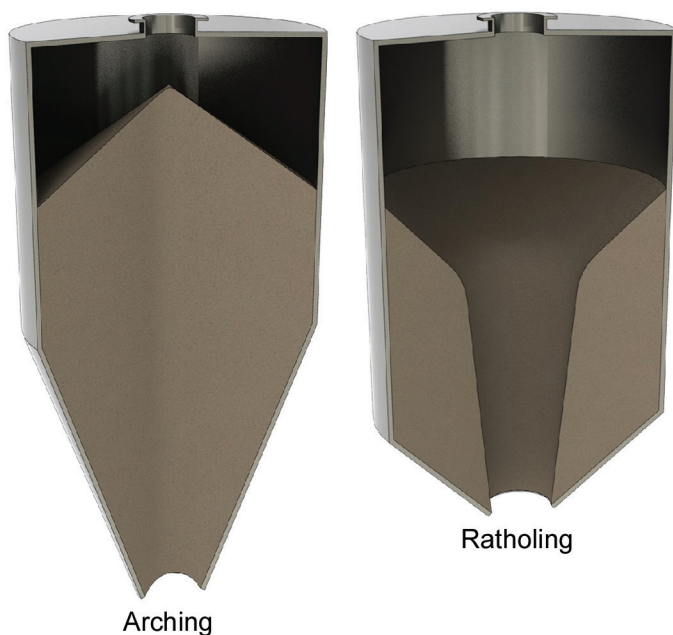
2.2 Storage Conditions

2.2.1 Providing Reliable Flow after a Defined Storage Time

The storage of raw materials is an important capability that a handling system needs to provide as part of continuous manufacturing. Powder volumes that are on hand cannot be expected to be in motion at all times, given that the goals of flexibility and inventory management involve having extra quantities of material on hand that are not in-process. As a result, the material may be stored in a warehouse for some period of time prior to its use. During this storage period, the stresses applied to the powder due to its own weight or from stacking of bags, for instance, can result in a gain of cohesion (caking, agglomeration), making flow more difficult to initiate when required. This behavior is material specific; some powders will not gain cohesive strength at all, while others will only do so if handled in larger volumes (resulting in higher compaction stresses) or in particular situations (storage temperature and humidity, starting moisture content, particle size/shape, impurities, etc.). These stresses impact the powder's ability to flow by gravity and may result in flow obstructions by arching or ratholing as illustrated in Figure 2.2.

Figure 2.2: Example Arching and Ratholing Flow Obstructions

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2.2.2 *Providing Total Capacity Needed*

The system design will have to provide the desired total capacity for each raw material. This can be accomplished in a variety of ways, likely involving the way in which the raw material is packaged by the supplier. Factors that should be considered include the package type, the total volume needed based on the amount of material desired to be on hand, and the manner in which total capacity is achieved. Stacked flexible bags can have an implication for the material within due to the total weight in the stack compacting material in the bottom package. Drum size can also influence compaction, with higher head pressure and settlement occurring in larger vessels. The need to transfer material for active use, such as into an Intermediate Bulk Container (IBC), may be part of the consideration for a storage system as well, given that the final use at the process will have to be provided.

2.2.3 *Reducing Risk of Moisture Gain or Caking in Storage*

The risk of moisture gain or caking can also be material specific, as some powders can be prone to moisture pickup and caking if stored in an environment that has high humidity and temperature fluctuations. The protective ability of packaging, use of desiccants, and use of the material from larger quantities (exposing the remaining material to varying conditions) can have a role as well. The direct result can be poor processability of the material due to increased cohesion or lumps that have formed. Broader goals can be affected as well, including blend uniformity due to the presence of agglomerates and final product quality due to moisture pickup.

2.2.4 *Reducing Risk of Segregation during Transfer*

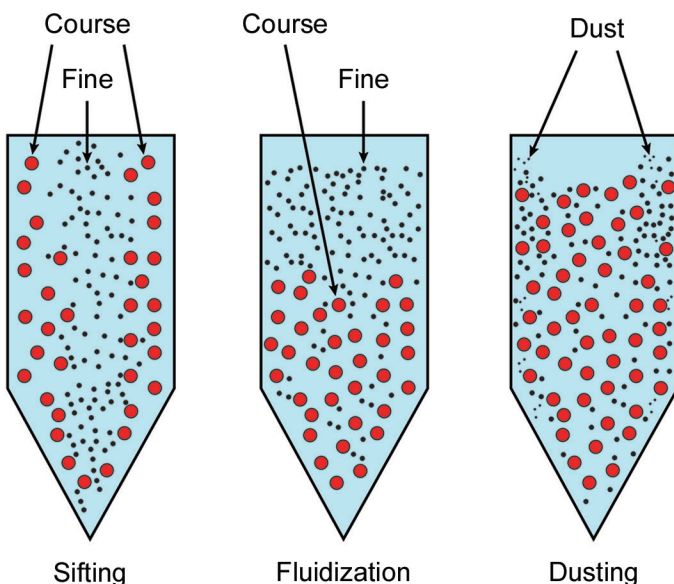
Segregation is defined as the unintended concentration of particles with a particular attribute within a larger quantity of material. Particle size is the biggest driver, but particle shape and density can play a role as well. Segregation can occur due to a number of fundamental mechanisms, most often during transfer steps (e.g., from storage to process feeding) when applied forces are high and interparticle motion occurs. The most common mechanisms include [7]:

- **Sifting:** Under appropriate conditions, fine particles tend to sift or percolate through coarse particles. For segregation to occur by this mechanism, there must be a range of particle sizes (a minimum 2:1 ratio of coarse to fine particle sizes can be sufficient) [8]. In addition, the mean particle size of the mixture generally must be greater than about 100 µm, the mixture must be relatively free flowing, and there must be relative motion between particles. This last requirement is very important, since without it even highly segregating blends of ingredients that meet the first three requirements, will not segregate. The result of sifting segregation is usually a side-to-side variation of particles. In the case of a bin, the smaller particles will generally be concentrated under the fill point, with the coarse particles concentrated at the outside of the pile.
- **Air entrainment (fluidization):** Variations in particle size or density of fluidizable powders often result in a vertical striation pattern, with the finer/lighter particles concentrated above larger/denser ones. This can occur, for example, during the filling of a bin. Whether the powder is pneumatically conveyed into the container, or simply drops free-fall through an air stream, it may remain fluidized for an extended period of time after filling. In this fluidized state, larger and/or more dense particles tend to settle to the bottom. Unlike sifting segregation, fluidization segregation becomes more likely as the particle size gets smaller.
- **Particle entrainment (dusting):** Similar to the air entrainment mechanism, particle entrainment occurs primarily with fine powders that vary in particle size or density. As a result of these variations, the finer/lighter particles remain suspended in air longer than larger/denser ones. The result can be unusual patterns of segregation. For example, a pneumatic conveying line that terminates at the side wall of a receiver will induce various patterns of air current within this vessel depending upon the incoming velocity, the solids loading ratio, the amount of material already in the receiver, as well as the location and type of dust collection system within the receiver.

See Figure 2.3 for a comparison of these common mechanisms for the case of filling a bin.

Figure 2.3: Common Segregation Mechanisms

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For a single raw material, segregation can result in the concentration of fine versus coarse particles and, when the material used in this behavior, can affect bulk density or blending in downstream operations. For a pre-blend with API, this issue can be more significant as it could result in variations in API being fed to a continuous blending process over time, even if the mass feed rate is comparatively constant. In addition, segregation of an inter-granular or final blend during transfer between process steps must also be analyzed and mitigated.

2.3 Container Type

2.3.1 Bin/Intermediate Bulk Container Systems

Bins and IBC systems are typically stainless steel construction, and consist of a constant cross-section area at the top (typically round or square; both shapes can be referred to as a cylinder section), followed below by a converging hopper to a smaller outlet where a valve is placed to open for discharge. These types of containers have the advantages of being mechanically robust, while providing good containment, ease of cleaning, and an opportunity for reuse. A typical downside is that they are inflexible, i.e., the container features or capacity cannot be changed without a significant investment. These containers often rely on gravity to promote flow, and hence their design must consider the range of characteristics for the powders handled in them.

2.3.2 Drums/Drum Inversion Systems

There are different types of drums and drum inversion systems that can be used, but the basic approach is that a cylindrical drum is the vessel used for storage and transport. These drums are typically plastic lined and can be stainless steel or fiber construction. To recover the material within, the drum is generally inverted with a drum inversion system at the point of use. This mechanism involves securing the drum into position and mating it with a hopper section that often includes a valve to control discharge. Drum inversion systems can be automated to align the hopper outlet with the downstream equipment during the inversion. These systems offer good flexibility in that multiple drums and hopper sections can be used, but can be subject to contamination concerns from the drum and liner materials based on how the units are handled.

2.3.3 Flexible Bag Systems

Flexible bag systems (and flexible IBCs) have flexible and sometimes clear (plastic sheet) walls, which allow for the advantage of manual manipulation with visual confirmation to promote discharge of the material within. These systems are often single-use/disposable, reducing the need for material transfer and cleaning. Total weight can be a concern, depending on whether they are handled by personnel or by lifting equipment. If they are stacked during storage, the cumulative weight on the material in the bottom bags can result in excess powder consolidation that has a negative effect on flow and caking (as discussed in Section 2.2.3). Flexible bag systems can also be supplied with integrated valves and mated to gravimetric feeders for smaller raw material additions (e.g., lubricants).

2.4 Container Features

2.4.1 Unit Storage Capacity

The storage capacity of a single container is based on its size and shape, but determining what is best from cost and efficiency standpoints requires an evaluation of the process goals. Multiple small units can provide more flexibility than fewer large units but requires more frequent filling.

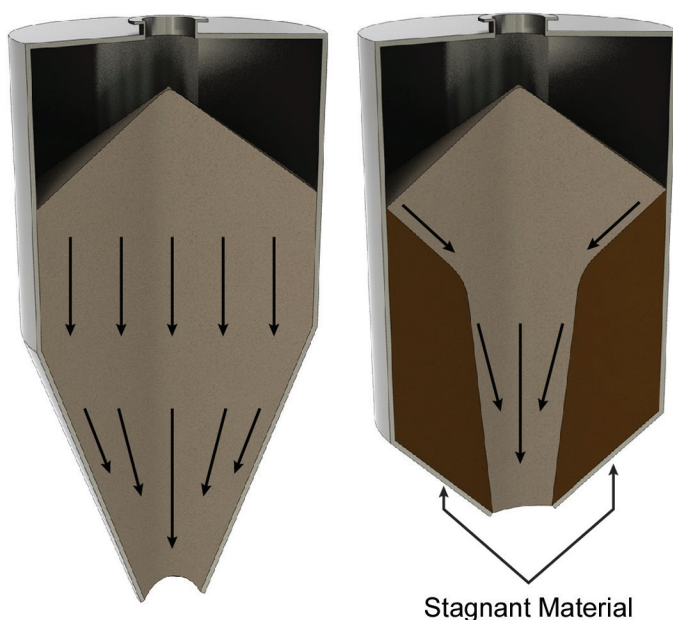
2.4.2 Geometry Features (Cylinder/Cone/Cone Angles)

The geometry features of a storage container have the greatest influence on its flow performance. The selected hopper shape, and whether the walls are sufficiently smooth and steep can promote *mass flow* (flow along the walls) during gravity discharge. In mass flow, all of the material is in motion whenever any is withdrawn from the hopper. Material from the center as well as the periphery moves toward the outlet. Mass flow hoppers provide a first-in-first-out flow sequence and prevent stagnation. Mass flow will eliminate the potential for some flow problems, such as ratholing, while reducing the potential for others, such as arching and the effects of sifting segregation. Mass flow is also a significant consideration for performance factors such as residence time. For mass flow to take place, the hopper walls must have sufficiently low wall friction with the material being handled and be steep enough to achieve flow along them [9].

The alternative discharge pattern is *funnel flow*. Depending on the material, funnel flow can result in a higher potential for flow and segregation problems and can promote variations in bulk density for the discharged material over time. In funnel flow, an active flow channel forms above the hopper outlet, with stagnant material at the periphery. As the level of material in the hopper decreases, material from stagnant regions may or may not slide into the flowing channel, depending on the material's cohesive strength. Funnel flow results in a first-in-last-out flow sequence and generally increases segregation tendencies as a result. These flow patterns are shown in Figure 2.4.

Figure 2.4: Flow Patterns during Gravity Discharge

Used with permission from Jenike & Johanson, <https://jenike.com/>.



Note: Mass flow pattern is shown on the left. Funnel flow is shown on the right.

2.4.3 Interior Surface Finish

The product contact surface is an important consideration with respect to cleaning. Depending on the usage being considered, it can also impact flow performance. Higher degrees of polish on hopper surfaces, i.e., lower Roughness Average (Ra), can often provide mass flow with shallower angles; however, this relationship does not always hold, and in some cases, friction between the powder and surface increases with surface polish. Cleanability and flow performance should be evaluated through testing prior to equipment construction.

2.4.4 Outlet Size (to Downstream Equipment Interface)

In gravity flow, the outlet size is an important consideration for the prevention of cohesive arching, which is material and process condition dependent. A smaller opening that appears most appropriate for feeder and connection sizing may not support the desired flow performance [10]. In some cases, this mismatch can be appropriately addressed with mechanical flow aids (discussed in Section 2.5). However, since flow aids come with added operating and maintenance costs compared to gravity, it is best to understand how much aid is needed ahead of time. In addition, the flow performance of equipment below the outlet can influence the behavior of the container above. Pre-feeders, if used to control the refill of feeder hoppers, must ensure the entire outlet area is active if mass flow is a desired outcome for the container.

2.4.5 Discharge Isolation Valve

Containers typically include a shutoff valve (e.g., gate valve, butterfly valve) to isolate the material within from downstream equipment and to allow for container replacement or refill. The selection of this feature should be made with the downstream process in mind. Factors to consider include response time, containment, space, cost, maintenance, and cleaning. Shutoff valves should be operated fully open, since metering of material flow is accomplished by other equipment (e.g., a feeder), and a partially open valve can negatively impact the flow performance of the container (e.g., even changing the flow pattern from mass flow to funnel flow).

2.4.6 *Incorporated Sealing/Mating Equipment*

Isolation of powder dust, equipment vibrations (to ensure accurate load cell readings), interface size, and transfer rate will all play a role in the selection of connection and docking equipment.

2.5 Mechanical Flow Aids

2.5.1 *Range of Types Available*

If gravity flow proves insufficient to ensure reliable discharge of a given powder, then a mechanical flow aid may provide benefit. Note that the use of this type of flow aid can be highly process dependent. In applying a mechanical flow aid, there are two broad categories of desired enhancements: achieving flow at all (overcoming a cohesive arch) or emptying out a container or hopper that has residual material on the walls (dust, adhered buildup, or possibly material trapped in a rathole). See Figure 2.2 for examples of arching and ratholing flow obstructions. Typical approaches that can be considered include external vibration, internal agitation or vibration, or gas injection. Other solutions may be available or desired that are not considered by these categories.

2.5.2 *External Vibrator*

If external vibration is to be considered, effectiveness will be based on location(s) and activation. Variables that can be considered include sizing, the use of high versus low frequency, high versus low amplitude, activation cycle, and control scheme. Performance testing at or near full scale is one approach to gain insight, given that the problems being addressed may not be well-represented by a small test bed.

2.5.3 *Internal Vibrator or Agitator*

As with external vibration, the effectiveness of internal devices will be based on location(s) and activation. Product contact features and surfaces can raise additional concerns in terms of cleaning and area of influence, as well as the potential for unintended consequences to the material itself (attrition and/or segregation).

2.5.4 *Gas Injection*

Gas (e.g., air or nitrogen) can be injected at one or more locations of a storage and feed system to promote powder flow based on the induced force and reduction in solids stress in the affected area. The interaction of the gas with the powder is a point of concern, as the excess gas can promote segregation and will have to be separated out of the bed if only the powder is desired downstream. Success will be influenced by the location(s) selected, dispersion and contact area, gas flow rate/fluidization velocity for the powder, activation cycle, and control scheme.

2.6 Milling and Screening

2.6.1 *Available Milling Features*

Within a continuous manufacturing process, milling may be included to overcome agglomeration of a powder (de-lumping) as a raw material is moved from storage to a feeder. Milling may also be used to reduce the fundamental particle size downstream of a granulation process. Success factors should be considered in advance to guide the process development, including desired Particle Size Distribution (PSD), shape, and uniformity over time. Different mill types can be evaluated, including roll compression, impact/hammer, or shear/attrition. Some mills can operate in a flood loaded mode, where the incoming solids stream is full, and mill throughput will dictate the flow rate. However, in some situations, a greater degree of control and uniformity can be achieved if a pre-feeder is used, and the flow rate to the mill is less than the throughput it is capable of. Ultimately, the throughput and outcome for the material being milled will be dictated by the screen area, drive arrangement, impeller design and speed, as well as details for the screen itself (mesh size, construction, and opening shape).

2.6.2 Available Screening Features

Screening is typically used when a segmentation of the PSD is desired, and can involve removing larger particles or contaminants that do not pass through a particular screen size and/or fines that do pass through a particular screen size. Similar to milling, success factors should be considered in advance to guide the process development, including desired particle size range for acceptance, as well as flood loading versus use of a pre-feeder. Ultimately, the throughput and outcome for the material being screened will be dictated by the screen area, drive arrangement, screen orientation and recovery of the different size fractions, features for de-blinding the screen(s) (balls, ultrasonic excitation of screens, etc.), as well as details for the screen(s) used (mesh size, construction, and opening shape).

2.6.3 Adjustability based on Performance

Adjustability should be considered based on the range of use intended, such as impeller shape/speed and screen type, opening size, and orientation. These features will influence the resulting PSD for the material, screener efficiency/carryover, material buildup on a screen, and process yield.

2.6.4 Features to Address Dust Explosion Hazards

This is a separate area of concern whenever airborne dust can be present within a unit operation. Since mills and screens are highly prone to dusting, it is best to perform combustible dust tests (K_{St} , P_{max} , Minimum Explosible Concentration (MEC), Limiting Oxygen Concentration (LOC), Minimum Ignition Energy (MIE), etc.) and then evaluate the risk of a dust explosion as part of a formal Dust Hazard Analysis (DHA) [11]. For material and process combinations that are at risk, precautionary measures can be deployed where needed (mill speed reduction, inert gas purging, grounding, explosion vents, suppression systems, etc.).

2.7 Sampling and Monitoring

2.7.1 Sampling Method/Device for Recovery and External Analysis

Mechanical sampling probes or access points can be included within system components for collecting specimens that are sent to a laboratory and analyzed for properties of interest in an off-line mode (e.g., moisture content, particle size, assay, etc.). The degree of representativeness for such a sample (compared to the larger mass of material it was pulled from at a given time point) can be dependent on location, device size, and method of collection. These considerations, along with statistical justification, would need to be factored in as part of a broader sampling plan development. Sampling thief type systems have long been used in batch processes for this purpose [12], with known limitations and bias that can occur based on the disturbance of the bed and limited area that samples are pulled from.

2.7.2 Integrated Monitoring of Material over Time

As an alternative for sampling systems that extract and remove discrete portions of powder, PAT can provide a path for instrumentation that can be added directly to a process for real-time monitoring of a property for the powder that is passing by. Factors to consider include the relevance of the method compared to information desired, device location, maintaining an active field of view for the instrument, proper calibration, and ensuring the sampling rate is sufficient for the process information desired. The utilization of such devices as part of a sampling plan has its own set of considerations in continuous manufacturing. The plan should be statistically justified, and the test duration should consider the process residence time to allow for timely decisions.

2.8 Pneumatic Conveying

2.8.1 System Classification – Conveying Mode and Line Loading

Pneumatic conveying can be used in continuous manufacturing to deliver raw materials from storage to a feeder, as well as to transfer in-process powder (e.g., transfer of an inter-granular blend between process steps). It can occur over a wide range of conditions bounded on one end by gas alone with no entrained powder and at the other extreme, by a completely full pipe where the solids are essentially extruded through the line. Most industrial conveying systems operate somewhere between these two extremes and are classified broadly as either dilute phase or dense phase, depending on the relative solids loading and velocity of the system. Dust collection is an example of conveying that operates at very low solids loading, where the performance is governed almost entirely by the gas flow.

2.8.1.1 Dilute Phase Conveying

Dilute phase conveying occurs when particles are conveyed in the gas stream at a velocity that is greater than the saltation and choking velocities. Most powders can be conveyed in dilute phase; however, potential adverse effects such as pipeline wear or particle attrition could result due to a high conveying velocity, as well as the risk of segregation of an inter-granular or final blend. Additionally, dilute phase conveying can make matters for static-sensitive materials worse, resulting in particle adhesion to pipe wall surfaces (buildup).

2.8.1.2 Dense Phase Conveying

Dense phase conveying occurs when particles are conveyed in the gas stream at a velocity that is less than the saltation velocity and can be used to reduce the risk of particle attrition. Only certain powders can be effectively conveyed in a dense phase mode. In plug flow, coarse, permeable materials such as large granules and tablets can likely be reliably conveyed. In moving bed flow, some fine and impermeable powders can be effectively conveyed.

2.8.1.3 Positive Pressure Conveying

A positive pressure conveying system utilizes gas pressure to entrain the powder and transport it to one or multiple destinations. Conversely, a vacuum conveying system can pick up the powder at atmospheric pressure and pull it into a vessel that is under vacuum. Positive pressure systems can convey materials over longer distances than vacuum systems. Vacuum systems are well suited for handling dust forming or toxic materials, given that any leakage in the pipeline will be inwards.

2.8.2 Blower/Vacuum Pump Considerations

The air (or gas) mover is one of the most critical components of a pneumatic conveying system. It must provide the required pressure and flow rate to move the material through the line, and might need an adjustment for varying feed rates or material handled. It is generally sized based on a performance curve of pressure versus flow rate.

2.8.3 Feeder (to Conveying Line Inlet) Considerations

This feeder introduces the powder at a controlled rate into the pipeline where it is mixed with the conveying gas. Positive pressure systems require devices (e.g., a rotary valve) to feed material from atmospheric pressure into a pressurized pipeline, while vacuum systems may require a pressure sealing feeder to minimize leakage of gas into the pipeline. This feeder must maintain feed rate and consistency during a conveying cycle to prevent line plugging.

2.8.4 Pipeline Considerations

For the pipeline layout, an acceleration zone is required right after the feed point to bring the powder up to a steady transport velocity. The pipeline consists of straight sections, both horizontal and vertical, connected together with bends or elbows. These points can be sources of material buildup, wear, and pressure loss, and hence should be selected based on the application.

2.8.5 Filter/Receiver (Gas/Powder Separator) Considerations

In the filter/receiver, or separator, the powder particles are decelerated and recovered from the gas stream in which they have been transported, and then dropped into a hopper or other target vessel for the next step in the process. The clean gas is typically released into the atmosphere. In closed loop systems, the gas is recirculated and used to convey additional solids. The type of separator used can vary based on the application (e.g., fabric filter/receiver, cartridge filter/receiver, cyclone), along with the required separation efficiency. The size of the unit will be based on the required air:cloth ratio (e.g., typically 1–10 fpm for excipients versus < 1 fpm for a fine or toxic APIs). The method for material release from the filter surface could include shaking versus reverse pulsing, and it is likely to have a cleaning sequence with controls (monitoring pressure drop, for instance) built in. The filter media selection is another important consideration, based on operating temperature, abrasion resistance, and filtration properties.

2.8.6 Instrumentation and Controls

Typically, pneumatic conveying systems include instrumentation to monitor line performance and possibly provide feedback control for critical components such as the gas mover or powder feeder. Parameters of interest (at multiple points) can include powder mass, gas pressure, temperature, and gas flow rate.

2.8.7 Performance Considerations

One important reason to monitor the pneumatic conveying line performance is to prevent problems that could have serious consequences, such as line plugging and material buildup in the filter-receiver. These unintended consequences, such as particle attrition and segregation, can be reduced based on how the system is designed and operated.

2.8.8 Dust Explosion Considerations

Similar to the concern raised with milling and screening, pneumatic conveying systems increase the risk for dusting and associated explosion hazards. Combustible dust testing and a DHA can be used as a basis to consider precautions or controls (inert gas purging, grounding, venting, isolation, suppression, etc.).

2.8.9 Maintainability Considerations

A line cleaning cycle (e.g., high velocity gas through the line) can be used after a conveying cycle to ensure it is empty. The line and its major components can be designed for quick disassembly and access for inspection or replacement of items that wear out, such as the separator's filter element. A range of factors can be considered for maintainability features, including frequency of access and preventative maintenance that will be required.

2.9 Chutes Between Unit Operations

In continuous manufacturing, chutes are gravity flow connection points between unit operations and can take on a variety of configurations.

2.9.1 Flexible Connection Considerations

Where relative motion or weighing isolation is anticipated (such as the interface to screeners or gravimetric feeders), flexible connections must be used to direct and contain the powder between the unit operations. Considerations include rigidity, degree of movement possible without degradation, and selection of the product contact material to reduce buildup and static charge, while maintaining the alignment of the connection itself.

2.9.2 Rigid Chute Considerations

Fixed (rigid) chute connections can be used when relative motion is not anticipated or required for scale measurements. Important considerations for these components include the chute angle (if a slope is required) to ensure powder flow and prevent buildup, chute cross section to support the process feed rate, and interior surface finish to minimize adhesion.

2.9.3 Intermediate Valves

Intermediate valves can be used as a part of interconnections for isolation purposes. They should provide full port openings to prevent buildup and uneven flow (a particular concern when sensors are relied upon), while also ensuring complete sealing when closed. Finally, quick disassembly can be advantageous for cleaning.

2.10 Cleaning

2.10.1 Use of Wash Stations/Clean Out of Place

The discontinuous use of smaller material handling components or sub-systems can support the use of Clean out of Place (COP), where the equipment is removed and reassembled after cleaning. COP can involve either manual washing or the use of machine washers. Equipment access, ease of assembly, and manipulation are among the considerations for this type of cleaning process, along with the selection of detergent, cleaning fluid velocity to provide sufficient physical action, complete coverage of internal surfaces by cleaning solution, use of ultrasonic energy, rinse cycle definition, as well as process controls such as timing and temperature.

2.10.2 Wash in Place/Clean in Place Capability

Clean in Place (CIP) is generally used for large systems with components that cannot easily be taken apart, and often results in less downtime since it eliminates the associated equipment handling. Automated systems, spray systems, and immersion are examples of CIP operations. To ensure coverage and containment, specific details must be determined, e.g., nozzle design and locations, activation sequence, etc. Some of the same considerations for CIP remain as for COP, such as the selection of detergent, cleaning fluid velocity, coverage of internal surfaces, rinse cycle definition, as well as process controls such as timing and temperature.

2.11 Other Considerations

2.11.1 Robustness

In a continuous manufacturing setting, the material handling systems must be capable of operating for long periods of time to match the overall process train (for example, up to 8 hours per shift, 3 shifts per day, 6 days per week, or 144 hours total per week) without breakdown, loss in performance, excessive noise, vibration, heat buildup, undue frictional wear, or generation of contaminants.

2.11.2 Containment

Depending on the materials involved and the overall strategy being used, the material handling system will need to provide a minimum level of containment. Typical requirements are stated in terms of Occupational Exposure Band (OEB) and should be considered for all components and features during running, setup, and disassembly. OEB 3 is common, while OEB 4 and OEB 5 (and future classifications) may be necessary for some situations.

2.11.3 Changeover

To support a continuous manufacturing process, rapid docking of IBCs, flexible IBCs, or emptying of drums is likely necessary. Adequate capacity in a feed chute or hopper section to maintain operation during changeover must be provided, which is a particular concern if more complex docking activities are required.

2.11.4 Flexibility

Depending on the product mix for a continuous manufacturing line, changes to the material handling system may be necessary. For instance, a single feed point may need to accommodate materials with different handling properties and/or usage rates, while a varying number of raw materials may be used for different products.

3 Feeding and Blending

3.1 Introduction

LIW feeders and in-line continuous blenders are the dominant type used for OSD continuous manufacturing. Feeder performance is determined by the achievable mass flow rate accuracy and associated precision, while the goal of the blending step is to achieve a uniform mixture of the input components at the required concentration by the time the material exits the blender. This chapter reviews the necessary elements for the design and implementation of continuous feeding and blending operations as part of a continuous manufacturing platform.

Table 8.2 provides additional information on the unit operation equipment attributes.

3.2 Feeding

3.2.1 Background

Unlike in batch processing, where individual raw/intermediate materials are dispensed in the required ratios prior to downstream processing, continuous manufacturing requires that raw/intermediate materials are continuously supplied to the downstream process in the required ratios in real time. The individual feeder mass flow rates entering the continuous process are determined by the formulation and the overall manufacturing line rate. Each feeder is set up to target its respective mass flow rate as a percentage of the line rate, which is determined by the formulation. However, each feeder may contain more than one raw material. In some cases, a blend of two or more materials may be desired.

Essentially there are only a few LIW feeder designs: vibratory feed, screw feed, or belt feed. This chapter focuses on screw feeders, since they are the most common type used in continuous manufacturing of powders in the pharmaceutical industry.

The LIW screw feeders dispense a specified amount of material per unit time using feed screw(s) to convey the raw material from its hopper into a downstream unit operation, typically a continuous blender. Alternatively, the feeder can be configured to deliver a specified mass of a component into a semi-continuous blending system. Mechanical flow aids in the hopper can be used to assist the flow of powder into the feed screws to ensure the flights of each screw are consistently full of powder during operation, typically referred to as screw fill. The screw speed is then used to control and maintain a mass flow rate via feedback control where the screw speed is automatically adjusted to deliver the precise amount of mass per unit time.

3.2.2 Equipment

Most LIW feeders designed for pharmaceutical operations use corotating twin screws to convey material from a hopper into the blender. The sets of screws may be of different lengths or diameters but are encased within a barrel having appropriate clearance to ensure a forward conveyance of the material. The screws extend into the feeder hopper, where they are exposed for filling.

Screw pitch capacity (i.e., screw free volume) is determined by the number of lobes, pitch, flight profile, and core dimensions. Twin screws can be intermeshed in such a way that the profiles of each screw have a small clearance between each other and can wipe one another with each rotation, as is the case for concave screws. This is desirable for cohesive powders, which tend to cake up and stick to the screws. Auger screws have a larger clearance between each other, where the benefit of wiping is eliminated, but the free volume is increased. The balance of self-wiping versus free volume requirements must be determined by the user. Single screws can only adjust the free volume as there is no second screw and have a higher risk for pulsation of flow for cohesive powders.

The selection of the appropriate screw flight volume and screw speed provides a volumetric displacement per unit revolution over time [13, 14]. The density of the particular material can then be used to determine the theoretical mass flow rate. Other bulk material properties such as flowability or compressibility have also been shown to influence the choice of screw, but this approach typically requires a material property library and significant feeding experience across a range of screw types and flow rates. Therefore, multivariate methods can be employed to predict the appropriateness of the screw selection to meet the desired feeder mass flow rate [15].

The hopper for the feeder is designed to accommodate a variety of powder characteristics. Hopper size influences the choice of load cell, as it must provide suitable resolution and linearity across the cycle of emptying a full hopper for a range of mass flow rates and the refilling strategy for the feeder. Hopper geometry influences how the powder flows into the screws under the force of gravity [16].

The key feature is to ensure there is constant flow into the screws. For example:

- Flat bottom cylindrical hoppers may utilize an impeller that guides powder from the hopper bottom into the screws; gravity acts to fill the void left in the wake of the impeller.
- Hemispherical hopper bottoms may have a rotating paddle that turns over the powder and disrupts any stagnant regions, guiding the powder into the screws.
- V-shaped hoppers that have flexible walls in the lower section of the hopper massage the powder to disrupt stagnant flow.

In each of these examples there may be vendor-specific solutions to further enhance the flow of powder into the screws, such as baffles, bridge disruptors, and other means of mechanical or vibrational agitation.

Aside from housing the material, the objective of the hopper is to ensure that the screw(s) are always full; however, because powder is compressible¹, the hopper design impacts the density of the powder in the screw. The powder weight from a full hopper exerts a peak consolidating force on the material entering the screws resulting in a maximum density of powder in the screw [17]. During normal operation, the fill level of the hopper decreases as the powder is dispensed causing an eventual reduction in consolidation force and screw fill density. There are a number of papers that have described this effect [13, 14, 18, 19].

3.2.3 Operation

3.2.3.1 Physical Connection

LIW feeder balances are quite sensitive in order to achieve the desired accuracy of mass flow rate. Physical connections such as stiffness of bellows (i.e., flexible connections) as well as changes in pressure or airflow near the scale can impact the scale's weight measurement. Thus, it is critical for the connection or transfer points both upstream and downstream of the feeders to be carefully designed and properly vented to not influence the scale during operation. A valve or seal may be used to eliminate influence from upstream equipment; however, it is preferred for the mechanical design to minimize product contact surface area where material may build up and/or create bulk flow issues (e.g., powder bridges). Flexible connections and/or mechanical compensators should be used as appropriate, and the airflow/pressure should be monitored or maintained for the best operational results. An approach to mitigate pressure changes is to sufficiently vent the feeder hopper and outlet such that pressure cannot build within the system.

¹ The bulk density of a powder varies as a function of the consolidating pressure applied and the state of aeration of the powder. Powders that are highly compressible can exhibit variations in mass stored (on a volume basis) or being fed over time, depending on factors such as head stress (weight of material above) or applied energy (vibration or shearing).

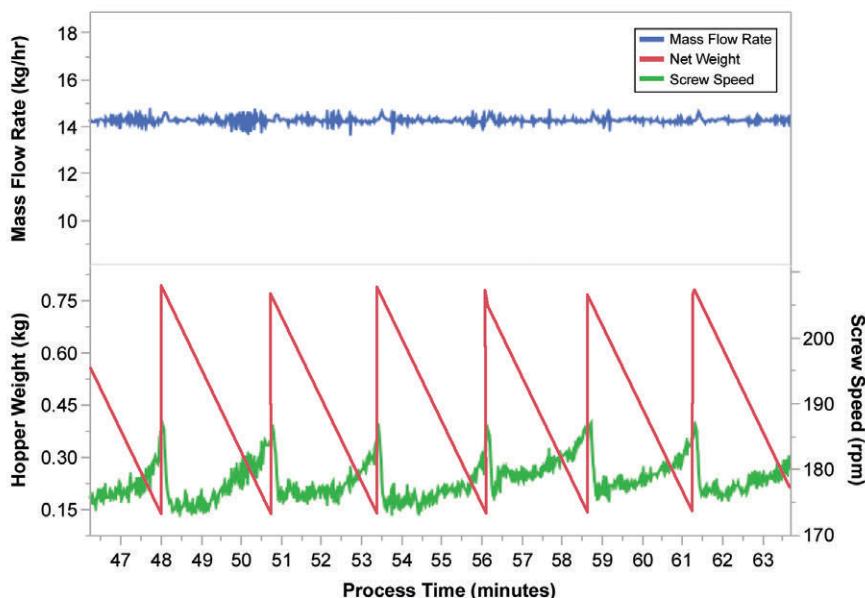
3.2.3.2 Automation and Controls

During routine production, the feeders primarily operate in gravimetric mode, where any shift or trend in bulk density affecting the screw fill density will be corrected immediately by an automated feedback control loop (i.e., the screw speed is dynamically adjusted to achieve the target mass flow rate). If the continuous batch requires more material than a single hopper charge can sustain, it is required to refill the hopper at a periodic frequency based on the mass flow rate and the volume of the hopper. A minimum hopper weight, or refill limit, is therefore selected to trigger a refill action. If the hopper weight goes below this value, it is advisable to pause the process until the hopper is refilled.

During a refill period, a charge of material is deposited into the feeder hopper typically while simultaneously discharging material from the screws into the downstream unit operation. The load cell cannot be used to accurately predict the loss-in-weight mass flow rate during this short time due to the gain-in-weight nature of the refill, so it is common for the feeder to momentarily enter volumetric operation (i.e., operation at a fixed screw speed set by the feeder's controller) to ensure stable performance during refill events. Once gravimetric operation has resumed, if there is any residual set point error, the feedback control drives the mass flow back to set point. This behavior can be used to adjust the screw speed during volumetric control during future refill periods.

While the refill event is usually triggered during continuous operation, this is not necessarily a requirement for a robust process. Although not typical, the equipment train may also be paused for refills and restarted upon completion. An example of the refill cycle and the interplay of feeder controls is shown in Figure 3.1, where the top graph is the mass flow rate and the bottom is the net weight of the hopper and screw speed, both per unit time. The feeder refill cycle repeats throughout production to ensure the continuous and consistent supply of powder for the feeder to deliver the target mass flow rate of each material.

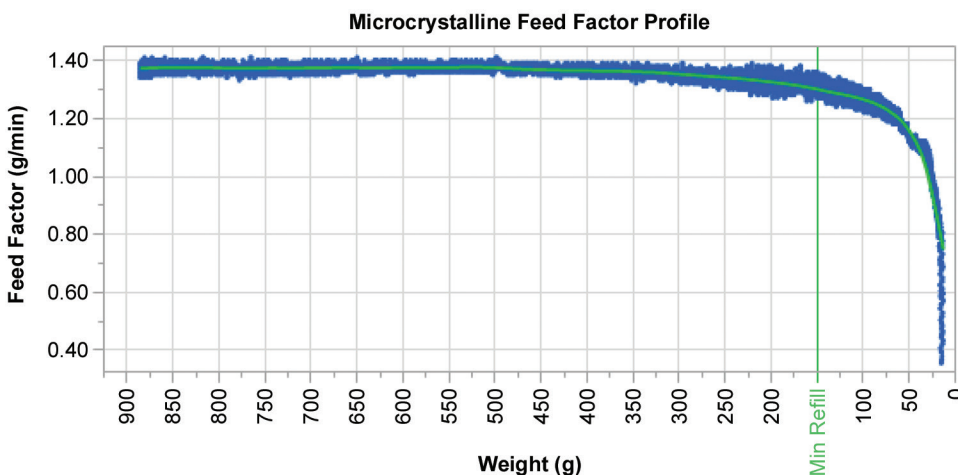
Figure 3.1: Feeder Refill Cycle



The refill limit ensures that the feeder does not run empty and continues to operate within the range of the screw speeds required to deliver the desired mass flow rate.

Some feeders define a state variable (often known as the feed factor) that is relevant to the current feeding capacity or screw fill density as a function of the hopper fill level. Its profile over time can be used to determine the optimal lower refill limit. If the refill is triggered within too steep a decay region of this state variable, depending on the feed rate and the time to refill, the mass flow rate during volumetric operation may be off target. An example of how the profile can be used to define the minimum weight of material in the hopper to trigger a periodic refill charge to the hopper is depicted in Figure 3.2.

Figure 3.2: Example of Feed Factor Profile



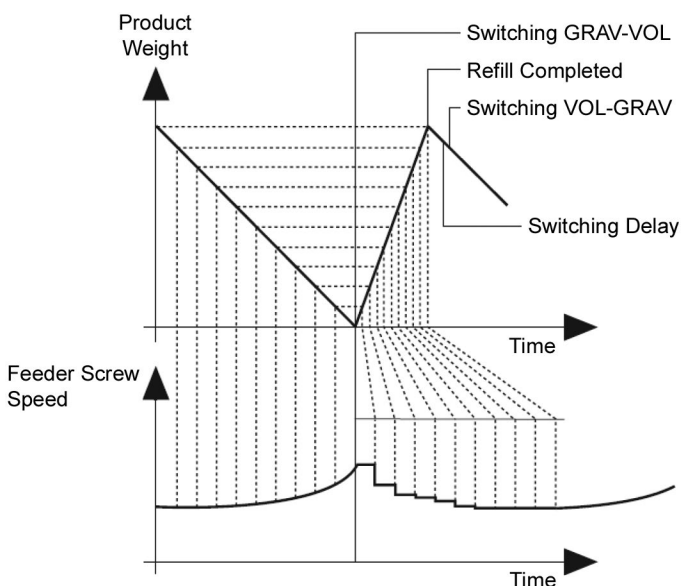
Another consideration related to feeder hopper refills is the frequency of refill and the corresponding outcome. For instance, using relatively tight refill limits (e.g., 40% to 60% of the maximum fill), refills will occur frequently resulting in a relatively constant feed factor, and by design, minimal mass flow deviation. However, the gravimetric ratio (the percentage of the time the feeder is in gravimetric mode versus volumetric mode) will be lower than an alternative strategy of applying wide refill limits (e.g., 10% to 90%). In this case, the opposite effects are directionally seen.

The method and degree of automation for refills must be considered when optimizing the strategy during process development.

Multiple control options are available to minimize the potential mass flow rate deviation during refill by accounting for changes in feed factor by adjusting screw speed.

Typically, the motor speed is stepped downward to accommodate the increasing material density in and above the screws as the refill occurs; an example is shown in Figure 3.3. When the refill is finished, the motor speed is closer to the correct value and thus minimizes set point error and subsequent speed corrections (typically a period of overfeeding would be seen without the refill array).

Figure 3.3: Example of Refilling Profile versus Elapsed Time using a Refill Array



3.2.4 Considerations on Feeding Performance

3.2.4.1 Material Properties Influence on Performance

The most challenging aspect of feeding is conveying poor flowing powder at low, consistent mass flow rates. The feeder is designed to manage and mitigate risks to Critical Quality Attributes (CQAs) such as assay and content uniformity that may result from poor powder flow and variable bulk density by using a combination of mechanical flow aids and feedback controls respectively, as briefly mentioned in Section 3.2.1. The risk is further compounded when the feeders operate at very low mass flow rates, where the signal-to-noise ratio is low relative to the load cell capacity. This is typical for lubricants and potent APIs, where the flow of material being dispensed into the process may manifest as discrete on a 1-second basis. Effects of consolidation, triboelectric charging, and adhesion to the screw barrel all play roles to resist the continuous flow of material out from the feeder [20, 21, 22].

Poor powder flow is a material attribute that results from the many different powder properties (e.g., cohesive, compressible, aeratable², static-sensitive³, frictional⁴ etc.), which inherently may cause a number of flow issues such as bridging in the hopper, ratholing, or stagnation [23, 24]. It can be effectively managed using mechanical flow aids to ensure the screws are always uniformly filled. In some cases, if the screw fill density is too low, an outlet mesh can be employed to provide backpressure on the screws and improve mass flow rate consistency. Caution is needed as too much backpressure can lead to blinding of the mesh during extended operation and a loss of the mass flow rate. Using bridge-disrupting elements, mechanical agitation, impellers, and algorithm-driven vibration/impactor devices in the hopper improve robustness to poor powder flow and are generally available as options provided by the equipment supplier. While each solution may be equipment specific, feeder vendors typically work with the customer during development to hone the most practical design.

Bulk density (i.e., *in situ* density) is an extrinsic property: a representative state of the powder consolidation, and often correlated with the powder flow of the material. For example, many low density ($< 0.3 \text{ g/cm}^3$) powders are also very cohesive and therefore poor flowing. As it relates to screw fill, bulk density is typically dynamic in nature, which results from poor powder flow into the screws. However, it is actively managed through feedback controls and can manifest in several ways.

There are two main types of disturbances arising from transients of bulk density that may occur during the LIW feeding operation: shifts and trends, or sharp disturbances. Shifts and trends are gradual and expected within defined acceptable limits. Sharp disturbances are generally unexpected. Shifts and trends often have little to no effect on the CQAs due to the feeder controller's response when the tuning parameters are properly set; whereas sharp disturbances may impact the mass flow rate and therefore composition of the material entering the blender. Unexpected disturbances are typically short in duration and due to a sharp change in the bulk density or a mechanical failure that causes the feeder motor to try to operate at a speed beyond its mechanical limit. Both of these cases are rare when the material being fed has acceptable powder flow, but in more cohesive formulations at low flow rates, the risk is magnified. In either case, the performance is monitored by alarms, which may provide a warning, stop the process, or flag the material to be diverted downstream if the disturbance is outside the acceptance criteria. However, alarms alone are not a viable control strategy element and the feeders must be designed and configured accounting for the particular material to be fed. A properly designed feeder and line rate can prove to be robust to many of the non-optimal material attributes mentioned above.

² Two-phase (air:solid) flow behaviors can result with fine particle size powders below a general threshold of 100 microns. These behaviors can include air retention in powder beds, resulting in such problems as flushing through feed equipment and long settling times needed to fit intended masses into fixed volume containers. Further, two-phase flow issues can occur once powder beds settle, resulting in limited discharge rates through processing equipment, or secondary problems with packing or gravimetric feed uniformity.

³ Powders that have a high coefficient of sliding friction against surfaces can also be resistive to flow, but the effect will be dependent on the surface in contact. Potential behaviors associated with highly frictional powders include a resistance to sliding on a chute surface, funnel flow discharge and the potential for ratholing (if the powder is cohesive), buildup on a surface, or a lack of release after some time in contact (this time effect can be described as adhesion).

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3.2.4.2 Load Cell Performance

There are several critical aspects of the load cell component of a LIW feeder that contribute to the overall feeding performance. Most importantly, the load cell must demonstrate linearity (or consistent accuracy across its capacity range), stability and repeatability over time, and appropriate precision for the intended purpose. It is also important that the load cell can properly measure disturbances in the mass flow and adjust accordingly so that product CQAs downstream are not impacted. Thus, a load cell must be properly designed such that its overall capacity accommodates the desired mass flow rate for a given material while operating in a proper signal-to-noise ratio range, even at low feed rates. To achieve this, the load cell must be stable, properly isolated from other equipment and atmospheric influence, and sufficiently filter out noise in order to not actively control or react to said influence. In cases where pressure changes occur near the scale with a noticeable influence, pressure can be continuously measured within the feeder hopper and/or at the outlet of the feeder, and the signal sent to the feeder controller for appropriate compensation. In cases where ambient air currents or laminar flow drafts are present, a draft shield or enclosure can be used.

3.2.4.3 Determination of Performance

Poor feeding performance can potentially impact CQAs, such as the assay or the content uniformity of the final dosage form (e.g., tablet, capsule, sachet, etc.). To design against this risk, feeder performance is typically described by accuracy and precision.

- Accuracy accounts for how closely the feeder can maintain a mass flow rate at the target set point
- Precision considers the variation around the mean operating point, which may not be at set point if the accuracy is poor

In both metrics, feeder performance and its impact on CQAs cannot be completely decoupled from the performance of downstream blending. However, optimized feeding accuracy and precision should be primary considerations when designing a continuous manufacturing process. Any residual variation in feeding performance will need to be managed by the continuous blender.

There is currently no universal standard to assess feeder performance. NAMUR-40 [25] was designed for older feeding systems that can be used as a starting point. In this standard, the feeder is operated in gravimetric control at the desired set point for 30 min and samples collected at 1 min intervals. The 30 samples are then individually weighed and the resulting overall mean of sample weights compared to the target set point represents the accuracy, and the standard error of the mean is the variance.

This evaluation is agnostic to the downstream blending as the duration and sample size that represents the desired operating conditions can be tuned appropriately.

There are also approaches that consider the feeding-blending system that uses the Variance Reduction Ratio (VRR) [26], where it is assumed that the accuracy is acceptable. A more detailed review of the VRR is described in Section 3.3.2.

When evaluating the performance of the feeder, it is important to remember:

- For any particular specification limit on accuracy and precision, the selected timescale should consider the downstream Residence Time Distribution (RTD) (see Section 3.3.3 for an explanation on residence time) before manufacture of final unit dosage form to define the desired balance between process risk and process response.
- An external scale can be used in off-line experiments to capture the gain in weight leaving the LIW feeder and it is not influenced by the feeder controls and algorithms.
- All feeder operating limits that may impact the resulting mass flow rate and/or output concentration should take resulting product CQAs into account.

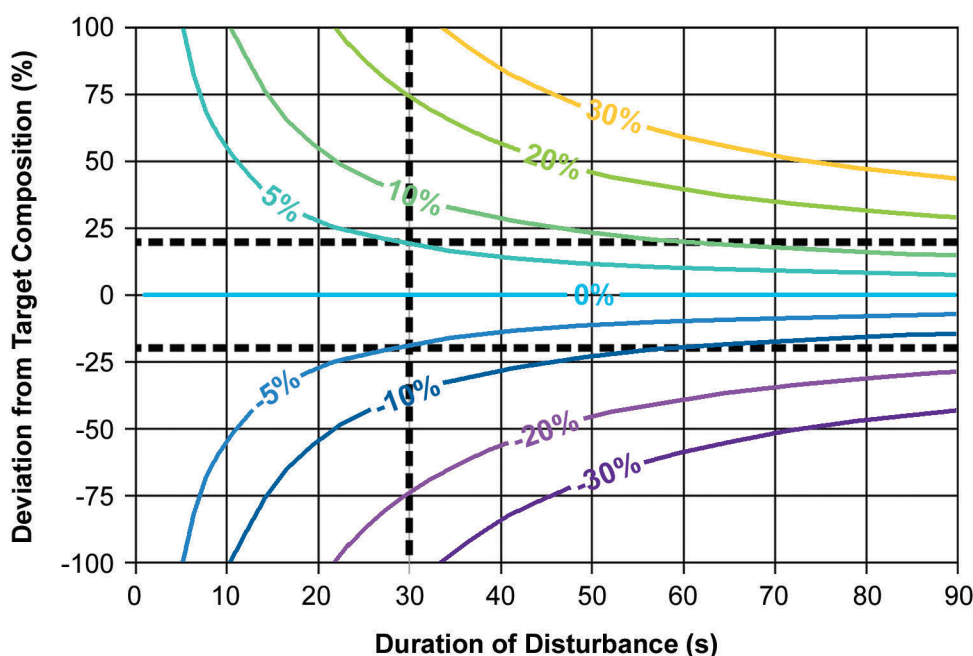
As the continuous manufacturing line usually includes multiple feeders, there is always the potential for an unexpected disturbance in the net composition entering the blender due to the multivariate nature of multiple materials being fed simultaneously. Alarms on each feeder can monitor for univariate disturbances, where alarms on the composition can protect against multivariate disturbances.

Additional control methods may be beneficial for some systems such as ratio control to further drive the concentration of ingredients to set point.

Finally, another method to ensure sufficient accuracy on the composition is to tune the blender dispersion to average or smooth out a disturbance, while accounting for any subsequent downstream means of dispersion from other unit operations. The process can be designed inherently to be robust to disturbances by selecting a sufficiently sized RTD. The residence time essentially dampens the resulting concentration fluctuations proportionally to the magnitude and duration of the disturbance.

A funnel plot [27] is one method used to visualize the maximum tolerable disturbance as shown in Figure 3.4. In the figure, the black dotted lines represent a $\pm 20\%$ disturbance in concentration for 30 s. The contours represent the concentration after dampening of the disturbance. The example shows that the disturbance would not result in an outlet concentration greater than a 5% deviation from target. It should be noted that funnel plots require the use of many assumptions (e.g., a square shaped disturbance) and may represent an idealized representation of the continuous processing system; however, they can be useful tools to guide the direction of development. Regardless, feeder control strategy elements such as mass flow rate or concentration limits should be set considering the effects on product CQAs downstream.

Figure 3.4: Example of a Funnel Plot



Finally, the robustness of feeders to operate with acceptable performance for short or extended periods of time hinges on their ability to tolerate material variability and nullify signal noise from the surrounding environment (which can affect the controller's response leading to inaccuracy in mass flow output). The former has been discussed throughout this section. The latter is primarily a result of the ability of the feeder to be isolated mechanically and electrically from surrounding equipment.

Flowing powders transfer and buildup electrostatic charge (i.e., tribo-charging) that can lead to safety concerns from dust explosivity, or inaccurate feeding due to bearding at the outlet of the feeder. It is important that the feeder has proper bonding and/or grounding to avoid these scenarios. In some cases using larger screws can reduce friction and additional static charge transfer.

Additionally, the feeder cannot truly be mechanically isolated and must connect to the blender as well as the upstream refill device. Each connection point increases the risk to transfer vibration (periodic and continuous) to the feeder and increase the noise on the loss-in-weight signal and ultimately reduce the ability to maintain control of the mass flow rate.

3.2.5 Changeover and Maintenance

Like any other piece of powder processing equipment, feeders will need to be cleaned for maintenance or changeover to a new product. Furthermore, when manufacturing under GMPs, products may have a required cleaning frequency to minimize by-products from active ingredient degradation and cross-contamination between products. The more parts and surfaces the equipment has, the greater the effort and duration it takes to clean and changeover equipment.

Upon initial introduction of a continuous manufacturing process to a plant, it may take a significant amount of time to completely change over the entire line due to the many product contact surfaces and complex geometry of the system. With experience, efficiencies and procedures can drive that time down, but the authors feel there is an opportunity to further design continuous manufacturing equipment to minimize the cleaning and changeover time (see Appendix 1).

Arguably, the feeder is mechanically complex, necessitating a large number of parts to be cleaned, especially considering that there is typically one feeder for each ingredient in the formulation. This increases the impact of minor design inefficiencies in assembly, disassembly, and cleaning. It also drives up the number of product contact surfaces and subsequently the complexity of the cleaning validation. Sharp corners and many removable parts result in an increase in swab locations used to verify equipment cleanliness for the next campaign or product. Finally, additional footprint and storage capacity needs to be considered for cleaning the vast number of parts in order to be ready for the next production campaign.

Another consequence of having a large number of parts is that assembly and disassembly may take a long time. In addition to the inefficiencies of changeover, the length of time under disassembly before cleaning increases the safety risk of the responsible personnel. Upon breaking containment, regardless of the exposure limit of the powder ingredients, the use of Personal Protective Equipment (PPE) may be required. Ideally, a CIP system is available to eliminate exposure risks. However, this option has not typically been a standard offering. In some cases, Wash in Place (WIP) is an adequate substitute. The advantage of a CIP system is that the equipment could theoretically be turned around for the next product without needing to disassemble and reassemble.

With many moving parts there are many requirements for seals between motors, refill mechanisms, and connections to downstream unit operations to ensure reliable containment. Specifically, around the feeder, inflatable seals are typically a robust solution. However, this drives up the air utility requirements and also the risk for pressure-induced errors on the sensitive feeding equipment during operation. A short circuit of compressed air through an inflatable seal may force powder outside of the process onto external surfaces, which are typically not required to be cleaned to the same level as product contact surfaces. Another failure mode occurs if the inflatable seal is not seated properly when replaced, and when inflated the seal may touch surfaces that negatively impact the feeder's delicate balance and feeder controls.

3.3 Blending

3.3.1 Background

Virtually all medicines in tablets produced by the pharmaceutical industry contain a mixture of components: at least one active ingredient combined with multiple inert excipients. In order to ensure that every tablet contains the required proportions of each formulation component, it is necessary that the powder mixture from which the tablets are compressed be uniformly blended. This operation plays a critical role in the process and may significantly impact quality and robustness.

Traditionally, blending operations for pharmaceutical products have been designed as batch processes: all the individual components for a given production run are combined in a vessel, which is then rotated or stirred to obtain a homogenous powder and all the material reaches the end point of the operation at the same time. Various PAT measurement systems have been developed to monitor batch blending processes, optimize process parameters, and determine end points. Issues with determining end points, dead zones, and scale up in traditional batch blenders can be challenging but may not be of particular concern once the process has been developed.

Various designs of in-line blenders are available for use in continuous manufacturing. Generally, they include one or more inlet ports for formulation components, a small amount of powder hold-up mass (i.e., hundreds of grams as opposed to hundreds of kilograms in batch manufacturing) in the mixing chamber, a mixing device, and powder exit port. A representation of a section of a continuous manufacturing line and possible positions of in-line blenders is shown in Figure 3.5.

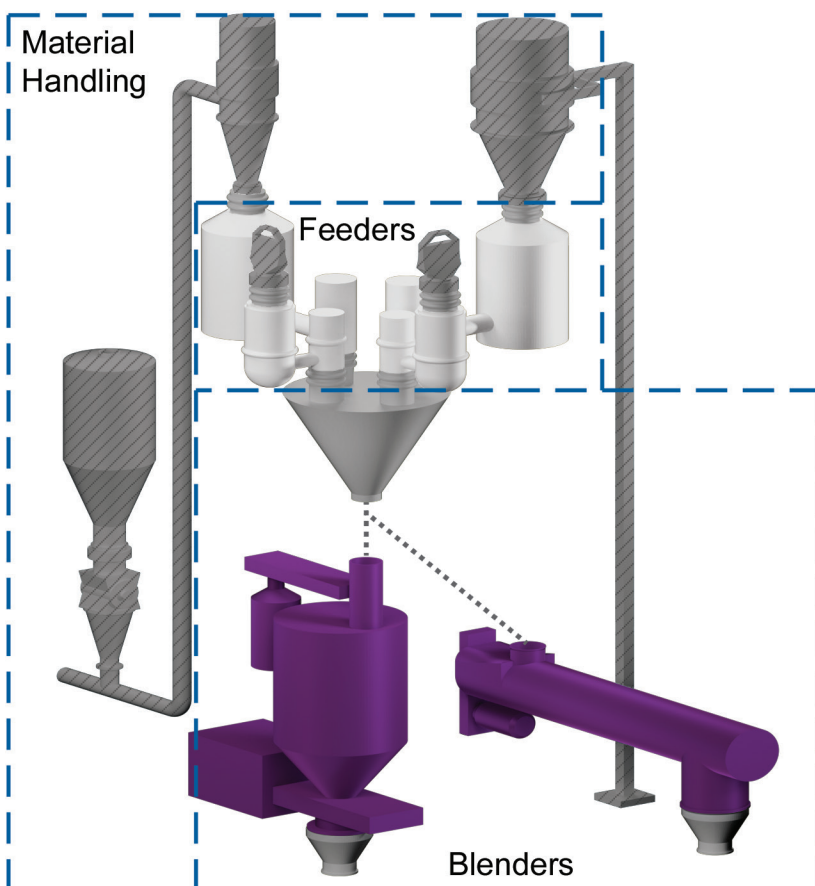
In-line blenders can be defined as continuous blenders when they operate in a simultaneous mass-in equal to mass-out regime, with some internal residence time associated, and therefore are able to dampen out any powder feeding variability.

Alternatively, the blender can be designed to run on a semi-continuous basis to collect, blend, and then feed a defined aliquot of material into downstream processing. This mode of operation removes residence time variability but supports continuous line running and flexible tuning of overall batch size.

Sections 3.3.2 discuss in-line blenders for pharmaceutical manufacturing in terms of their mixing performance including the influence of operating conditions, geometric designs, powder properties on mixing efficiency, and evaluation of RTDs. These blenders must be able to accommodate a wide range of material properties while producing uniform mixtures with desired blend quality attributes at the exit prior to further processing.

A general description of the most common commercially available in-line blenders (linear and vertical) are described in the following sections, all falling under convective mixers according to the FDA Post-Approval Change guidances [28]. It is noted that other continuous blending equipment may be available commercially. Based on the Guide authors' experience, these are less frequently utilized and are not discussed here.

Figure 3.5: Example Representation of a Continuous Manufacturing Line (Material Handling, Feeding, and Blending)



3.3.2 Characterization of Continuous Blenders

The performance and characterization of continuous blenders is commonly described in literature using three key statistics:

- Mean Residence Time (MRT) – driven by residence mass in the blender
- Number of blade passes – extent of mixing
- RTDs

Additionally, a means to quantify mixing efficiency or ability to reduce the incoming feeder variability is the VRR. The following sections will describe these terms in further detail.

3.3.2.1 Mean Residence Time

The MRT of a blender describes the average amount of time that a particle spends in the system before exiting. The MRT is a ratio of the residence mass (amount of powder contained within the blender), which can be actively controlled in some systems, and throughput rate passing through the blender at steady-state. In general, a larger MRT will lead to increased dampening capabilities of fluctuations from upstream gravimetric feeders.

$$MRT \text{ (in minutes)} = \frac{\text{Holdup mass (in kg)}}{\text{Overall line mass throughput (in kg/hr)}} \times [60 \text{ min/hr}]$$

3.3.2.2 Number of Blade Passes

Efficient blending requires a combination of macro-mixing occurring at the bulk level via dispersion effects, leading to an ability to dampen upstream fluctuations, and micro-mixing occurring at the particle level via shearing or diffusion. Total blade passes of a blender with the same impeller configuration may be used to describe the extent of energy applied by the rotating impeller(s) to the powder over the average duration of time that the powder spends within the blender. The number of blade passes is the product of the MRT and the impeller rotational speed. The larger the number of blade passes, the more shear is applied to the powder, which can lead to both positive and negative (for example, deterioration of tabletability with shear sensitive formulations) effects on the output blend properties.

$$\text{Number of Blade Passes } (n) = \text{Mean Residence Time } (min) \times \text{Rotation Rate } (rpm)$$

3.3.2.3 Residence Time Distribution

The RTD has been broadly used to characterize continuous powder mixing in pharmaceutical processes [29, 30]. The RTD measurement is commonly completed via the impulse response method, although other experimental methods are possible. In these studies, upstream gravimetric feeders typically deliver the formulation components into the inlet of the continuous blender at a constant target overall mass line rate. The blender impeller(s) is operated at the desired rotational speed until steady-state is reached (i.e., constant residence mass by measurement, or mass-in equal to mass-out determination).

At an arbitrary timepoint, a tracer material (chosen to both have minimal process impact and appropriate detection for analytical/in-line sensing method) is inserted into the inlet of the continuous blender as a pseudo-instantaneous pulse. The tracer is blended into the formulation components residing within the blender and after some time exits the blender. The blend discharging from the blender can be sampled at the desired frequency from the outlet manually or via an automatic sampling interface device. Alternatively, the blend can be presented in real time to an in-line PAT sensor (e.g., Near-Infrared (NIR) spectroscopy) via an appropriate interface.

The experiment continues typically until the tracer concentration returns to 0, after which the concentration, $C(t)$, of the tracer in the output stream can be analyzed as a function of time and used to determine the RTD function $E(t)$ as shown:

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

It is noted that several other approaches to measure the RTD of a system are also acceptable that may have different advantages in terms of minimizing processing impact during measurement, such as assessments of dynamic process change responses or extinction experiments.

The experimental MRT can also be calculated using this data:

$$\tau = \int_0^{\infty} tE(t)dt$$

Obtaining this characteristic behavior of the continuous blender for example can be used to calculate mass flow of single formulation components at the exit, given the incoming mass flow data from the feeders and a generalized RTD description of the blender. Continuous blender process parameters, configuration of mixing elements, line rate, as well as material attributes of the incoming blend may all impact the RTD profile. In most cases, the flow behavior of a blender is expected to reside between the two extreme conditions of a Plug Flow Reactor (PFR, perfectly unmixed system) and a perfectly mixed Continuously Stirred Tank Reactor (CSTR), described as:

$$E(t) = e^{-t/\tau}$$

3.3.2.4 Variance Reduction Ratio

Due to the possibility of incoming feeder variability having an effect on the variability of the final mixture, an important characteristic of the continuous blender is to what extent variability of feed composition can be eliminated within the unit. A way to measure this characteristic is through the VRR [31, 32]. The VRR is defined as the ratio of variance in concentration at the blender inlet and outlet, and can be defined in general terms or related to specific frequencies of incoming disturbance:

$$VRR = \frac{\sigma_{in}^2}{\sigma_{out}^2}$$

These are determined using the following equation:

$$\sigma^2 = \frac{1}{n} \sum_{i=1}^n (X_i - \bar{X})^2$$

A higher VRR value therefore indicates a better performance of the blender in question, as it will have a better ability to reduce incoming fluctuations.

As an illustrative example of a continuous blender's potential to reduce incoming feed rate variability, Figure 3.6 shows a created set of input feeder data having some amplitude and frequency (top), along with examples of two characteristic RTDs (middle) having different fitting parameters (i.e., number of tanks, MRT, and delay time) which represent two different blenders. With the input feed rates and RTD known, the predicted concentration at the outlet of the blender can be calculated (bottom). As can be seen, for the same input concentration, the two blenders represented by the RTD curves will result in different dampening capabilities (i.e., the VRR) in the output stream.

Figure 3.6: Depiction of the Dampening Capability of Two Continuous Blenders Dampening with Different RTD Profiles

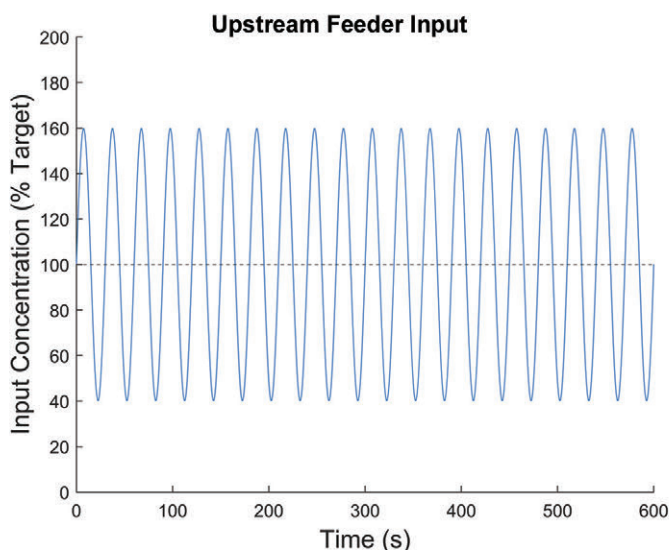
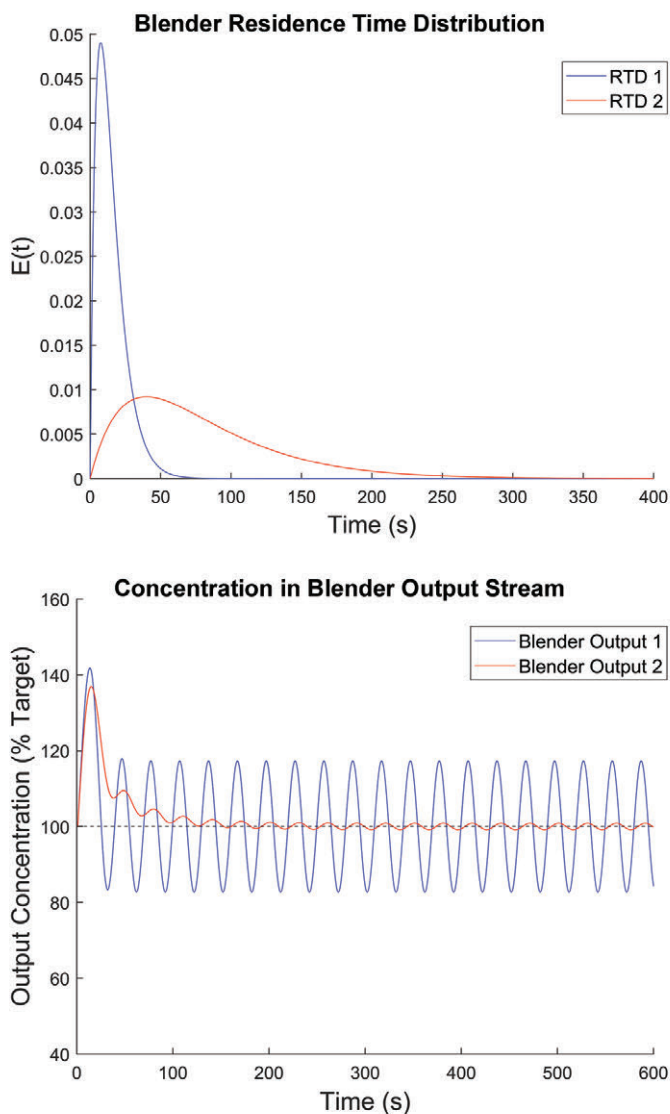
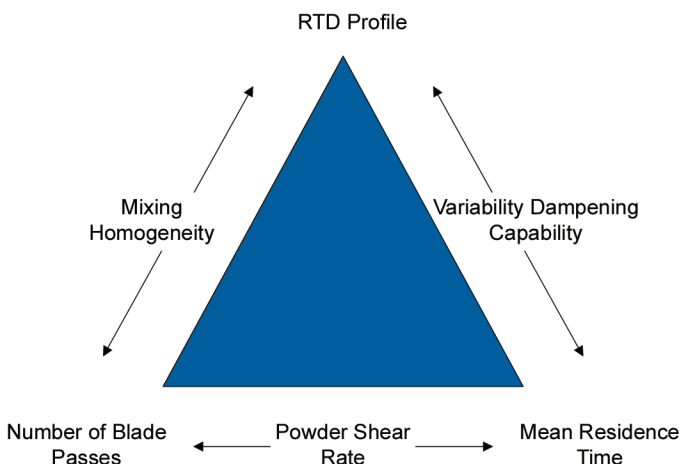


Figure 3.6: Depiction of the Dampening Capability of Two Continuous Blenders Dampening with Different RTD Profiles (continued)



3.3.2.5 Continuous Blender Optimization

As depicted in Figure 3.7, optimization of the blending process space includes selecting appropriate operating setpoints or ranges for the line rate, impeller speed, and resulting residence mass (or when possible setting the residence mass as an independent control set point) of the blender in order to achieve the desired number of blade passes, MRT, and RTD profile. Ultimately, this balance is rooted in the ability to achieve three objectives: a uniform blend (mixing homogeneity), with an appropriate extent of mixing (number of blade passes), and the capability to dampen incoming feeder variability (VRR).

Figure 3.7: General Considerations for Continuous Blender Process Space Optimization

The objective for optimization of the continuous blender can be achieved via modeling or through the use of PAT, however, the ultimate approach should be a risk-based one. It is not appropriate to measure the objective (i.e., mixing homogeneity, extent of mixing, or feeding variance reduction) within the blender as the material is blended in space (see Section 3.2.2.3) not time as in batch-based blending. Furthermore, operations downstream of the continuous process further influences these objectives and so extrapolation of the result from the blender alone to predict the final product quality is not advised.

The objectives for development may be very different than routine commercial production. An example of a risk-based optimization is where the formulation components being fed have demonstrated to flow freely, with low adhesion to surfaces, cohesion to agglomerate, or be insensitive to shear. In this case, modeling approaches or use of PAT for blend monitoring during development only may be appropriate. However, if incoming powder has a known risk of poor flow or likely probability for inhomogeneity or lubrication sensitivity, it may be warranted to include PAT for blend monitoring and product diversion during routine production.

3.3.3 Types of Blenders for Continuous Manufacturing

3.3.3.1 Linear Blenders

Figure 3.8 shows a schematic of commonly available linear continuous blenders usually consisting of the following features:

- One or more powder inlet locations for incoming formulation components
- An agitated linear or near-linear mixing chamber for hold-up of powder mass
- A rotating shaft with adjustable impeller blade configurations and designs
- A powder exit location

During normal operation, upstream process equipment (often comprised of an array of LIW feeders) deliver a constant flow of material into the blender section. The mixing chamber provides a fixed volume for hold-up of powder, which undergoes convective and axial mixing from the rotating blade(s) or other blending components. During steady-state operation, these blenders typically operate in a truly continuous mode, with the mass flow of materials in equal to the mass flow out. This leads to some amount of residence mass inside the powder chamber, which is a function of material properties, blender configuration, and process conditions. This hold-up of powder mass then results in an RTD of particles inside the blender, which has been described [33].

As shown in Figure 3.9 and described in the Section 3.3.2, the RTD profiles shown may vary based on process parameters (input rate, speed of the mixing elements), as well as mechanical design and incoming material properties. The powder is then able to exit the blender and transition to the next unit operation with reduced variability compared to the input stream, due to the RTD as mentioned. Note that multiple blenders can be assembled in series with the output of one blender feeding the next, typically with additional formulation components fed via gravimetric feeders in the subsequent blender location.

Figure 3.8: Generic Representation of a Linear Blender

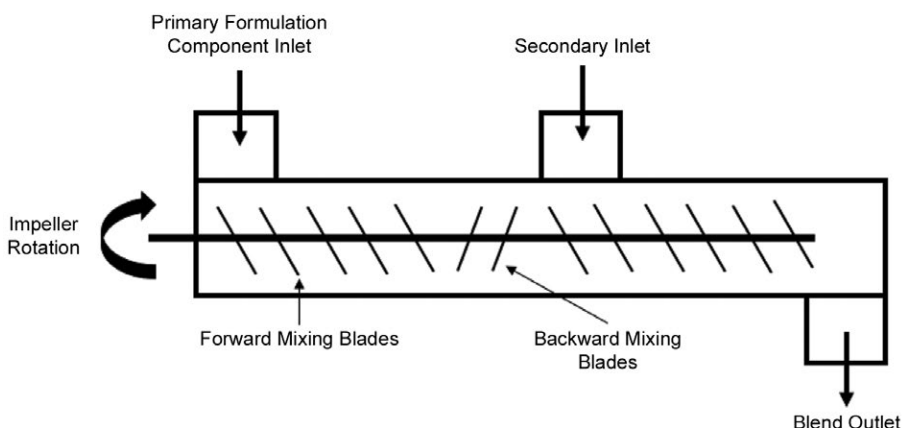
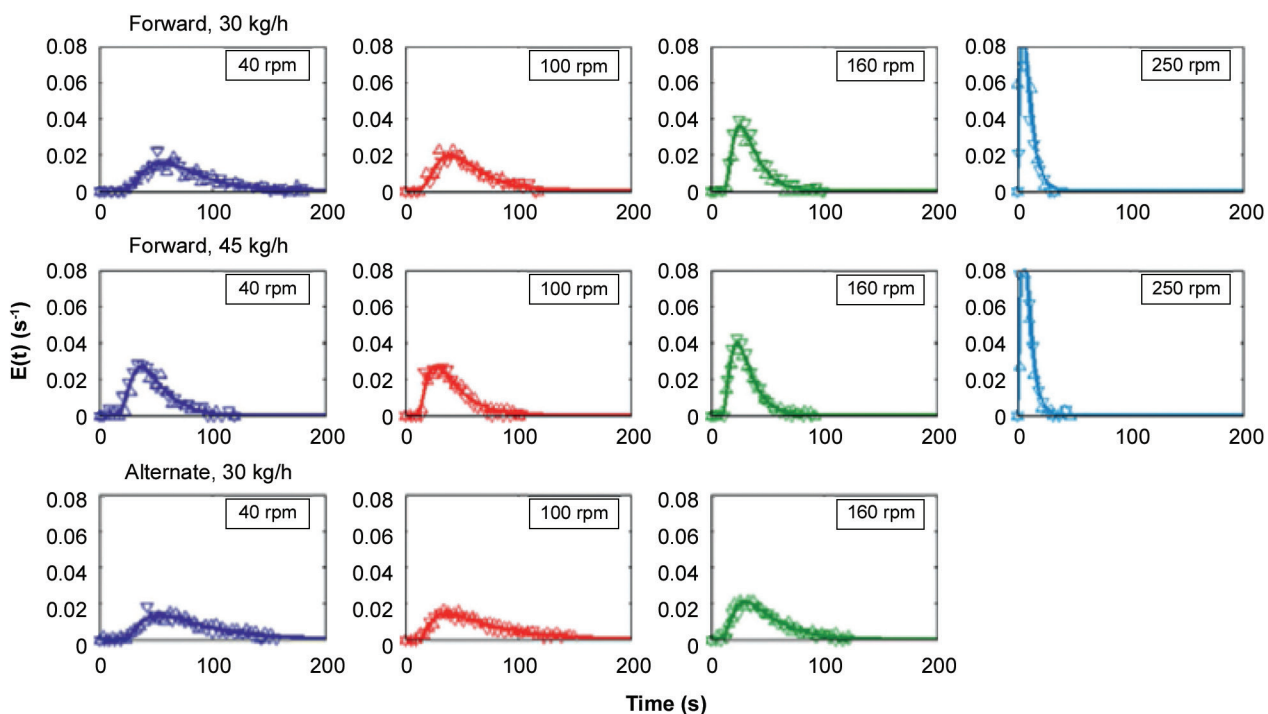


Figure 3.9: Example RTDs for a Linear In-Line Blender as a Function of Various Process Parameters [33]

Reprinted from *Chemical Engineering Science*, 66(3), Y. Gao, A. Vanarase, F. Muzzio, and M. Ierapetritou, "Characterizing continuous powder mixing using residence time distribution," pp. 417-425., Copyright 2011, with permission from Elsevier.

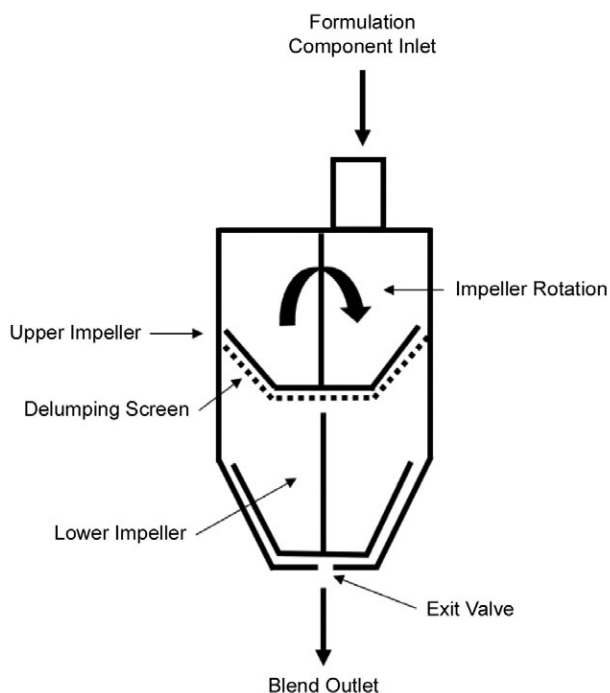


3.3.3.2 Vertical Blenders

As with linear blenders, during normal operation, upstream process equipment (often comprised of an array of LIW feeders) deliver a constant flow of material into the blender section. These blenders typically operate in a truly continuous mode, yielding a constant mass-in equal to mass-out flow of material and have the ability to start up and shut down appropriately. Figure 3.10 shows a representative schematic of a commercially available vertical continuous blender consisting of the following features:

- A material inlet port for incoming materials
- An upper mixing chamber with delumping screen and rotating impeller
- A lower mixing chamber with rotating impeller for hold-up of powder mass
- Load cells for real-time measurement of powder hold-up mass
- A material exit port with motor-controlled valve

Figure 3.10: Representation of a Continuous Vertical Blender



During normal operation, incoming material enters the upper region of the blender where it undergoes delumping via a rotating impeller and an appropriately sized screen. The powder spends the majority of the residence time in the lower mixing chamber, where the powder hold-up mass is subject to shear and mixing energy from the lower impeller. The vertical blender can mix new material into the system with old material present. Material exits to the next unit operation through the exit valve, which is continuously adjusted to ensure hold-up mass is maintained at the target set point and to preserve the line mass throughput. These features allow for the vertical blender to independently set and control the line rate, hold-up mass within the blender, and rotational speeds of both impellers, which allows for independent control of shear applied to the powder and feeder fluctuation dampening capability.

During development activities, an in-line PAT sensor may be situated at the outlet of the vertical blender to allow for real-time potency measurements. These measurements are used to understand the mixing dynamics and obtain an RTD at a variety of processing conditions and/or ingoing material properties. An example RTD study is shown in Figure 3.11 [34], where impulse experiments were carried out using a chosen tracer with various process parameters (hold-up mass, impeller speed).

Figure 3.11: Example Residence Time Distribution Study [34]

Copyright 2019 Wiley. Used with permission from D.O. Blackwood, A. Bonnassieux, and G. Cogoni, "Continuous Direct Compression Using Portable Continuous Miniature Modular & Manufacturing (PCM&M)," *Chemical Engineering in the Pharmaceutical Industry: Drug Product Design, Development, and Modeling*, Wiley.

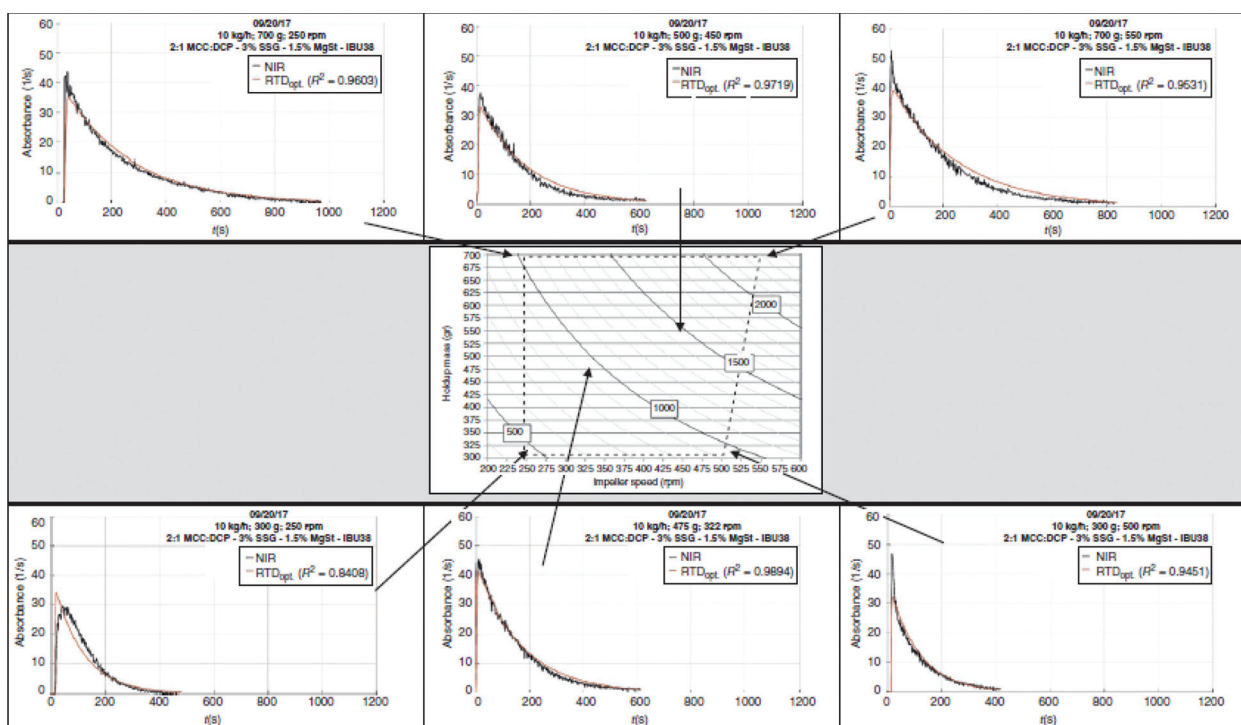


Figure Note: Spike Study with 38 μ m D50 Ibuprofen and 2:1 MCC/DCP, 3% SSG, 1.5% MgSt as a Function of Hold-Up Mass (g) and Impeller RPM at 10kg/hr.

3.3.3.3 Semi-Continuous Blenders

Figure 3.12 shows a representative schematic of a semi-continuous blender. These blenders typically allow a defined fixed amount of upstream process material to accumulate in the mixing zone or chamber, after which this zone may be isolated with a series of interlocked valves while the blending takes place via rotating paddles or other mixing components. This allows separation of mixing intensity and residence time in the blending operation and can provide effective damping of short time-frame feed disturbances when feeding challenging minor components. However, the downstream line must be appropriately designed to handle the variable output of material from the blender.

The mixing paddle geometry creates axial and radial dispersion of individual formulation components inside the blender. At the end of the mixing time, blended material is discharged through an outlet valve where it is forward processed to the next unit operation. A subsequent amount of material to be blended is collected in the empty blender housing again, and the process repeated. These units may vary in terms of the geometry of the blender body as well as the geometry and motion of the impeller components; however, the overall operating concept remains the same.