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Chapter X
Continuous powder feeding: Equipment design and material considerations

Brian M. Kerins and Abina M. Crean

Abstract

The continuous feeding of raw materials is a fundamental initial step in the continuous production of solid dosage forms. The continuous feeding process is considered critical as deviations or disturbances in individual feeders may produce compositional variability in the following mixing steps. This variability may then impact downstream unit operations and result in a detrimental change to the quality attributes of the final product. To design a robust feeding process and optimise the feeding performance, it is essential to understanding feeder design and the underlying relationships between the material properties, feeder tooling configuration, and feeding process parameters. In this chapter a brief overview of continuous feeding equipment and feeder operation modes is provided. The chapter describes the equipment and process considerations for the design of a continuous feeding process, with a primary focus on loss-in-weight (LIW), twin-screw feeders, primarily employed during the continuous production of pharmaceutical solid dosage forms. The chapter finishes with a description of modelling approaches employed to investigate feeder performance and the integration of the feeding process to the subsequent steps of the overall continuous manufacturing process.

1. Introduction

Continuous feeding of raw materials is a critical step of all continuous manufacturing (CM) processes. The function of the feeder is to transfer material into the following operation using an accurate and reliable feed rate. In the case of solid oral dosage forms, the predominant materials fed are active pharmaceutical ingredients (APIs) and excipient powders. If there is variability in the feeding process, there is a risk that downstream processes will be impacted, leading to the material critical quality attributes (CQAs) being outside the specified limits (Berthiaux et al. 2008). All feeders share this primary function to control the rate of powder flow, however the underlying feeding mechanism varies depending on the equipment design. The most common feeder types employed in the pharmaceutical industry are based on one of the following moving elements: screw, vibratory channel, belt, or rotary valve (Coperion 2021; Gericke 2021; Schenck Process 2021). Feeder selection is carried out by assessing the compatibility with several key aspects of the CM process.

The material properties of fed API and excipients can vary significantly (Van Snick et al. 2018a; Escotet-Espinoza et al. 2018). Therefore, it is important to employ a suitable feeder design to minimise unwanted powder flow patterns. Table 1 outlines some of the main points for feeder-material compatibility. Feeder design also impacts the degree of feed rate control. For example, twin-screw feeders can better regulate powder flow in comparison to single-screw configurations. This is because twin-screws tend to dispense material in smaller pulses (Messmer 2013). Closed-loop feedback control is often incorporated into pharmaceutical feeders to further reduce feed rate variability and is used in loss-in-weight (LIW) systems which are discussed in more detail in section 3.2. The maximum volumetric capacity of a feeder is dependent on the moving element used. To ensure a feeder is compatible with the CM process, the feed rate required in the next unit operation must be comfortably within the operational limits of the chosen feeder.

Table 1 Overview of material compatibility with feeder types (Messmer 2013; Nowak 2015)

Feeder Design		
Screw	**Vibratory Channel**	**Belt**
▪ Various screw types available which allows the feeder to handle a wide range of materials. ▪ Available in single-screw or twin-screw setups. ▪ Single-screw feeders may encounter issues when dispensing fine/cohesive powders as they can build-up on the screw and decrease feeder efficiency. Certain twin-screws designs can overcome this by using screws which intermesh, providing a self-cleaning function.	▪ Gently handles powders. ▪ The vibrations may generate dust for low-density materials. ▪ The vibrations may promote powder segregation. This is particularly relevant if feeding blends. ▪ Adhesive powders can build up on the feeder tube or on the tray.	▪ Gently handles powders. ▪ Ideally want the powder to form a stable bed on the belt, which may make it suitable for low-density materials that aerate and form dust. ▪ Adhesive material may stick to the belt which can produce feed rate variability and affect the belt tracking.

2. Overview of Feeding Fundamentals

Pharmaceutical feeders may vary in design; however, the core elements of the feeding process remain the same. This section will discuss these shared fundamentals and outline how they impact feeding control.

2.1 Volumetric Feeding

Conventional volumetric feeders operate using open loop control where there is no feedback signal integrated into the process. In relation to screw feeders, this means the screws will rotate at a constant speed unless the operator manually intervenes. While running in this fixed manner, there is often variability in the produced feed rate. Investigations into the volumetric feeding process have highlighted physical mechanisms behind these mass flow deviations, with several examples being discussed in the chapter.

If fluctuations are present, it suggests that the mass of powder being conveyed by the screws is inconsistent. Screw design will be discussed in more detail in section 2.4, but in brief, the screws transport material within channels between the screw flights. The first source of variability may be identified here as the volume of material contained within these pockets may not be consistent. There are several root causes that could contribute to this. Cohesive material may adhere to the screws, form stagnant zones, and limit the volumetric transport capacity (Hanson 2018). Alternatively, with each screw rotation a uniform volume of powder may struggle to flow into the screw flights from the hopper. This is called inconsistent flight filling which again is more commonly seen in poorly flowing and cohesive materials. Powder bridging is one form of flow obstruction which can cause this non-uniform filling (Engisch and Muzzio 2012).

Next it must be considered if the volume of material being transported remains constant (i.e. consistent flight filling). If the mass flow is still not stable, this suggests that the bulk density of the material is variable. One possible cause for fluctuating powder density is the hopper refilling process. Compressive forces generated by the incoming material can result in the densification of powder in the lower portions of the hopper. An increase in density would allow a greater mass of material to be transported within the screws resulting in higher feed rates (Bostijn et al. 2019).

For these reasons outlined, volumetric feeding has an increased risk of mass flow variability. Accordingly, this type of feeder is usually used if feed rate accuracy and precision is not critical which is seldom applicable for pharmaceutical manufacturing.

2.2 Gravimetric Feeding

Feeding complications which occur during volumetric feeding similarly occur when using gravimetric, loss in weight (LIW) feeders. However, in LIW feeders there is an in-built gravimetric system which enables minimisation of feed rate deviations. LIW feeders can consist of the same volumetric feeding component, but also require a weighing platform and a control module (Fig. 1). The control module is often a type of proportional integral derivative (PID) controller and is the primary enabler for the closed-loop gravimetric system. During operation, the load cell within the platform continuously monitors the net weight of the material in the feeding unit. This sensory data is transferred back to the control module to calculate the instantaneous feed rate. If there is any disparity between the actual feed rate and the setpoint (i.e. the input feed rate target selected by the operator), the controller will determine a desired actuator output. This will signal the motor to adjust the screw speed and to minimise this deviation from the defined setpoint.

The main advantage of this gravimetric system is that the feeder can self-regulate the screw speed to compensate for feeding inconsistencies. For example, if the material density increases, the controller will detect the higher feed rate produced, and it will signal the motor to reduce the screw speed. Conversely, if screw flight filling worsens, the controller will detect a lower feed rate, and increase the screw speed.

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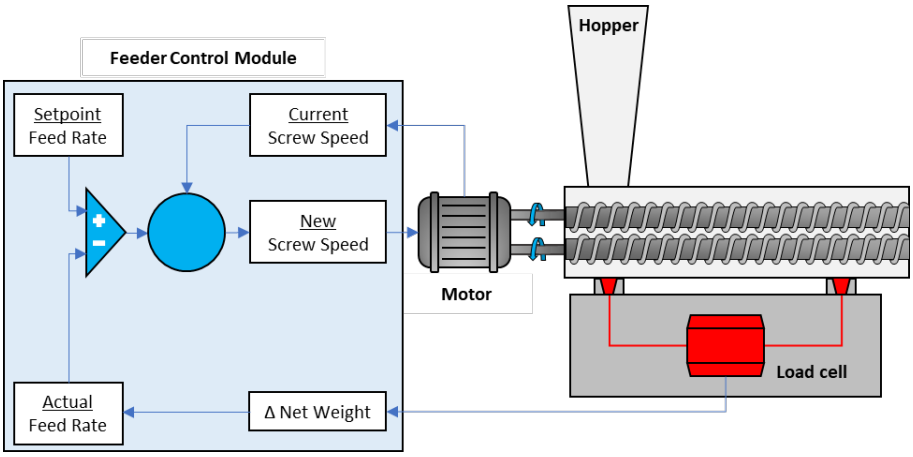


Fig. 1 Schematic of a LIW system for a twin-screw feeder

2.3 Hopper Refill Procedure

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During the feeding operation the hopper depletes and when it reaches a predefined level, the feeder controller initiates a refill cycle to replenish the material back to a preset upper fill level. The fresh powder entering the hopper can create compressive forces, causing densification of the lower portion of material (Hopkins 2006). With a greater density, a higher mass of powder can enter the screws flights and cause a spike in the feed rate. Refilling also has the potential to aerate the powder, an unwanted effect, as the material may then behave more like a liquid and flush uncontrollably through the screws, again causing over-feeding (Engisch and Muzzio 2015).

As discussed above, gravimetric feeding uses a feedback signal (derived from the net weight changes in the hopper) to regulate the screw speed, thereby reducing feed rate deviations. This feedback system is compromised during hopper refill as material is entering and leaving the feeder at the same time, obscuring the weight readings, and as a result the feed rate cannot be calculated. Without a feedback signal, the feeder temporarily switches from gravimetric to volumetric mode. Operating in volumetric mode the process is essentially blind to the density changes that can occur which can result in temporary feed rate deviations. It will remain operating in this manner for the duration of the refill and for a short post-refill delay, after which it will return to gravimetric feeding. Once the feeder switches back to gravimetric mode, it can recognise the feed rate deviation and begin to regulate the screw speed. However, this can lead to an abrupt speed change which can further contribute to feeding variability (Nowak 2016). Feed rate variability during refills can impact downstream processes as shown by Berthiaux et al. (2008) where the refilling procedure produced feed rate deviations which negatively affected the following mixing operation.

While establishing a hopper refill procedure, several factors must be considered to optimise the process and minimise any unwanted effects. These factors include: the frequency/size of refills; the material properties; the post-refill delay duration; and the refilling device. All these factors cannot be decided in isolation as they are highly interlinked. Two refill procedures which differ in the frequency/size of refills is shown in Fig. 2. Larger, low frequency refills (a) mean that less refills are needed in total and that the feeder doesn't have to revert to volumetric mode as often. The downside is that a greater mass of refill material is added to a shallower bed of bulk powder. This can accentuate the alteration to the powder properties. In contrast, smaller, high frequency refills (b) minimise this effect, although as more refills are required, the gravimetric system is more regularly disengaged.

Engisch and Muzzio (2015) investigated the impact of refill scheduling for a zinc oxide powder and a acetaminophen/silica blend. In both cases the feed rate deviation was highest using the larger, less frequent refills, and improved as the refills became smaller. Although the same trend was observed for each material, the mechanism behind the deviation was different. The over-feeding for the zinc oxide was primarily caused by powder densification due to compressive effects. In contrast, the deviations for the acetaminophen/silica blend were due to fluidisation and flushing of materials through the feeder screws.

During the refill process, there are vibrational disturbances created which distort the net weight readings of the load cell. Accordingly, in LIW feeders there is often a post-refill delay function which designates a waiting period once the refill has completed before switching back to gravimetric mode. The post-refill delay function allows time for the vibrational disturbances to dissipate before the weight readings are utilised for the feedback loop. Engisch and Muzzio (2015) compared a 5 and 10 s post-refill delay. No improvement was observed using the longer delay which indicated that the majority of the deviation occurred while the hopper was physically being refilled, rather than the period directly after.

The refilling device is another important factor as it controls how the new material is transferred into the hopper. Various options are available such as gate vales, rotary valves, pneumatic receivers, and volumetric screw feeders. Ideally the rate of the refilling should be quick to reduce the time spent in volumetric mode. Although, adding material too quick and with too much force can result in greater feed rate deviations by altering the powder density (Engisch and Muzzio 2015). Therefore, the selection of a suitable refill device should be tailored to the properties of the fed material and the acceptable level of feed rate deviation of the feeding process.

As discussed, the overall problem with the hopper refill process is that the feeder switches to volumetric mode and the screw speed is fixed for the duration of the refill. To directly address this issue, more advanced approaches are being developed to improve control during this period. One example of this is the "Refill Array" function (Nowak 2016). In brief, this method allows the screw speed to change during the refill based on previously stored feeding data which can reduce feed rate deviations and lead to a smoother transition back to gravimetric feeding.

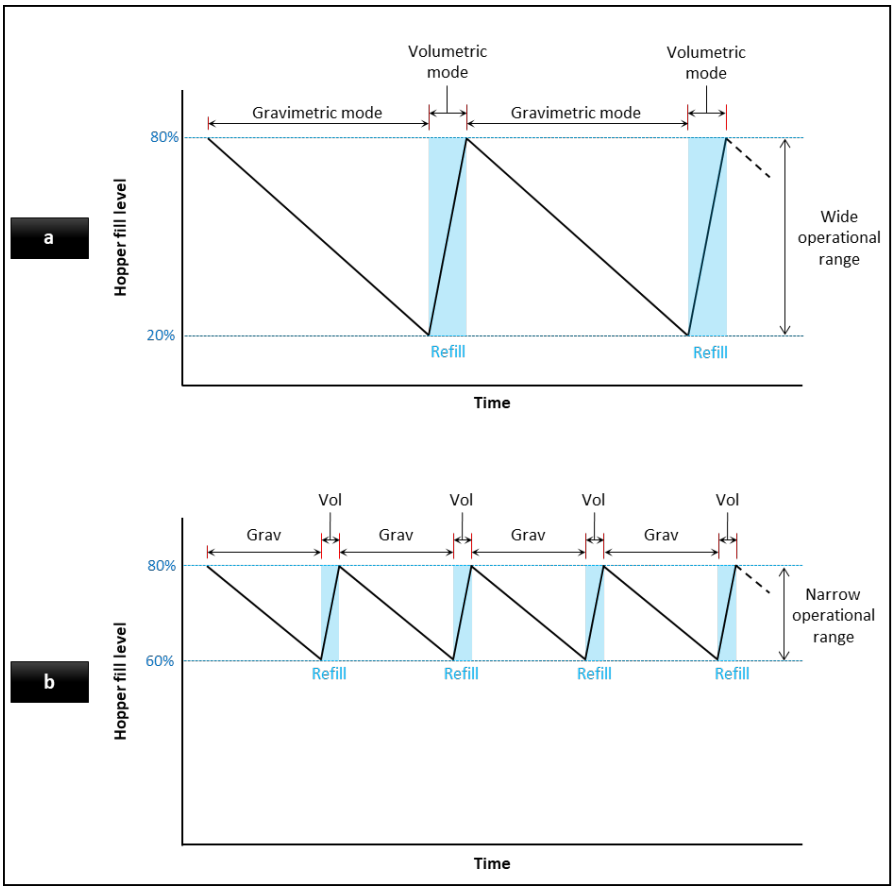


Fig. 2 Examples of a (a) low and (b) high frequency hopper refill schedule

2.4 Volumetric Capacity & Feed Factor

The screws in pharmaceutical feeders are often flood fed from the hopper (Bates 2000). Flood feeding the screws means material flows directly into the screw conveyor by gravity without assistance from additional pneumatic or conveyor systems. The volume of powder that the screws can transport is dependent on the screw design and its dimensions. Several of the primary screw design features are illustrated in Fig. 3. Material entering from the hopper flows into the channels between the screw flights. As the screws rotate, the material is then conveyed through the barrel. The pitch (distance between adjacent screw flights) and the flight depth are among the key factors that dictate the size of these pockets, which then controls the volumetric transport capacity (Dai et al. 2012). Selection of an appropriate screw configuration is essential during process design as the feed rate required by the next unit operation must be within the screws volumetric range.

An important parameter used to describe the transport efficiency of screws is the feed factor. Feed factor represents the mass of powder delivered per revolution of the feeder screw (g/rev) (Tahir et al. 2020). Feed factor can be affected by several equipment and process variables which range from

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the physical design of the screw, the screw speed, the hopper fill level, and by the bulk properties of the fed material. In regard to screw design, a study by Yadav et al. (2019) highlighted that screws with a larger pitch produced higher feed factors due to larger channels within the flights to accommodate material. Moreover, the magnitude of difference in feed factor due to the pitch sizes was dependent on the material being fed. Using a multivariate approach, Bostijn et al. (2019) correlated the maximum feed factor for 15 pharmaceutical powders with the raw material properties. The resulting analysis highlighted that the feed factor was linked to the bulk density and flowability of the materials. Additionally, this study demonstrated how the feed factor decreases as the hopper gradually depletes. The feed factor can also be used to help detect feeding complications as fluctuations may be indicative of inconsistent flight filling and material density changes.

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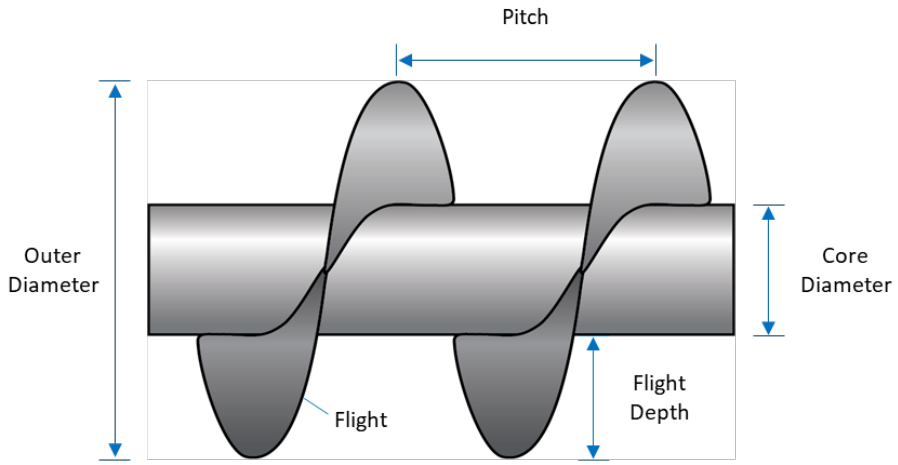


Fig. 3 Diagram of the typical screw geometries

3. Twin-Screw Feeders - Equipment Considerations

Twin-screw feeders are commonly used during pharmaceutical continuous manufacturing and offer a range of designs and tooling configuration options. Therefore, a specific feeder can be tailored to the process and material requirements to improve feeding performance. In this section, several of these equipment options will be discussed such as screw type, discharge screen type, and hopper/agitators.

3.1 Screw Type

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While selecting an appropriate screw type for a feeding process there are two primary considerations: (i) the feed rate required to the next unit operation, and (ii) the properties of the powder being fed. As discussed in section 2.4, the volumetric capacity of the screws is impacted by the screw design. Several twin-screw setups are displayed in Fig. 4. Note that the primary difference between the fine and coarse screws is the pitch size, with the coarse design having a greater capacity. To optimise the screw configuration to a specific material a thorough characterisation of its physical properties is required. Feeding behaviour of material is linked to its flow, which in turn is related to powder properties such as: particle size and shape, bulk and true density, electrostatic charge, moisture content, and surface texture (Faqih et al. 2007; Wong et al. 2015; Jager et al. 2015; Garg et al. 2018).

Cohesive, low-density, and poorly flowing powders can be some of the most difficult to feed. Firstly, these powder particles have a greater tendency to adhere to available surfaces. If this occurs on the screws, it can lead to the formation of stagnant powder zones. Throughout the feeding process, this can cause the feeder efficiency to gradually decrease resulting in a reduced volumetric capacity (Hanson 2018). Cartwright et al. (2013) encountered a similar issue where a low density API compacted within the barrel housing. To compensate, the LIW feeder progressively increased the motor torque to meet the feed rate setpoint. This eventually led to the feeder shutting down as the upper torque limit was reached. These unwanted flow patterns also raises concerns regarding material traceability and degradation (Engisch and Muzzio 2014). Auger screw types have been shown to be particularly prone to these issues and therefore should be used with care if processing very cohesive materials (Engisch and Muzzio 2012). Due to the design of concave screws, in a twin-screw setup they are capable of a self-cleaning ability which helps to reduce material build-up (Engisch and Muzzio 2014). An additional consideration if using concave screws with a cohesive material is the size of the screw pitch. A study by Engisch and Muzzio (2014) found that colloidal silicon dioxide, which is a low-density and highly cohesive powder, had difficulty fully filling the flights of the fine concave screws. Therefore, the screw configuration was unable to reach the desired feed rate capacity. One method which was found to improve the flight filling was the use of a larger feeder with bigger screws.

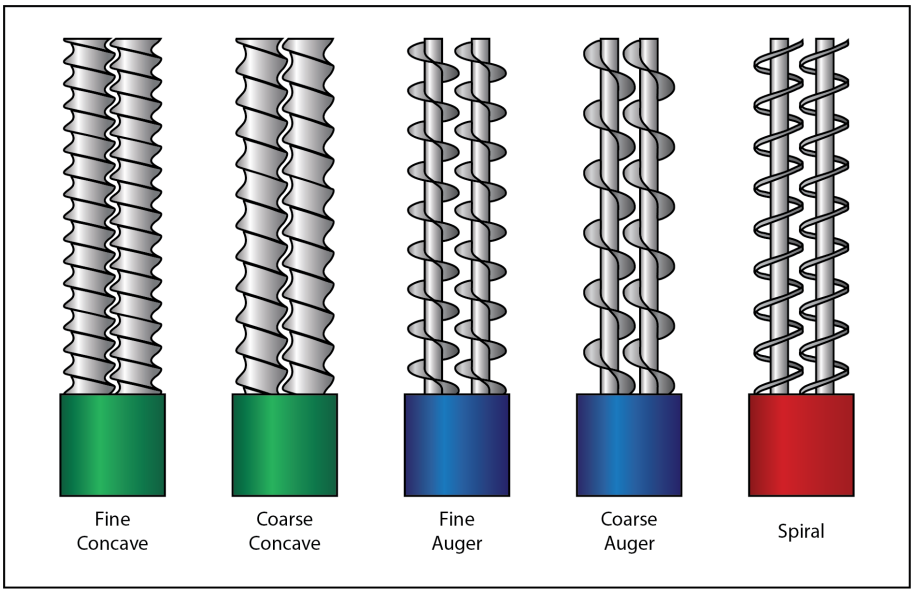


Fig. 4 Example of twin-screw types

In contrast to cohesive powders, the feeding performance of free flowing materials is less dependent on screw type (Wang et al. 2017). However, if powders are allowed to flow too freely through the screws it can impact feed rate control and lead to increased variability. In this scenario auger screw types offer less control in comparison to concave screws. Concave screws have smaller pockets to convey the material and as a result can dispense powder in smaller pulses which reduces the tendency of material to flush through the screws, thereby improving the performance (Engisch and Muzzio 2014).

3.2 Screen Type

In some twin-screw feeder models, there is an option to place a discharge screen at the outlet directly after the screws. Like the screws, by providing tooling choices it grants the operator more flexibility to optimise the process based on the fed material. There are two primary functions of the screen component: to help regulate flow, and to break up powder aggregates (Engisch and Muzzio 2014). An example of two screens which can be placed at the outlet of a K-Tron MT12 twin-screw feeder is shown in Fig. 5. The size and shape of the screen gratings impact its ability for flow regulation, with smaller gratings providing increased resistance. Feeders can also be operated without a screen in place.

Materials, particularly those with good flowability, may flush out of the screws too freely if the feeder configuration lacks control. This can result in increased feed rate variability. A good example of this was shown by Engisch and Muzzio (2014). In this study, a free-flowing excipient, Prosolv HD90, was gravimetrically fed using various tooling configurations. It was found that the feed rate variability could be reduced with the inclusion of a screen at the outlet. In a subsequent study, the additional flow control gained with the screen was shown to help reduce feed rate fluctuations caused by hopper refills (Engisch and Muzzio 2015).

Screens may be beneficial for some cohesive materials as they can help to break up powder clumps, however they can also cause other issues. If the powder is prone to adhering to the equipment, the addition of a screen will provide extra available surface which could accentuate the problem of material adherence. Material may accumulate on the screen and then fall off periodically causing feed rate fluctuations (Engisch and Muzzio 2014). The flow regulation of the screen occurs by forcing the powder to pass through the gratings. Poorly flowing material may struggle to get through finer screen gratings which can lead to the powder building up and compacting before the screen. The powder compaction causes the feed rate to drop and due to the gravimetric feedback system, the controller then increases the screw speed to compensate for the drop off in feed rate. As more and more powder compacts, the torque needed by the motor to rotate the screws increases. If an upper torque threshold is met, the motor can shut down, halting the feeding process (Engisch and Muzzio 2012).

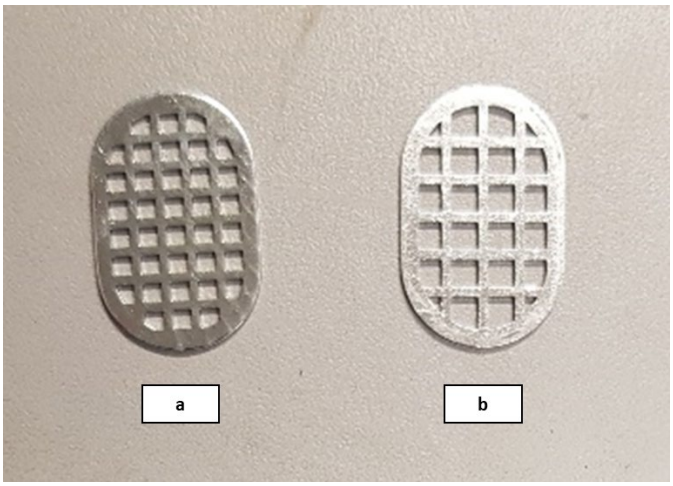


Fig. 5 Example of 2 discharge screens: (a) a fine square screen, and (b) a coarse square screen

3.3 Hopper & Agitator

Flow patterns in the hopper are an important aspect of continuous feeding as it controls how the material transitions into the screws. There are two primary modes of flow seen within the hopper: mass flow and funnel flow. Mass flow is the desired behaviour and works under the principle of first-in, first-out (Fig. 6). In this mode, all particles in the hopper are in a uniform motion which provides a steady discharge. Funnel flow, which is often described as first-in, last-out, occurs when a preferential flow channel develops directly over the hopper outlet (Søgaard et al. 2017). During funnel flow the material in the centre flows faster versus the material at the edges, which can also lead to the formation of stagnant zones. Ratholing is a term used to describe extreme cases of funnel flow where the material nearer the walls is completely stationary and only the central material is discharged (Polizzi et al. 2016). Ratholing was observed by Santos et al. (2018) which resulted in a feed rate reduction for a poorly flowing material. Funnel flow can also have other negative effects on the bulk powder. It has the potential to induce powder segregation into non-

uniform fractions (Ketterhagen et al. 2009). Additionally, it raises concerns regarding material residence times.

Aside from funnel flow, powder bridging is another undesirable flow issue which can occur in the hopper (Fig. 6). Obstruction to flow due to bridging arises when a stable arch forms over the hopper outlet, which prevents material from being discharged (Polizzi et al. 2016). The obstruction to flow would have a significant impact on the overall CM process as it would starve the feeder screws, and the continuous stream of material into the next unit operation would cease.

Similar to screw and screen selection, thorough material characterisation is recommended prior to selecting a hopper design. Choosing a suitable design can help mitigate the flow issues of troublesome materials. The shape of the hopper, including the wall slope and outlet width, can have a significant impact on powder flow behaviour (Schulze 2016). A rotating agitator can be installed inside the hopper which can facilitate improved flow and screw flight filling. However, these agitators may not be compatible in all processes. Cartwright et al. (2013) observed significant ratholing during a feeding study and noted it was partly due to the agitator. The rotating blade aided the compaction of the low-density API which required repeated operator intervention to resolve. The solution used in this study was to select a feeder with a flexible hopper design. These specialised hoppers allow the bulk powder to be gently massaged from the outside via external agitators, thereby improving flow behaviour (Messmer 2013).

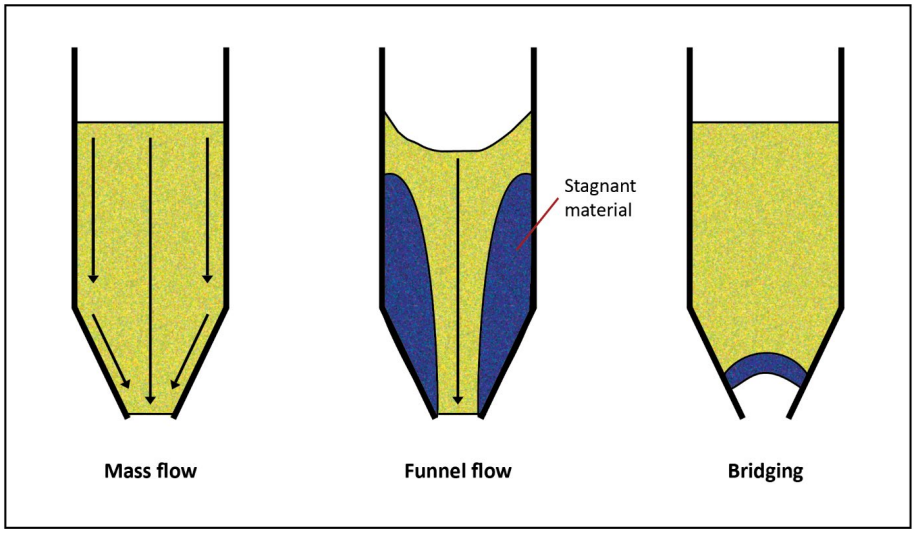


Fig. 6 Flow patterns in the hopper

4. Additional Process Considerations

4.1 Time to Reach Steady State

The start-up procedure of a CM processes must be given careful consideration as the unit operation must be allowed to achieve a steady state. The time required is heavily dependent on factors such as the feed rate employed and the material being fed. While steady state can be achieved in a relatively short time frame during the feeding process, it is important to understand this time frame as large

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fluctuations may occur prior to reaching steady state which can produce significant feed rate variability. Simonaho et al. (2016) investigated this by monitoring the individual feeding of microcrystalline cellulose and acetylsalicylic acid at 17.14 kg/hr and 2.86 kg/hr respectively. In both cases it was shown that a steady state mass flow was achieved after 3 min from start-up. Blackshields and Crean (2018) also studied the feeding of microcrystalline cellulose, although a much lower feed rate of 0.25 kg/hr was used. Additionally, the definition of the time to reach steady state employed was the time taken until the feed rate remained within ± 3 standard deviations of the gravimetric setpoint. In this study, approximately 12 min was needed for the mass flow to remain within these limits. Ervasti et al. (2015) investigated a continuous process for manufacturing extended release ibuprofen tablets. Within the experimental design, the API was fed at 3 different mass flow rates: 0.070, 0.525 and 0.770 kg/hr. A settling time of under 5 min was seen for both the higher feed rates. In contrast, the 0.070 kg/hr feed rate required approximately 10 min to stay within the ± 3 standard deviations limits.

4.2 Powder Triboelectrification

Triboelectrification or tribo-charging is a charge transfer process which can occur when particle contact involves frictional forces generated by rubbing, sliding, rolling or impaction (Wong et al. 2015). Triboelectrification can apply to anywhere in the manufacturing process where particles frequently collide with other powder particles, or with the surfaces of equipment. Pharmaceutical powders are often dielectric materials, giving them a greater tendency to tribo-charge (Pu et al. 2009). These insulating properties additionally mean the accumulated charge will decay slowly, which may be of particular concern to CM processes where each unit operation connects directly to the next (Beretta et al. 2020). The electrostatic charge generated can be quite problematic during manufacturing as it can:

- Increase the risk of powder handling hazards such as creating an electrical spark or causing a dust explosion (Glor 2003)
- Lead to powder agglomeration and segregation
- Reduce powder flow
- Increase particle adhesion

Due to the influence of electrostatic charges, there have been many studies investigating its impact on unit operations such as feeding (Bostijn et al. 2019; Stauffer et al. 2019; Beretta et al. 2020; Allenspach et al. 2021), and blending (Engers et al. 2006; Pu et al. 2009; Karner and Urbanetz 2012). There has also been several reviews discussing tribo-charging in a pharmaceutical setting (Wong et al. 2015; Naik et al. 2016; Sarkar et al. 2017).

Engisch and Muzzio (2014) encountered electrostatic issues when feeding colloidal silicon dioxide which lead to significant powder buildup at the feeder outlet. Using an electrostatic eliminator, the tendency for powder adhesion was reduced although not completely resolved.

A study by Beretta et al. (2020) investigated the tribo-charging of various pharmaceutical powders and found the magnitude of the charge generated was highly material dependent. Additionally, the particle charge density was compared after (i) allowing the powder to flow through a GranuCharge™ instrument, and (ii) feeding using a twin-screw feeder. There was a good correlation between these results which suggests that the tribo-charging may be mainly due to frictional interparticle forces rather than interaction with equipment surfaces.

While feeding controlled release grades of hypromellose, Allenspach et al. (2021) reported significant electrostatic material buildup on the feeder barrel. The accumulated material occasionally fell and caused feed rate fluctuations, which was reflected in the higher feed rate variability of those samples. Another finding of this study was that the location of the material buildup changed when the powder was fed directly from the feeder into another hopper. In this case, instead of

accumulating on the feeder barrel, the powder adhered to the output of the following hopper which highlights the additional considerations when integrating the feeder into a continuous process.

5. Low-Dose Powder Feeding

Special consideration must be given to feeding processes which require very low feed rates. In relation to pharmaceutical manufacturing, this is most frequently seen with excipients, such as flow aids and lubricants, that are only required in small quantities proportional to the overall formulation. Low-dose feeding also applies for feeding highly potent active pharmaceutical ingredients. An increasing number of highly potent active pharmaceutical ingredients have emerged from development in recent years (Wollowitz 2010). Fluctuations in the feed rate can occur with all feeders, although when using lower feed rate setpoints this can become particularly troublesome (Santos et al. 2018). One solution is to pre-blend the API or excipient with another material in the formulation and then feed at a higher feed rate where there is greater control. The drawback of this approach is that it necessitates an additional processing step. Alternatively, the issue can be directly addressed by establishing a feeding process capable of dispensing a continuous and reliable powder stream at lower feed rates.

Bostijn et al. (2019) investigated feed rates of 100 and 550 g/hr using a twin-screw LIW feeder. The relative standard deviation (RSD) of the feed rate was significantly higher in the lower 100 g/hr runs. Additionally, the powder properties were a critical factor which impacted the feed rate variability. A micro-pump feeder setup has been utilised in several studies where accurate feed rates were achieved at 1-25 g/hr (Besenhard et al. 2017), 1-15 g/hr (Fathollahi et al. 2020), and 1-5 g/hr (Sacher et al. 2020). In this design the feed rate is primarily controlled by the displacement of the powder from a cartridge via a pump/piston. Besenhard et al. (2016) assembled a vibratory sieve and chute system which produced a stable flow from 4-90 g/hr. However, the powder had to be pre-processed via sieving prior to feeding.

6. Modelling to Predict Feeder Performance

The APIs and excipients used in pharmaceutical formulations can differ significantly in relation to their material properties. These differences affect the materials performance in all operations throughout the manufacturing process, including: blending (Vanarase et al. 2013), tableting (Van Snick et al. 2018b), granulating (Willecke et al. 2017), and feeding (Engisch and Muzzio 2014; Bostijn et al. 2019). Therefore, research which aims to investigate and further our understanding of these interactions is an indispensable tool during process design. The key benefits of this modelling are:

- It can predict which tooling configurations would be most suitable.
- It can lead to a faster and more efficient drug development process.
- It can reduce the consumption of materials, which are often in limited supply during the early design phases.

The first step in the modelling process is to create a database of the material properties. To improve the quality and reliability of the data, standardised characterisation methods should be used (Hlinak et al. 2006). From this material library a model can be produced using multivariate analysis techniques such as principal component analysis (PCA). In technical terms, PCA is a mathematical algorithm which reduces the dimensionality of data while still retaining most of variation (Ringnér 2008). PCA can position the materials within a design space so the relationship between the properties can be assessed. During process design, this method can also be used to identify a surrogate material which shares the same critical material attributes.

Partial least squares (PLS) regression is another multivariate analysis technique which can be used. While PCA determines the relationship between the material properties, PLS correlates the independent variables (material properties) to output responses. In relation to continuous feeding, the responses studied include the feed rate RSD, and deviation from the feed rate setpoint. The established correlation can be used to predict feeder performance based on the material properties. Examples of studies using multivariate analysis methods are shown in Table 2.

Powder behaviour during the feeding process has also been investigated using discrete element modelling (DEM) (Hou et al. 2014; López et al. 2020; Bhalode and Ierapetritou 2020). The DEM modelling approach determines the trajectory of individual particles using simulations which focus on particle-particle and particle-wall interactions. Important information regarding powder behaviour can be extracted using these simulations while not consuming any physical material.

Table 2 Examples of studies which used modelling to investigate the feeding process

Study	Brief outline
(Polizzi et al. 2016)	PLS was used to model the relationship between the material properties and the flow in conical hoppers.
(Wang et al. 2017)	Both PCA and PLS were used to create predictive correlations between material flow properties and feeder performance.
(Escotet-Espinoza et al. 2018)	PCA and hierarchical clustering were used to analyse a material library based on flow properties. The material clusters were linked to the performance in the characterised equipment.
(Van Snick et al. 2018a)	A material library was created using over 100 raw materials descriptors. It was then analysed with PCA to identify the relationship between the properties.
(Bostijn et al. 2019)	PLS was used to correlate several feeding responses to the material descriptors. Two volumetric (the maximum feed factor and its relative decay), and 2 gravimetric (the feed rate RSD and deviation from the setpoint) feeding responses were assessed.
(Wang et al. 2019)	PCA and hierarchical clustering were used to analyse a material library. The feeding performance of several materials were assessed to determine if samples within the clusters exhibited similar feeding behaviour.
(Yadav et al. 2019)	A PCA model was used to investigate the relationship between the material properties, the feeder tooling configuration, and the feeding performance.
(Stauffer et al. 2019)	PCA and PLS models were used to optimise the feeding performance of a blend and to identify the critical material properties.
(Tahir et al. 2020)	First, material specific PLS models were generated. Then PCA was used to cluster the materials, and a generic PLS model was developed for each cluster to predict the feed factor profile.

7. Considerations for Feeder Integration into CM Lines

In a CM process, it is common for APIs and excipients to be fed using individual feeders, then blended in the following operation. As previously discussed (section 3.2), gravimetric feeders can improve feeding performance of materials. Further levels of control are also of interest when integrating multiple feeders into a continuous process. Three types of control systems have been described (Weinekötter and Gericke 2000) (Fig. 7):

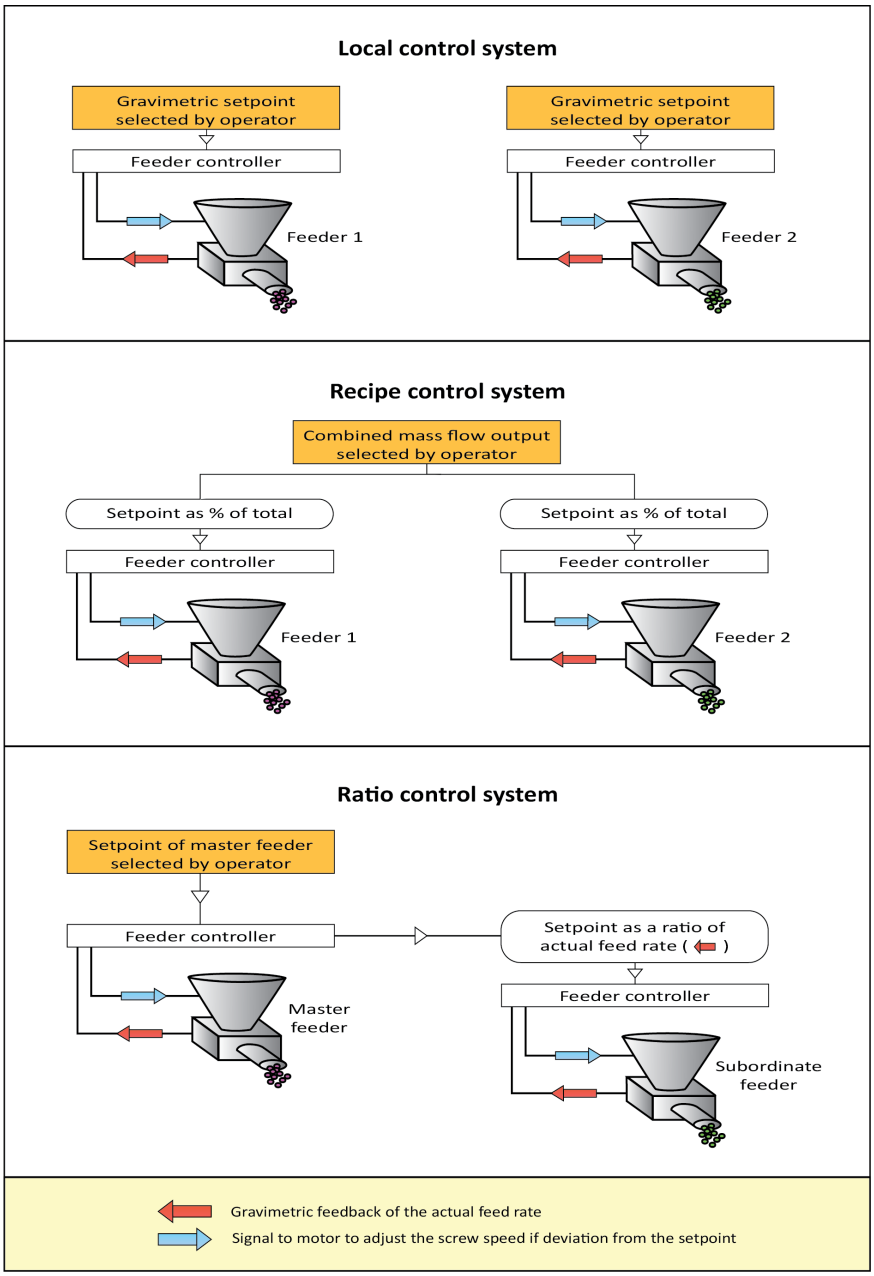
1) Local control – Each feeder independently controls its feed rate.
2) Recipe control – The feed rate of each feeder is determined as a percentage of the main recipe (i.e. overall combined feed rate)
3) Ratio control – One feeder is assigned as the master while the other feeders are assigned as subordinates. The subordinate feeders determine their feed rate targets as a percentage of the master feeders output. This means they can react to the actual mass flow of the master feeder.

A study by Hanson (2018) compared feeding performance while using local and ratio control. It was found that the variability of the fed concentrations of the API and excipients were lower while using ratio control.

While designing the feeding step it is important to define the acceptable level of feed rate variability that the following unit operations can tolerate without compromising the quality of the final product. For example, variability in feed rate can result in subsequent blend variability and variability in the final dosage uniformity of content. The frequency of feed rate fluctuations should be assessed, as continuous blenders can only offset short-term (i.e. high-frequency) fluctuations (Pernenkil and Cooney 2006). Vanarase and Muzzio (2011) were able to reduce feeding variability by using higher feed rates, however this did not improve blend uniformity after the blending step. It was suggested that the variability due to the feeding process was almost completely filtered out by the continuous mixing step. In contrast, Berthiaux et al. (2008) found that the feeding variability caused by the hopper refill process resulted in the post-mixer blend being outside the specified uniformity limits.

In contrast to batch processing, material traceability is a key requirement and challenge for integrated pharmaceutical CM processes. From patient safety and product quality perspectives, it is a regulatory requirement to identify the batches of raw materials input at the feeding stage which compose a specific batch/lot of the final drug product. To trace materials through the CM process, measurement of residence time distribution (RTD) is proposed (U.S. Food and Drug Administration 2019). RTD is defined as a probability distribution that describes the amount of time a mass or fluid element remains in a process. Addition of a tracer compounds, the application of online measurements of a specific material attribute (e.g. near infrared or Raman spectral properties) and process modelling can be used to measure RTD (Pedersen et al. 2021). RTD profiles of materials in LIW feeders is influenced by material feed rate but also powder flow patterns (i.e. mass flow versus funnel flow and bridging) and feeder equipment design, configuration and settings.

A study by Van Snick et al. (2019) established a PLS regression model which linked the properties of a range of pharmaceutical excipients and feeder process variables with RTD responses as outputs, for two twin-screw feeders. RTDs for both feeders could be represented by a combination of plug-flow and mixed-flow. Material flow rate, hopper level and density of the material were identified as critical factors for both feeders. Plug-flow and mixed-flow time were reduced to a similar extent by an increase in powder flow and decrease in material density. However, difference in RTD profiles were noted for both screw feeder types. Therefore, feeder type, configuration and processing parameters should be considered and investigated as critical process factors in relation to material traceability for a pharmaceutical continuous process.



484

485 **Fig. 7** Example of 3 feeder control systems using multiple LIW feeders

8. Summary

Continuous feeding is an integral step in the continuous manufacturing of pharmaceutical products. As highlighted in this chapter, there is no one feeder setup suitable for all APIs and excipients. For this reason, many studies have been carried out to further our understanding of the underlying feeding mechanisms, and to correlate feeding behaviour with elements of the process design. Of the various considerations, the properties of the fed material have been identified as a highly influential factor. It has been repeatedly shown that the feeder type, the relative tooling, and the process parameters must be tailored to the material properties to optimise feeding. High emphasis is put on this relationship in the pharmaceutical sector as highly accurate and precise feeding is required. A nonoptimal feeding process with high variability could cause failures of downstream processes, reducing the quality of the final drug product. As the industry follows its current trajectory towards an increased uptake of CM, it is essential that we continue to develop our understanding of the mechanisms behind the feeding process. Research to date has been primarily focused on how the equipment and process parameters affect feeder performance. An area which may warrant more research in future work is if the feeding process itself is affecting the physical properties of the fed material, as this could impact the following unit operations.

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