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REVIEW

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Critical review on the role of excipient properties in pharmaceutical powder-to-tablet continuous manufacturing

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ABSTRACT

Introduction: The pharmaceutical industry is gradually changing batch-wise manufacturing processes to continuous manufacturing processes, due to the advantages it has to offer. The final product quality and process efficiency of continuous manufacturing processes is among others impacted by the properties of the raw materials. Existing knowledge on the role of raw material properties in batch processing is however not directly transferable to continuous processes, due to the inherent differences between batch and continuous processes.

Areas covered: A review is performed to evaluate the role of excipient properties for different unit operations used in continuous manufacturing processes. Unit operations that will be discussed include feeding, blending, granulation, final blending, and compression.

Expert opinion: Although the potency of continuous manufacturing is widely recognized, full utilization still requires a number of challenges to be addressed effectively. An expert opinion will be provided that discusses those challenges and potential solutions to overcome those challenges. The provided overview can serve as a framework for the pharmaceutical industry to push ahead process optimization and formulation development for continuous manufacturing processes.

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Continuous manufacturing; continuous processing; excipients; material characterization; material properties; Quality-by-design; lactose; microcrystalline cellulose

1. Introduction

The pharmaceutical industry is continuously looking for strategies and solutions that can improve the quality and efficiency of drug product manufacturing processes. Stimulated by Pharma 4.0 [1], batch-wise production processes are gradually changing to continuous production processes. Continuous manufacturing (CM) is a strategy that allows the movement of materials through an integrated equipment train, eliminating holding times between process steps, while ending up with a product having the desired quality attributes. At steady-state conditions, the material enters and exits each unit operation at the same mass flow rate. Compared to batch processes, particles spend only a short period in each operating unit before continuing to the next process step. CM has been used for many decades in the food, consumer, petrochemical, and automotive industries [2]. In the pharmaceutical industry, however, implementation is considerably slower. This may be explained by the regulatory hurdles related to changing registered processes, the relatively low costs of production as a fraction of the entire price and the risk-avoiding approach toward innovations in production technology. With the growing competition, however, pharmaceutical manufacturers are forced to increase production efficiency and quality to reduce costs – justifying investments in the development and introduction of continuous processes [3,4].

Figure 1 shows a visual representation of a continuous powder-to-tablet manufacturing process. Each process includes feeding of the raw materials (a), blending (b), final blending (e.g. lubrication) (g) and tableting (h). Granulation is an optional step. Wet granulation steps include wet granulation (c), drying (d), and milling (f). Dry granulation steps include roller compaction (e) and milling (f). In continuous production processes, all relevant unit operations are integrated [5,6]. Continuous operation is associated with many advantages, including increased flexibility of production [7–9], no or limited need for scale-up [9,10], the reduced equipment size [9,10], decreased environmental impact [11], and a reduced waste and material (including API) consumption [9,10]. Additionally, a reduced inventory of intermediates can be obtained by alignment of the throughput of different unit operations [4,10]. Furthermore, an improved consistency of product quality through the use of in-process feedback systems can be achieved [2,12].

Multiple major pharmaceutical companies have stated they are going to adopt CM as their production method for the future [9,13,14]. Since the first Food and Drug Administration (FDA) approval using CM in 2015, the FDA has approved over 10 drug products that are labeled to be manufactured by CM [15,16], and many more are in the pipeline. Continuous manufacturing is encouraged by regulatory bodies since it is in line with the Quality by Design (QbD) paradigm for pharmaceutical development [17,18]. QbD requires a deep understanding of the relationships between the raw material properties, the process parameters, and the final product quality. This

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Article highlights

- Continuous processes are inherently different from batch processes.
- Knowledge on the role of raw material properties in batch processing is not directly transferable to continuous processes.
- Prior knowledge of physical chemical material properties can provide indications of how the powder will behave during processing and can support the optimal selection of equipment design and tooling.
- Excipient innovations that support the implementation of continuous processes include a good feedable lubricant, regulatory-wise accepted customized co-processed excipients, cleaning excipients, and improved insights in data, consistency, and modeling.
- Fast wetting kinetics and fast drying of excipients can help to achieve higher throughputs in twin screw granulation processes.

understanding can be obtained via CM, by correlating the continuous data stream of raw material properties, process parameters, and intermediate product properties with the final product properties.

QbD principles emphasize that robust formulations and processes should be able to accommodate all typical variation. In particular, the product's manufacture, stability, physical-technological properties, or performance should not be compromised by the variation in active pharmaceutical ingredients (APIs), processes, and excipients [18–20]. In order to transform batch production to continuous production, each processing step needs to be re-designed. Much knowledge has been generated on the role of raw material properties in batch processing [21,22]. This knowledge is however not directly transferable to continuous processes, due to the inherent differences between batch and continuous processes.

To enable the design of robust continuous processes, a thorough understanding of the impact of intrinsic material properties on the result of each unit operation in a continuous manufacturing line is required. Additionally, an understanding of the effect of the material properties on the integrated process and the used integration processes is required [23]. The current review will evaluate the relevance of excipient properties for different unit operations used in continuous manufacturing processes. Unit operations that will be discussed include feeding, blending, wet granulation, dry granulation, and compression. After discussing the excipient's needs per operating unit, further requirements relevant to continuous processing and process integration will be discussed.

The research methodology for this systematic review involved a structured approach to identify and evaluate relevant literature primarily using databases Scopus and Google Scholar. Key search terms included descriptions of general continuous manufacturing as well as specific unit operations. Search results were screened based on titles and abstracts, followed by a full-text review when potentially relevant articles.

In general, it can be assumed that the impact of intrinsic excipient properties will reduce as the material moves through the CM process. In the first unit of operation, the material properties are fully determined by the raw material. Moving through the CM process however, the properties of the blends may substantially be altered by the processing. The further a material has passed through the CM process the more dominant the impact of the process-induced properties will become. This phenomenon is also reflected in this review, since early process steps are discussed more extensively than latter steps.

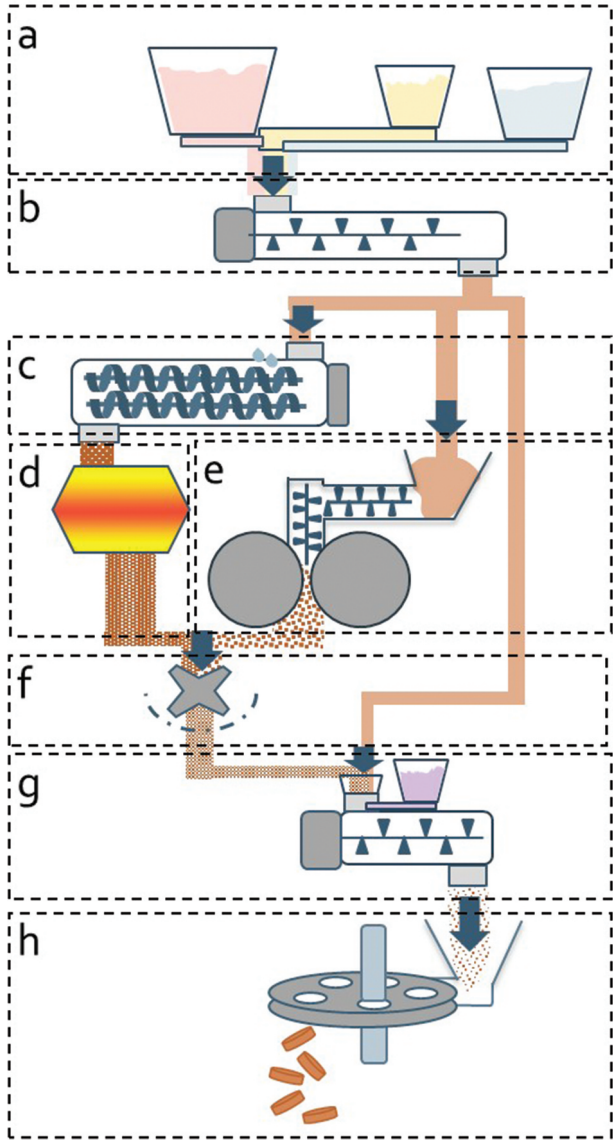

Figure 1. Visual representation of three continuous powder-to-tablet manufacturing processes. Each process includes feeding the raw materials (a), blending (b), final blending (g), and tableting (h). Granulation is an optional step. Wet granulation steps include wet granulation (c), drying (d), and milling (f). Dry granulation steps include roller compaction (e), and milling (f). The material moves through an integrated equipment train, eliminating holding times between the various processing steps.

2. Feeding

A continuous manufacturing process typically starts with the feeding of raw material into the processing line, as shown in Figure 1(a) [24]. The feeder performance determines the amount of a component that ends up in the final product and is therefore critical for product quality [25–27]. The inability to maintain targeted material concentrations in the process stream can lead to quality defects, including out-of-specifications regarding drug content and content uniformity

[27–29]. Ensuring a consistent mass flow is crucial in CM, unlike in batch manufacturing where only the final dispensed masses need to be accurate. Consequently, feeding becomes exceptionally critical to quality and is one of the most closely examined unit operations in a CM line [27].

Because of the large impact of inconsistent feeding, loss-in-weight or gravimetric feeding is the most commonly used continuous feeding method for pharmaceutical powders [30,31]. Loss-in-weight (LIW) feeders consist of a hopper that contains the material, screws to transport the material and a weighing system to regulate the material transport. LIW feeders can operate at a fixed rotational screw speed, which is referred to as volumetric mode, or in gravimetric mode. In the gravimetric mode, the actual weight loss per unit time is compared to the desired weight loss. Any discrepancy between actual and desired weight loss results in a correction to the speed of the feeding device, ensuring maintenance of a constant feed rate [32]. During refill, however, a feeder is unable to run in gravimetric mode. Material is simultaneously entering and leaving the hopper. As a result, it is challenging to precisely determine the weight loss from material leaving the hopper [33]. It will therefore transiently be run in volumetric mode, with constant volumetric dosing per unit of time. During these periods, the mass feed rate can vary as the process is essentially rendered blind to any changes in the incoming material, such as changes in density [34].

2.1. Material characteristics impacting feeding

Many papers discuss the importance of understanding the physical properties of raw materials and their impact on feeding [27,31–33,35]. Prior knowledge of physical chemical material properties can provide indications of how the powder will behave during processing and can support the optimal selection of feeder design and tooling. Due to the multivariate nature of raw materials, however, it is typically not straightforward to determine which properties influence the feeding process most significantly and how the different properties interact with each other [27,36]. This is mainly because flow or feeding behavior is the result of the combination of several factors. Factors contributing to the powder flow include material physical properties, the equipment and the process parameter settings used for handling, storing, and processing the material [37]. Flowability or feeding behavior can never be expressed as a single value or index. There are however specific bulk characteristics that are commonly mentioned as being known to impact the accuracy of powder feeding. These flow properties include among others bulk density, particle size distribution, shape, electrostatic charging, and moisture content [27,32,38,39]. Powder flow is the result of all forces driving the powder flow and forces preventing powder flow [40]. Powders normally flow under the influence of gravity, and therefore higher density results in better powder flow. The particle size of a particle determines the surface area-to-volume ratio. Smaller particles have relatively more surface area, resulting in higher limiting van der Waals and electrostatic forces. The shape of particles also affects the interparticle friction. Spherical particles typically have the least interparticle friction, while irregular shaped particles tend to interlock. Moisture can create liquid bridges between particles, resulting in limiting capillary forces that bind the particles together and to the equipment walls. Generally, cohesive powders have the risk of adhesion to the screws and hopper walls, potentially causing blockages. Extremely free-flowing materials, on the other hand, risk pulsating flow rates by uncontrolled variable flooding through the feeder during refill [39].

2.2. Sources of variation

Variation in the mass flow out of a feeder can have different origins and can be categorized into two types, namely intrinsic or extrinsic material property variation. Intrinsic material property variation refers to variation in the raw material that is already present when the material is added to the process. Intrinsic density differences in the raw material can be an issue when switching over to a new portion of raw material. But also when the intrinsic density of the raw material is consistent, the density of the material that is fed can vary due to process-induced variation. Extrinsic material property variation refers to variation that is introduced by the process. Extrinsic material property variation can originate from disturbances in the process, like external vibrations or fluctuating pressure on the powder bed during refill. The density of the powder in the process can for example increase due to vibration-induced compression of the existing powder bed, or decrease due to aeration of the powder [38]. Compressible materials typically show a decay in feed factor (amount of material per screw revolution), due to reduced pressure on the material when the hopper level decreases. Additionally, process stops could result in time consolidation of the powder bed and the powder flow could vary as the result of segregation (based on variations in particle size, shape, or density) in the hopper [40]. The screws of a LIW feeder could be starving as the result of flow challenges like ratholing, bridging, or caking. Additionally, the volume of screws could decrease due to powder adhering to the screws. Friction between particles or between the particle and equipment could lead to electrostatic charging. Consecutive changes in repulsive and attractive forces could result in powder sticking to the equipment, powder clumping together or different powder flow characteristics.

2.3. Feeding challenges

Feeding is a continuous operation that is substantially different from all unit operations in a batch manufacturing line. In batch processes, materials are manually dosed via dispending in a blender. While in continuous processing with adequate blending, the dosing is fully determined by the feeding process. Feeding is therefore associated with certain potential challenges. The following section discusses potential challenges and solutions related to the specific unit operation feeding. General challenges, like consistency and data modeling, will be discussed separately in section 8.

2.3.1. Number of hoppers

Drug products are typically developed with six or more ingredients in the formulation. This is in general not a challenge for batch manufacturing, as the manual addition of various

amounts of ingredients to a blender is not limited. All ingredients in continuous manufacturing operations, however, are added by feeders. Each feeder incurs substantial expenses and demands space within the manufacturing environment. Additionally, each feeder requires the development of a control strategy. Manufacturing lines therefore are limited in the number of feeders around a single processing unit. Especially clustering more than six feeders around a single processing unit is difficult and expensive [41]. This limitation of feeders forces formulators to carefully select which raw materials to use in a specific formulation.

Different strategies have been identified to deal with a limited amount of feeders. It can for example be an advantage when one feeder can be used to dose an advanced or composite (co-processed) excipient that adds multiple functionalities to the formulation. Granulated anhydrous lactose, for example, can be used to achieve higher compactibility and flowability in the formulation than other direct compression lactose grades (e.g. granulated lactose, anhydrous lactose or spray dried lactose) [42]. Another option to reduce the amount of feeders needed is by combining multiple raw materials in one feeder. The use of physical blends in one feeder provides the formulator with an additional flexibility in composition, although this comes with risks regarding segregation. As the unit of scale is low, small-scale homogeneity from the beginning onwards is key. Downstream segregation could be minimized by using efficient blenders, by minimization of the distance of powder flow, internal lags and by elimination of semicontinuous steps [43]. Blend uniformity can also be improved through granulation of the powder blend immediately after blending to avoid segregation [9]. In such cases, the main risk for inhomogeneity is at the start of the process, for example due to segregation during transport or blending. Co-processed mixtures of excipients overcome the potential risks for segregation of excipients. Segregation of the API in the mixture can however not be prevented by this. Co-processed mixtures at the same time reduce the flexibility in the composition, which may be required to fulfill the needs of an individual formulation. Customized co-processed excipients might therefore be required to generate the flexibility necessary for optimal process performance, although the costs of such customized excipients should justify the benefits. Additionally, regulatory concerns about using co-processed excipients or ready-to-use physical blends might exist due to the absence of a monograph. So far, silicified microcrystalline cellulose is the only co-processed excipient that has its own monograph. In the future, however, co-processed excipients are expected to find their way to regulatory acceptance [44]. In 2010, the USP-NF published a stimuli article describing criteria for acceptance of requests to review inclusion of an excipient in the NF [45]. In 2017, the International Pharmaceutical Excipients Council (IPEC) published a co-processed excipient guide to support both manufacturers and users of co-processed excipients [46]. This guide should facilitate communication between excipient users and suppliers regarding the safety information required for regulatory filing of a product containing a novel co-processed excipient.

2.3.2. Consistency of feeding

Due to the constant feedback loops in loss-in-weight feeders, stable feeding of raw materials can in general be obtained with a wide variety of materials having different physical chemical characteristics [32]. In certain cases, however, deviations in feeding performance can be observed. Controlled mass flow might be challenging for example due to material adherence to the feeder screws and walls, or due to densification dynamics during refill. These challenges have been addressed by manufacturers by providing advanced control algorithms adapting the screw speed during refilling in combination with automated refill systems [47]. The impact can also be minimized by using raw materials that show limited densification and screw adherence. Other unanticipated events that cannot easily be corrected via gravimetric feedback include the sudden detachment of an agglomerate from the screw outlet or intermittent starvation of material from the hopper (e.g. because of bridge formation). Feeding is especially challenging when the material is cohesive and/or dense, and when it needs to be dosed at very low rates [48], as is the case for high potent APIs and lubricants. In these situations, the powder–wall interactions are highly relevant, due to a high surface-to-volume ratio.

Challenges related to low quantity feeding of cohesive materials have been addressed in multiple ways. Specialized precision micro feeders have been developed to achieve consistent low feeding rates for materials with a wide variety of properties [49]. One strategy is by prevention of low-quantity feeding. This can be achieved by increasing the throughput of the system or by using batch made pre-blends to get rid of the individual low feed rates [48–50]. Cohesive raw materials could also be replaced by materials with better flow properties. For example, sodium starch glycolate might be selected as a superdisintegrant, due to the improved flow properties compared to croscarmellose sodium or crospovidone [51]. Engineering of API particles has led to morphologies with improved flow properties [52], although this might not be possible for all potential ingredients.

3. Blending

Feeding of raw material into the processing line is typically followed by blending (Figure 1(b)). The key purpose of blending is to create a homogeneous mixture, to enable a dosage form which delivers the API consistently at the desired dose. Compared to batch blenders, materials spend only a small amount of time in a continuous blender before continuing to the next operation.

Research on continuous powder blending has primarily been focused on the effect of process parameters and design on process performance [7,53–60]. Multiple studies have, however, been published that compare batch blending processes to continuous blending processes [26,61–63]. Batch blending is more dependent on the material properties of the powders being blended than continuous blending [26,61,62]. The optimization of batch blending settings depends therefore on the material properties of the API and excipients. The output of the continuous blender, in contrast, depends less on material properties, due to the high fill ratio and the limited freedom for the components to segregate. Typically, the homogeneity of a blend is not related to the performance of the continuous blender, but to the accuracy of API feeding [26,61,64]. Powder properties that might influence the performance of a continuous blender include density, cohesion, and electrostatics [60,65–67].

These powder properties impact the residence time distribution, which is directly correlated to the blending time. Additional factors that impact the residence time distribution are related to the design and operation of the blender, like the geometry, mixing elements, and mixing speed [68]. One risk associated with higher residence times in the blender is the high shear that might damage the powder particles. Kulkarni et al. [69] evaluated the impact of material properties on the risks for attrition. Brittleness and irregular shapes were identified as risk factors. In most formulations, however, attrition during blending was concluded to have a low impact on the functional performance [69]. Vanarase et al. [60] published a study that shows that the mean residence time in a blender is primarily affected by the bulk density, whereas the axial dispersion coefficient was affected by cohesion. Particle size affects the occurrence of triboelectric forces, where the average charge per unit mass decreases with increasing particle size [55]. Optimal blender performance could therefore be obtained when excipients are used with a high density (i.e. higher residence times in the blender) and low triboelectric potential. However, in conclusion, the performance of a continuous blender is only minimally affected by the material properties of the powders.

4. Granulation

Granulation is a commonly applied particle enlargement technique that improves detrimental raw material properties, like powder flow, segregation tendency, density, cohesiveness, and electrostatic charging [68]. It is seen as a safe technique as it is suitable for all kinds of drug doses. Granulation is an optional step that can be by-passed using a direct compression (DC) process. Unit operations of continuous DC lines include feeding, blending, and tableting. Compared to granulation techniques, direct compression offers several advantages. Those advantages include fewer manufacturing steps and pieces of equipment, faster development, reduced processing times, reduced labor costs, less process validation, lower consumption of raw materials, and the absence of heat or liquid in the process [70]. For granulation processes, the flow and compaction properties of the granules are driven by the process settings [71]. Disadvantageous properties of the raw materials are overcome before the powder is dosed and compressed into tablets. For DC processes, in contrast, the flow and compaction properties of the blends are driven by the intrinsic properties of the API and the excipients [72]. The continuous introduction of new DC excipients with improved flow and compaction properties therefore allows formulators to extend the amount of formulations that can be produced via DC processes [73].

4.1. Dry granulation

In continuous dry granulation processes, the compaction and densification of powder (Figure 1(e)) are combined with a milling step (Figure 1(f)) to ensure the controlled formation of granules. Dry granulation is a popular granulation method because of the fewer processing steps compared to wet granulation [74]. Additionally, the absence of water is a benefit when formulating moisture-sensitive drugs. Roller compaction is of particular interest for integration in a continuous manufacturing line, due to the inherently continuous nature of the process [75].

A major challenge in dry granulation is the reduction of tablet tensile strength as a result of recompression [76]. Multiple papers have been published to relate material properties to the loss of compactability [77–82]. Brittle materials that show extensive fragmentation upon compaction, like anhydrous lactose, were concluded to be most suitable for dry granulation due to the limited loss of compactability upon dry granulation. Plastic deforming materials, like microcrystalline cellulose (MCC), can also be used because of the high initial compactability, although this parameter reduces significantly upon densification [83]. To limit the loss of compactability, Jaspers et al. recommended the addition of superdisintegrants in the blends [84]. Croscarmellose sodium was shown to introduce some defects in the granule structure that increase the propensity for fracture.

4.2. Wet granulation

The wet granulation step consists of three substeps, which are the wet formation of granules (Figure 1(c)), followed by drying (Figure 1(d)) and milling (Figure 1(e)) of granules. Wet granulation is a popular method, as the flow and compaction properties of the granules are highly controlled by the process settings that the formulator can choose. Continuous high shear granulation (HSG) and continuous fluid bed granulation (FBG) are semicontinuous steps with small alternating granulators for continuous throughput. Twin screw granulation (TSG) is the most commonly used continuous wet granulation technique [85–89]. In TSG, the powder blend is kneaded using two corotating screws with a modular configuration, which allows the efficient blending of the raw materials, the distribution of the liquid during the wetting phase, and the densification of the formed granules [90]. Compared to high shear granulation, twin screw granulation requires less water to obtain granules of a desired size [91,92]. In general, less spherical and more porous granules are produced with TSG than with high shear granulation [93]. These properties are favorable, as more fragmentation could occur during compaction, increasing tablet tensile strength. Material properties that are relevant for the performance of a wet granulation line include the solid form, particle size, particle shape, morphology, surface area, moisture content, solubility, wettability, density, type of diluent, type of disintegrant, type of binder, binder solution viscosity, and surface tension [94].

4.2.1. Production capacity

In a twin screw granulation process with a continuous subsequent drying process, the residence time in the granulator is limited by the throughput. Granulation needs to occur in 5–20 s, in contrast to a time period of (tens of) minutes for batch processes [89]. It is therefore important that binders are activated and exert their binding potential in a short timeframe. Consequently, fast wetting kinetics of all ingredients is more important than in batch processes [89].

Besides the limited time for granulation, there is also limited time for drying. The amount of water that can be evaporated

during drying after TSG is therefore lower than in batch processes [95]. This is in line with the lower amounts of liquid that are typically needed in TSG, due to efficient blending and kneading interactions. A further reduction of granulation liquid can be desirable to achieve higher throughputs in the drying unit. Formulators could adapt to this by optimizing the composition of the formulation. For example, a reduction of MCC content in lactose-based formulations could lead to a reduced liquid-to-solid ratio. MCC has a high water binding capacity, but also requires more water to be added to ensure binding [96]. Portier et al. evaluated the addition of the surfactant sodium lauryl sulfate (SLS) to a formulation of mebendazole, lactose, and MCC. Similar granule quality could be obtained after TSG, while allowing a significant reduction in the required liquid-to-solid ratio when SLS was in the formulation [95]. In conclusion, TSG can benefit from excipients with fast wetting kinetics and high binding potential at low liquid-to-solid ratio.

5. Final blending

Just before compression into tablets, an additional blending step is typically performed (Figure 1(g)). During this final blending step, minor components like anti-adherents, glidants, and lubricants can be added to the blend [97]. Anti-adherents prevent sticking of the powder to the tooling and as a consequence counter the picking or sticking of a tablet [98]. Glidants improve the flow properties of powders and granules by reducing the inter-particle friction [98,99]. This ensures the uniform filling of tablet dies. Lubricants reduce the friction between a tablet's surface and the die wall during ejection. Lubricants are required to eject tablets from dies without defects, and they reduce the wear of punches and dies [100,101]. Materials that are used as lubricant, glidant, or anti-adherent typically have more than one of those qualities and are often all referred to as lubricants [97,98,101]. Lubricants can reduce the compactability via the formation of a thin layer that covers APIs and excipient particles. The correct use of lubricants can therefore be challenging. Hebbink et al. compared the lubricant sensitivity of different raw materials in batch-wise and continuous blending processes [102]. They showed that the impact of material properties on the magnesium stearate sensitivity is similar for batch and continuous blending. In general, brittle fragmentation and irregular surfaces with cavities are beneficial to prevent over-lubrication. Plastic deforming materials with flat surfaces provide the highest risk for over-lubrication.

A main challenge for particle engineering of excipients is still present for lubricants. As lubricants are added just before the compression step, they typically require separate addition through a specific inlet port. Traditional lubricants include magnesium stearate, stearic acid, and sodium stearyl fumarate, and are added in concentrations of 0.25–5.0% w/w [103]. So far, a good feedable, easy-to-mix lubricant is still missing. Alternative lubrication solutions have been suggested, including external lubrication. Effective lubrication has been obtained by spraying a lubricant, as a powder or as a rapidly evaporating solution, directly onto the punches [104].

6. Compression

The final step of a power-to-tablet continuous manufacturing line is the tableting process (Figure 1(h)). Commercial tableting processes are inherently continuous, and they can be combined with preceding unit operations to create a continuous process. In comparison to granulation techniques, direct compression has fewer manufacturing steps and pieces of equipment, reduced processing times, reduced labor costs, less process validation, lower consumption of powder, and there is no need to use heat or liquid in the process [70]. The intrinsic properties of the raw materials used in a direct compression process are more important to the final product quality than with a dry or wet granulation process. Due to its importance in batch-wise processing, the impact of material properties on compaction processes has intensively been studied [105]. The success of the compaction process depends mainly on the material properties of the ingredients, especially their compaction behavior. The ratio between fragmentation, plastic flow, and elastic deformation is the main determinant of the final tablet properties. However, directly or indirectly, properties such as moisture content, surface properties, flow properties, particle size distribution, polymorphism, and amorphism were identified to impact the results of a compaction process [73,105–110].

In general, the process stability over time is significantly improved in an integrated continuous direct compression (CDC) process, as compared to batch processing. Especially formulations with high API content and consequently poor powder flow provide better uniformity of tablet weight and subsequently API content in continuous processing [63,111]. This is explained by the continuous addition of powder to the tableting machine and the fluidization of powder in the continuous setup. In batch-wise processes, in contrast, hoppers are typically filled in portions creating variable pressure rates on the powder bed.

7. Conclusions

This review summarizes the impact of excipient properties in pharmaceutical powder-to-tablet continuous manufacturing. Unit operations feeding, blending, wet granulation, dry granulation, lubricant blending, and compression were discussed. For each unit operation, an overview is provided of recent literature that indicates which existing knowledge of batch processing is transferable to continuous processing. The increased understanding of those processes has led to new needs regarding excipients. The limitation in the number of ingredients that can be added through feeding results in increased interest in multi-functional (co-processed) excipients and excipient blends. The feeding of low quantity raw materials highlighted the need for better feedable excipients, in particular lubricants. Feeding is the critical step for content uniformity in continuous processing, in contrast to blending as the critical step in batch processing. Dry granulation by roller compaction is inherently continuous, and therefore no new needs were identified. Twin screw wet granulation can be optimally performed with excipients that are instantly activated upon contact with the granulation liquid and have fast

drying kinetics. Compression is an inherent continuous step, although the continuous addition of powder and fluidization of the powder in continuous processing could lead to lower weight variability. Based on the evaluated situation, some gaps between the current and the desired situation can be identified. Needs that deal with the general advantages will be discussed in section 8.

8. Expert opinion

Continuous manufacturing has the potency to become the major manufacturing route for the production of tablets. As described above, developments are fast and the potential advantages of CM are recognized by many pharmaceutical companies. However, full utilization of the potency of CM still requires a number of challenges to be addressed effectively. These challenges comprise equipment-related challenges as well as material-related challenges. Equipment-related challenges that require attention include the feeding precision, the PAT control for real-time-release, the easiness for cleaning, and the integration and coordination of different unit operations. Even so, raw materials can be optimized to expedite the development of CM processes. Excipients that traditionally have been used in batch manufacturing can typically also be used for CM. Increased understanding and characterization of their behavior in continuous manufacturing lines is however required to achieve optimal performance in a CM line. Additional excipient innovations that would help CM move forward include a good feedable lubricant and regulatory-wise accepted customized co-processed excipients. Additionally, fast wetting kinetics and fast drying can help to achieve higher throughputs in TSG processes. In general, some major challenges deserve future attention before CM can be applied to more production processes. These challenges are described below.

8.1. Cleaning challenges

One commonly mentioned advantage of continuous manufacturing is the improved flexibility of production. The flexibility in batch size allows more products to be produced with the same manufacturing line [4,8,9]. Using the same line efficiently for the production of different products, however, requires validated and intensive cleaning procedures during switch-overs. Cleaning is however challenging, time-intensive, and often uses organics solvents, detergents and/or heating [112]. Wet cleaning procedures need to be completed with effective drying steps, which is time and energy consuming. It would be a huge advantage, if the equipment could be cleaned by flushing it with an inert, nontoxic solid excipient without dismantling the line. Research has identified excipients that can support in-line cleaning by the removal of ibuprofen residues effectively from the hopper, feeder screw, mixer paddles, shaft, and stream sampler [112]. Dismantling and manual cleaning was however still required to clean the rotating feeder screws and mixer paddlers. So far, no cleaning excipient has been identified that allows complete cleaning of an entire CM line without dismantling it.

8.2. Consistency

A major difference between batch and continuous manufacturing is the processing scale. Compared to batch manufacturing, continuous processing has a small unit of scale with reduced degrees of freedom [62]. Continuous manufacturing is more constraint on adjusting variables, because any change needs to be consistent and sustainable over the entire operation period. Batch mixing in contrast, allows for dynamic changes and adjustments at any point during the mixing process, for example based on intermediate results. This means that any variation in how a product flows into a continuous manufacturing line can affect the final product quality. Excipient manufacturers have different

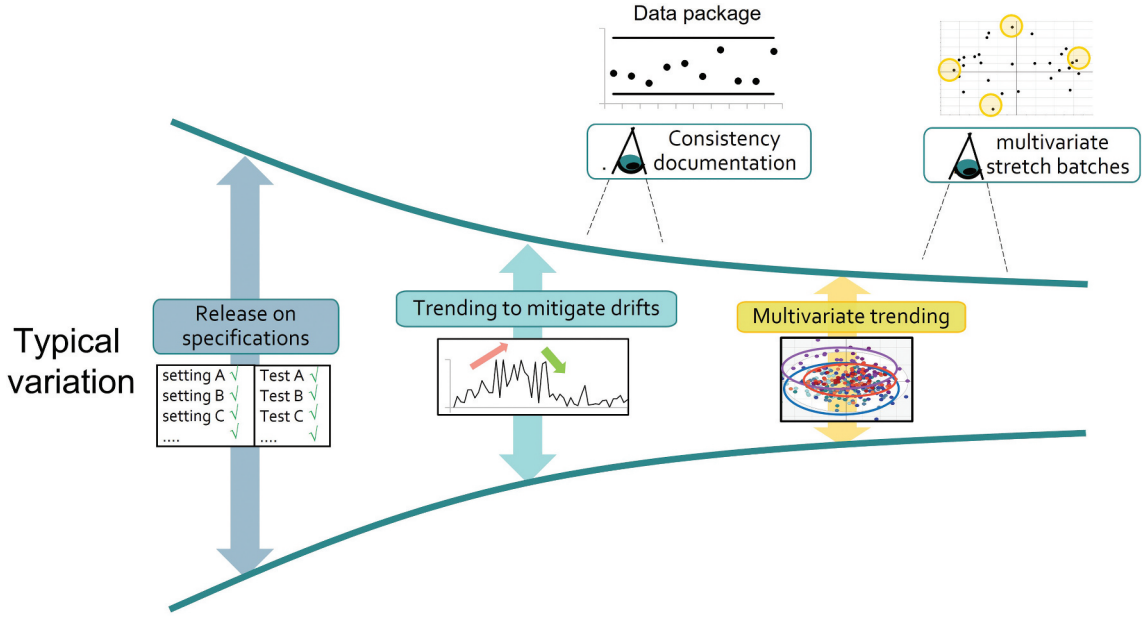

Figure 2. Different quality levels that are provided by different excipient manufacturers. Increased effort to control the process and share insights on consistency is of benefit to the design of continuous manufacturing processes.

quality levels, and they make different efforts to improve the process stability and product consistency (Figure 2). All suppliers release their materials with specifications, but only some do univariate and/or multivariate trending to mitigate any drifts in the processes and thereby in the product quality. Performing this trend analyses, and linking the product properties with raw material and process data allows the further refinement of production processes and the supply of more consistent excipients [113].

Although variability in the properties of excipients can be minimized, some level of variability is inevitable [114]. Understanding the level of excipient variability is therefore crucial in the formulation development. This is also in line with the recently published ICH Q13 guidelines, in which formulators are recommended to pay additional attention to understanding the impact of input material attributes and their variability [23]. Understanding the total variability of a raw material, however, is something that requires an open supplier/buyer relationship. Suppliers have a wealth of product data, while users know which part of this data and variability is relevant to the quality of the products produced with their processes. Open communication and confirmation on how tested batches relate to the total variability is key to convince regulatory agencies of the reliability and consistency of developed processes.

8.3. Multivariate models and modeling

Due to the complexity of particle interactions, predictive methods for powder flow through a continuous manufacturing line based on one or only a few powder properties are difficult to develop. Therefore, in many cases, multivariate analysis (MVA) tools are needed for the evaluation of the impact of material properties on performance [33,35,36,115,116]. MVA models mainly have been used to predict the feeding behavior of new powders based on similarities in material properties [33,35,36]. This allows more efficient and faster development of new drug products, by guiding the selection of raw materials, required feeder capacities, feeding mechanisms, and screw types.

Another way to deal with the complexity of particle interactions is by advanced mechanistic modeling. This way of modeling can reduce the amount of experiments required to test any hypothesis. For example, discrete element modeling (DEM) simulation techniques can model the feeding process down to the particle level [39,117]. DEM is typically used to screen formulation options – resulting in savings in time and resource investment [118]. Important to note is that modeling can provide insights and understanding of the impact of changing certain parameters, but always require confirmation and validation of the simulation results in practice.

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•• **Extensive description of material properties and their impact on formulation.**

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