

Roller compaction in pharmaceutical manufacturing: Comprehensive insights into processes, equipment, and formulation development

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ABSTRACT

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Received: 27 September 2024

Revised: 19 April 2026

Accepted: 5 May 2026

Published: 23 September 2026

Citation:

Thareesucheevakul, T.,
Pornpitchanarong, C.,
Opanasopit, P.,
Patrojanasophon, P., &
Chaksmithanont, P. (2026).
*Roller compaction in
pharmaceutical manufacturing:
Comprehensive insights into
processes, equipment, and
formulation development.*
*Science, Engineering and
Health Studies*, 20, 26010002.

Roller compaction is a crucial operation in pharmaceutical manufacturing, offering a versatile approach to granulation and powder processing. This review provides a comprehensive overview of roller compaction in pharmaceutical production, including its principles, advantages, disadvantages, and recent trends. In addition, it explores formulation development for roller compaction, emphasizing critical quality attributes, suitable excipients, and the influence of material properties. Ultimately, this review is intended to serve as a valuable resource for pharmaceutical researchers, process engineers, and industry professionals aiming to enhance their understanding of roller compaction and its pivotal role in modern pharmaceutical manufacturing.

Keywords: roller compaction; pharmaceutical manufacturing; process parameter; drug development; solid dosage form

1. INTRODUCTION

1.1 Background on roller compaction

Oral solid dosage forms are widely used for delivering active pharmaceutical ingredients (APIs) due to their convenience, stability, and ease of administration. Tablets and capsules are the most common, often manufactured via direct compression, which is a straightforward approach that involves blending APIs with excipients, followed by compression into tablets or filling into capsules. However, this approach can be unsuitable when the blend has poor flowability or contains a low API content, leading to issues

with mixing homogeneity and content uniformity. To overcome these limitations, granulation techniques are employed to improve the physical properties of powder blends by agglomerating the particles.

Roller compaction is a widely used dry granulation method that enhances powder properties by mechanically compacting the drug powder between two counter-rotating rollers to obtain free-flowing granules. Particles with diameters less than 50 μm typically exhibit poor flowability due to strong cohesive forces that overpower gravity, which can result in unacceptable drug product content uniformity (Lee, 2010). Compared to wet granulation,

which involves binder solutions and a drying step (Wade, 2019), roller compaction avoids the challenges associated with the instability of water- or heat-sensitive drugs, the presence of residual solvents in finished products, and the need for stringent environmental controls (Grodowska & Parczewski, 2010; Kristensen & Schaefer, 1987; Propst, 2002). In scenarios where direct compression is unsuitable due to poor powder flow or wet granulation is not feasible due to moisture or heat sensitivity, roller compaction is the method of choice (Lee, 2010; Miller, 2005; Parikh, 2010). According to a manufacturing classification system developed by experts from academia and the pharmaceutical industry, roller compaction is ranked between direct compression and wet granulation in terms of process simplicity and risk. Although it receives a lower score than direct compression, it is rated as superior to wet granulation in terms of the risks associated with API properties and desired attributes of the final product (Leane et al., 2015). A flowchart of the three previously mentioned manufacturing routes for

tablet and capsule production, along with their key processing conditions, is shown in Figure 1. Furthermore, roller compaction offers substantial advantages over slugging, another dry granulation technique that involves compressing powder into large tablets before milling. Unlike slugging, roller compaction supports continuous processing and provides enhanced control over product quality, which makes it highly compatible with modern continuous manufacturing lines.

This article focuses on pharmaceutical manufacturing using roller compaction, emphasizing how process design, operating parameters, excipients, and material properties influence potentially critical quality attributes (CQAs). Figure 2 presents an overview flowchart summarizing these relationships. Overall, the goal is to provide a comprehensive understanding of how these factors influence quality attributes, offering insights to optimize the roller compaction process and enhance the CQAs of the final product.

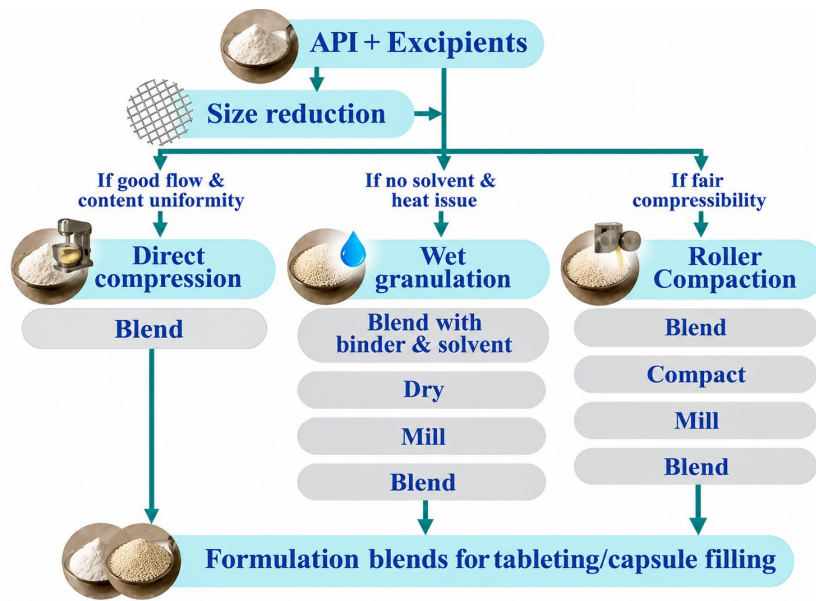


Figure 1. Flowchart of tablet and capsule production pathways and their key process selection criteria

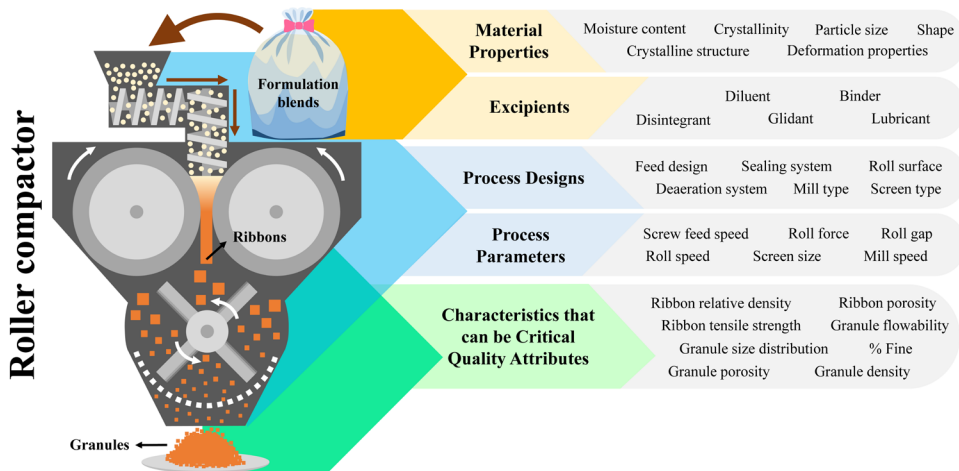


Figure 2. Overview flowchart illustrating the factors influencing ribbon and granule properties, which can be critical quality attributes in roller compaction

1.2 Advantages and disadvantages of roller compaction

Roller compaction offers several advantages, making it a preferred granulation method in pharmaceutical manufacturing. These advantages include:

1. A solvent- and heat-free process, making it particularly suitable for moisture- or heat-sensitive APIs (Shaikh et al., 2018).
2. Continuous operation, enabling integration with other unit operations.
3. A standalone process, which reduces the number of steps compared to wet granulation.
4. Compatibility with automation, which is easily implemented through control panels, enhancing process control and consistency (Miller, 2005).

However, the mechanical compaction during the process is not well understood, given the diversity of parameters and material attributes involved in process operation (Rogers et al., 2013). Furthermore, the process still presents some challenges, including the following:

1. Loss of compressibility of the drug powder due to granule hardening at high compaction forces (Propst, 2002; Sun & Kleinebudde, 2016).
2. Generation of large amounts of fines, particularly from ribbon edges, due to poor powder feeding across the ribbon width. This issue may require additional steps for fine recompaction, thereby increasing labor and processing time (Miller, 2005; Omar et al., 2018; Propst, 2002).
3. Dependence on material properties, which necessitates the use of excipients with good compressibility and flowability, generally requiring the use of specialized excipients to ensure acceptable product quality (Rowe et al., 2017).

Despite these limitations, roller compaction remains a vital technique when other approaches are unsuitable.

1.3 Recent trends of roller compaction in pharmaceutical manufacturing

A notable recent trend in pharmaceutical manufacturing is the integration of roller compaction into continuous processing systems. This continuous manufacturing approach links multiple unit operations into a single uninterrupted process line (Wilms et al., 2022). Material transport between units is achieved using gravity, pneumatic conveyors, pressure differentials, compressors, or pumps, thereby reducing the need for intermediate transfer and storage. The process thus becomes less dependent on human intervention and external factors. This setup reduces material handling, minimizes losses, and improves process efficiency (Ganesh & Reklaitis, 2020).

Roller compaction is also aligned with Quality by Design (QbD) principles, which emphasize a scientific and risk-based understanding and control of manufacturing processes to ensure consistent product quality (Mishra et al., 2018; Muliadi et al., 2020). Several strategies and technologies have been implemented to support this framework, including:

1. Process analytical technology (PAT) has been integrated to enable the real-time monitoring of CQAs, such as granule size distribution, ribbon density, and drug content. Tools such as near-infrared spectroscopy, thermal effusivity, image analysis, microwave resonators, and Raman spectroscopy have been employed for this purpose in many studies (Ghorab et al., 2007; Gupta et al., 2015; McAuliffe et al., 2015; Omar et al., 2018).

2. The design-of-experiments methodology has also been used to optimize roller compaction parameters. This approach involves systematically investigating key process parameters affecting CQAs and their interactions, typically employing multivariate or response surface analysis to define a design space for controlled, robust processing (Jang et al., 2021; Karkala et al., 2018).

3. Process simulation is garnering interest as a promising predictive and optimization tool. Depending on the material and process characteristics, models can be developed based on physical principles, engineering fundamentals, empirical techniques, or hybrid approaches. These models enable *in silico* experimentation, which allows the prediction of process outcomes and the refinement of models and operational parameters without extensive physical trials (Pandey et al., 2017). Several models have been developed to simulate compaction behavior and ribbon properties, including the Johanson model, the slab method, the finite element method (FEM), the combined discrete element method (DEM)-FEM, and artificial neural networks (Cunningham et al., 2010; Johanson, 1965; Katashinskii, 1966; Mazar et al., 2018; Muliadi et al., 2013, 2020; Sajjia et al., 2017). For the subsequent milling step, predictive models, namely DEM, multivariate analysis, population balance modeling (PBM), and DEM-PBM hybrids, have been employed to forecast granule properties (Amini & Akseli, 2021; Amini et al., 2020; Hare et al., 2016; Loreti et al., 2017).

2. ROLLER COMPACTION PROCESS

2.1 Principles of roller compaction

Roller compaction consists of three main compartments: (a) the feed compartment, where the drug powder is delivered from a hopper to the compaction compartment using feeders; (b) the compaction compartment, where two counter-rotating rollers compact the drug powder into ribbons; and (c) the mill compartment, where the ribbons are cut using mill rotors and subsequently sieved into granules using a screen beneath the mill (Figure 3) (Kleinebudde, 2004).

Regarding powder behavior during compaction (Al-Asady, 2016; Miller, 2005), four primary stages occur (Figure 4):

1. Particle arrangement: The applied pressure causes particles to move closer together, filling the space between them. This reduces porosity without densifying the particles. This step continues until the particles are tightly packed, thereby preventing further reduction in porosity.
2. Particle fragmentation: As higher pressure is applied, particles begin to fracture into smaller fragments, thereby increasing the available bonding surface area. These newly formed fragments can undergo repeated cycles of rearrangement, deformation, and further fragmentation until they reach their fracture limit.
3. Particle deformation: With additional pressure, densification changes the particle geometry, which can result in either permanent (plastic) or temporary (elastic) deformation. The type and extent of deformation depend on the material's mechanical properties and the processing parameters, such as temperature and applied pressure.
4. Particle bonding: Following the deformation and fragmentation of particles, consolidation occurs through intermolecular forces, such as van der Waals forces, and mechanical interlocking between particles.

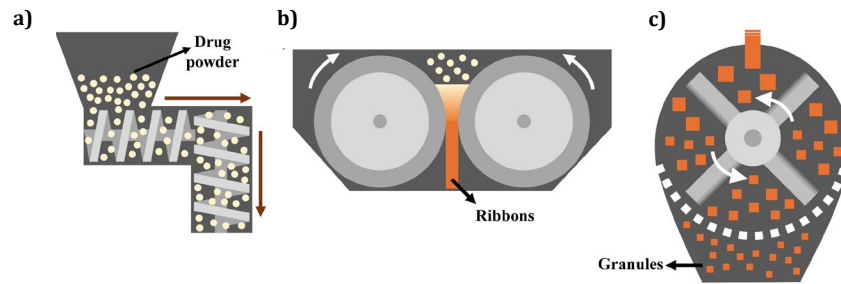


Figure 3. The three main compartments of roller compaction, including (a) feed, (b) compaction, and (c) mill compartments

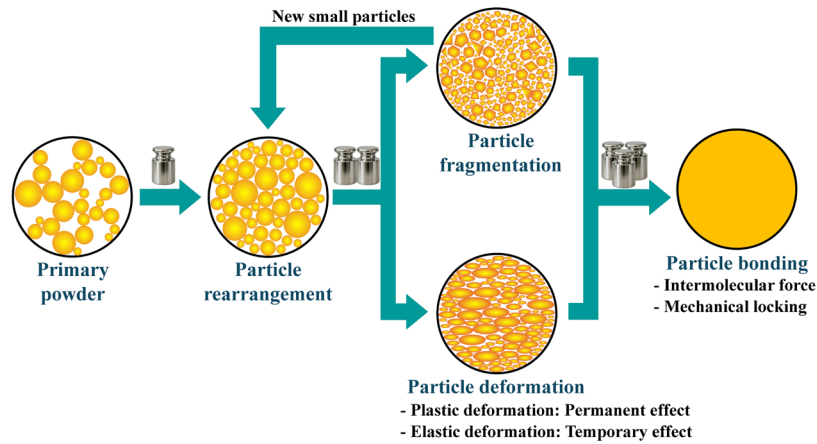


Figure 4. Flowchart illustrating powder behavior during compaction

In the compaction compartment, the area is divided into three zones: the slip, nip, and release zones, as shown in Figure 5 (Bindhumadhavan et al., 2005; Johanson, 1965; Singh et al., 2012; Sousa et al., 2020). The slip zone is where the powder has not yet been densified and is still in the particle rearrangement stage, during which deaeration occurs. The nip zone is where the powder is trapped and densified into a ribbon by the rollers. The release zone is where the compacted ribbon is relieved of pressure. The geometry of the ribbon may change in this zone if elastic

recovery occurs after compaction. The nip angle (α) defines the transition from the slip zone to the nip zone. It can be determined by the intersection of two curves derived from equations based on distinct assumptions: one assumes slip occurs along the roller surface, whereas the other assumes no slip between the powder and rollers. Dwell time is the duration that the powder spends under compaction in the nip zone, serving as a measure of compaction duration (Omar et al., 2018).

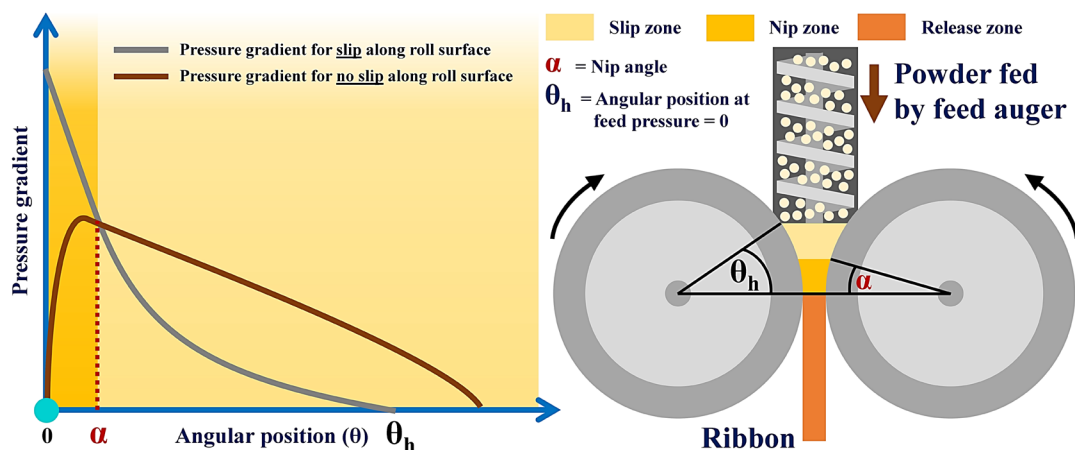


Figure 5. Schematic diagram of the compaction compartment of a roller compactor and the vertical pressure gradient at various angular positions

2.2 Types of roller compactors

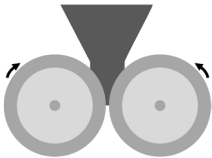
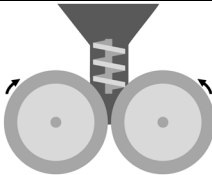
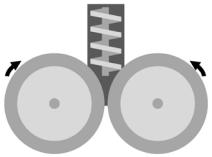
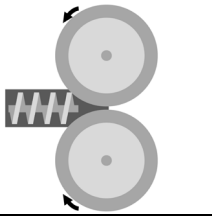
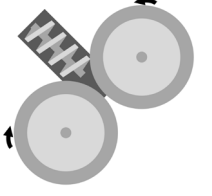
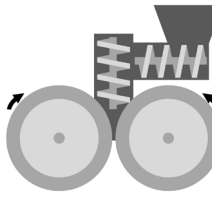
Currently, roller compactors in the pharmaceutical field are distributed by several suppliers worldwide. Consequently, roller compactors come in diverse designs, including various dimensions, feed mechanisms, feed orientations, roller orientations, and roller configurations. In this review, roller compactors are classified by the design of the fixed parts of the equipment, namely the feed mechanism, feed orientation, and roller orientation. The design of the changeable parts is discussed in subsequent sections.

2.2.1 Types of roller compactors based on the feed mechanism

The most commonly used feeding systems in roller compaction are gravity and force feeders, as summarized in Table 1 (Al-Asady, 2016; Miller, 2005; Muliadi et al., 2020; Teng et al., 2009). In a gravity feeder, a simple hopper delivers powder to the compaction unit without

applying external pressure. Because this mechanism relies solely on gravity, the powders must possess good flow properties. Otherwise, issues such as nonuniform ribbon density and reduced production efficiency may occur. Consequently, gravity feeders are generally limited to small-scale or laboratory applications. In contrast, a force feeder uses a feed auger, which is a screw-shaped feeder placed beneath the hopper, to transport the drug powder into the compaction compartment. The force feeder is particularly effective for handling powders with low density or poor flowability, as it provides continuous, uniform feeding. However, if the force feeder is not properly controlled, it may interfere with the removal of air from the powder bed. Today, force feeders are widely implemented in modern roller compaction equipment used in the pharmaceutical industry due to their consistent performance and process reliability.

Table 1. Types of roller compactors based on the fixed components design

Name	Image	Description
Types of roller compactors based on the feed mechanism		
Gravity feeder		A hopper is used to feed drug powder into the equipment. A distributor and a tongue can be placed at the end of the hopper to aid flow. Gravity is a crucial factor in controlling powder delivery. Therefore, powder with good flow properties is required for this feed mechanism.
Force feeder		A feed auger is positioned beneath the hopper to deliver the drug powder from the hopper to the compaction compartment. Some auger designs are capable of lightly compacting the powder before it reaches the rollers. The force feeder is especially suitable for processing powders with low bulk density or limited flow characteristics.
Types of roller compactors based on the feed and the roll orientation		
Vertical feed & horizontal roll orientation		This type benefits from gravitational head pressure, which aids in the delivery of drug powder, resulting in more consistent feeding and easier flow into the compaction compartment. However, this setup may result in greater leakage of uncompacted powder through the roll gap due to gravity.
Horizontal feed & vertical roll orientation		This type typically results in less leakage of uncompacted powder through the roll gap. Conversely, the lack of gravitational assistance may hinder the efficient transfer of drug powder into the compaction zone.
Inclined feed & roll orientation		This type combines the advantages of the two orientations above.
Combined horizontal and vertical feed & horizontal roll orientation		Multiple types of feed augers can be integrated into the equipment to enhance feeding capacity and ensure continuous powder flow.

2.2.2 Types of roller compactors based on the feed and roller orientation

In a force feeder system, the feed auger and compaction rollers can each be configured in vertical, horizontal, or inclined orientations (Muliadi et al., 2020; Teng et al., 2009). These components are typically arranged so that the roller orientation is perpendicular to the feed direction. For example, vertical rollers are commonly paired with a horizontal feed auger, whereas horizontal rollers are often combined with a vertical or gravity feeder, as summarized in Table 1. Other angular configurations are also possible, depending on the design and process requirements. Each type provides specific advantages. The vertical feed and horizontal roller orientation benefits from gravitational head pressure, which assists powder delivery and results in more consistent feeding and easier transfer into the compaction compartment. However, the horizontal feed and vertical roller orientation typically results in less leakage of uncompacted powder through the roller gap.

The inclined feed configuration combines the advantages of vertical and horizontal systems. It is frequently used for manufacturing-scale applications. In addition, more than one type of feed auger can be installed in the equipment to increase feeding capacity and maintain continuous material flow.

2.3 Design and process parameters of the roller compaction

As mentioned earlier, the roller compaction process is not fully elucidated due to the wide range of factors that influence it. Consequently, many researchers have investigated and discussed the effects of these factors. This section summarizes the critical elements that affect roller compaction, including the design of interchangeable components and operator-adjustable parameters. These factors are organized by the specific compartments they affect, as shown in Table 2, and are discussed further in the following subsections.

Table 2. Process designs and parameters of roller compaction involved in each compartment

Compartment	Process design	Process parameter
Feed	- Feed design • Straight feed auger • Tapered feed auger	- Screw feed speed
Compaction	- Sealing system • Side sealing • Rimmed roll sealing - Roll surface • Smooth • Rough - Deaeration system	- Roll force - Roll gap - Roll speed
Mill	- Mill type • Pocket mold-grooved rotor • Open star rotor • Knife rotor • Bar rotor • Etc. - Mill screen type • Round • Grater • Etc.	- Mill speed - Mill screen size

2.3.1 Design and parameters involved in the feed compartment

1) Feed design

A feed auger in a roller compactor can be either straight or tapered, as shown in Figure 6. A straight-feed auger features a standard screw configuration with uniform spacing between flights for various materials. In contrast, a tapered feed auger gradually reduces the volume of conveyed powder along its length, thereby deaerating and predensifying the powder. This design provides benefits for light, bulky powders but may lead to clogging when the material consists of drug powders that are dense and highly compressible (Teng et al., 2009).

2) Screw feed speed

Screw feed speed is an adjustable parameter that governs the rotational speed of the feed auger, particularly in roller compactors equipped with a force feeder operating in gap-controlled mode. In this system, a proportional-integral-derivative (PID) controller automatically regulates the roller

gap by responding to changes in the user-defined parameters through an internal feedback loop (Muliadi et al., 2020; Toson et al., 2019). Increasing the feed speed elevates the feed rate, thereby influencing the powder throughput. For a force feeder with a multi-feed auger, the nomenclature for feed speed parameters may vary with design and orientation, such as horizontal and vertical feed speeds, or feed auger and tamp auger speeds (Bacher et al., 2007; Falzone et al., 1992). Some studies have evaluated the ratio of auger speeds as a distinct processing parameter (Bacher et al., 2007; Clarke et al., 2020). Regarding the effects on ribbon properties, Omar et al. (2018) reported that increasing the feed speed increased the ribbon porosity and decreased the tensile strength. This occurred because a greater quantity of powder was fed into the compaction zone, causing the feedback system to increase the roller gap. The resulting wider gap allowed the powder to disperse more broadly across the roller width, thereby reducing the maximum compaction stress and weakening the ribbon.

An increase in feed speed while keeping other parameters fixed led to reduced fines in the resulting granules. The increased roller gap provided more space for powder distribution across the rollers. Improved powder distribution enhanced the compaction efficiency at the

ribbon edges, thereby reducing the formation of fines (Omar et al., 2018). Moreover, Weyenberg et al. (2005) reported that this can substantially improve the density, size, and flowability of the resulting granules, particularly in the 125–355 μm size range.

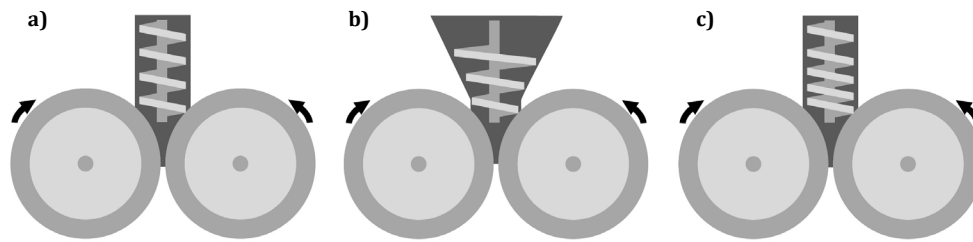


Figure 6. Various feed auger designs for roller compaction, including a) a straight feed auger, b) a feed auger with a tapered flight, and c) a feed auger with a tapered pitch

2.3.2 Design and parameters involved in the compaction compartment

1) Sealing system

Sealing plates are typically installed in roller compactors to reduce powder loss from the sides during compaction. Contemporary designs feature either side sealing or rimmed roller sealing, as illustrated in Figure 7. Side sealing involves the use of two stationary plates, known as cheekplates, positioned adjacent to the rollers without direct attachment. In contrast, rimmed roller sealing consists of flat plates fixed to both sides of a movable roller, also

referred to as a concave–convex roller, which enables them to rotate with the roller during compaction (Muliadi et al., 2020). Csordas et al. (2018) reported that denser ribbons were obtained with side sealing compared with rimmed roller sealing, regardless of whether the rollers had smooth or knurled surfaces. However, Wiedey & Kleinebudde (2017) reported that rimmed roller sealing produced ribbons with a more uniform density. With cheekplates, the ribbon density tended to be higher in the center and lower at the edges due to friction between the powder and stationary plates, which disrupted powder flow.

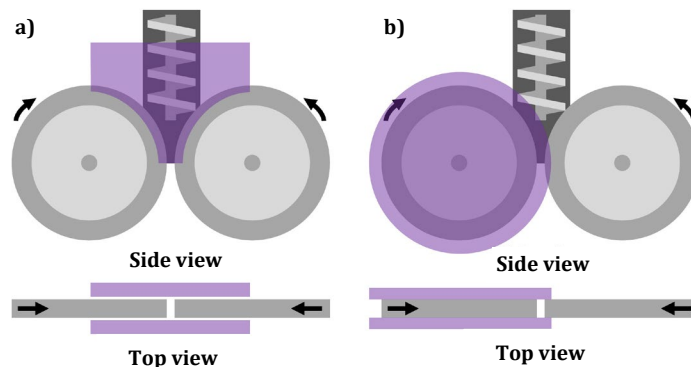


Figure 7. Configurations of the sealing system, including (a) side sealing and (b) rimmed roller sealing

2) Roller surface

Roller surfaces in contact with the drug powder are broadly classified as smooth (polished, flat) or rough (textured). Due to its increased surface friction, the rough roller draws drug powder more effectively into the compaction compartment (Johanson, 1965). This may be essential for powders with low bulk density or poor flowability. A smooth surface is recommended for formulations prone to sticking (Muliadi et al., 2020). Roller surface type can interact with the sealing system. For instance, Csordas et al. (2018) found that switching from rough to smooth rollers enhanced the effect of the sealing system on ribbon density.

3) Deaeration system

Air entrapped within the powder can lead to fluidization, uneven feeding, reduced throughput, and powder leakage. Therefore, deaeration systems are implemented to overcome these issues. One approach is the use of a tapered

feed auger, as discussed earlier. Alternatively, a vacuum deaerator—a filter connected to a vacuum pump—can be installed upstream of the rollers or at the feed auger to remove interstitial air (Miller, 2005; Muliadi et al., 2020).

4) Roller force

Roller force is an adjustable parameter that governs the pressure applied between the stationary and movable rollers to compact powder into ribbons (Muliadi et al., 2020; Omar et al., 2018). It is typically expressed as a specific compaction force (kN/cm), calculated by dividing the total compaction force by the roller width. This parameter is frequently manipulated in experimental studies to investigate compaction behavior (Herting & Kleinebudde, 2008; Janssen et al., 2022; Lück et al., 2022).

An increase in roller force generally leads to higher ribbon density, reduced porosity, and increased tensile strength (Csordas et al., 2018; Omar et al., 2018; Souihi et al., 2013). In a study by Omar et al. (2015), higher roller

forces reduced fines in lactose granules due to greater particle fragmentation and increased surface area, thereby enhancing interparticle bonding via van der Waals forces. Similarly, Weyenberg et al. (2005) demonstrated that increasing roller force improved the density, flowability, and size of the resulting granules while reducing granule porosity.

5) Roller gap

Roller gap is an adjustable parameter that defines the distance between the counter-rotating rollers in screw-controlled mode, where a PID controller automatically controls the feed speed to maintain consistent compaction conditions (Omar et al., 2018; Toson et al., 2019).

Generally, a wider roller gap yields thicker ribbons (Souihi et al., 2013) but results in lower ribbon density and tensile strength, as well as higher ribbon porosity (Csordas et al., 2018; Omar et al., 2018). As explained in the section on screw feed speed, a larger quantity of powder enters the compaction zone, distributing pressure more widely and reducing the peak stress applied. Regarding granule properties, a wider roller gap facilitates better powder spread across the ribbon width, thereby increasing ribbon width and reducing fines in the resulting granules (Omar et al., 2018).

6) Roller speed

Roller speed is an adjustable parameter that controls the rotational speed of the rollers. Higher roller speed increases process throughput but reduces dwell time under pressure, potentially compromising interparticle bonding during compaction (Muliadi et al., 2020; Omar et al., 2018).

According to studies by Csordas et al. (2018) and Omar et al. (2018), increased roller speed resulted in a slight reduction in ribbon density and tensile strength and an increase in porosity due to insufficient bonding time. Furthermore, Gupta et al. (2004) reported that at constant screw feed speeds, higher roller speeds reduced the upstream powder buildup, resulting in thinner, more fragile ribbons. Shorter dwell times also impair lateral powder spread, yielding narrower ribbons (Omar et al., 2018). Regarding granule properties, Weyenberg et al. (2005) reported that increased roller speed led to higher granule porosity and lower density, flowability, and particle size in the 125–355 μm range. In addition, fine material content increased due to poor bonding at the ribbon edges caused by limited powder distribution (Omar et al., 2018).

2.3.3 Design and parameters involved in the mill compartment

1) Mill type

The rotor mill design in roller compactors varies among equipment suppliers. Some commercial mills offer flexible configurations that can be freely changed, thereby influencing the production rate and granule shape (Rekhi & Sidwell, 2010). Several types of mills are commercially available, such as pocket mold-grooved rotors, open star rotors, knife rotors, and bar rotors (Muliadi et al., 2020; Rekhi & Sidwell, 2010).

2) Mill screen type

The type of screen installed in the mill compartment plays a critical role in determining the granule size distribution and proportion of fine particles generated (Perez-Gandarillas et al., 2016; Samanta et al., 2012). Common screen types include square wire mesh, round-hole screens, and conidur screens (Farrenkopf, 2009).

In a study by Samanta et al. (2012), granules were

produced by milling compacted flakes made from lactose monohydrate and microcrystalline cellulose (MCC) using different screen types and mill speeds. The granule size, represented by the mass median diameter (d_{50}), was substantially affected by mill speed when a smooth screen was used. However, with a grater-type screen, adjusting the mill speed did not notably affect the d_{50} . This is because the grater screen's edge design can trap the flakes, leading to faster release of the milled granules, whereas the smooth screen increases residence time due to the lack of such trapping.

3) Mill screen size

Screen size is a critical process parameter that determines the maximum granule size after milling and has a direct influence on the granule size distribution, flowability, and compressibility (Kazemi et al., 2016; Rowe et al., 2017).

Using a design-of-experiments approach, Sun et al. (2018) investigated the effect of milling parameters on the granules obtained from simulated ribbons composed of MCC and dibasic calcium phosphate anhydrous. Their findings indicated that larger screen sizes substantially reduced the extent of fines. Among the factors studied, including screen size, ribbon density before milling, and mill speed, screen size was identified as the most critical parameter influencing the generation of fines.

4) Mill speed

Mill speed is an adjustable parameter that controls the rotational speed of the mill rotors. Briefly, higher mill speed results in smaller granule sizes (Sakwanichol et al., 2012). This parameter can interact with other factors, such as screen type, as demonstrated by Samanta et al. (2012). The interaction between mill speed and screen design can considerably influence granule size and should therefore be considered during process optimization.

3. FORMULATION DEVELOPMENT FOR ROLLER COMPACTION

3.1 CQAs of roller compacted formulations

Within the QbD framework, CQAs are key product characteristics that should be maintained within the acceptance range to guarantee product quality. These attributes can be identified through risk assessment to justify their criticality. This is followed by a design-of-experiments approach to evaluate the effect of critical variables in building a knowledge space (Sangshetti et al., 2017; Teng et al., 2009).

As ribbons are the primary intermediate products in roller compaction, several of their physical attributes have been investigated as potential CQAs in numerous studies. One of the most commonly studied attributes is ribbon relative density, also referred to as the ribbon solid fraction (SF), which is defined as the ratio of the ribbon envelope density to the material's true density. It has been frequently evaluated because it notably influences granule attributes (e.g., extent of fines and flowability), final product properties (e.g., dissolution, hardness, and friability), and downstream processing (e.g., milling into granules and tableting) (Csordas et al., 2018; Gupta et al., 2005; Iyer et al., 2014; Muliadi et al., 2020; Rowe et al., 2017; Yu et al., 2013).

Another relevant attribute is ribbon porosity (ϵ), which represents the void space within the ribbon. It has an inverse relationship with ribbon relative density, as shown in the following equation:

$$SF = 1 - \epsilon \quad (1)$$

A porosity of zero ($\epsilon = 0$) corresponds to a fully dense ribbon ($SF = 1$) (Omar et al., 2018; Rowe et al., 2017). Ribbon porosity is targeted in parametric studies to investigate how different material and process variables influence this property (Khorasani et al., 2015; Muliadi et al., 2020; Omar et al., 2018; Souihi et al., 2015).

Ribbon tensile strength is another important ribbon attribute that is derived from the breaking force of ribbons using a three-point bend test. Ribbons with low tensile strength are more susceptible to fracture during milling, which potentially results in a higher proportion of fines, and compromises flowability and blend uniformity (Gochioco, 2014; Gupta et al., 2005; Iyer et al., 2014; Omar et al., 2015; Osborne et al., 2013; Rowe et al., 2017). Ribbon tensile strength has also been shown to correlate with ribbon density (Omar et al., 2018; Rowe et al., 2017).

In addition to ribbon attributes, granule-related CQAs are vital to ensuring the quality of the final dosage form. One such attribute is granule flowability, which is essential during tableting and capsule filling. Poor flow can lead to inconsistent fill weights, which impacts content uniformity (Lee, 2010; Teng et al., 2009). Flowability is influenced by particle size and shape, as smaller, elongated particles generally reduce flow performance (Lee, 2010).

Granule size distribution is another CQA that affects compressibility and flowability (Nordström & Alderborn, 2015; Teng et al., 2009). A wide size distribution or excessively large granules can cause segregation, leading to weight variation during tableting (Teng et al., 2009).

The proportion of fines should also be monitored as a key attribute. Excess fines can cause poor granule flow, tablet picking, and unacceptable variation in weight during tableting or capsule filling. This may require recompaction to agglomerate the fines (Miller, 2005; Teng et al., 2009).

Granule porosity and density are also often identified as CQAs. Granules with higher porosity (or lower density) tend to fragment more readily, increasing the surface area for interparticle bonding, which can enhance the tensile strength of the final tablets (Teng et al., 2009). These attributes also influence compressibility, thereby reflecting the material's ability to be compacted during tablet formation (Nordström & Alderborn, 2015).

3.2 Excipients for roller compaction

In the context of formulation development, excipients play a critical role in enhancing the performance and stability of the final product, aiding processability, and mitigating in-process defects by improving the drug powder's physicochemical properties (Darji et al., 2018). In addition to their functional role, a primary objective of adding excipients to the roller compaction formulation is to improve the powder blend's compressibility and flow properties, ensuring suitability for compaction (Muliadi et al., 2020). The excipient types used for roller compaction are similar to those used in direct compression. Generally, a formulation for the roller compaction process is prepared by blending a drug substance with excipients (e.g., diluents, binders, and disintegrants) and subsequently adding lubricants to obtain a blend with the desired compaction properties. The mixture is then roller compacted to form ribbons, which are subsequently milled into granules. These granules may undergo further blending with additional excipients (e.g., diluents, glidants, and disintegrants) and a second lubrication step before final compression into tablets or filling into capsules (Muliadi et al., 2020). Common pharmaceutical excipients used in roller compaction and their descriptions are summarized in Table 3 and discussed further in the following subsections.

Table 3. Commonly used excipients in roller compaction and their descriptions

Type	Excipient	Trade name	General description
Diluent	Microcrystalline cellulose	Avicel, Celolus, Vivapur	It is a well-known diluent recognized for its high tensile strength after compaction. Various commercial grades are available, differing in particle size and porosity, which influence their compressibility, flowability, and the disintegration time of resulting tablets and capsules.
	Silicified microcrystalline cellulose	Prosolv	A co-processed blend of microcrystalline cellulose and colloidal silicon dioxide, offering enhanced compaction properties and improved flowability.
	Lactose	FlowLac, Lactopress, Pharmatose, SuperTab	It is a well-known brittle diluent available in various grades, depending on its hydration state (anhydrous or monohydrate) and manufacturing process (e.g., spray-drying). These variations affect its compressibility and flowability. It should be avoided in formulations containing drugs with an amine group due to the risk of a Maillard reaction (Darji et al., 2018; Ohrem et al., 2014).
	Dibasic calcium phosphate	A-Tab, Di-Tab, Emcompress	A brittle inorganic insoluble diluent available in various hydration state (anhydrous or dihydrate), with each grade offering different chemical stability, porosity, compaction properties, and disintegration times for resulting tablets and capsules (Zarmpi et al., 2017).
	Mannitol	Parteck, Pearlitol	A brittle diluent that serves as a substitute for lactose, with direct-compression grades available to improve flow properties.

Table 3. Commonly used excipients in roller compaction and their descriptions (continued)

Type	Excipient	Trade name	General description
Binder	Povidone	Kollidon, Plasdone	A highly water-soluble binder.
	Hypromellose	Methocel, Vivapharm	It can be used as a dry binder, although it is less effective than when used as a wet binder (Dürig, 2010).
	Hydroxypropyl cellulose	AeroWhip, Klucel	Low-substitute grade may also function as a disintegrant (Desai et al., 2016).
	Copovidone	Kollidon, Plasdone	A povidone derivative with higher plasticity, which enhances compressibility while retaining its water solubility (Dürig, 2010).
Disintegrant	Corn starch	Farmal, Hylon, Meritena, Pure-Dent, Purity, Uni-Pure	A conventional disintegrant with a swelling mechanism (Desai et al., 2016).
	Pregelatinized starch	Starch 1500, Prejel, Unipure	A modified starch that functions as a disintegrant, primarily through a swelling mechanism (Desai et al., 2016).
	Sodium starch glycolate	Explotab, Primogel, Vivastar	A rapidly swelling superdisintegrant (Desai et al., 2016).
	Crospovidone	Kollidon CL, Polyplasdone	A superdisintegrant that functions through wicking and strain recovery mechanisms (Desai et al., 2016).
	Croscarmellose sodium	Ac-Di-Sol, Kiccolate, Primellose sodium	A superdisintegrant that utilizes multiple mechanisms including swelling, wicking, and strain recovery (Desai et al., 2016).
Glidant	Corn starch	Farmal, Hylon, Meritena, Pure-Dent, Purity, Uni-Pure	A conventional hydrophilic glidant (Builders & Arhewoh, 2016).
	Talcum	Luzenac Pharma	A conventional crystalline glidant that also functions as a lubricant (Sheskey et al., 2017).
	Colloidal silicon dioxide	Aeroperl, Aerosil, Cab-O-sil	An effective glidant consisting of fine particles with high surface area, which also acts as a moisture scavenger to maintain drug stability and enhance flowability.
Lubricant	Magnesium stearate	Cecavon, Synpro	A well-known hydrophobic metallic salt lubricant recognized for its high efficiency.
	Stearic acid	Edenor, Pristerene, TriStar	A fatty acid lubricant that can be used as a substitute for magnesium stearate when acid-base interactions with acidic drugs are a concern (Chaiya & Phaechamud, 2020).
	Sodium stearyl fumarate	Lubripharm, Pruv	A hydrophilic acid ester used as a lubricant, offering minimal impact on tablet and capsule disintegration time (Hölzer & Sjögren, 1979).

1) Diluents

Diluents are added to formulations to increase bulk volume and improve physical attributes, such as compressibility and flowability, thereby aiding the process (Darji et al., 2018). They are typically inert and cost-effective (Ohrem et al., 2014) and are classified as ductile or brittle based on their deformation behavior.

a) Ductile diluents typically undergo plastic deformation under compaction pressure (Mohan, 2012; Roberts & Rowe, 1987), such as MCC. MCC exhibits excellent compressibility and produces ribbons with high tensile strength and low fines due to strong hydrogen bonding under moderate compaction forces (Iyer et al., 2014; Kerche et al., 2023; Muliadi et al., 2020). However, it is sensitive to overlubrication, which can soften the ribbons and tablets, and is relatively hygroscopic (Darji et al., 2018; Otsuka et al., 2004).

b) Brittle diluents undergo particle fragmentation under pressure, creating new bonding surfaces (Mohan, 2012; Roberts & Rowe, 1987), such as dibasic calcium phosphate and lactose. This mechanism reduces sensitivity to overlubrication (Otsuka et al., 2004). Dibasic calcium phosphate anhydrous generally yields higher ribbon tensile strength, whereas lactose is easier to densify into a

very high-density ribbon (LaMarche et al., 2014; Muliadi et al., 2020). Mannitol is a brittle diluent that is less commonly used but is preferred when lactose may react with amine-containing drugs (Maillard reaction). Although direct-compression grade mannitol has good flowability, its performance does not match that of spray-dried lactose (Teng et al., 2009). Using pure mannitol (β -form, a typical commercial form) under high compression may result in capping during tableting (Yoshinari et al., 2003).

In addition to managing the compressibility and flowability of the formulation blend, achieving a balanced ratio of ductile and brittle components is a critical strategy in roller compaction formulation design. The advantages of adding both deformation types when selecting suitable diluents will be discussed further in the section on deformation properties.

2) Binders

Binders are typically ductile polymeric materials that are added to formulations to improve the binding properties of powders, thereby enhancing granule strength, flowability, and compressibility (Darji et al., 2018). In roller compaction, only dry binders are used. Although binders can be absent in roller compaction formulations, their addition provides considerable advantages and is especially beneficial in

brittle formulations to stabilize the ductile-to-brittle balance in the formulation by compensating for loss of compactibility and increasing tablet hardness while reducing friability (Arndt & Kleinebudde, 2018; Sun & Kleinebudde, 2016). However, excessive binder addition can delay disintegration and dissolution (Arndt & Kleinebudde, 2018).

3) Disintegrants

Disintegrants play a pivotal role in formulations, as they promote tablet and capsule disintegration, thereby reducing disintegration time and enhancing dissolution. They achieve this by attracting water into the product and then undergoing processes such as swelling, wicking (facilitating water penetration by generating capillary and micropore structures), strain recovery (recovering the disintegrant shape, which creates stress inside the product), disrupting particle bonds, or generating heat through interactions (inducing the expansion of entrapped air in the product) (Desai et al., 2016). Moreover, they may be included intragranularly, extragranularly, or in both parts to influence disintegration dynamics (Lee, 2010).

4) Glidants

Glidants are formulation components that improve powder flow by reducing interparticle friction, surface charges, or uneven surfaces, thereby preventing weight variation issues (Augsburger & Shangraw, 1966; Darji et al., 2018). Colloidal silicon dioxide is widely used because of its dual function as a flow enhancer and moisture scavenger, thereby increasing the product stability (Darji et al., 2018; Teng et al., 2009). In addition, silicified microcrystalline cellulose, a co-processed excipient, can be incorporated as a diluent, which reduces the need for additional glidants due to its benefits for compressibility and flowability (Tomar et al., 2018).

5) Lubricants

Lubricants are essential excipients used to reduce friction during compaction and tableting by preventing issues such as sticking and picking (Darji et al., 2018). They form thin films on particle surfaces, which aid in separating surfaces and minimizing adhesion (Miller & York, 1988). In roller compaction formulations, lubricants are typically added to the intragranular and extragranular phases (Teng et al., 2009). Lubricants reduce friction on the roller surface and in the feeding zone, promoting a more homogeneous powder feed across the roller width into the compaction compartment. As a result, lubricated powders produce ribbons with more consistent density distributions than unlubricated ones, even though the direct blending of lubricants with drug powder may reduce ribbon density (Miguélez-Morán et al., 2008). However, excessive lubricant levels can reduce the tensile strength of ribbons and resulting tablets (He et al., 2007; Yu et al., 2013). Lubricants can be categorized into three types: metallic salts (e.g., magnesium stearate), fatty acid esters (e.g., sodium stearyl fumarate), and fatty acids (e.g., stearic acid). Among these, magnesium stearate is the most widely used because of its efficient lubricating properties and cost-effectiveness (Muliadi et al., 2020).

3.3 Material properties that affect formulation development

The physicochemical properties of initial substances play a fundamental role in the success of roller compaction processes. Inadequate properties, such as very bulky drug powders with low compressibility, may limit their suitability for roller compaction (Rogers et al., 2013). In

addition, many ribbon and granule attributes, designated as CQAs, are influenced by material properties such as moisture content, crystallinity, morphology, and deformation properties (Gupta et al., 2005; Iyer et al., 2014; Omar et al., 2015; Soh et al., 2008). These material properties should be carefully evaluated during formulation development to ensure optimal performance and product quality.

1) Moisture content is a critical factor in the roller compaction process, especially for hygroscopic materials such as MCC (Darji et al., 2018). Previous studies have demonstrated that moisture can induce swelling in MCC, impacting tablet tensile strength and hardness (Khan et al., 1988; Reier & Shangraw, 1966; Shah & Wilson, 1968). Moreover, moisture can influence powder flowability (Dawoodbhai & Rhodes, 1989; Emery et al., 2009; Wu et al., 2010). The effect of moisture on flowability is complex; at low levels, moisture promotes particle agglomeration via liquid bridging, thereby improving flow (Emery et al., 2009). However, at higher levels, excessive water can lead to caking issues, hindering powder flow (Dawoodbhai & Rhodes, 1989). In roller compaction, studies have shown that an increase in moisture content or humidity slightly enhances the ribbon tensile strength at low moisture and humidity conditions but slightly decreases it at high moisture and humidity conditions (Gupta et al., 2005; Osborne et al., 2013). The rationale behind these findings is believed to be related to the cohesive forces exerted by liquid bridges under low-moisture conditions, which drive particle rearrangement and improve compressibility. In contrast, under high-moisture conditions, strong hydrostatic resistance due to a large volume of free water between particles impedes particle consolidation (Wu et al., 2010). In addition, increased humidity can also increase ribbon density by facilitating particle rearrangement. Regarding the resulting tablet properties, higher-humidity conditions during roller compaction markedly enhance tablet hardness across all compression forces and substantially reduce tablet friability, particularly at low compression forces (Gupta et al., 2005).

2) Crystallinity can influence the compaction, dissolution, and stability of pharmaceutical formulations (Hancock et al., 2002; Lee, 2010). Materials can exist in crystalline or amorphous forms, each exhibiting different mechanical and physical behaviors. Lactose, a widely used diluent in pharmaceuticals, illustrates how crystallinity affects compaction properties. Crystalline forms, such as α -lactose monohydrate and β -lactose anhydrous, typically undergo fragmentation, thereby increasing the surface area under compression. In contrast, amorphous lactose deforms plastically with no change in surface area (Lerk, 1993). Commercially available lactose in the pharmaceutical industry is often in crystalline form, with α -lactose monohydrate and β -lactose anhydrous being the most commonly used forms. Some commercial lactose products may contain amorphous content, typically in spray-dried grades, which enhances ribbon tensile strength due to plastic deformation. Comparative studies have confirmed that amorphous lactose tends to produce ribbons with higher tensile strength than its crystalline counterpart, especially under high roller force (Gochioco, 2014; Omar et al., 2015).

3) Morphology, including particle size and crystal shape and structure, can affect powder characteristics and compaction behavior.

3.1) Particle size is generally expressed as diameter or equivalent diameter. In many studies, particle size distribution

is reported using percentiles such as d_{10} , d_{50} (median), and d_{90} , which are derived from the cumulative frequency data. Particle size can influence drug stability, dissolution, mechanical strength, and compressibility (Hintz & Johnson, 1989; Merkus, 2009). The particle sizes of excipients, in addition to the API, can affect the granule properties, further affecting the attributes of the resulting tablets. Previous studies have shown that finer particles tend to increase tensile strength due to a larger surface area for interparticle bonding (McKenna & McCafferty, 1982). For roller compaction processes, Herting & Kleinebudde (2007) reported that increasing the particle size of materials in blends (MCC or theophylline) resulted in smaller granules, reduced tablet tensile strength, and increased tablet friability.

3.2) The crystal shape and structure of a drug powder are critical parameters that can influence its flowability, compaction behavior, and the final product's dissolution rate (Lee, 2010; Merkus, 2009). Certain crystal shapes can lead to defects during tablet production. For example, needle-shaped paracetamol crystals are more prone to capping and lamination than layer- or cube-shaped crystals (Hong-Guang & Ru-Hua, 1995). Furthermore, studies on lactose reported that its crystal structure (primary crystals, agglomerates, and milled particles) notably affected the tablet tensile strength due to variations in surface area, porosity, and particle size (Grote & Kleinebudde, 2019). In roller compaction, Omar et al. (2015) reported that the crystal structure of lactose influenced the tensile strength of ribbons and resulting granules, as the surface area plays a crucial role in particle bonding. Moreover, the crystal structures of isomalt (primary crystals, milled particles, and agglomerates) were found to affect the resulting granule size after roller compaction, as reported by Grote et al. (2019). Agglomerates yielded the largest granules, whereas primary crystals produced the smallest, regardless of the roller force. This is because agglomerates fragment into many smaller primary crystals during compaction, thereby increasing their surface area for bonding.

4) Deformation properties are crucial in roller compaction, as they determine how materials respond to the applied compaction forces. Materials can be broadly classified as ductile or brittle based on their dominant deformation behavior, which is similar to the classification of diluents discussed earlier. Previous studies have compared the effects of ductile and brittle materials in the roller compaction process, indicating that:

4.1) Ductile materials are often more sensitive to process parameters than brittle materials. A study by Lück et al. (2022) found that the density of MCC ribbons was correlated with the dwell time at high roller speeds and low compaction pressure. However, a substantial correlation was not observed for lactose under the same conditions. Similarly, Iyer et al. (2014) demonstrated that adjusting the roller force caused more notable changes in the density and tensile strength of ribbons made from Avicel DG (a co-processed blend of 75% MCC and 25% dibasic calcium phosphate) compared with those made from lactose monohydrate, thus highlighting the greater sensitivity of the ductile component.

4.2) Ductile materials are more susceptible to lubricant effects. Yu et al. (2013) reported that increasing the amount of magnesium stearate in the formulation considerably reduced the density of MCC ribbons but did not affect the

density of ribbons made of brittle materials such as dibasic calcium phosphate dihydrate.

4.3) Ductile materials typically yield ribbons with higher tensile strength than brittle materials due to their superior binding capacity through plastic deformation (Perez-Gandarillas et al., 2015). A study by Iyer et al. (2014) found that ribbons made of Avicel DG exhibited higher tensile strength than those made of lactose monohydrate, which was attributed to the higher proportion of ductile material in the formulation.

4. FUTURE ASPECTS

While an incomplete understanding of powder behavior during compaction persists, particularly for multicomponent formulations with complex deformation profiles, integrating roller compaction into fully continuous manufacturing lines, guided by QbD and PAT frameworks, holds promise for enhancing overall process efficiency and product consistency. Future development is expected to focus on improving mechanistic understanding of the compaction process and integrating advanced modeling and real-time monitoring technologies. The adoption of artificial intelligence for predictive analytics may enable improved control strategies, resulting in more robust, efficient, and scalable manufacturing processes.

Process simulation and machine learning are increasingly being explored for their feasibility and benefits in roller compaction. Mechanistic models have demonstrated the potential to simulate powder behavior, ribbon formation, and granule characteristics. These models enable *in silico* experimentation, thereby reducing reliance on trial-and-error approaches and accelerating process development. Furthermore, machine learning algorithms offer promising capabilities in recognizing patterns from complex, multivariate datasets generated during formulation and processing. When integrated with PAT, machine learning may enable the real-time prediction of CQAs, adaptive control of process parameters, and early detection of deviations. This data-driven approach aligns well with the principles of QbD, thereby supporting the development of more robust, scalable, and continuous roller compaction systems.

In the future, a greater emphasis on hybrid modeling, combining first-principles simulations with machine learning, is expected to enhance predictive accuracy and process understanding. In addition, continued advancements in excipient technology and material engineering may expand the applicability of roller compaction to a broader range of drug products. Overcoming current limitations will require interdisciplinary collaboration across formulation science, process modeling, and regulatory strategy to fully realize the potential of this technique.

5. CONCLUSION

In pharmaceutical roller compaction, various process designs and parameters, as well as material properties, must be precisely controlled to ensure product quality. Key material attributes, such as moisture content, crystallinity, morphology, and deformation behavior, directly influence ribbon and granule characteristics. Similarly, process variables such as feed speed, roller force, roller speed,

screen size, and mill speed should be carefully optimized, as they affect granule size, density, and flowability. Excipients are essential in formulation development and can enhance product performance and stability. In addition to compressibility and flowability, the ductile-to-brittle balance in the formulation should be stabilized to leverage the advantages of both deformation types.

Moreover, the integration of QbD principles enables the identification and control of CQAs across formulation and process design. Future advancements should focus on improved material characterization, real-time process monitoring, and predictive modeling to enhance robustness and scalability. Therefore, a comprehensive understanding of material science and process engineering is essential for the successful development of consistent, high-quality, roller-compacted products.

AUTHOR CONTRIBUTIONS

T.T. conducted the literature search and data curation, developed figures and visualizations, and drafted the original manuscript. C.P. and P.O. supported the development of visual materials and validated the accuracy and consistency of the reviewed information. P.P. and P.C. were responsible for conceptualization, supervised the overall work, and handled project administration. P.P. and P.C. also provided critical review and substantive revisions to improve the intellectual content and clarity of the manuscript. All authors read and approved the final manuscript.

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