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Review article

Systematical approach of formulation and process development using roller compaction

Yue Teng, Zhihui Qiu *, Hong Wen

Pharmaceutical Development Unit, Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA

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ABSTRACT

The roller compaction process has gained heightened interest in the pharmaceutical industry. In this review, common excipients and equipment used for dry granulation are described. Roller compaction process parameters and their impact on the critical quality attributes of the final product, as well as evaluation methods for roller compaction product such as ribbons and granules, are discussed. Overall, a systematical approach of formulation and process development has been proposed for excipient selection, critical process parameter identification, and necessary tests.

1. Introduction

Dry granulation process is a particle-bonding process. Miller [1] described the theory of granule bond formation as:

a. particle rearrangement
b. particle deformation
c. particle fragmentation
d. particle bonding.

In the roller compaction process, powder blends first pass a feeding zone, where most of the rearrangement occurs. The densified powders then go through a compaction zone, where increasing force is being exerted by two counter-rotating rolls. As the pressure goes up further into the compaction zone, the particles deform, fragment, and bond to form ribbons.

Roller compaction is widely applied to dry granulation. It offers many superior characteristics, e.g., good control of process and cost-advantages compared to wet granulation. As no liquid or drying is involved, this process is more suitable for water or heat-sensitive drugs. Compared to direct compression, roller compaction can handle high drug loading, improve flow and content uniformity, and prevent segregation. Like any other processes, dry granulation has its own issues, such as loss of compactibility or dissolution problem. A systematic approach of formulation and process development is the key to high quality drug products.

This review intends to discuss dry granulation formulation and process development from three aspects:

a. formulation design strategy
b. equipment and process overview
c. quality by design strategy.

Fig. 1 outlines a brief flow chart for formulation and process development using roller compaction. At high drug loading, the compactibility and flowability of drug substance will be critical for roller compaction and tableting processes. Different excipients need to be evaluated in formulation development to achieve desirable chemical stability, tablet properties, and process control. After selecting a suitable roller compactor, potential critical process parameters and material attributes can be identified using a risk management strategy. The fishbone diagram and Failure Mode and Effects Analysis (FMEA) are useful tools for risk management. Design of experiment (DOE) can be used to identify the critical quality attributes and design space for the overall process.

2. Formulation design strategy

A successful formulation strategy starts with studying the physical and chemical properties of drug substances carefully and recognizing the main challenge(s) in drug product development correctly. The issue(s) could be high drug loading, poor flow, poor compactibility, high compressibility, low density, etc. Proper selection of formulation composition and excipients level can balance the poor physical properties of drug substance, thus greatly improve the processiblity of the powder mixture. This section focuses

* Corresponding author. Pharmaceutical Development Unit, Novartis Pharmaceuticals Corporation, Ridgedale Ave., East Hanover, NJ 07446, USA. Tel.: +1 862 778 2824.
E-mail address: Zhihui.qiu@novartis.com (Z. Qiu).

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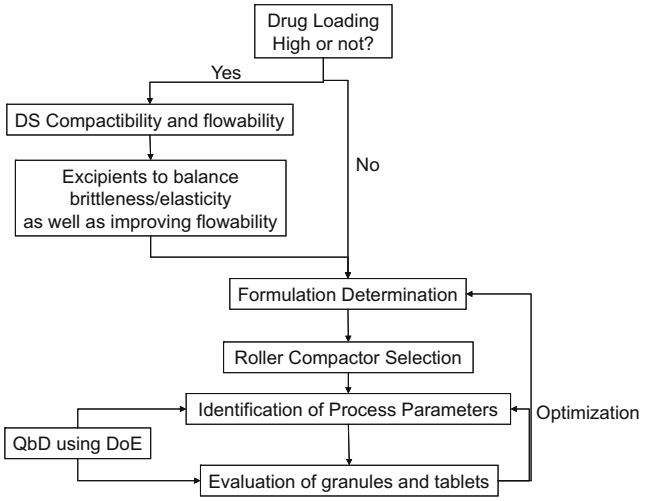

Fig. 1. A brief flow chart for formulation and process development using roller compaction.

on excipients such as fillers, binders, disintegrants, glidants, and lubricants [2–6]. The impacts of roller compaction equipment and process parameters are discussed in Section 3. Fig. 2 describes the decision tree on formulation development strategies.

The excipients are selected based on their chemical/physical compatibility with drugs, regulatory acceptance, and processability. First, excipients should be chemically compatible with drug substances. Second, in the time of globalization, excipients should meet the requirements of not only the FDA or EMEA but also the regulatory agencies of other potential marketing countries. By applying do-it-right-the-first time during excipients selection, development time and cost can be greatly reduced. Third, excipients can significantly impact the properties of a powder mixture, such as flowability, density, compactibility, and adhesiveness. For example, different fillers can be selected carefully to balance the plasticity, elasticity, and brittleness of the pre-compaction powder mixture, in order to make large-scale production feasible.

2.1. Filler

The primary function of fillers in roller compaction is to facilitate formulation design and process development. Fillers play a critical role in modifying the pre-compaction blend properties to achieve desirable compactibility, flow, and density. For a very plastic or brittle drug substance, the selection of filler may be the most important step in formulation design. By balancing the plasticity/elasticity/brittleness of the pre-compaction powder, fillers are critical in making roller compression process feasible and in ensuring good ribbon and granule quality [7–9]. The most commonly used fillers in roller compaction are summarized in Table 1. Among those excipients, microcrystalline cellulose (MCC) is more plastic, mannitol and $CaHPO_4$ are more brittle, while lactose is mostly brittle and partially plastic. Some excipients like MCC and starch derivatives can play dual roles of both fillers and binders.

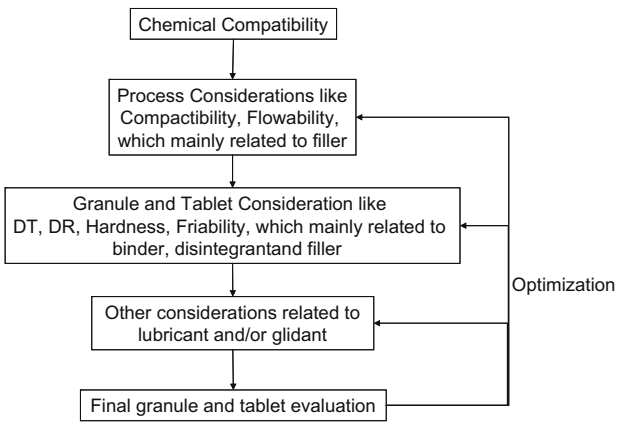

Fig. 2. Formulation screening process.

2.1.1. Lactose, mannitol and sorbitol

As a brittle excipient, lactose is one of the most popular choices to design formulations with desired compressibility and friability. Its wide application partially is because of the fact that lactose is available in many grades: anhydrous and hydrous forms, α-lactose or β-lactose monohydrate, various particle size distribution and bulk density [13–15] (http://www.pformulate.com/lactose-rev.htm). A suitable grade of lactose should be selected based on the requirements on powder flowability and the particle size distribution of other ingredients, especially drug substance. For example, spray-dried lactose, generally recommended for direct compression, is very useful in improving powder flowability at high drug loading. With all the good properties of lactose, there is one concern when selecting lactose: lactose can undergo the Maillard reaction in the presence of primary and/or secondary amine drugs, which can lead to tablet browning [16].

Compared to lactose, mannitol does not have the concern of undergoing the Maillard reaction. In addition, direct compression grade mannitol has large particles and good flow. However, due to its lower density, the contribution of mannitol to overall powder performance is not as good as spray-dried lactose. Sorbitol, another common filler, has been used in achieving good compactibility for calcium carbonate formulation [17]. Hygroscopicity in humid environment is the main concern for sorbitol.

2.1.2. Microcrystalline cellulose (MCC)

MCC, with the trade name Avicel, is another most commonly used filler. MCC has very good flowability and compressibility. Different grades of MCC can be chosen, depending on requirements on particle size distribution, compressibility, and moisture content. For example, MCC with large particle size can improve powder flowability significantly, and help to achieve excellent content uniformity with minimum weight variation. At high drug loading, if the drug substance is a plastic material, suitable brittle excipients

Table 1
Commonly used fillers in roller compaction.

Filler	Comments
MCC	Many grades available Select based on desired flowability, density, and/or compactibility. (www.fmcbiopolymer.com)
SMCC	Silicified MCC has much higher flowability than regular MCC (www.jrspharma.com)
Starch	Starch 1500
$CaHPO_4$ [10]	Anhydrous and dihydrate forms (www.jrspharma.com)
Lactose	Many grades available Anhydrous and monohydrate forms Concern of Maillard reaction
Mannitol [11]	A good alternative for lactose
Sorbitol [12]	An optical isomer of mannitol Hygroscopic at humidity above 65%
Sucrose	Various sucrose-based excipients – not very popular due to diabetic concern
Dextrose	Anhydrous and hydrate forms

like lactose or mannitol should be added to the formulation to achieve balanced compressibility. Otherwise, the powder blend may be too sensitive to compaction force during roller compaction, considering the excellent compressibility of MCC. SMCC, silicified MCC, has become very popular recently, due to its excellent flowability and compressibility. Moreover, low dosage drug substances can be adsorbed to the rough surface of SMCC to achieve good content uniformity.

2.2. Binder

The function of binders is to agglomerate drug substance and excipients to form better granules with suitable density, particle size distribution, strength, and thus tablets with acceptable friability [18,19]. Most dry granulation binders are plastic materials, which can form thin films on particle surfaces. Therefore, the tensile strength of granules can be improved with increased cohesive and adhesive force between solid particles. Selection of binder is very important for brittle drug substances. Binders, together with plastic fillers, can balance the plasticity/brittleness of the pre-compaction powder mixture, control the granule size and strength, and reduce tablet friability. Binders can affect the granules properties from the following perspectives: binder level, binder particle size, and binder type.

Binder levels are very important in generating granules with proper strength. At low binder levels, there are not enough binders to cover particle surfaces. Consequently, even though ribbons may be formed after roller compaction, the strength and particle size control of granules can be very poor. On the other hand, if the binder level is too high, tablet disintegration and dissolution may suffer.

Generally, binders with fine particle size are preferred for roller compaction. Smaller binder particles with a larger surface area give better surface coverage of other ingredients, thus enhance the binder efficiency. For both direct compression and roller compaction, Herting and Kleinebudde reported that decreasing particle size of MCC (as binder) can increase tablet tensile strength [18]. Using small-sized MCC can generate larger granules with better flowability than using large-sized MCC. It was suggested that higher drug loading could be achieved by reducing particle size of MCC (as binder) and similar tablet tensile strength could be maintained [18].

Compared with wet granulation, roller compaction has limited choices of binders, e.g. cellulose and starch derivatives, PVP, etc. The commonly used binders in roller compaction are listed in Table 2.

Many cellulose and starch derivatives have been used as binders in roller compaction. These binders include methylcellulose, ethylcellulose, hypromellose (hydroxypropyl methylcellulose), HPC (hydroxypropylcellulose), pregelatinized corn starch, and MCC (microcrystalline cellulose) [20,21]. Low viscosity HPC, especially HPC EXF and L-HPC (low substituted), are commonly used binders in roller compaction [22–24]. (http://www.herc.com/aqualon/pharm/pharm_products.html). HPC EXF with fine particle size is highly recommended for roller compaction, and has been successfully used to decrease acetaminophen tablet capping and to improve tablet friability [25]. For HPMC, those grades with relative low viscosity like E5, E15LV, and K3 (5, 15, and 3cP, respectively) can be used as binders in roller compaction.

Polyvinylpyrrolidone, trade name Kollidon from BASF, is also one commonly used dry binder [26] (http://www.pharma-solutions.basf.de/binders.aspx). Kollidon VA 64, especially VA 64 Fine, is designed for roller compaction. Polyvinylpyrrolidone should be used with caution for oxidation sensitive drugs as it has trace amounts of hydroperoxides which can lead to oxidation of amine and thio containing compounds.

2.3. Disintegrant

A disintegrant is used to break tablets into granules and further into fine particles, and to achieve satisfactory disintegration time and dissolution rate. Disintegrants can draw water into the tablets, swelling and breaking the tablets into granules. Thus, proper control of ribbon and granule porosity can lead to improved disintegration efficiency. For roller compaction, disintegrants can be used in both intragranular and extragranular portions. The three most common choices are crosscarmellose sodium (Ac-Di-Sol), crosspovidone (Polyplasdone XL), and sodium starch glycolate (Explotab) [27–30]. Starch and pregelatinized starches are also widely used disintegrants (Table 3).

Particle size of the disintegrants may affect tablet disintegration. Zhao and Augusburger [31] reported that tablets containing enlarged Primojel and Polyplasdone XL10 had a slightly longer disintegration time. However, Ac-Di-Sol is less sensitive to particle size.

2.4. Lubricant

The function of lubrication is to reduce the friction between contacting equipment surface and granule/tablets. Lubrication is similar to coating process. Lubricants can form thin films on particle surfaces, thus modifying the interaction between solid bulk and contacting equipment surface. For roller compaction, lubricants are used in both intragranular and extragranular portions. Intragranularly, lubricants reduce the friction between ribbon and rolls, while extragranularly, lubricants reduce the friction between tablets and die walls. The commonly available lubricants are listed in Table 4.

The particle size of lubricant plays a critical role in maximizing lubrication efficiency. For all types of lubricants, the finer the particle size, the more effective they are. Thus, it is recommended to sufficiently screen lubricants before final blending.

Magnesium (Mg) stearate is the most commonly used lubricant [32–34]. It should be noted that Mg stearate from different suppliers can have different lubrication effects because the lubrication efficiency of Mg stearate is very sensitive to particle size. To make full use of the lubrication effects of Mg stearate, sieving through a size 30–60 mesh screen is recommended. Over-lubrication is the

Table 2
Commonly used binders in roller compaction.

Binder	Comments
Polyvinylpyrrolidone (PVP)	Concern of oxidation
Cellulose derivatives	Methylcellulose, hydroxypropyl methylcellulose (HPMC), hydroxypropyl cellulose (HPC)
Polyethylene glycol (PEG) [23]	Concern of oxidation
Carbopol [23]	Produce tablets with excellent hardness and low friability

Table 3
Commonly used disintegrants in roller compaction.

Disintegrant	Comments
Croscarmellose sodium	Trade name Ac-Di-Sol, Cellulose derivatives
Crospovidone	Trade name: Polyplasdone XL cross-linked polyvinylpyrrolidone
Sodium starch glycolate	Trade name: Explotab, Primojel
Alginate	Not compatible with strong oxidizing agents
Starch and pregelatinized starch	Typically used at 5–20% of tablet weight

Table 4
Commonly used lubricants in roller compaction.

Lubricant	Comments
Stearic acid	Stearic acid and derivatives
Stearic acid salts	Magnesium, calcium salts, sodium stearyl fumarate
Talc	Concern of residual iron
Polyethylene glycols (PEG)	High molecular weight PEG
Surfactant	e.g., Na lauryl sulfate
Compritol	Glyceryl behenate

main concern of using Mg stearate, which may lead to poor disintegration and dissolution of drug products.

Talc is the second most commonly used lubricant. It is less efficient than Mg stearate, but does not have over-lubrication concern. Due to the trace amount of iron in most talc, special attention should be paid when drugs degradation may be catalyzed by iron.

As a new lubricant, Compritol® 888 ATO is not prone to over lubrication compared to magnesium stearate, and does not interfere with tablet disintegration or dissolution. Besides, it is an effective problem solver for those metal–ion sensitive compounds [21,35–37]. Compritol is generally used at 1% to 3 % level for the formulation of tablets and capsules.

2.5. Glidant

Glidants are added to a great number of roller compaction formulations to improve the flowability of pre-compression powder. They act as ball bearings to reduce the friction among particles. The commonly used glidants are listed in Table 5. Silicon dioxide is the most commonly used glidant. For low dosage drug, silicon dioxide can also help to improve content uniformity by adsorbing the drug to the surfaces of silicon dioxide [38].

2.6. Excipient/granule particle size

Generally, fine particles show better compactibility than coarse particles. The effects of particle size on compaction properties are more prominent for plastic materials than for brittle materials [40,41]. This effect can be best explained by particle bonding theory. In roller compaction process, particles rearrange, deform, fragment, and bond. Under increased pressure, plastic materials, like MCC, deform and bond without creating extensive fracture. Larger plastic particles or granules have less surface area available for bonding, thus produce tablets with lower tensile strength. Under high pressure, brittle material fragmentation creates new surfaces for bonding; therefore, initial granule size differences are minimized.

It is well known that MCC loses compactibility after repeated roller compaction, possibly due to granule size enlargement. Sun and Himmelspach [42] reported that particle size enlargement lowered the tabletability of Avicel powders. Avicel PH-105 and PH-200 were roller compacted, milled, and sieved. Two sieve cuts, 44–106 μm, 250–500 μm, from each granulated powder were compressed. Despite significantly different tableting properties between Avicel PH-105 and PH-200, tabletability of their granules with similar size was minimal. Tabletability of granules of the same sieve fraction from different batches always decreased with increasing granule size (decreasing granule surface area). Tabletability of larger granules, 250–500 μm, was roughly a half of that of finer granules, 44–106 μm. Tableting properties of these granules were determined by size and surface properties of the granules but not by those of the original Avicel particles. One or a maximum of two re-compaction steps are suggested, in case multi-compaction (rework) is needed to reduce the amount of fine particles and increase granule size, density, and flowability [43].

The granule size does not affect compaction properties of brittle materials as much as those of plastic materials. Riepma et al. studied the consolidation and compaction properties of α-lactose monohydrate granules and β-lactose monohydrate granules, respectively. Their results showed that the type of lactose and the granule size had an impact on the granule compactibility [44]. Fichtner et al. investigated the impact of particle size distribution of free-flowing particles on tablet structure and tablet strength. Sucrose, sodium chloride and paracetamol with different size distributions were studied [45]. It was concluded that the size distribution of free-flowing particles is not critical for tablet porosity but may impact tablet tensile strength significantly.

Table 5
Commonly used glidants in roller compaction.

Glidant	Comment
Silicon dioxide and derivatives	Typically 0.1–3% concentration [39]
Talc	Typically 5% concentration
Corn starch	Typically 5–10% concentration

3. Equipment and process parameters

In the process of product development, the formulations need to be evaluated on roller compactor with process parameters taken into consideration. Fig. 3 outlines an evaluation process for determining equipment and process parameters.

Typically, roller compactors used in the pharmaceutical industry are double roll presses. Powder materials flow through the hopper(s) and are compacted by two counter rotating rollers (Fig. 4). As loose bulk powder approaches the end of hopper, particles are rearranged and densified. At this stage, the particles are exposed to very little force. After the particles enter the nip area, brittle particles break and plastic particles deform with the steeply increased compaction force. The maximum pressure is achieved at the neutral nip angle, which typically is slightly before the minimum roll

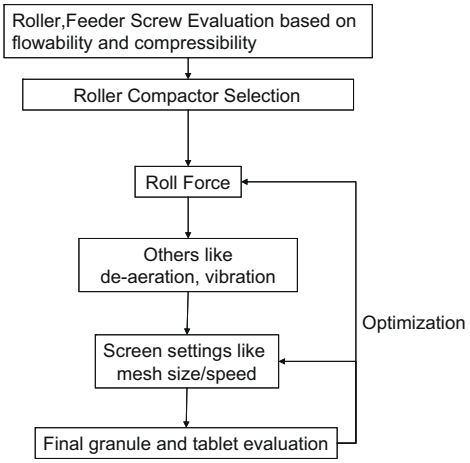

Fig. 3. Flowchart for equipment selection and process parameters evaluation.

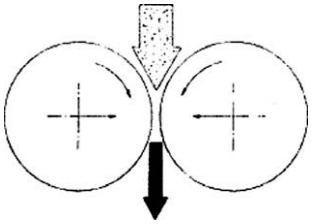

Fig. 4. Schematic diagram of roller compaction [50].

gap. It is reported that the higher the compaction force or the feeding–rolling ratio, the further peak pressure moves away from the minimum roll gap [46]. The nip angle is the angle where pre-densified powders enter the nip area, which depends on the material friction angle and the roll surface friction angle [47,48]. While the nip angle is large for readily compressible material, it is small for incompressible material [49]. After the roll gap, the ribbons are extruded from the rolls, then chopped and milled to form granules of desired particle sizes.

3.1. Roller compactor

There are several factors to consider in equipment selection, namely, the roll design, the feeder design, and mills and other accessories. A brief comparison of different roller compactors commonly used in pharmaceutical industry is listed in Table 6 [51,52].

3.1.1. Roll design

Depending on the manufacturer, the roll design can be different in terms of orientation, mounting, arrangement, pressurizing system. Manufacturers also offer variety of choices in the roll surface design.

As shown in Fig. 5, the orientations of rolls could be horizontal (aligned side by side), inclined, or vertical (one on top of the other) [46]. Most equipment has the horizontal orientation, especially for the large-scale equipment. The roll orientation defines feeder orientation. Vertically aligned rolls are equipped with horizontal feeder(s). Vertical or inclined feeders are used for horizontally aligned rolls. The pros and cons of the two commonly used orientations, horizontal and vertical, are discussed in feeder design, Section 3.1.2.

The surface of rolls can be smooth, corrugated, or fluted (Fig. 6). Smooth and corrugated rolls are the most commonly used in pharmaceutical industry. Smooth rolls can help when alleviating sticking problems and can reduce the amount of lubricant needed. They are widely used when powder gripping is not an issue. When lack of gripping force leads to inadequate feeding and uneven compact, corrugated rolls can be selected to provide more gripping force to the powder, but powder sticking may be an issue, in this case.

3.1.2. Feeder design

Feeding system is critical for achieving a good compaction product. When a hopper is loaded, there is a pressure difference between the bottom and top of the hopper, called head pressure. As a result, particles are continuously densified and deaerated. By regulating powder flow, powder densification, and powder deaeration, the feeding system plays a vital role in achieving good processibility and product quality.

Table 6
Comparison of roller compactor used in pharmaceutical industry.

Manufacturer	Roll orientation	Feeder design	Deaeration
Alexanderwerk	Horizontal/vertical	Screw	Y
Bepex	Horizontal	Screw/gravity	Y
Fitzpatrick	Horizontal	Screw	Y
Freud/vector	Horizontal	Screw	Y
Gerteis	Inclined	Screw	Y

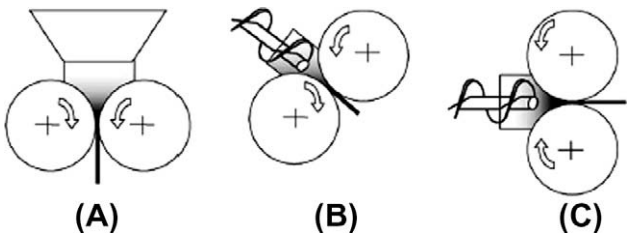

Fig. 5. Roll orientations. (A) Horizontal; (B) inclined; (C) vertical [46].

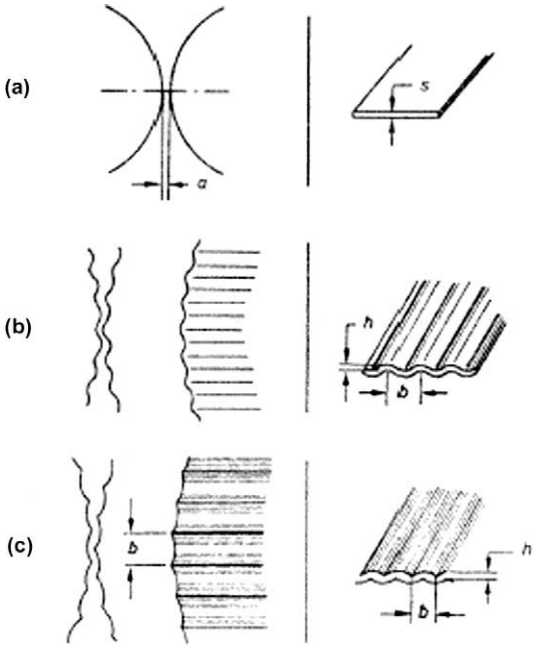

Fig. 6. Roll surface (a) smooth roller; (b) corrugated; (c) fluted [50].

3.1.2.1. Feeding mechanism. The feeder can be either a gravity feeder or a force feeder. In a gravity feeder, the feed control can be achieved by installing an adjustable tongue and a distributor at the end of hopper. Without an external driving force to feed the compaction zone and to densify the powder, the gravity feeder works well for powder with a good flow and a reasonable density or for the lab scale roller press. In a force feeder, a rotating screw is installed in the center of the hopper. The rotating flight forces the powder to move toward the nip area. Force feeders work well for powder mixtures with a poor flow. It provides continuous and consistent flow of particles to the nip area to accomplish the desired densification and compaction. Force feeders also help overcome "fluidization" of fine particles in hoppers, in which trapped compressed air disrupts powder feeding (discussed in Section 3.1.3.1). However, if not properly selected/operated, a force feeder can hinder proper deaeration and may cause the failure of the compacted product due to the expansion of compressed gas.

3.1.2.2. Feeder orientation. Depending on the equipment design, the orientation of the feeder could be vertical, horizontal, or inclined (Fig. 7). Feeder designs are important in obtaining positive pressure to feed the powder and providing a more versatile means of control.

Vertical feeders take advantage of the head pressure in the hopper above the horizontally aligned rolls. The feed screw could be either straight or slightly tapered. Straight screws are a somewhat standard design. For light, fluffy and aerated powder, tapered screws are better, as the volume reduction in the taper enhances the deaeration and pre-densification effect. On the other hand, tapered screws may cause jamming when powder mixtures are highly compressible. In this case, distance between flights should be increased to reduce the feeding force.

Horizontal feeders are used for vertically aligned rollers. Compared to vertical screw feeders, horizontal screw feeders are advantageous in minimizing leakage and improving press capacity.

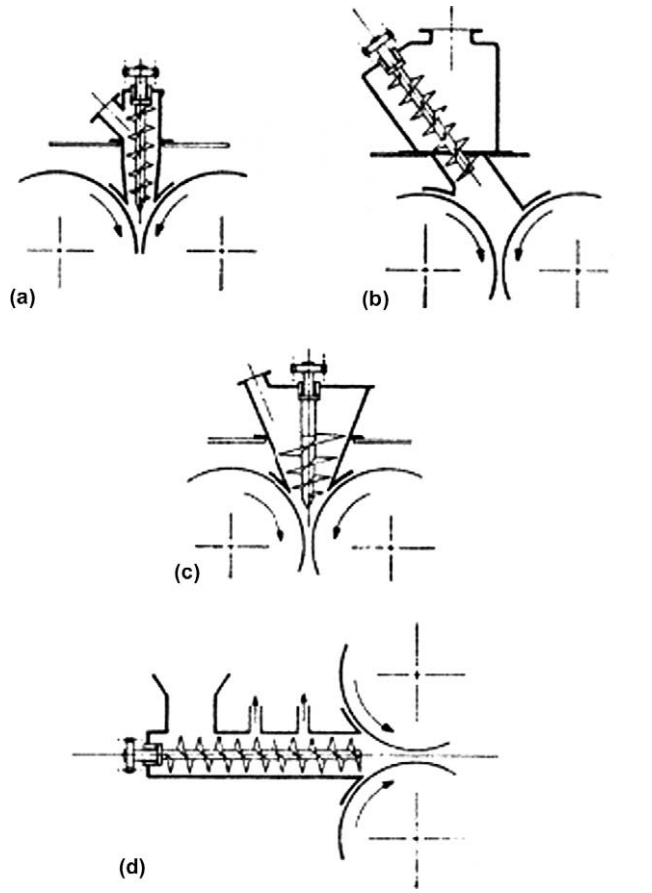

Fig. 7. Feeder orientations. (a) Vertical, straight; (b) inclined; (c) vertical, tapered; (d) horizontal. [50].

For some equipment, inclined screw feeders are used as they utilize gravity to feed powder but have less powder leakage. The inclined screws are more common for multi-screw feeders in large scale equipment.

3.1.2.3. Feeding issues. There are fundamental problems in feeding the nip area for both gravity and screw feeders. For gravity feeders, when particles flow through the hopper, there is a velocity gradient layer close to the wall due to wall friction, which resembles laminar flow in a pipe. Consequently, powder feeding condition is poor at the edges of the rolls [50]. The result is less compaction and possibly excessive leakage between rolls and the cheek plate. Therefore, ribbons are inherently non-homogenous in terms of density, porosity, and strength. The granules produced tend to have a wide particle size distribution and excessive fines.

For screw feeders, the non-uniform feeding is more complicated. First, the nip area is rectangular in cross section, while a rotating screw results in a circular delivery area. As a result, the center portion of the nip is overfed and the edges are poorly fed. The leakage at the cheek plate and the lack of feed on edges exaggerate the uneven feeding, which produces ribbons with thinner and more fragile edges. Using a screw with a diameter larger than the roll diameter does not help, because bigger screws tend to exert pressure directly on the rolls. It does not only waste energy but also exaggerates uneven feeding. Typically, screw diameter is approximately 50% of roll diameter [52]. Second, for a single flight screw, the rotating flight exerts pressure on the compact in the roller gap. This feed pressure is inhomogeneous, which results in uneven distribution of the powder compaction in nip area. Therefore, the ribbons could be more compacted in one area than the other [53]. There are multiple ways to reduce this effect:

a. round off the end of screw flight
b. use double flight screws to obtain more uniform force distribution
c. use multiple feeder screws
d. elevate the position of the screw.

3.1.3. Accessories

Some other accessories are also important in roller compaction process, such as deaeration, vibration, and/or temperature control. For some difficult drugs, these accessories could act as critical elements that make the roller compaction process feasible.

3.1.3.1. Deaeration. For the typical poor flow, low density pre-compaction mix, trapped air could be a big issue, especially in the large scale. If not effectively removed from the powder, trapped air may accumulate in the powder bed to a very high pressure. The pressurized air may intermittently fluidize the powder bed and lead to uneven feeding. Air can also get trapped in ribbons. If the ribbon porosity is high, air continues to leave after ribbon is released from rolls, which results in weaker ribbons. If the ribbon porosity is low, the trapped air may cause the ribbon to break horizontally into segments or even "burst" into small pieces [50]. Therefore, it is very critical to remove the air trapped between particles to maintain good product quality.

Typically, there are three pathways for air to escape:

a. between the feeder base and the top of the roller
b. between the rolls and the cheek plates
c. against the flow of feed through the loose bulk material.

For small-scale equipment, deaeration via space between rolls and cheek plates is the major route. As the roll diameter increases, this route becomes insufficient and may force air to leave through the center of the bulk powder, which will fluidize the bed and disrupt the powder flow. To remove the trapped air, choosing a suitable screw feeder can help solve the problem to a certain extent. At large scale, applying a vacuum at the top and bottom level of the powder bed can force the trapped air out.

3.1.3.2. Feeder vibrator. For a poor flow powder, a simple gravity feeder or force feeder may not prove to be good enough. Installation of a feeder vibrator can be an easy and effective way to improve the flow. By providing a constant driving force, feeder vibrators can break the stagnant powder bed, drive the powder toward the rolls, and help densification and deaeration.

3.1.3.3. Temperature control. As described in the feeder design section, the screw flight can generate a lot of heat when rotating in the powder bed. In a highly packed powder bed, excessive heat may elevate the local temperature, and cause the powder to be partially melted and stuck to the flight. This may even cause batch failure. In this case, special flight with a cooling jacket can be used to improve processibility.

3.2. Impact of process parameters

Even with suitable roller compactor and parts, roller compaction process parameters have very significant effects on the process feasibility, ribbon quality, and granule tabletability. Compaction force, roll speed, and feeder screw speed are the critical parameters needed to be optimized to improve product quality.

3.2.1. Compaction force

A minimum compaction force is needed to compress the loose powder into ribbons. As described earlier, under pressure, solid particles densify, deform or fracture, and bond to form ribbons. At a higher compaction force, stronger compact with a lower porosity and less fine is produced [17,54–56]. Over-compaction may break the ribbon and result in poor granule quality. Since the purpose of roller compaction is to produce granules for compression, excessively high compaction force tends to result in loss of granules' compactibility [42,55,57,58]. As a result, tablets prepared from over-compressed granules may suffer from low hardness and high friability. This is especially prominent for plastically deformed materials [56].

While fragmentation is the major mechanism for bonding, compaction force may become the most important factor in controlling granule quality. Inghelbrecht and Paul Remon [59] studied roller compaction of various lactose and found out compaction force was the most important factor that affects the quality of a good compact. Wu and Sun [41] also pointed out that brittle material is less susceptible to compactibility loss.

For most pharmaceutical formulations, the powder mixtures usually contain both plastic and brittle materials. An optimum operating range of compaction force should be defined on a case-by-case base during process development for quality control.

3.2.2. Screw speed

For equipment with force feeding, screw speed is a critical process parameter to obtain high granule quality. The force generated by a rotating flight produces a downward compression force that not only forces the powder into the compaction zone but also pre-densifies the powder [52]. The operating range of the screw speed should be determined based on powder flow, aeration condition, and the roll speed. Low screw speed may cause insufficient feeding to the nip and poor ribbon strength. High screw speed may cause a highly densified zone in the nip area, and even cause melting/caking of particles on the flight, which may interrupt powder flow. Setting the screw speed too high or too low may cause poor product quality, or even batch failure. It should be noted that an increasing screw speed is not the "magic bullet" for poor flow powder. Necessary formulation modification, the proper deaeration, or the addition of feeder vibrator may be needed to improve process feasibility. Detail discussion on screw speed and roll speed is given in Section 3.2.4.

When two screws are used consecutively for feeding, usually the one farther away from rollers is more critical. Its particular speed determines the overall feeding rate.

3.2.3. Roll speed

Roll speed controls the dwell time of the compact and eventually the throughput of the roller compactor. The selection of roll speed depends on the flowability, plasticity, and elasticity of the powder.

For plastically deformed materials, such as MCC, which are sensitive to dwell time, a low roll speed tends to produce granules with better flow and lower friability [60,61]. However, longer dwell time may also cause the material to lose compactibility and results in tablets with low hardness and high friability. High roll speeds and low screw speeds tend to minimize the dwell time dependency of the plastic material. Even for partially plastic deforming materials, such as lactose, a higher roll speed is preferred. Inghelbrecht and Paul Remon [59] reported that at higher roll speed, the lactose granule quality improved and the tablet friability is lower.

For materials with a significant elastic recovery, such as pregelatinized starch [62–64], the compact strength depends on the dwell time in the compaction zone, because there may be significant elastic recovery upon release of the ribbon from the compaction zone. High roll speed or short dwell time may cause cracking, weakening, or even the destruction of the ribbon. Pietsch [52] proposed that theoretically there is a maximum roll speed (shortest dwell time) that the compacted material will disintegrate completely upon depressurization. Therefore, for highly elastic material, the overall process throughput may be limited due to the physical property of starting material. For brittle materials, the compact strength tends to be independent of dwell time, because fragmentation is achieved rapidly and extended exposure to compaction force tends to have a limited effect on the ribbon strength [62,65,66].

3.2.4. Inter-dependence of roll speed and screw speed

The roll speed and screw speed are inter-dependent in controlling ribbon quality. At constant roll speed, a low screw speed may lead to insufficient feeding, thinner ribbons, and weaker ribbon strength. On the other hand, a high screw speed may lead to overfeed and thicker ribbons [17]. In both cases, the ribbon quality is compromised. Hervieu et al. [67] reported that to produce granules with desirable compression capacity, it is critical to control the ratio of roller speed to screw speed. Gupta et al. [60] also reported that when roller speed and screw speed ratios are kept constant, the ribbon density and strength is independent of roller speed.

The selection of roll speed to screw speed ratios depends heavily on the properties of the powder mixture [68,69]. For plastically deformed materials, granules prepared under high roll speed to screw speed ratio and low compaction force give the best tablet friability, hardness, and dissolution rate. Even for partially plastic deforming materials, such as lactose, a higher roll speed is preferred to improve granule and tablet quality [59].

3.3. Scale up

Inherently, roller compaction is not easy to scale up. As the roll diameter increases, the nip shape and size change unproportionally. The complications become more unpredictable when the roll surface is not smooth. Generally, as roll diameter increases, the roll gap also increases. When the peripheral speed is kept constant, the angle of nip remains approximately the same. There are many ways to carry out scale up.

Pietsch [50] proposed the following relations for roller compaction process scale up:

$$\sqrt{\frac{D2}{D1}} = \frac{P_2}{P_1} \quad \text{or} \quad \frac{F_2}{F_1}$$

where D is the roll diameter, P is the compaction pressure and F is the compaction force.For gap width, it is usually between

$$h_1\left(\frac{D_2}{D_1}\right) > h > h_2\left(\sqrt{\frac{D2}{D1}}\right)$$

However, due to the enlarged compact zone, the densification and compaction behavior are quite different for different scales.

Sheskey et al. [70] used different ways to scale up a controlled release theophylline formulation from lab scale to pilot and full scale:

linear roll velocity = constant
roll speed/screw speed = constant
force per linear inch (roll) = constant.

The tablets from all trials had similar good friability and tight weight control. However, full scale productions tend to have more fines that led to better compression during tableting and faster release in dissolution rate.

The compaction simulator is also a very useful tool in scale-up. The simulation enables prediction of the impact of critical parameters such as roll speed, pressure and radius on the properties of ribbons. When compacted to the same solid fractions, the real ribbons and simulated ribbons exhibited similar compression behavior and equivalent mechanical properties (tensile strengths) [71].

4. Build quality into roller compaction

In drug product development, quality should be built into a product, rather than achieved by control. For a roller compaction product, quality should be ensured from both formulation and process development perspectives. Risk management and building knowledge space and design space by design of experiment (DOE) are two important aspects to come up to a quality by design strategy to ensure desired quality profile of product. Fish bone analysis and FMEA (Failure Modes and Effects Analysis) are powerful tools for risk assessment, which can be used to identify critical formulation and process variables and critical quality attributes, and then to build design space by DOE. For both techniques, their successful application highly depends on thorough understanding on the drug substance properties, mechanism of excipients functionality, and the interactions between formulation and process parameters.

Table 7 lists the general formulation and process variables for a roller compaction product. Good scientific judgment should be applied to give the best evaluation of each variable including the likelihood of variation detection and the potential impact of such variation. Being overcautious may lead to identification of an unreasonable number of critical variables for DOE. On the other hand, being overoptimistic may miss some critical variables. Either way will result in less reliable control for drug product qualities.

Table 8 lists the critical quality attributes. A summary of evaluation methods can be found in the Appendix A. The physical and mechanical properties of granules are important because of their impact on the down stream process to the final dosage forms. Among various granule properties, most commonly checked properties are particle size distribution, bulk/tapped densities. Other properties like porosity, flowability, moisture content, morphology are also useful information. For example, it is reported that change in granule morphology may cause capping if trapped air cannot escape. The surface morphology of granules can be studied with a Scanning Electronic Microscopy (SEM) [70,72].

Table 7
Formulation and process variables.

Formulation variables	Drug substance	Density Particle size and distribution Flowability LOD Compactibility
	Excipients	Compactibility Density Particle size and distribution Compatibility Flowability Hygroscopicity
Equipment variables		Roll orientation Roll surface
Process variables		Screw design Screw speed Roller speed Compaction force Mill screen size Mill speed

Table 8
Critical quality attributes.

Roller compaction	Granules density Strength Flow Particle size distribution Ribbon porosity
Compression or encapsulation	Disintegration time Dissolution rate Weight variation Content uniformity Tablet hardness Friability

Among critical quality attributes, consistent granule particle size distribution and densities as well as suitable ribbon/granule porosity are the most important. If a batch contains too much fine, problems such as poor flow, weight variation, and picking may arise during compression. However, if a batch contains too much large granules, weight variation during compression may be an issue. Granules with a higher porosity has higher fragmentation tendency, thus higher surface area for bonding and smaller pore volume during compression. This results in tablets with high mechanical strength [73–75].

5. Conclusions

To develop a high quality product using roller compaction, systematic approaches with built-in quality measures are the key. A good starting point is to understand the physical, chemical, and mechanical properties of the drug substance, and identify the potential main challenges during product development, e.g., chemical and physical stability, flowability, densification, etc. This leads to the identification of desired quality profile of the drug product.

During drug development, formulation design, equipment selection, and process development, as well as necessary ribbon and granule evaluation should be carried out as an integrated task instead of individual tasks. This is critical because formulation, equipment, and the process are all highly inter-related in drug development using roller compaction. Overall, developing high quality of drug products is based on good science, and there is no standard way suitable for all drugs. Scientific judgment should always be applied in every aspect of product development.

Appendix A

A.1. Ribbon (compact) evaluation

Commonly used ribbon evaluation methods are summarized in Table 9.

A.2. Particle size

Table 10 lists some commonly used method to test powder particle size.

A.3. Relative density/bulk density/tapped density

Bulk density is a measure of the mass of the "as poured" granules per unit volume (g/cc). Pour granules in an undisturbed cylinder, the mass of the granules divided by the volume they occupy is the so-called bulk density. The volume includes the space between granules, as well as the space inside the pores of individual granules. Generally, granules with high bulk density have low porosity and reduced compactibility [15,81].

Table 9
Ribbon evaluation methods.

Key ribbon properties	Measurement
Ribbon strength	Three-point beam bending method on a texture analyzer [76].
Solid fraction	Calculated by dividing the weight of the compact by its length, width, thickness, and true density [40,77,78].
Ribbon density	Oil immersion technique: place several roller compactor compacts into a heavy mineral oil, then measure the weight and volume of oil before and after addition of the compacts. The compact density can be calculated with the following equation: Density = $(Wf - Wi)/(Vf - Vi)$ [15]
True density	Helium–air pycnometry [60]
Microhardness	An instrumented hardness measurement system can be used to measure the indentation load and penetration depth at all time, evaluate loading and unloading curves, and analyze the viscoelastic–plastic behavior of the ribbon by comparison with the loaded and unloaded states [55].

Table 10
Particle size evaluation methods.

Method	Comments
Sieve analysis	The particle size distribution of a 50–100 g granule can be analyzed on a sieve-shaker using a series of sieves with different sizes [76]
Malvern Mastersizer (Malvern Instruments Ltd., Worcestershire, UK).	Approximately, 5 mL of powder is for each measurement [79]
Microscopy	The particle size distribution and mean particle size can be evaluated randomly using 500 particles in a fixed field of inspection under the microscope on various degrees of magnified photographs
Diffuse reflectance near-infrared (NIR)	Gupta and his colleagues used (NIR) spectrum of the ribbon as a non-destructive and real-time tool to study the resulting ribbons and granules [76,80]

Table 11
Evaluation method of porosity.

Method	Comments
Mercury porosimetry	Pore volume and pore size distribution obtained with mercury porosimetry explain densification of mass better than those obtained with nitrogen adsorption [87–89]
Nitrogen gas adsorption	Used to determine fine porosity. Surface area values measured with mercury porosimetry were larger than those determined with nitrogen adsorption [87]
Hexadecane imbibition and hexadecane permeability	Used to characterize pore size distribution of the samples, mercury porosimetry [88]

Tapped density refers to the bulk density of the granules after a specified compaction process. As described in US Pharmacopeia (USP), tapped density can be measured in a device that lifts and drops a volumetric measuring cylinder containing the powder a

Table 12
Evaluation method of flowability.

Methods	Comments
Carr's compression index (CI)	CI = $100 \times (D_T - D_B)/D_T$ D_T: tap density D_B: bulk density CI value can reflect the ease of powder consolidation. A high CI value means poor flow • Excellent flow: 5–15%; • Good flow: 12–16%; • Fair flow: 18–21%; • Poor flow: 25–35%; • Very poor: 33–38%. [49,61,70,90]
Hausner's ratio (HR)	HR = D_T/D_B HR value can reflect the interparticulate friction. A high HR value means poor flow [61,90]
Heckel equation	$\ln 1/1 - D = KP + A$ D: density of the compact relative to the particle density of the material being compacted P: the applied pressure K: the slope of the straight line portion [91]
Kawakita equation	Kawakita plots: $N/C = N/a + 1/ab$ a and b: constants; a (compactibility): constant, describes the degree of volume reduction at the limit of tapping $1/b$: constant, describes cohesiveness C: the degree of volume reduction, calculated from the initial volume V_0 and tapped volume V as: $C = (V_0 - V)/V$ N: number of taps Kawakita constants, obtained from the slope $(1/a)$ and intercept $(1/ab)$ of the line from graphs N/C versus N, indicates the behavior of the powder from the bulk density state to the tap density state. Small value of the Kawakita equation indicates good flowability and small cohesiveness [92]
Flow function	Powder flow property can be expressed as a flow function (ff), which describes the unconfined yield strength (f) as a function of major principal stress. From the fitted FF plot of each set of data, (f) at a certain pressure could be calculated [93].
Angle of repose	When powders or granules are poured onto a horizontal surface, a conical pile will form. The internal angle between the surface of the pile and the horizontal surface is called the angle of repose $\tan Ø = 2h/D$ ø is the angle of repose h is the height of the pile D is the diameter of bottom of the pile. Ø between 20° and 40° indicates good flow potential, while indicates poor or no flow if the value is bigger than 50° [15,94].
Flow funnels	Flow rate = sample weight/elapsed time to empty [15]
Ring shear cell tester	The flowability of powders after roll compaction can be characterized by the ff_c ratio
RST-01.pc with RST-CONTROL (Schulze Schuettgutmesstechnik, Germany)	ffc < 1 Non-flowing 1 < ffc < 2 Very cohesive 2 < ffc < 4 Cohesive 4 < ffc < 10 Easy flowing 10 < ffc Free flowing [18]

Table 12 (*continued*)

Methods	Comments
Powder flowability analyzer (API Aero-flow, Amherst Process Instruments Inc., Hadley, MA)	50 ml powder was placed in a transparent rotating drum, and the resultant avalanche was detected by the obscuration of photocells located behind the drum. The data were collected using a data acquisition software [79]
FT4 powder rheometer	FT4 powder rheometer is a relative new equipment for flowability characterization. This equipment can evaluate many aspects of powder flowability at different conditions to simulate the storage and process environment. http://www.freemantech.co.uk/

fixed distance. (US Pharmacopeia. *USP Chapter ⟨616⟩ Bulk Density and Tapped Density.* Rockville, MD: USP; 2006:2638.) [15].

True density, also called absolute density, is commonly measured using helium pycnometry. Helium gas can access to any voids in bulk granules and any open porosity in an individuale granule. The volume excludes the space between granules, as well as the space inside the pores of individual granules [79,82]. However, for most water containing powders, such as amorphous material, helium pycnometry gives higher true density value due to water release. For this category of materials, Sun [83–85] proposed that powder true density can be calculated from compaction data.

Relative density is defined as the ratio of bulk of tapped density to true density. Hancock and his colleagues reported that relative densities of the roller-compacted microcrystalline cellulose samples varied measurably with changes in the roller compaction conditions such as roll pressure, therefore could be a useful tool to ensure consistent product performance [86].

A.4. Porosity

Two types of porosity evaluation methods are described in Table 11.

A.5. Flowability

Some commonly used flowability testing methods are listed in Table 12.

A.6. Moisture content

Low levels of moisture content may lead to capping during tableting, while high level of moisture content may cause sticking or stability issues. The moisture content can be measured using the following methods: Loss on drying (LOD) method [60,76,82], Karl Fisher and on-line NIR [76].

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