38

DESIGN AND SCALE-UP OF DRY GRANULATION PROCESSES

Omar L. Sprockel and Howard J. Stamato
Biopharmaceutics Research and Development, Bristol-Myers Squibb Co., New Brunswick, NJ, USA

38.1 OVERVIEW OF THE DRY GRANULATION PROCESS

Granulation offers the opportunity to alter the properties of solid particulate material. An increase of particle size reduces potential hazards or nuisance from dust. The granule structure can improve the flow and compression properties of the powder and helps to assure that the composition remains uniform throughout the powder mass if a mixture of materials is used.

Nishii and Horio [1] have described how dry granulation can be achieved during mixing, or as a powder is passed through a screen. As reported by Horio [2] particles can be dry granulated by a fluidization technique where the particle size of the starting materials is small, for example, lactose at a particle size of approximately 3 μm. However, granulation without a solvent to help with the binding is usually accomplished by subjecting powders to pressure.

Dry granulation by slugging is achieved by compressing powders in a cavity formed by a set of tools and a die, similar to the way tablets are made. Pietsch [3], in a review of granulation technology, described dry granulation by slugging among the methods and referenced a patent for a tabletting machine from 1843. Slugging and tabletting use similar technology and the patent shows how long slugging may have been available. When comparing slugging with tabletting it is apparent that tablets are typically much smaller than slugging compacts and can be the final product, whereas slugging compacts are reduced to granules feeding a subsequent tabletting or capsule filling operation. As the purpose of the slugging operation is to form granules with larger particle size, better flow and improved compression properties, the feed to a slugging press often consists of very fine powder with poor flow properties when compared to a tabletting operation.

Johnson [4] described dry granulation by roller compaction noting that passing powders through the nip of two rollers in order to produce larger sized material was originally used in coal processing. One of the earliest patents for a roller compaction system, “A Method for Converting Fine Coal into Lumps,” was issued in 1848. The largest volume applications of roller compaction are in the coal, soda ash, potash, calcined lime, and magnesium oxide industries. Bakele [5] gives an example of soda ash production of 160,000 ton/year. In pharmaceutical applications, Kleinebudde [6] has reviewed the advantages of granulation and the application of roller compaction to form granules used in tabletting and filling of hard gelatin capsules. Mouro et al. [7] showed how granulation via roller compaction improved the processing of low bulk density materials in a capsule filling operation.

The roller compaction unit operation is actually comprised of several subprocesses. Once the components and composition have been selected, the powder to be compacted must be mixed so that the feed to the compactor is relatively homogeneous. The container with the prepared powder is placed in position to feed the roller compaction machine and the powder must be metered to the area in front of the compaction rollers. A variety of devices and configurations such as valves, stirring devices, and feed screws are used in order to convey the powder from the holding container, to the roller compaction unit, and inside the machine to the area in front of the rollers. The resulting powder bed is dragged by

Chemical Engineering in the Pharmaceutical Industry: R&D to Manufacturing Edited by David J. am Ende

the rollers to the nip area where it is compacted. During the compaction the powders are deformed to a degree that causes the formation of a continuous sheet. The compacted output is commonly referred to as a ribbon but has also been referred to as a compact, flake, or tape.

The last step of the roller compaction unit operation is the reduction of the ribbon to granules. This can happen in one or more steps where mechanical elements impact the ribbon, break it into pieces, and force the broken pieces through a screen. The size reduction subprocess of roller compaction may be integral to the roller compaction machine or performed as a separate operation. In either case the size reduction typically yields particles with a distribution of sizes. Because one of the objectives of the compaction process is to increase size, a large fraction of granules below a minimum size may be undesirable. In some cases fines are separated from the granulation and returned for another pass through the compaction step.

The sections of this chapter will give an overview of the roller compaction unit operation, followed by consideration of material behavior and measurement. A step-by-step review of the subprocesses that comprise the roller compaction unit operation including various types of models and control strategies is offered next. In the final section, case studies including scale-up, one for a parametric-based scale-up approach and one for an attribute-based scale-up approach are presented.

38.2 GENERAL CONSIDERATIONS FOR ROLLER COMPACTION OPERATIONS AND EQUIPMENT

Although the roller compaction process is used to improve the flow of material, the incoming feed needs to have sufficient flow properties in order to be delivered with as consistent a composition, flow, and density as possible. The requirements may include limitations on the micromeritic properties of the active ingredient. Excipients are usually selected to dilute the active ingredient to an appropriate concentration and enhance various aspects of the powder properties. Some of the flow properties to help feed the roller compactor and compression properties to assist in ribbon formation can be provided by the addition of materials called binders because of their compression properties (e.g., microcrystalline cellulose (MCC), and lactose). Including these materials is often necessary to achieve the desired granulation properties. Flow aids (e.g., silicon dioxide) may be needed to achieve the desired mixture flow properties. A lubricant (e.g., magnesium stearate) typically added to modify interaction with the equipment surfaces, may also be necessary to achieve the desired performance of the roller compactor. Other components necessary for performance of the final product, rather than performance in the roller compactor, such as disintegrants (e.g., croscarmellose sodium, cross-linked polyvinyl pyrrolidone, or sodium starch glycolate) may also be used.

The next selection for the overall roller compaction operation is the unit operation that will prepare the powder blend for roller compaction. A diffusion mixer is one of the more popular choices for the mixing subprocess of roller compaction used to prepare the roller compactor feed. The batch size, sequence of loading, number and speed of revolutions, and the shape of the blender may be considered when designing the process. Multiple steps involving a geometric dilution strategy or intermediate milling between blending steps may be necessary to distribute the ingredients and achieve the appropriate level of uniformity and handling properties. Although a homogeneous powder feed will reduce variability in the roller compaction operation, content uniformity of the powder blend is not required at the same limits that would normally be applied to pharmaceutical dosage forms. Issues with blocking, bridging, segregation, or adhesion to equipment surfaces may result from poor selection of materials or insufficient blending prior to roller compaction.

The arrangement of the blender, bin, or other container relative to the roller compactor is also to be considered. Powder needs to flow evenly from the container to the equipment without bridging, flooding, or segregating between the bin and the roller compactor feed hopper. A general arrangement of the elements of a roller compaction process is shown in Figure 38.1.

Once the powder reaches the integrated roller compaction machinery there will be various means of conveying the powder toward the rollers depending on the manufacturer, model, and user requirements. Typically there is a feed hopper to receive material from the main powder container. The hopper may have a device to break any powder bridges and help move the material for further processing. The hopper may feed directly to the rollers by gravity, but a majority of designs also use one or more feed screws to deliver the powder and consolidate it in front of the rollers. In all cases the feed screw is oriented in-line with the roller nip. The orientation of the screw will depend on the orientation of the rollers.

The powder bed must be contained to assure it travels to the rollers and through the gap. The most typical system involves plates mounted to cover the powder bed before the gap, which extend over the gap itself, preventing powder migration outside the compaction area. It is important to assure proper mounting of the plates and sufficient maintenance to prevent the leakage of powder from the compaction area. Unprocessed fines could join the product stream if powder leaks from the seals. A different type of sealing system also uses ridges on the roller edges such that one roller fits into a channel in the surface of the other in order to form a tighter seal.

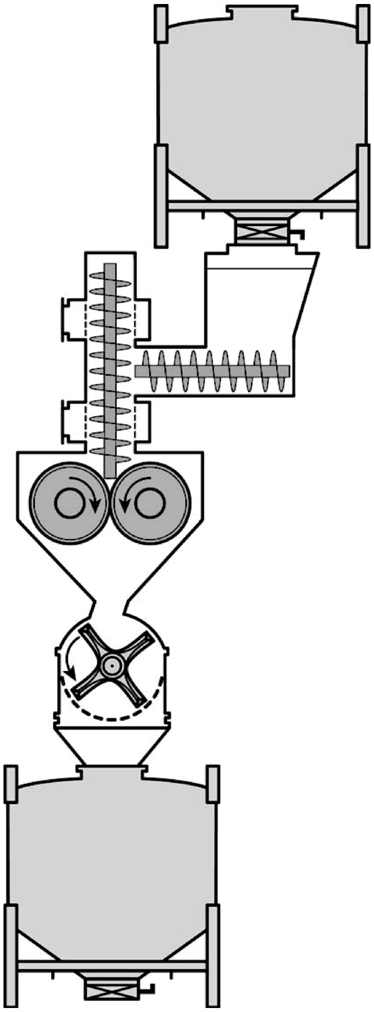


FIGURE 38.1 General arrangement of the roller compaction process. (*Courtesy*: The Fitzpatrick Company.)

Kleinebudde [6] surveyed various manufacturers with regard to their roller and screw configurations, offering a list of suppliers correlated to references focused on the various designs. Some machines have the powder conveyed to the nip vertically such that the open space between the rollers—the gap—is vertical and a line drawn between the roller axes is horizontal. A system with this configuration may lose a small amount of powder through the nip as conditions are stabilized in the beginning of the run. Other roller compaction machines have this configuration turned on its side so that the powder feed and the nip opening are oriented horizontally and a line drawn between the roller axes is vertical. This reduces the possibility of powder flooding the machine at start-up and depends entirely on the action of the feed screw to move powder to the rollers. A third configuration, used in other types of roller compactors, orients the powder flow and nip at an angle to the vertical giving some of the advantages of both the horizontal and vertical configurations. An illustration of the various configurations is shown in Figure 38.2. Typical roller compactors from laboratory to production scale from different manufacturers are shown in Figure 38.3. A unit shown in an expanded view so that all of the parts are visible is shown in Figure 38.4.

During roller compaction, the porosity of the powder is reduced in the compaction step to form the ribbon. The air filling the pores must escape through the forming compact and adjacent powder bed. In some types of roller compaction machines the powder is deaerated before reaching the nip by passing over a porous plate with vacuum applied underneath. The deaeration is intended to reduce any disruption from air moving through the powder as the compact is formed. Miller [8, 9] described the effects of air entrainment and

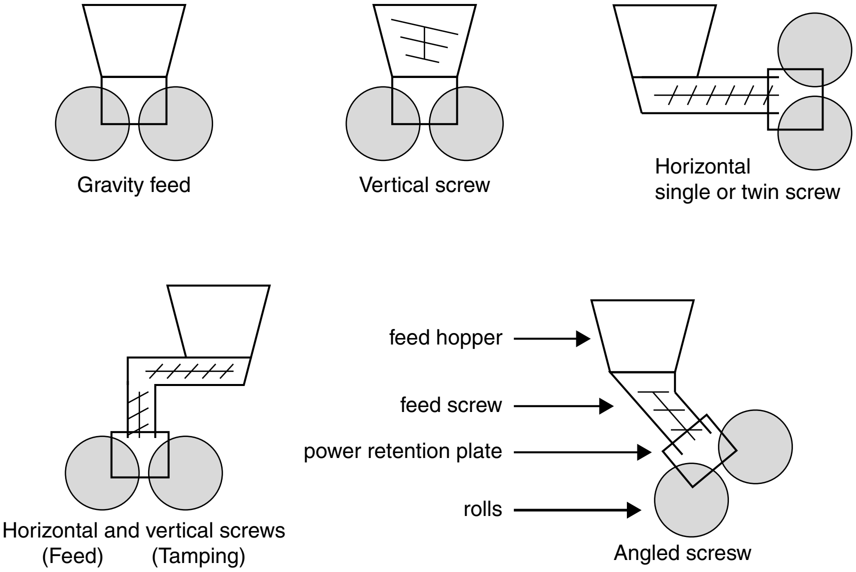


FIGURE 38.2 Common feed, feed screw, and roller configurations.

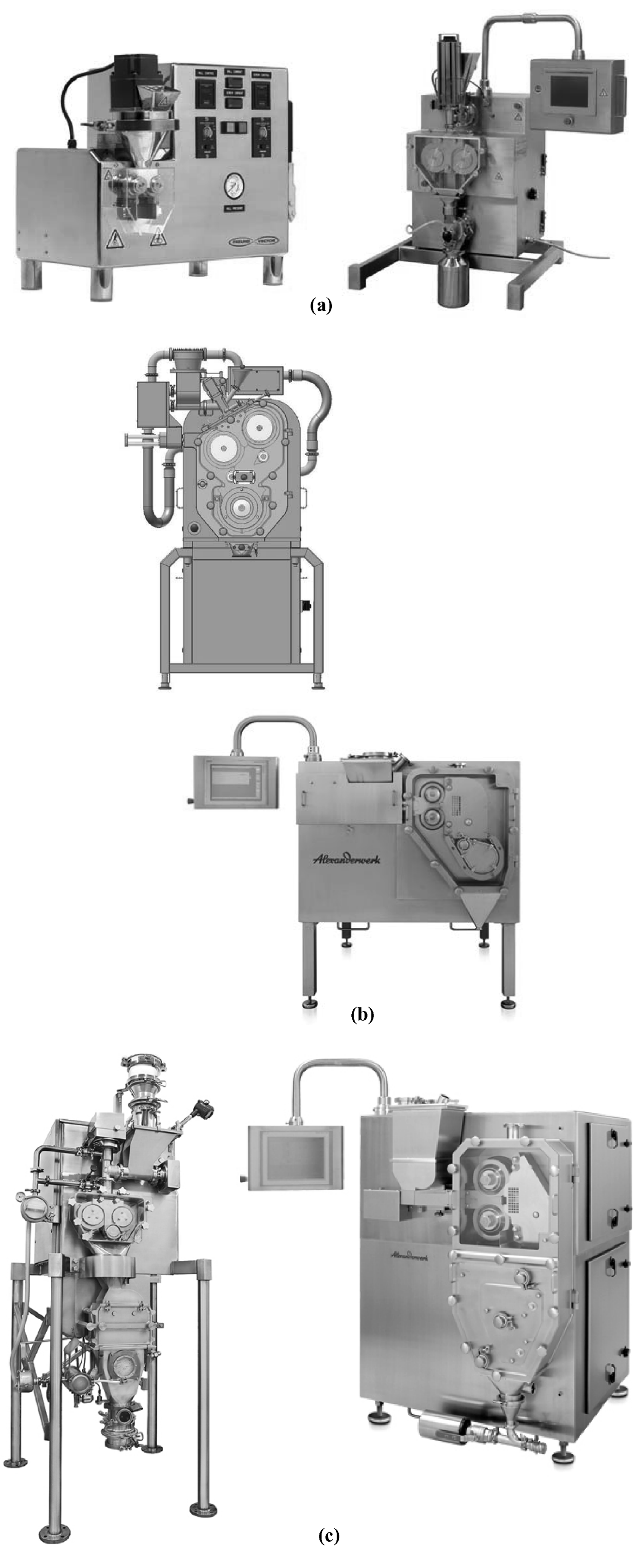


FIGURE 38.3 Examples of roller compactor units from laboratory to commercial scale. (a) Lab-scale roller compactors; (b) pilot-scale roller compactors; (c) production-scale roller compactors. (*Courtesy*: Vector Corporation, The Fitzpatrick Company, Gerteis Maschinen + Processengineering AG, Alexanderwerk AG.)

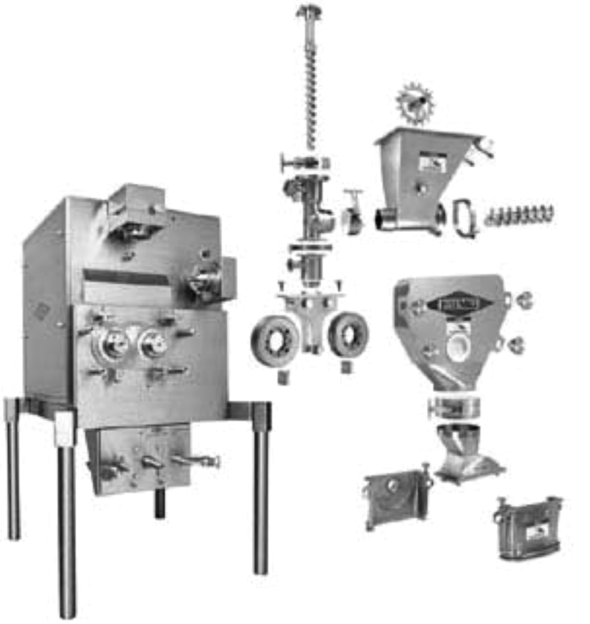
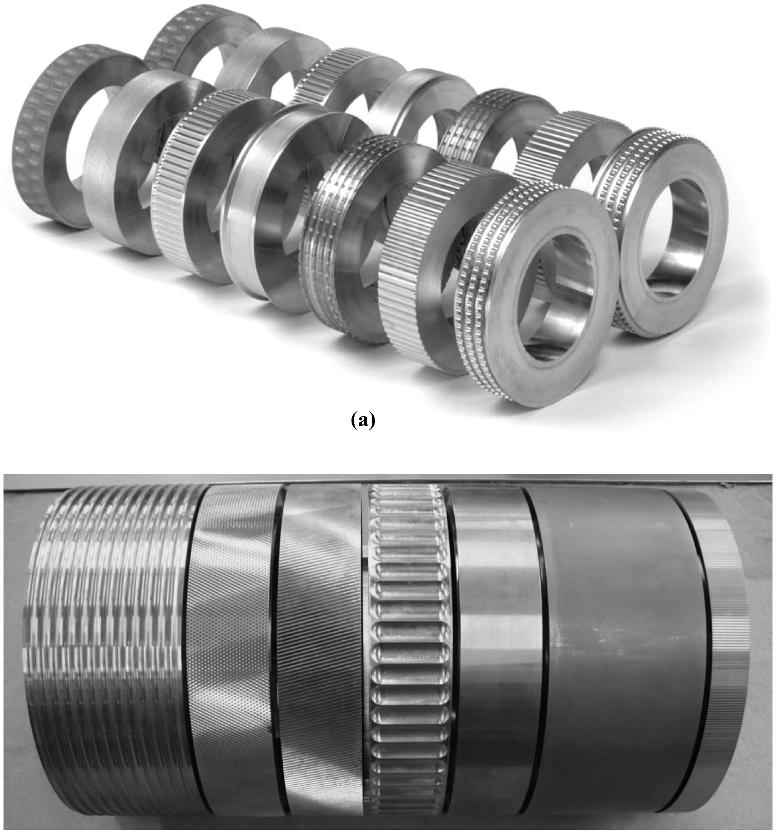


FIGURE 38.4 Expanded view of a roller compactor showing the components. (*Courtesy*: The Fitzpatrick Co.)

improvements in the roller compaction operation due to deaeration of the powder feed.

In the simplest case the roller faces in contact with the powder are smooth. However, other types of roller finishes, such as grooves or other inscribed patterns, are used in an attempt to change the interaction with powder and the surface of the rollers are also available. Rollers with different surface finishes and the resulting ribbons are shown in Figures 38.5 and 38.6. Daugherity and Chu [10] studied the effect of roller surfaces on the compacted ribbon properties. Rambali et al. [11] also noted differences attributed to the use of smooth versus grooved rollers. Pietsch [12] described a briquetting application in which the faces of the rollers are indexed so that shaped indentations in each roller face form the desired final product shape during the compaction step. Rollers with internal channels for cooling liquid may be used for temperature sensitive products that might melt from the energy of compaction as mentioned by Pietsch [3].

Even on a relatively small compaction machine the nominal roller pressure may be set to a value of 50–70 bar. This pressure is typically applied by use of a hydraulic cylinder pushing on the roller axle. The pressures involved are in a



(a)

(b)

FIGURE 38.5 Rollers with different surface treatments. (*Courtesy*: The Fitzpatrick Company and Gerteis Maschinen + Processengineering AG.)

FIGURE 38.6 Examples of product produced from rollers with different surfaces. (*Courtesy*: The Fitzpatrick Company.)

range where deflection of the axle can actually affect the operation of the machine. Most manufacturers of roller compaction machinery have carefully considered the design of the hydraulic system and axle deflection so that the width of the gap is consistent across the roller width. It should be noted that the pressure on the powder may be different than the nominal pressure set on the hydraulic system although the two values are related.

Guangsheng et al. [13] described an application for roller compaction of magnesium alloy powder to form sheets. In this case, after some posttreatment, the roller compacted ribbon is the final product. However, in most roller compaction operations the ribbon itself is not the useful product and is broken into granules that have the desired properties for further processing. Although used in some high volume applications, briquetting rollers, as described by Pietsch [12], are not used to form the final product in pharmaceuticals due to the need for tight uniformity of finished product. Different types of output from roller compaction operations including broken ribbons with different surfaces, granules, and long briquettes are shown in Figure 38.7.

The size reduction step for the ribbon typically consists of an impeller without a screen to start the process followed by one or two stages of milling, this time with an impeller mounted in proximity to the screen. The mill configuration may take the form of an oscillating screener, hammer mill, or conical mill. The screening mill may or may not be integrated with the roller compaction unit.

Fines may be present in the resulting granulation from several sources. The sealing mechanism at the edges of the rollers may not contain all of the powder or powder may not be completely incorporated into the ribbon and is carried over into the final product. The milling operation itself can create fines. In some cases the amount of fines are considered unacceptable for the final granulated material.

For operations where more fines are present the equipment may be fitted with mechanisms to separate the fine fraction. Some fines reduction can be accomplished by collecting powder which did not get properly compacted by use of a chute into which the fines fall while the ribbon is collected separately prior to milling. However, this method will not completely assure a low fines fraction as some fines are generated during the milling process. In other cases the entire output after the milling operation is size separated to remove fines from the granulation caused by the milling operation along with any carry over of uncompacted fines. In both cases the undersized material may be returned to the

FIGURE 38.7 Examples of roller compactor output. (*Courtesy*: The Fitzpatrick Company.)

roller compactor to improve yield of granules with the desired size.

It should be noted that repeating the compaction step can reduce the performance of the granules in subsequent processing. If reprocessing is necessary the number of passes through the compaction should be limited and the combination of reprocessed material with the main granulation should be monitored. Material behavior and the characterization of raw material, and finished granules, and compacted ribbon are discussed in the next section.

38.3 MATERIAL BEHAVIOR, ATTRIBUTE TESTING, AND PROCESS SENSORS

The performance of the roller compaction unit process and the resulting products (e.g., ribbon, granules, tablet, or capsules) depend on the properties of the powder being processed. Some considerations of the choices for the unit operation related to material behavior are described in this section.

38.3.1 Material Behavior During the Roller Compaction Process

38.3.1.1 Powder Handling of Feed and Granulated Product Powder handling is important in the feed of the roller compaction unit and is also applied to the granules produced by the roller compaction operation. The particle size distributions, densities, and flow properties of the powders going into the roller compactor must be matched, manipulated, or modified by additives (e.g., lubricants and flow aids) and preprocessing (e.g., milling and blending) in order to feed material evenly and with the appropriate levels of the components to the compaction machine. The powder mix will have to maintain these properties throughout the compaction run that may be an extended time because roller compaction is typically performed as a semicontinuous operation. The powder to be compacted will be subjected to various conveying and consolidation operations that may induce segregation due to material or air motion, and vibration. Bacher et al. [14] reported that the shape and size distribution of calcium carbonate and sorbitol used to prepare roller compacted granules affected the granule content as a function of granule size. Similarly the output granules must have appropriate flow, resist segregation, and have sufficient strength to withstand handling when being conveyed to various downstream process or packaging into the final product presentation.

38.3.1.2 Compaction In addition to the feeding properties, the raw material properties can also have an effect on the compaction of the powder into ribbons. Material properties were considered an input for the earliest mathematical models, such as Johanson [15] who suggested measuring the internal and surface friction of the powder, to more recent studies including process analytical technology, such as Soh et al. [16, 17], who studied twenty material parameters and suggested particle size, span (a measure of size distribution), and angle of fall as the most interesting measurements to characterize the input material.

Many studies have focused specifically on the behavior of an excipient or class of excipients in the roller compaction operation and can give insights to assist in selection of excipients. In many studies a formulation including a model active ingredient was used to simulate the response of the excipient under typical use conditions. Because the material in a roller compactor undergoes some of the same physical processes as in a tablet press many of the same considerations of material behavior apply. For example, Sheskey and Dasbach [18] noted that slower roller speeds, giving a longer dwell time under pressure, allowed plastically deforming materials to perform better as binders. Falzone et al. [19] noted differences in behavior between plastically deforming microcrystalline cellulose and lactose that exhibited behavior influenced by brittle fracture.

Some roller compaction studies of specific materials are summarized in Table 38.1.

TABLE 38.1 Selected References Reporting Material Behavior in Roller Compaction

Material	Reference
Microcrystalline cellulose	Inghelbrecht and Remon [20]
Lactose	Riepma et al. [21] Inghelbrecht and Remon [22]
Hydroxypropylmethylcellulose	Sheskey et al. [23]
Hydroxypropylcellulose, methylcellulose, polyvinylpyrrolidone, starch, and microcrystalline cellulose	Sheskey et al. [18]
Magnesium carbonate	Freitag et al. [24]
Magnesium carbonate in combination with powdered cellulose	Freitag et al. [25]
Hydroxypropylmethylcellulose, hydroxypropylcellulose, microcrystalline cellulose, and polyvinylpyrrolidone	Herting et al. [26]
Calcium carbonate and sorbitol	Bacher et al. [14, 27]

The addition of small amount of components to influence the powder properties is common practice, but may have an effect on the compaction operation. He et al. [28] studied the effect of lubricating the roller compactor feed with magnesium stearate on the strength of tablets compressed from the resulting granules. The authors noted that lubricant is often added to roller compaction feed to prevent sticking to the rollers. One caution offered was that the lubricant can change the interaction of the powder and rollers resulting in a smaller nip angle and reduced process efficiency. It was found that tablets produced from roll compacted granules of unlubricated microcrystalline cellulose did not show a significant decrease in strength at two of the three levels of ribbon densification studied. At the highest level of ribbon densification there was approximately a 30% drop in tablet strength. For microcrystalline cellulose lubricated with 0.5% magnesium stearate the drop in tablet strength was 90% over a much broader range of ribbon densities.

Many excipients can absorb water from the environment under typical processing conditions. The moisture can affect the material properties, perhaps causing unwanted effects in the roller compaction operation. The effect of moisture on the behavior of microcrystalline cellulose in roller compaction with ambient relative humidity ranging from 15% to 75% was studied by Gupta et al. [29]. It was found that as water content increased; the powder yield strength decreased, indicating better powder rearrangement, while tensile strength of the resulting ribbons decreased, indicating poorer bonding. Inghelbrecht and Remon [30] intentionally added water to blends of lactose, microcrystalline cellulose and hydroxypropylmethylcellulose, and other ingredients in order to reduce the amount of fines in the roller compacted granules. They found that the fines produced during the compaction step were negligible and the fines fraction produced during the milling operation were reduced. The resulting granules and tablets had lower friability and the tablets had higher strength.

A more typical strategy to reduce fines is the recycle of the fine fraction to the inlet of the roller compaction step. However, the change in material properties when subjected to roller compaction can be cumulative and has been reported by many investigators. Bultmann [31] studied this phenomenon as a function of the number of repeated roller compactions for microcrystalline cellulose and found the repeated compactions decreased the amount of fines but also decreased the compressibility of the resulting granules. Up to 10 cycles of roller compaction were studied with most of the losses in material properties seen in the first and second processing by the roller compactor. Shesky et al. [23] found a similar reduction in compressibility for hydroxypropylmethylcellulose which decreased with increasing roller pressure after a single pass through the machine. In contrast Riepma et al. [21] found that for material displaying brittle fracture characteristics, such as lactose, dry granulation had minimal influence on the compatibility during subsequent tabletting.

A review of specific material attributes and their effect on the products from a roller compaction process are discussed in the following sections.

38.3.2 Incoming Powder and Outgoing Granule Properties

The performance of the roller compaction process and the quality of the output materials (granules) depends on material characteristics as well as on process parameters. The types of attributes and measurements that may be considered for roller compaction operations are considered in this section. For example, Miguelez-Moran [32] showed that the size of the three flow regions in the roller compaction zone and the transition from one to the other depends on the properties of the input powder. Examples of powder properties that affect the powder flow behavior in the compaction, zone are internal friction, cohesion and friction between the powder and the rollers and side shields. Particle size distribution is an attribute that is commonly measured for the input and output materials. Density and flow are characteristics that are influenced by particle size distribution, and often monitored. Offline characterization techniques are covered in the respective property section below, but online methods are covered in Section 38.3.4.

38.3.2.1 Particle Size Distribution Much of the knowledge gained on the influence of input material properties from the tablet compaction field can be applied to roller compaction. The influence of particle size and compression characteristics (plastic or brittle nature) is dominant in ribbon and granule quality.

Several authors have reported on the importance of selecting the proper diluent particle size. Herting et al. [33, 34] reported on the effect of microcrystalline cellulose particle size on granule and tablet properties. Under similar processing parameters, a reduction in the particle size of the input material (MCC and theophylline) resulted in larger mean granule size and higher compactability. Inghelbrecht and Remon [20] evaluated the effect of MCC particle size in ibuprofen/MCC drug mixtures. They found that smaller MCC particles produced stronger granules. The irregularity of the MCC particles was ascribed a secondary role for the differences seen in granule strength.

In evaluating the effect of particle size of sorbitol on granules properties, Bacher et al. [27] found that smaller sized sorbitol produced granules that had higher compactability due to the increase in surface area with smaller particles of sorbitol.

Inghelbrecht and Remon [22] evaluated the influence of lactose particle size as well as the type on granule and tablet properties. As with MCC and sorbitol, they found that reducing the lactose particle size (regardless of type) improved the granule quality (less friable). They showed that anhydrous lactose produced granules that were less friable, because the crystals were more compactable and less elastic.

In summary, the work cited above shows that selecting a smaller particle for the input material (MCC, sorbitol, or lactose) results in granules that are larger, stronger and less friable. The effects were ascribed to the increased surface area.

As with input materials, particle size of the resulting granules is often used as a metric to determine input or parameter effects. The granule size is controlled by the roller compaction process as well as downstream processing. The initial granule size is a result of the material properties and the process parameters. Granule attrition during postroller compaction processing (blending) will determine the final particle size distribution.

The quality of the ribbons (density and strength) produced has a direct impact on the granule size distribution. Ribbons with higher solid fractions (lower porosity) produced granules with larger mean sizes that resulted in a better flowing powder (Herting and Kleinebudde [33, 34]). Ribbon solid fraction is correlated with ribbon strength, which is sometimes used as an alternate measure of ribbon quality and the effect on granule size. Under similar milling conditions (mill speed and screens) ribbons with higher strength produced larger granules compared to ribbons with lower strength (Shesky and Hendren [35], Inghelbrecht and Remon [20, 22], Weyenberg et al. [36]). Farber et al. [37] hypothesized that during roller compaction the particles deform under load, causing them to interlock. Upon milling, the break in the ribbon occurs at the weakest interlocking junction, but the deformed particles remain intact in the resulting granules. Rambali et al. [11] showed that the mean granule size produced from thicker ribbons was smaller that that for thinner ribbons. The ribbon thickness effect on granule size was marginal.

Methods for particle size determination fall into two general categories: laser light scattering (LLS) and sieve analysis.

A secondary way in which the particle size of the granules is affected is in processing downstream from the roller compaction operation. This is primarily governed by the strength of the granules. This is assessed by determining the friability of these granules by measuring the change in particle size distribution under stress (e.g., due to additional mixing). There are two ways by which the friability of the granules can be determined. An indirect way is to compare the particle size distribution of the granules after milling with that of the final blend after additional mixing. After accounting for any extragranular materials added, the change is size distribution would be indicative of granule friability.

Inghelbrecht and Remon [20] quantified granule friability directly by tumbling granules of a particular particle size range with glass beads for certain duration, and then determined the change in particle size. The reduction in mean particle size was ascribed to particle attrition. Patel et al. [38] used stress–strain analysis on single particles using a 2 mm flat probe to determine the particle fracture potential. Inghelbrecht and Remon [22] ranked the process parameters for their effect on granule friability in order of decreasing influence: roller pressure, roller speed, and feed rate.

38.3.2.2 ***Density***

Soh et al. [16] and Freitag et al. [24] investigated the effect of raw material attributes on their performance in roller compaction. One attribute tracked was material density. Since, material density was confounded with other materials properties, such as particle size or morphology; a clear relationship between input density and output (ribbon or granules) properties was difficult.

Herting and Kleinebudde [34] characterized the hardening of granules postroller compaction by measuring the yield pressure. They showed an increasing relationship between the applied roller pressure and the apparent yield pressure. They ascribed the increased resistance to deformation as granule hardening. Traditional density measurement techniques typically used include bulk density, tap density, and true density by helium pycnometry. Derived parameters, such as porosity, Carr Index, Hausner ratio, also have been used (Soh [16]).

38.3.2.3 ***Flow***

For processing downstream from the roller compaction operation powder flow dominates process stability. Flow of the powder blend into the compression operation controls the variability in tablet weight. Weyenberg et al. [36] reported that the fastest powder flow was obtained with a combination of low roller speed and high roller pressure. These conditions yielded ribbons with high strength that resisted attrition during the milling operation. The rate of powder feeding had a minor impact of granule flow properties. These conditions also produced the largest and strongest granules with the lowest friability. Granule size increased with higher roller pressure, lower roller speed and higher powder feed in order of importance.

There are several techniques used to gauge the ability of a powder to flow. A mass flow determination can be obtained by measuring the flow time of a certain mass of powder passing through a certain orifice. An alternative method would be to determine the minimum orifice opening that would support continuous flow (Flow index). Other techniques rely on indirect means to assess flow, such as Carr Index, shear cell, and other measures of powder rheology.

38.3.2.4 ***Compactability***

One of the common objectives of a roller compaction process is to improve the performance of granules in a downstream capsule or tablet operation. Compactability, the ability to form tablets of a desired strength at an acceptable pressure, is one of the main attributes to consider for the roller compacted granules. Compactability is typically studied by experiments on a tablet press or compaction simulator to assure that the desired tablet properties can be achieved.

Several articles report a reduction in powder compactability of the roller compacted material (Sun and Himmilspach [39], Herting and Kleinebudde [26], Herting and Kleinebudde [30], Malkowska and Khan [40], Shesky and Cabelka [41]). Investigators have identified two possible causes for this reduction: work hardening and size growth. Malkowska and Khan [40] describe the effect as a loss of bonding capacity between the particles. Plastically deforming materials are more susceptible to work hardening.

Sun and Himmilspach [39] ascribed the reduction in compactability to an enlargement of granule size relative to the input particle size. The growth in particle size reduces the area available for bonding. Herting and Kleinebudde [30] concluded from their investigation that the reduction in compactability is due to both size enlargement and hardening of the granules. They observed that work hardening could be countered by producing smaller granules.

38.3.3 Ribbon Properties

38.3.3.1 Density and Porosity The packing in a ribbon after roller compaction can be stated by three related terms: density, solid fraction (density relative to the true density), and porosity (measured or calculated from the solid fraction). Ribbon solid fraction is an attribute that indicates the degree to which the powder has been compressed (Zinchuk et al. [42]). The density across the width of a ribbon can vary (Miguelez-Moran et al. [43]).

The density of the ribbon is often highest in the center and lowest at the edge. This density gradient is caused by the friction between the powder and the face plates covering the rollers (Guigon and Simon [44]) and can be reduced by the inclusion of lubricant. Funakoshi et al. [45] showed that density distributions are related to the force distribution across the ribbon. Funakoshi et al. [45] and Parrott [46] evaluated an alternate roller design (concave–convex roller pair) to address the nonuniform distribution of pressure on the rollers during roller compaction. Several incline angles were evaluated and a 65° angle was shown to be optimum for a uniform pressure distribution over the roller surface (Funakoshi et al. [45]).

The force distribution is related to the flow patterns of the powder passing between the rollers (Miguelez-Moran et al. [32]). This effect is accentuated at high roller speeds (Funakoshi et al. [45], Miguelez-Moran et al. [32]). The mean ribbon density is higher at a narrower gap setting compared to a wider gap setting. Guigon and Simon [44] also showed that if the screw feeding in a roller compactor is nonuniform in time or space, and this produces ribbons whose solid fraction varies over the width of the ribbon.

The solid fraction of the ribbons produced is a result of powder properties, process parameters, and equipment geometry factors. The increase in solid fraction affects the mechanical properties of the granules and the material behavior. However, when comparing ribbons made from different materials, solid fraction is insufficient as a sole descriptor of quality. Ribbons with similar solid fractions could have dissimilar mechanical properties such as strength. Ribbon strength is an attribute that is indicative of performance during the milling operation postribbon production. Solid fraction can be used as a surrogate for ribbon strength within a single composition.

Two physical techniques were reported by various authors for determining ribbon density (sectioning, enveloping). Additional methods using NIR or ultrasound are described in Section 38.3.4. With the sectioning method, a portion of the ribbon is removed and the volume and mass measured to yield the density. The dimensions of the section must be carefully measured. With the enveloping method a volume displacement approach is used so that the precise dimensions of the section are not critical. In determining the ribbon solid fraction, Soh et al. [16] argued that envelope volume is required for higher precision rather than using sectioning. The reason stated for this is the imprecise nature of the edges during sectioning.

In place of the techniques cited above that provide the average overall density of a ribbon specimen, Miguelez-Moran et al. [43] used X-ray microcomputed tomography to obtain the distribution of the densities in a given ribbon sample. This enabled the investigators to not only determine the effect of roller compaction process parameters on ribbon density, but also on the density distribution.

38.3.3.2 Thickness Investigators use a micrometer to measure the thickness of the ribbons produced (Miguelez-Moran et al. [32, 43]). This measurement has to be repeated at several places across the ribbon sample to account for variation in the ribbon thickness. This average thickness then is used for density calculations using the sectioning technique or for feedback control of the roller compaction process. In lieu of measuring the ribbon thickness, some investigators use the roller gap as a surrogate. This approach ignores the relaxation that may occur postconsolidation.

38.3.3.3 Strength Many investigators use ribbon density as a metric for comparing ribbons made under different conditions to determine equivalency. Zinchuck et al. [42] argued that a ribbon's resistance to milling postribbon production is a better metric. They determined the tensile strength of ribbons using a three-point beam bending analysis. Miguelez-Moran et al. [43] used a microindentation technique to determine the hardness of ribbons at a microscale. The size of the indentation made depends on the shape of the indentor, the force used to make the indentation and the hardness of the ribbon.

Within a composition the ribbon tensile strength or hardness varies directly with the solid fraction of the ribbons. Similar to tablets, the ribbon tensile strength or hardness is directly proportional to the pressure used to make the ribbons. Farber [37] hypothesized that during roller compaction the particles, deform under load, causing them to interlock. This is the reason for the increased strength of ribbons postcompaction. The strength of ribbon varies across the width of the ribbon, due to the variation in ribbon solid fraction across the width of the ribbons. This variation is due to a nonuniform distribution of stress across the roller width. Guigon and Simon [47] used a series of pressure transducers on the rollers to obtain the distribution of the pressure on the rollers during roller compaction. They observed that the pressure varied with a period that coincides with the screw feeder pushing the powder into the nip region. Guigon and Simon [47] showed this variation in applied force across the rollers visually by adding charcoal particles to lactose. The areas of high stress were identified by the large number of broken charcoal particles.

38.3.4 Online or At-Line Process Sensors

38.3.4.1 Particle Size Distribution There are several examples in the literature of technologies for determining the particle size of powders online, but Zhang and Yan [48] made the point that development of cost-effective online particle size instruments is challenging. Zhang and Yan [48] used an electrostatic sensor combined with digital signal processing to determine particle size distribution. A slip stream of particles was carried on an air stream toward the sensor causing the particles to acquire a charge; the magnitude of the charge was size dependent. Frake et al. [49], Rantanen et al. [50] and Gupta et al. [29, 51] used a near infrared technique to quantify the particle size of granules. The near infrared spectrum was affected by physical properties such as particle size, particle surface and density (Rantanen et al. [52]).

Two additional means of ascertaining the particle size distribution of the granules as they exit the milling chamber postribbon production are laser light scattering and high-speed image analysis. For the LLS method a slip stream sampling of the falling granules is needed. Traditional LLS techniques can be used on the sample of granules (Bordes et al. [53]). Image analysis would require high-speed image capture that is processed against a predictive model of pixels versus volume or diameter. Liao and Tarng [54] developed a high-speed optical inspection system to determine particle size. A CCD or CMOS camera was used to acquire the image that was processed and analyzed against a reference.

38.3.4.2 Ribbon Density Two general methods were reported by various authors: physical (sectioning, enveloping) and associative (NIR, ultrasound). The physical methods were described previously and can be used only at-line. Several investigators have reported on the associative methods (Sprockel et al. [55], Gupta et al. [29], Feng et al. [56]). Even though the fundamental principles of the associative methods differ, both rely on a predictive model that correlates density to the underlying measurement. The associative methods lend themselves to online or at-line measurements, whereas the physical methods can only be used at-line.

Ghorab et al. [57] reported on their evaluation of the relationship between ribbon physical attributes (such as density and strength) and thermal effusivity. They found strong correlations between thermal effusivity and ribbon density or strength. The relationships were first- or second-order polynomials depending on the composition. Even though these relationships are composition dependent, the utility of this method is intriguing. Herting and Kleinebudde [33] reported a means of calculating the in-gap porosity by calculating the volume of ribbon produced per unit time. The mass of granules corresponding to this time unit was used to calculate the ribbon porosity.

38.3.4.3 Composition and Uniformity Bacher et al. [13] investigated the cause for the nonhomogeneous distribution of calcium carbonate in roller compacted granules containing sorbitol. They showed that the particle size of the sorbitol diluent was the main contributing factor. Using the smaller particle size sorbitol produced granule fractions with near theoretical mean calcium carbonate content. When sorbitol with larger particle sizes was used a higher content of calcium carbonate was seen in the fines.

They postulated that the weakest interparticulate bond in the granule was the calcium carbonate–calcium carbonate bond. It is at this juncture that the ribbons fractured during the milling process. This rupturing of the ribbons at the weakest point exposed the calcium carbonate to attrition. Gupta et al. [29] investigated near-infrared coupled with multivariate analysis to relate the spectral data to content uniformity of the ribbon.

The material properties of the raw materials and the resulting products determine the type of equipment selections for the roller compaction unit operation. The various tests of input, output, and intermediate material properties help to understand the operation of the equipment and selection of parameters described in the next section for each subprocess of the roller compaction operation.

38.4 PRINCIPLES OF OPERATION

Roller compaction is a unit operation composed of several subprocesses the principles of, and considerations for operations are described for each subprocess in the sections below.

38.4.1 Roller Compactor Feed Preparation and Delivery

The preparation and handling of powder fed to the roller compactor has challenges common to similar operations in other equipment trains. Powder and handling are specialized areas with adequate sources from which to assemble information for the design of the mixing and handling subprocesses of a roller compaction process. Blending and blend batch size increase was discussed by Alexander and Muzzio [58]. Prescott [59] presented aspects of powder handling, and the metering and dispensing of powders was reviewed by Yang and Evans [60].

Some common themes from powder handling technology are important to the powder handling for roller compaction. For example, it is commonly held that powder flow can be affected by particle size and shape, factors which can be important considerations in the selection of material for a roller compaction process. Yang and Evans [60] mentioned how humidity and electrostatic charge can affect powder flow, knowledge that can also be applied to the conveying of powder to the roller compactor. Pietsch [12] has described how air entrainment can influence powder handling, including the densification step and the postcompaction recovery in the roller compaction process. A study by Miller et al. [8] showed that the leakage of uncompacted powder was reduced from 20–30% to <2% of the material by the use of a vacuum deaeration system fitted to the roller compactor. The throughput of the roller compactor was also increased by 20–40% with the deaeration system activated.

Most roller compaction equipment configurations move the powder toward the rollers via a screw feeder. Sander and Schonert [61] showed that the delivery of powder from an unconstricted feed screw follows a linear relation with the screw speed. It was found that the screw feed needed to have a minimum speed in order to feed sufficient material to the rollers at a given roller speed assuring the roller compactor operated properly. At higher screw speeds the screw throughput was less than predicted by the unconstricted delivery rate indicating that the screw exerts a pressure on the powder before the rollers (Figure 38.8). The screw feed increased the throughput of the roller compactor by causing consolidation of the powders before the nip. Similar results showing the behavior of the screw feeder and its effect the roller compaction throughput were also reported by Guigon and Simon [44].

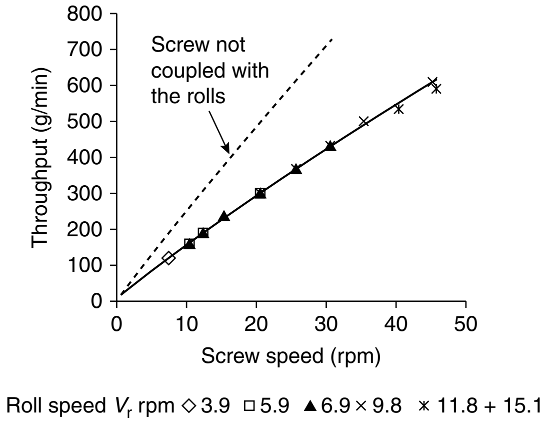


FIGURE 38.8 Screw throughput as a function of screw speed with and without the influence of the rollers. Reprinted from Ref. 44, Copyright (2003), with permission from Elsevier.

The design and rotation of the screw can have unintended effects on the compacted ribbon. Patterns of color or differences in ribbon properties oriented along the main axis of the ribbon in a sinusoidal pattern were reported by Simon and Guigon [62] for operations with a single screw (Figure 38.9). They used piezoelectric sensors in the rollers to study the pressure during compaction, and image analysis of the ribbons to determine the density of the ribbon. Both sets of data showed a periodic variation that could be correlated with the frequency of the feed screw rotation. Experiments with a piston device to feed the powder did not show periodic variations confirming that the screw feeder was causing the powder to consolidate differently depending on the screw rotation. It was postulated that the screw is preferentially applying pressure where the clearance between the flight and the nip are at the minimum, a position corresponding to the screw flight terminus. Miller [9] reported that a dual screw feed design in combination with vacuum deaeration of the powder minimized any influence of the screw rotation on the ribbon.

Lecompte et al. [63] did not find screw-related variations in similar experiments with an instrumented roller compactor. It was proposed that because the screw terminated further

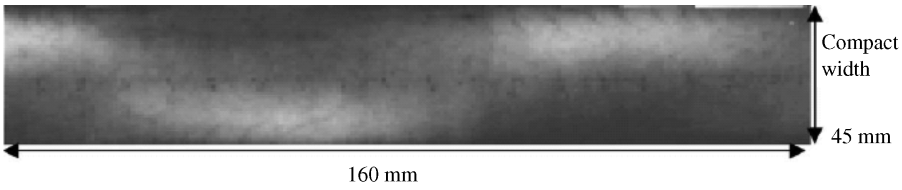


FIGURE 38.9 Variation in ribbon color due to variation in ribbon compaction induced by the motion of the feed screw. Reprinted from Ref. 44, Copyright (2003), with permission from Elsevier.

from the rollers in the experimental setup used by Lecompte, variations due to screw rotation were not carried forward into the ribbon. The authors also examined how various combinations of parameters such as feed screw speed, roller speed, and gap could be adjusted to assure that the powder spread evenly across the rollers and was converted to a ribbon with consistent properties. Settings which increased the amount of powder entering the nip region, such as high screw speed, low roller speed, and a narrow gap setting, promoted the distribution of powder across the roller width.

The sealing plates can have an influence on the distribution of powder and compaction of the ribbon. This phenomenon was studied by Miguelez-Moran et al. [32, 43] using an instrumented laboratory roller compactor, and several techniques to characterize ribbon density. A distribution of density was found across the ribbon (parallel to the roller axes, transverse to the ribbon motion) with lower density found at the ribbon edges. The effect was less pronounced for slower roller rates, smaller gaps and powders that slipped along the seal surfaces more readily. The authors suggested that the lower density at the ribbon edges was attributed to drag induced in the powder feed by the sealing plates.

From the end of the screw feed to the gap, the powder is typically contained by plates that may also be considered part of the feeding system. Some leakage of powder from the seals may contribute to the amount of fines in the granulation. If not properly installed so that the leakage is at a minimum, and sufficiently maintained so that the performance of the seal plates is consistent, the sealing plates may cause an isolated batch-to-batch variation or trend in the granule properties over time.

To improve the powder sealing and process performance some manufacturers offer rollers that interlock. One roller has a rim on the edge such that the edge of the second roller fits the channel and seals the powder into the nip. A system of this type was explored by Funakoshi, et al. [45]. Several roller designs with different modifications to the rim geometry were explored. The amount of leaked powder was reduced from ~20% to ~5% by use of the interlocking rollers. When examining the resulting ribbons it was found that without the interlocking roller, the ribbon experienced the highest pressure and achieved the highest density in the center. With the interlocking roller system in place, the pressure experienced by the ribbon and resulting density was even across the ribbon width.

38.4.2 Consolidation and Compaction in Between the Rollers

Once powder is delivered to the area before the nip it begins its interaction with the rollers, moves forward and becomes compacted into ribbon as it passes through the gap between the rollers. Johanson [15] developed one of the most referenced descriptions and mathematical models of the roller compaction process. The roller compaction operation was described based on the machine geometry and assumptions of powder behavior.

Johanson took the pressure exerted on the powder bed from the feed screw as an input to the mathematical model but did not otherwise discuss the powder motion up to the rollers. From the feed area the powder moves forward and begins to be influenced by the roller motion. This region is typically referred to as the slip region because the rollers move faster than the powder with a boundary condition of slip between the powder and the roller surface. As the powder is dragged forward the space in between the rollers narrows so that the powder bed consolidates and the pressure between the roller surfaces and the powder increases. A schematic diagram of the powder and roller interactions is presented in Figure 38.10.

To describe the process in the slip region Johanson built upon earlier work describing steady-state powder flow originally developed by Jenike in 1961. The Jenike model and other powder flow concepts, developed more recently, has been summarized by Podczeck [64].

It was proposed that for a cohesive, compressible, isotropic powder, a shear test could give information about the

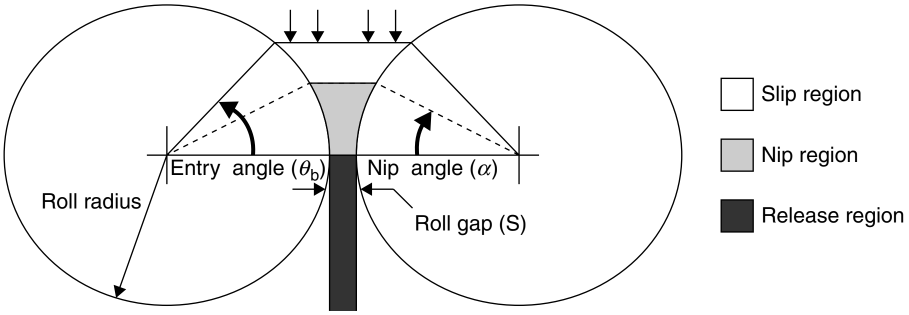


FIGURE 38.10 Schematic diagram of the roller and powder interactions. Reprinted from Ref. 65, Copyright (2005), with permission from Elsevier.

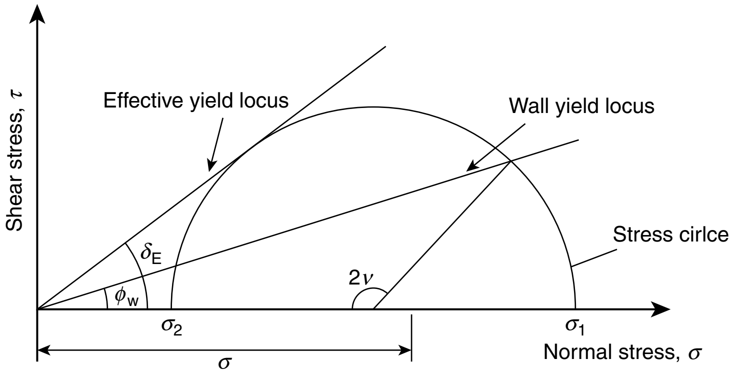


FIGURE 38.11 Jenike-Shield yield criterion for the slip region. Reprinted from Ref. 65, Copyright (2005), with permission from Elsevier.

effective angle of friction and the surface friction angle. This information could then be used to plot yield loci describing the response of the powder to shear and normal stresses (Figure 38.11). The intersection of the wall yield locus and the stress circle gives the resolution of shear and normal stresses at the roller surface. The angle between the normal stress and the tangent to the roller is then described by equation 38.1 (equations were prepared from Ref. [65] Copyright (2005) with permission from Elsevier).

$$2\nu = \pi - \arcsin\frac{\sin\phi_\omega}{\sin\delta} - \phi_\omega \qquad (38.1)$$

Johanson used the combination of the incoming pressure, roller geometry, and powder properties to predict a pressure distribution as a function of position as shown in equation 38.2.

$$\frac{d\sigma}{d\chi_{\mathrm{Slip}}} = \frac{4\sigma((\pi/2-\vartheta-\nu)\tan\delta_{\mathrm{E}})}{(D/2)[1+(S/D)-\cos\vartheta][\cot(A-\mu)-\cot(A+\mu)]} \qquad (38.2)$$

where A is given by

$$A = \frac{\vartheta+\nu+(\pi/2)}{2}$$

The pressure at the roller surface is typically plotted as pressure versus angle from the closest approach of the rollers, the gap. Typical curves constructed with this approach show a low starting pressure followed by a rapid nonlinear increase of pressure moving toward the gap (see Figure 38.12, line a).

At some point the pressure on the rollers increases such that the powder no longer slips along the roller surface but moves with the roller surface until the powder exits the gap as compacted ribbon. This region close to the gap is referred to as the nip region. In order to predict the pressure in this region, Johanson considered the densification of a cross section of powder moving between the rolls. This section of powder is compressed as if in uniaxial compression with density increasing as the distance between the rollers decreases. Powder property measurements from compression experiments with a die can determine the functional relationship between pressure and density. Johanson developed the expression shown in equation 38.3 to describe the pressure as a function of position in this region.

$$\left(\frac{d\sigma}{d\chi}\right)_{Nip} = \frac{K\sigma\vartheta(2\cos\vartheta-1-(S/D))\tan\vartheta}{(D/2)[(1+(S/D)-\cos\vartheta)\cos\vartheta]} \qquad (38.3)$$

This function can be used to construct a plot of pressure as a position from the gap in a similar fashion to the plot generated for the case where the powder slips along the roller surface. For the case of no powder slip the resulting pressure versus position curve typically has a different shape with a higher starting pressure and a more linear increase as

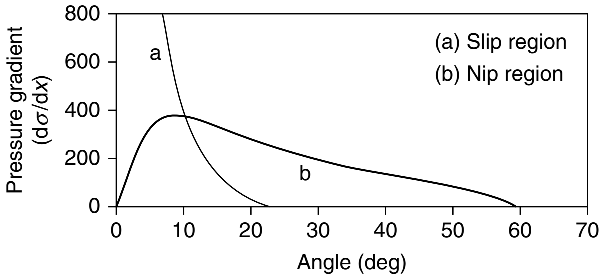


FIGURE 38.12 Pressure gradient versus angle from the nip. Reprinted from Ref. 65, Copyright (2005), with permission from Elsevier.

the gap is approached than the plot for the slip condition (see Figure 38.12, line b).

The difficulty is predicting when the powder behavior will switch from slip to no-slip at the roller surface, thereby transitioning from the slip to the nip region. Since the pressure is most often plotted as an angle from the gap, the position of this transition was referred to by Johanson, and is commonly called, the nip angle. The lowest pressure predicted by the slip and no-slip assumptions for the roller surface boundary condition is followed. At the nip angle the pressure predictions from the slip and no-slip condition are equal and the powder no longer slips at the roller surface from this point onward as no-slip is the lowest pressure needed to induce powder motion. This relationship is represented in equation 38.4.

$$\left(\frac{d\sigma}{d\chi}\right)_{\text{Slip}} = \left(\frac{d\sigma}{d\chi}\right)_{\text{Nip}} \tag{38.4}$$

or

$$\frac{4((\pi/2)-\alpha-\nu)\tan\delta_{\mathrm{E}}}{[\cot(A-\mu)-\cot(A+\mu)]} = \frac{K(2\cos\alpha-1-(S/D))\tan\alpha}{\cos\alpha}$$

A schematic illustration of the concepts from the Johanson model showing the two pressure predictions as a function of angle from the gap and the intersection of line a (slip condition) and line b (no-slip condition) defining the nip angle is shown in Figure 38.12. A graphic representation of the stress on the rollers is shown in Figure 38.13.

Forty years later, Bindhumadhavan et al. [65] compared the results of calculations using Johanson's model with experiments. Microcrystalline cellulose was roller compacted with the benefit of better instruments to measure powder properties, pressure sensors mounted in the roller faces to measure the compaction forces, and better computing power to calculate the model and evaluate the data. Good agreement was found between the predictions using the method of Johanson and the experimental values as shown in Figure 38.14 relating the pressure as a function of angle from the nip for different gap settings. Yusof et al. [66] also reviewed Johanson's model and conducted experiments with maize powder to compare the model and experimental values. Once again good agreement between the model and the experiments was found.

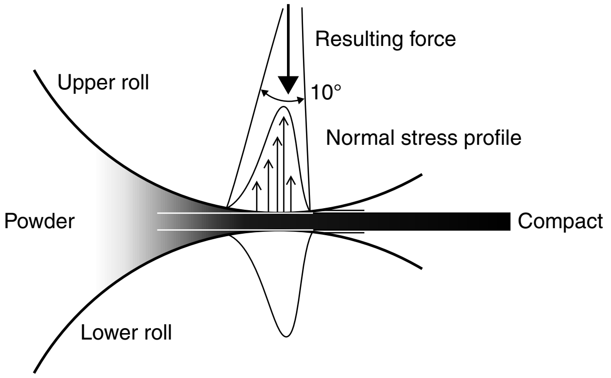


FIGURE 38.13 Graphic representation of the stress profile in the roller compactor nip. Reprinted from Ref. 44, Copyright (2003), with permission from Elsevier.

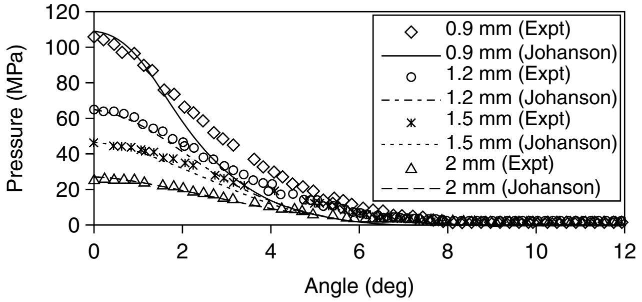


FIGURE 38.14 Predicted and experimental roller surface pressure as a function of gap. Reprinted from Ref. 65, Copyright (2005), with permission from Elsevier.

Sommer and Hauser [67] reviewed the Johanson model and found that predictions were useful given the limited number of inputs. However, they examined the assumptions, which Johanson used and concluded that there could be limitations from the assumptions, which might cause the model to deviate from the results found in practice. One example presented was the model's possible sensitivity due to the method of choosing the boundary condition for the point at which the rollers engage the powder feed. The boundary condition assumption could cause an unrealistic sensitivity to the feed pressure in the model results. Simple material models were used for the description of the nip region, and it was proposed that the limitations in these models could also lead to inaccuracies.

An additional mechanism of slip has been explored by Schonert and Sander [68]. They reviewed several theoretical models and concluded that there could be slip between the compacted ribbon from the point of maximum stress to the exit of the gap. Instrumentation embedded in the rollers capable of resolving the normal and tangential stresses at the roller surface confirmed that the powder does begin to move with the rollers at some level of consolidation. However, the maximum stress occurred slightly before the line of centers between the two rollers. From the point of maximum stress it was found that the compacted ribbon accelerates, moving faster than the rollers, toward the gap exit. A similar measurement showing the maximum pressure before the line of centers and an acceleration of the ribbon was obtained by Lecompte et al. [63].

Other approaches to predicting the process conditions have also been proposed. Yehia [69] described a simplified approach in which the change in bulk density going from the feed to the ribbon is considered when estimating the pressure during the roller compaction process. Rather than subjecting powder to a shear test, only measurement of the input and output bulk densities and the pressure response to uniaxial compression is needed. The author assumed that most of the powder densification occurs in the nip region and that the pressure at the beginning of the nip region could be estimated by a density measurement and information about the density–pressure relationship for the material studied. The speed and geometry of the rollers and gap width is used to estimate the change in volume, and therefore, density of the material as it is processed. It was proposed that the performance at scale could be predicted from the limited material testing required for the calculation and information obtained on a lab-scale roller compactor. The lab-scale machine would need to be adjusted to a variety of geometries and equipped with different roller finishes to determine an appropriate regime to predict the performance at scale.

Dec et al. [70] reviewed various models including a method of estimating roller compaction conditions. The “slab method,” originally developed for the compaction of metal powders, considers a section of material or “slab” passing as a single element through the nip region. The stepwise calculations assume a condition at the inlet of the nip and uses experimental data to determine the nip angle. Pressure is predicted by successive iterations of the calculation until the prediction matches the measured properties of the ribbon.

The mechanistic understanding of roller compaction developed by Johanson and others is useful to understand the processing history of the powder as it is compacted into ribbon. The approach of these investigators grew of an interest in designing roller compaction equipment. For most applications, the machine geometry, speeds, and pressure ratings have been predetermined by an equipment manufacturer for a range of materials similar to the proposed process. However, the preselected machine capabilities still leave the choice of the various processing parameters to be made in designing the roller compaction operation.

Other investigators reported studies designed to understand the interaction of the process variables and particular materials or combinations of materials to determine the most effective processing parameters. Most of the studies of this type used a statistical design of experiments to evaluate the affect of parameter changes on the ribbon, granule, and finished tablet properties but may also include raw material changes, composition or other variables as part of the study.

Falzone et al [19] studied the effect of the horizontal and vertical feed screw speeds, and roller speed on granule size and compactability for microcrystalline cellulose, lactose, and a model active blend consisting of 60% acetominophen. The results for microcrystalline cellulose granules and tablets were successfully modeled by a quadratic regression that included the horizontal feed speed and the roller speed with high feeder speed and low roller speed giving the highest values for both granule size and compactability. For lactose the vertical feed speed also had to be used to successfully model the results. The acetaminophen blend results showed granule size equal to or less than the starting material due to fracture of the acetominophen crystals. The results for granule size could not be modeled by a quadratic fit of the data, but the acetominophen granulation compactability could be described by the quadratic regression and showed a dependence on both the feed screw speeds and the roller speed.

Hervieu et al. [71] used a model powder to study the effect of feeder speed, roller speed, and compaction force on granule properties and the hardness and friability of the final tablet. The Box Wilson experimental design required 15 batches to complete. It was observed that at low feeder speeds compared to the roller speed, the powder could not be effectively compacted and had high friability. If the feed speed was too fast in comparison to the roller speed the material temperature increased and the roller compactor jammed. Compaction force only had a secondary effect on the results. Similar results showing dependence on the feeder to roller speed ratio were reported by Guigon and Simon [44]. At higher feed speeds, overfeeding resulted in a poor quality compact with loss of uncompacted powder while at lower feeder speeds underfeeding resulted in no compact being formed. The effect of feeder and roller speed selections at constant pressure on the gap opening is shown in Figure 38.15 with lower feed resulting in a smaller gap at constant roller

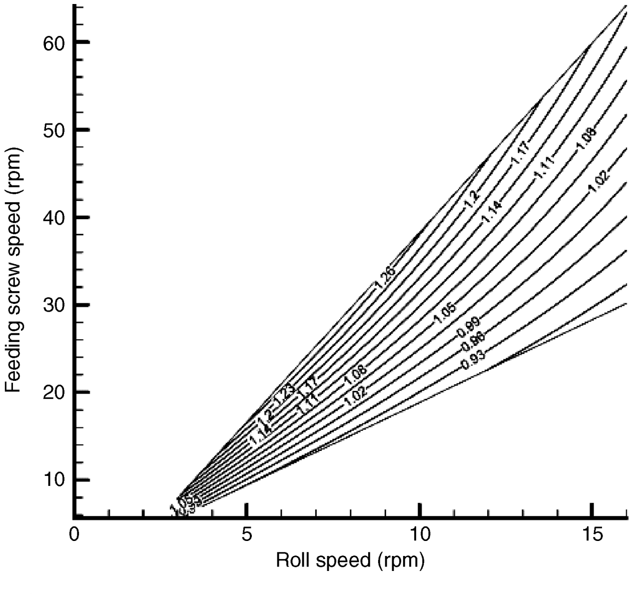


FIGURE 38.15 The effect of feed screw and roller speed on the gap opening at constant pressure. Reprinted from Ref. 44, Copyright (2003), with permission from Elsevier.

speed and lower roller speed resulting in a larger gap at constant feed speed.

Four parameters (pressure, gap, roller type, and sieve aperture) were studied for their effects on a buccal tablet formulation by Rambali et al. [11]. A partial factorial design showed that smooth rollers promoted larger granule size and higher tablet strength but resulted in slower dissolution compared to ribbed rollers. It was noted that smaller granule size typically gave higher tablet strength. The lower than expected tablet strength for small granules produced by ribbed rollers was attributed to the higher frictional force and powder rearrangement induced by the ribbed surface. Smaller gaps and higher pressures produced larger granules. However, the tablet strength was found to be inversely proportional to gap and pressure.

A factorial design was also used by Weyenberg et al. [36] to study the effects of roller speed, pressure, and horizontal feed speed on granule flow, granule size, granule friability, and the resulting tablet strength for a bioadhesive tablet formulation. The roller speed and the compaction force had the largest effects on the granule properties followed by the horizontal screw feed speed. Higher roller speeds combined with low compaction force had reduced granule flow, increased granule friability, and smaller granule size. The horizontal screw speed did not have a large influence on granule properties. The highest tablet strength was obtained from smaller granules prepared at high roller speed and low compaction force. Tablets from the smaller granules best matched the dissolution profile of tablets that were previously prepared by direct compression, tested *in vivo*, and used for comparison with tablet from a roller compaction granulation.

In a study by am Ende et al. [72], a two stage design was used to examine the effects of roller compaction on the content uniformity, granule properties, and tablet properties of a low active concentration granulation. The first stage of the experiment used a full factorial design to study the effects of compaction pressure, and gap width, where the feed screw was automatically adjusted to maintain gap. The study responses were the amount of uncompacted fines and the potency of the uncompacted fines. It was found that the amount of uncompacted fines was affected by the pressure and gap settings with a significant interaction between the pressure and gap variables. Higher levels of fines were present for low pressures and high gap widths. The potency of the fines, a measure of the uniformity of the granules, could not be predicted by these two variables alone.

The second stage of the experiment used a D-optimal design to examine the effects of roller speed, gap width, compaction pressure, and postcompaction mill sieve opening on granule and tablet properties. The granulation size increased with increasing pressure but had less of an effect as the mill sieve opening decreased showing the interaction between these two variables. Compaction pressure and sieve opening also had an influence on the uniformity of both the granulation and the tablets. As screen size increased the variability of the granulation potency increased. It was found that lower pressures and larger gaps during the roller compaction led to lower compaction forces to form a tablet of the desired strength. Tablet friability was unaffected by any of the roller compaction variables studied.

As discussed in this section a review of the mathematical descriptions and mechanistic understanding, combined with some knowledge of the materials being roller compacted and some studies of the system response to the parameter settings can be used to determine and even predict the settings of or system responses to the four main variables in the roller compactor: feed speed, roller speed, compaction pressure, and gap width.

38.4.3 Ribbon Breaking and Size Reduction

The roller compacted ribbon is typically broken and reduced in size to form the final granulation. The interparticle bonds in the ribbon need to be strong enough such that fractures form and lead to granules rather than a loosely compacted ribbon returning to powder. Ribbon of a consistent strength and density should give consistent granule particle size distributions. Bacher et al. [14] suggested that the ribbon breaks at the weakest interparticle bonds and that ribbons with uniform interparticle bonds give the better compactability.

The milling operation can be integral to the machine or a separate step and is usually accomplished with a screening mill. General considerations common to screening mills such as choosing the impeller type, screen type, speed (impeller or screen depending on type of mill), and spacing of the screen and impeller are steps to achieving the desired granulation particle size distribution. Proper selection, setup, and maintenance can eliminate the need for a metal detector at the mill exit. Effects of screen selection affecting the granule and tablet properties in a roller compaction operation have been reported by am Ende et al. [72].

Information on the operation of mills can be applied directly to the milling subunit operation of roller compaction. Rekhi and Sidwell [73] described how Kick's Law, Rittinger's Law, and Bond's Law have all been developed to relate the mill energy input to the size reduction process. It was reported that only a small part of the energy used by the mill is consumed in breaking the particles making the ability to predict performance limited in practice. Some experimentation is necessary to select the mill change parts (e.g., screen, impeller, spacers), and operating parameters due to the limitations of the predictive methods. These experiments can also identify common milling problems such as screen blinding, heat generation (with possible melting), and interactions with moisture either from the environment or liberated during the milling process.

38.4.4 Process Models for Roller Compaction

The area of the roller compaction operation that is unique to the unit operation and of most interest to model is the area where the powder is consolidated, begins to move with the rollers and is compacted into the ribbon. Several approaches to process predictions have been explored: mathematical models, multivariate regression of designed experiments, predictions from compaction properties, computational modeling of the material in the process, and artificial intelligence/neural network construction to predict outcomes from a set of training data.

The foundation of a mathematical description for the roller compaction process was described by Johanson [15] and has been further studied by many authors including Bindhumadhavan et al. [65], Yusof et al. [66], and Sommer and Hauser [67]. Alternate approaches were presented by Yehia [69] and reviewed by Dec et al. [70]. Several studies have used multivariate regressions to characterize the roller compaction operation such as Falzone et al. [19], Hervieu et al. [71], Rambali et al. [11], Weyenberg et al. [36], and am Ende et al. [72].

Although achieved by passing between rollers, the compaction of ribbon causes the same physical processes within the powders that are induced during compaction within a die. Borrowing or combining concepts from tablet compaction can be useful to understanding roller compaction. For example, Farber et al. [37] examined the loss in tensile strength when comparing tablets made via a roller compaction granulation to a direct compression prototype. The roller compaction process was considered as part of the overall compaction history of the materials. A "unified compaction curve" was constructed that described both the roller compaction and tablet forming processes. It was found that, for materials that bond primarily from plastic deformation, compaction information generated with a compaction simulator or single station press could be used with information about the pressure exerted by the rollers to estimate the tensile strength of the final tablets.

Hein et al. [74] used a three-dimensional model of compaction properties populated by data from a single station press to predict the change in final tablet properties as a result of roller compaction. A reduction in final tablet strength was shown for materials with plastic deformation. A minimal reduction in tablet strength was shown for the material with primarily brittle fracture. The model was considered effective at screening materials for use in roller compaction.

Computational methods can be used to understand and predict process behavior and can be applied to roller compaction. Dec et al. [70] reviewed several finite element method (FEM) applications as part of a review of modeling methods. However, most of the models reviewed were published from researchers in the metals industry. The simulations were dependent on estimates of the feed stress and friction to predict the process conditions and postcompacted material performance.

The use of neural networks and artificial intelligence approaches to modeling have been explored to correlate different types of inputs, process parameters, and granule or resulting tablet performance. Inghelbrecht et al. [75] studied a 60 experiment data set and then predicted the results for an additional 20 experiments. The speed of two feed screws (horizontal and vertical), roller pressure, and roller speed were used to predict the granule friability and particle size. It was found that the neural network was more effective than a quadratic mathematical model approach in predicting the granule performance results.

The binder type, binder concentration, number of compaction passes, and addition of microcrystalline cellulose extragranularly, were used as inputs to predict the performance of acetominophen tablets by Turkoglu et al. [76]. The results were poorly predicted using a typical neural network learning algorithm of adjusting the weighting of parameters relating model inputs and outputs. A second calculation method using a "genetic" algorithm that progressively selects best fit solutions in "generations" of calculations gave better predictions.

A variety of material inputs were used with projected process settings for roller speed, and roller gap to predict the roller pressure, nip angle, ribbon density, and ribbon porosity by Mansa et al. [77]. The commercial software package employed used neural network, genetic algorithms, and fuzzy logic in order to predict the outputs. Good agreement was found inside the training range. However, some rules generated by the system did not seem to correlate with the physical system (e.g., roller gap not having an effect on ribbon density) and predictions outside the training range did not compare well with experimental values.

38.4.5 Control Strategies for Roller Compaction

The overall roller compaction operation includes the powder preparation and handling, compaction by the rollers, and the subsequent breaking and sizing of the resulting ribbon. The variables affecting powder preparation and handling as well as sizing operations are not specific to the roller compaction and can be chosen for the roller compaction operation from a base of information devoted specifically to these fields.

For the compaction portion of the operation, several references such as Johanson [15], Yehia [69], and others have discussed how powder measurements with or without experiments can be used to design a compactor that will subject the material to a compression history resulting in the desired output ribbon and granule properties. The typical situation in many areas of manufacture, including pharmaceutical applications, is the reverse. An equipment vendor has already spent the effort to design a piece of equipment of general applicability for the typical range of powder properties encountered by their clients. The decisions regarding screw feeder arrangement, design, placement in proximity to the rollers, roller diameter, width, a mechanism to maintain position of the rollers, a system to apply pressure on the powder, and the milling arrangement have already been chosen.

The challenge in most practical applications of roller compaction technology is to find the appropriate settings for adjustable parameters given a set piece of equipment and control system previously engineered by the manufacturer. The four common variables discussed in most of the literature are the feeder speed, roller speed, gap, and pressure. These variables depend on one another and need to be set in combinations that are appropriately balanced. The experience of the vendor who configured the machinery and who has the benefit of the knowledge from working with many clients can help in designing the roller compaction process and selecting parameter values. Extreme settings of the controllers are usually not effective at making the best product unless there is something very unusual about the system under study. Several investigators, such as Rambali et al. [11], Weyenberg et al. [36], and am Ende et al. [72] used statistically designed studies to understand and even predict the granule and tablet properties as a function of the roller compactor variables and select the parameter values.

The simplest method is to choose a feed speed, roller speed, and pressure, which delivers the desired gap or ribbon thickness. The challenge for this method is to deliver the powder very consistently. A balance of the powder feed speed and the roller settings must be achieved to avoid over or under feeding the roller compactor. As discussed by Lecompte et al. [64] it is necessary to feed enough material to the nip region such that a compact is formed and the powder is being transported fast enough to encourage a uniform packing across the roller width with a uniform ribbon resulting. Guigon and Simon [44] discussed how the feed speed and compactor throughput should not be so fast that there is leakage of powder from the sealing mechanism or that air entrainment disrupts the powder flow or strength of the compacted ribbon.

In some studies, such as Guigon and Simon [44], a link between the gap and the resulting product quality is established. Given the difficulty of feeding powders without variation, control systems have been developed such that a roller speed, pressure, and gap distance can be set. The feeder speed is then adjusted in a feedback loop with the gap measurement in order to maintain a consistent ribbon thickness and strength.

More recent variations in control systems also recognize the importance of the feed and seek to monitor the feed screw output or the actual mass throughput of the roller compactor in order to make adjustments to the roller compactor settings.

Two different approaches to setting and scaling the operation of the roller compactor are discussed in the next section.

38.5 SCALE-UP OF ROLLER COMPACTION

38.5.1 Scale-Up Strategies

A common method for scaling up a roller compaction process from development equipment to commercial equipment is to use a parametric strategy. The parametric strategy focuses on determining the commercial equipment parameter values by using equivalency factors. Equivalency factors are based on aspects of the equipment. Some of the values used may be taken from the equipment manufacturer, who has assembled information from the design and testing of the unit as well as the collected experience of the client base in order to develop scale-up factors.

In selecting the roller pressure for the commercial equipment, the hydraulic pressure required to generate a needed force on the rolls can be estimated by considering the roller width and roller diameter. In selecting the roller speed for the commercial equipment, the rpm can be set to obtain a linear velocity of the rolls equivalent to that used in development. Alternatively, dwell time can be used as a metric for selecting the appropriate roller speed for the commercial equipment. Often, the selection of roller speed and roller gap is synchronized to obtain the desired throughput. This approach neglects the quality of the ribbons and granules produced, and the potential affects on downstream processes.

An alternative strategy focuses on the attributes of ribbons and calls for adjusting the ribbon production parameters to attain attribute values on the commercial equipment equivalent to that produced in development. The intent of controlling the quality of the ribbons produced is to control the downstream granule properties (size distribution, solid fraction, and compactability). The hypothesis underlying this approach is that under similar milling conditions (mill speed and screen opening) the output particle size distribution is determined by the ribbon input quality (Campbell et al. [78], and Morrison et al. [79]).

The roller compaction unit operation is composed of subprocesses focused on achieving two sequential, independent, but linked manipulations of the material: ribbon production and granule production by milling. The two quality attributes of interest for the ribbons are the thickness after recovery due to relaxation, and the solid fraction. As with the general consolidation theory, these two ribbon attributes control the breaking strength of the ribbon. Both of these attributes should, therefore, influence the behavior of the ribbons during milling. The indirect effects on ribbon recovery should be carefully studied, since extensive recovery could affect ribbon strength.

One crucial decision to be made when contemplating scaling up a roller compaction process is whether or not to use the automatic gap feedback control system or to proceed with a preset feed rate. This decision will determine what parameters need to be considered in scale-up. If the roller compactor is run under gap control, the effect on ribbon thickness is muted, unless purposely varied (by changing the gap). To determine what process parameter to alter to obtain the desired intermediate attribute requires a detailed knowledge of the interplay between process parameters and ribbon/granule attributes.

38.5.2 Case Study I: Parameteric-Based Scale-Up

Case Study I reports on the roller compaction of a model microcrystalline cellulose/lactose blend with 5% active using the manual operation. In manual operation, the three parameters for ribbon production (screw speed, roller speed, and roller pressure) were set at predetermined values that remained constant for the duration of the run. For reproducible ribbon production, this implied that the powder flow into the rollers had to be constant.

The behavior of the powder during roller compaction depends on the region it is in (Inghelbrecht and Remon [20, 22], Bindhumadhavan et al. [65], Zinchuk et al. [42], Yusof et al. [66]). The powder in the slip region is densified slightly by rearrangement as it travels toward the rollers. In this region there is slippage between the powder and the rollers. In the slip region the velocity of the powder is slower than the linear velocity of the rollers. In the nip region the powder undergoes densification by particle rearrangement and by deformation. In the compaction region further densification by deformation occurs proceeded by bonding to form the ribbon.

In the parameter optimization study three factors were evaluated: screw speed, ratio of roller speed to screw speed (powder delivery rate), and roller pressure. Based on the data set, various parameter combinations were identified that produced granules of the desired flow and particle size distribution. The process parameters (screw speed, roller pressure, and roller speed) for commercial-scale equipment were determined using equivalency factors.

38.5.2.1 Adjusting Pressure Several researchers have reported on the loss of powder compactability upon roller compaction (Kochhar et al. [80], Bultmann [31], Freitag et al. [24]) and ascribe it to a reduction in the binding potential due to the consolidation that occurs during roller compaction (Malkowska and Kahn [40], Falzone et al. [19], Kleinebudde [6]). To mitigate this reduction the authors state that only sufficient pressure should be applied during roller compaction to improve powder flow (the main benefit). The roller pressure for the commercial equipment was set considering the roller width and roller diameter. No modification to the calculated value was made during the run.

More recently, investigators have looked at instrumented rollers to gather data on the actual pressure curve on the rolls (Miguelez-Moran et al. [43]). Farber et al. [37] argued that the compression process (volume reduction) a powder undergoes during roller compaction is similar to that during tabletting. Therefore, instrumented rolls can be used in setting roller pressure on commercial equipment to achieve equivalent pressure on the commercial equipment (and hence similar powder behavior). The underlying principle being that similar ribbons would be produced on scale-up if the pressure is maintained.

38.5.2.2 Choosing Screw and Roller Speed The roller speed for the commercial equipment in Case Study I was set to obtain the desired process efficiency. In manual mode, the ratio of screw:roller speeds dictates, for a given material and roller pressure, the gap between the rollers. To attain a roller gap on the commercial equipment similar to that on the development equipment, the value of ratio of screw speed to roller speed obtained during development was used to set the screw speed on the commercial-scale roller compactor based on screw design and roller width and diameter. The force generated by the powder propelled by the feeder screw into the slip region is counter-balanced by the hydraulic pressure applied to the rollers. Based on the material properties, the balance between these two forces determines the gap between the rollers.

38.5.2.3 Mill Screens and Speeds The velocity at which the milling blade rotates affects the milling process in two ways: the force of the instantaneous impact on the ribbon and the residence time in the milling chamber. These two aspects have two different potential consequences. The higher impact could result in the ribbon shattering into smaller granules. Residence time in the chamber affects the amount of attrition the ribbon undergoes, which results in finer particles. Brittle materials are more susceptible to the impact, whereas pliable (viscoelastic) materials are more prone to attrition. The properties of the microcrystalline cellulose/lactose active blend in Case Study I suggested that the ribbons produced would posses both brittle as well as viscoelastic properties. Since ribbons are porous solid bodies, it is plausible that the ribbons fractured into smaller pieces that underwent size reduction by attrition. Hence, it was determined that residence time was the important factor to study and not the instantaneous impact.

A derived parameter was used for mill speed. The effect of milling speed is due to its effect on residence time of the ribbon in the milling chamber. To more accurately estimate the effect of residence time on granule properties, a ratio of mill speed to roller speed was studied as a derived parameter. Increasing the mill-to-roller speed ratio reduced residence time for the ribbons in the milling chamber by increasing the output rate for a given input rate. Increasing the mill-to-roller speed ratio (shorter residence time) increased the mass flow rate of the granules. This was due primarily to the increased mean particle diameter and reduced fines.

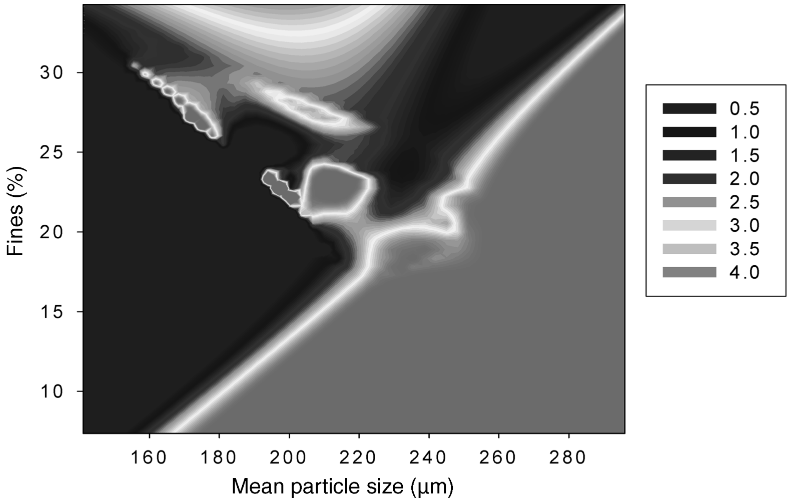


FIGURE 38.16 The interactive effect of mean particle size (μm) and amount of fines (%) on bulk mass flow (g/s).

The bulk powder property of interest for tablet compression is the mass flow. Powder mass flow should be governed by the properties of the particles making up the bulk. The two particle properties controlled by the roller compaction process are mean particle size and amount of fines. These two particle properties have an opposite effect on mass flow. Figure 38.16 is a contour plot showing the interactive effect of mean size and fines on flow. To maximize flow, the mean particle size would have to be increased to compensate for a higher amount of fines. The area of maximum flow is bounded approximately by the lower left to upper right diagonal in Figure 38.16.

Due to the statistical design used, the effect of screen size was nested within the effect of mill/roller speed ratio. The effect of the upper and lower screen could only be determined for a given mill to roller speed ratio. As expected, the effect of the lower screen was more pronounced than that for the upper screen. A maximum in mean particle size was observed with a 1 mm lower screen opening. This maximum mean particle size coincided with a similar maximum in mass flow with a 1 mm lower screen opening.

To understand the milling process in more depth, the difference between the upper screen opening and the lower screen opening was studied. It was theorized that this difference may be important since the upper screen controls the quality of the input for the lower screen, and because size reduction in this case is partially through attrition. Figure 38.17 depicts the relationship between mass flow and the difference in screen opening between the upper and lower screen. Equation 38.5 depicts the relationship, where M is the mass flow (g/s), M_{max} M is the maximum predicted flow (g/s), X is the difference in screen opening (mm) between the upper and lower screens, and X_0 is the difference at maximum flow.

$$M = M_{max}\, \mathrm{e}^{-0.5\left(\frac{X-X_0}{b}\right)^2} \qquad (38.5)$$

The fitted model strongly suggests an optimum for mass flow at 1.96 mm difference in screen opening. The maximum predicted flow is 3.99 g/s. The combination of the lower screen maximum at ~1 mm and the screen difference maximum at ~2 mm defines the upper screen optimum at ~3 mm. These same screen openings were used for scale-up in Case Study I.

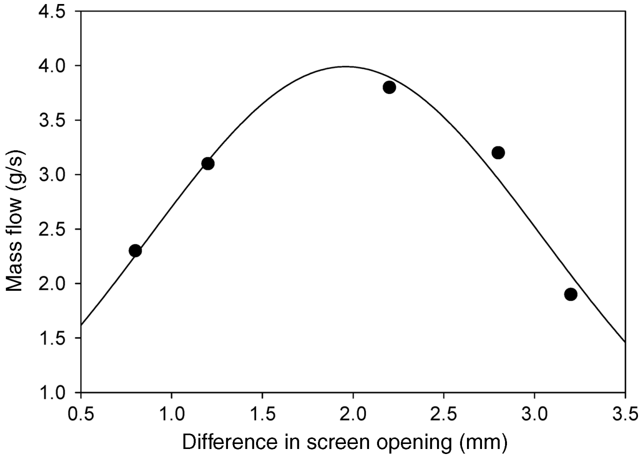


FIGURE 38.17 The effect of difference in opening between upper and lower screens on mass flow.

38.5.2.4 Parametric Scale-up With a Procedure and Parameters Recommended from the Equipment Manufacturer The example presented in this section illustrates scale-up recommendations similar to one of the major equipment manufacturers based on the design and experience developed with their equipment. In this case the pilot-scale equipment has a roller diameter ~60% of the size of the commercial equipment and a roller depth ~53% of the commercial equipment. It was recommended that the gap for the commercial machine be calculated from the acceptable values from the pilot-scale machine according to equation 38.6, which for this choice of equipment sizes leads to the larger machine gap setting about 1.7 times the pilot-scale machine.

$$G_2 = \frac{D_2}{D_1} \times G_1 \tag{38.6}$$

The screens on the postcompaction mill for the commercial machine are approximately five times the size of the pilot-scale machine so a throughput increase of approximately 4.5–5 times is expected in this example. The suggested scale-up procedure then uses machine parameters to calculate the roller speed based on equation 38.7. The throughput of the pilot-scale machine and the desired ribbon density are used as inputs with the remaining parameters coming from the machine geometry. The roller depth, B, may have an adjustment factor to be added for some machine designs. The roller speed calculation typically has a result with the commercial-scale machine about 1.7 times faster than the pilot-scale machine for the commonly available units this example was based on.

$$n_2 = \frac{T_1 \times 5}{D_2 \times \pi \times (B) \times G_2 \times \rho} \tag{38.7}$$

The next step in the scale-up is to relate the hydraulic pressure setting on the pilot-scale machine to the hydraulic pressure setting on the commercial machine. First the force per unit distance of roller width needs to be estimated from the manufacturer's conversion factor by a rearrangement of equation 38.8. The force per unit distance of roll width for the commercial machine is then calculated from equation 38.9.

$$P = F \times (\text{pressure conversion factor}) \tag{38.8}$$

$$F_2 = \frac{D_2}{D_1} \times F_1 \times t_c \tag{38.9}$$

where t_c is an adjustment factor related to the dwell time.

The hydraulic pressure setting for the commercial-scale machine is then calculated from equation 38.8 using the appropriate factor for the commercial-scale machine. Typical values are approximately an 8% increase in the hydraulic pressure as suggested by the manufacturer for the models in this example.

The screw feed is adjusted to achieve the calculated gap and the calculated pressure. It is recommended by this manufacturer to use a feedback loop to adjust the feed screw to maintain the gap. Typical values for screw speed on the larger unit are about 80% of the value for the pilot-scale unit for two typical models from this manufacturer but it should be noted that the larger system has twin screws compared to the single screw on the smaller machine.

Finally, the mill speed is set. From the manufacturer's experience, a mill speed setting on the commercial machine of about 75% of the pilot-scale machine will yield granules of similar size distribution when using screens with the same aperture.

38.5.3 Case Study II: Attribute-Based Scale-Up

Case Study II reports on the roller compaction of a model microcrystalline cellulose/lactose active blend with 2.5% active using the automatic operation. The roller speed for the commercial equipment was set at high speed to maximize operational efficiency. The roller gap and roller pressure were adjusted to produce ribbons with the attributes identified in development as optimal for downstream processing. The feed screw speed was allowed to float to maintain the powder feed rate sufficient to maintain an adequate flow into the nip area.

The optimum ribbon attributes were identified from development results by multiple constraint optimization of the granule properties such as powder flow and compactability. The variability in ribbon and granules properties depended on roller compaction process stability that is controlled by the powder flow to the feed screw during manufacture.

38.5.3.1 Ribbon Thickness and Density Roller speed had a marginal impact on the thickness, recovery, or density of ribbons produced. Increasing the roller pressure increased the ribbon density and reduced the ribbon recovery. The augmented load experienced by the powder during its transit through the rollers resulted in increased consolidation producing stronger ribbons. The increased interparticle bonding resisted the relaxation postcompaction, which explains the reduced recovery seen. Increasing the roller gap produced thicker ribbons, while reducing the recovery. The effect of gap on ribbon density was minimal.

There was little interactive effect between gap and pressure on ribbon thickness (Figure 38.18). The desired ribbon thickness could be obtained simply by setting the gap to the necessary setting (under gap control) allowing for the appropriate relaxation. Equation 38.10 depicts this relationship, where h is the ribbon thickness (mm), G is the gap setting

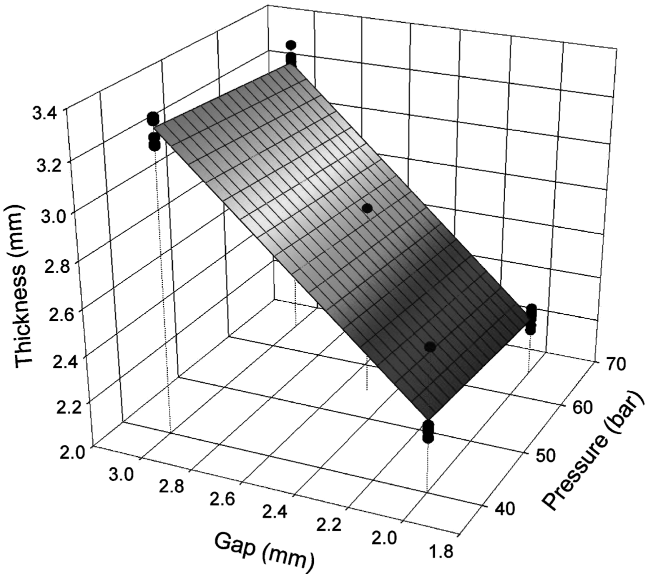


FIGURE 38.18 Effect of roller gap and roller pressure on ribbon thickness.

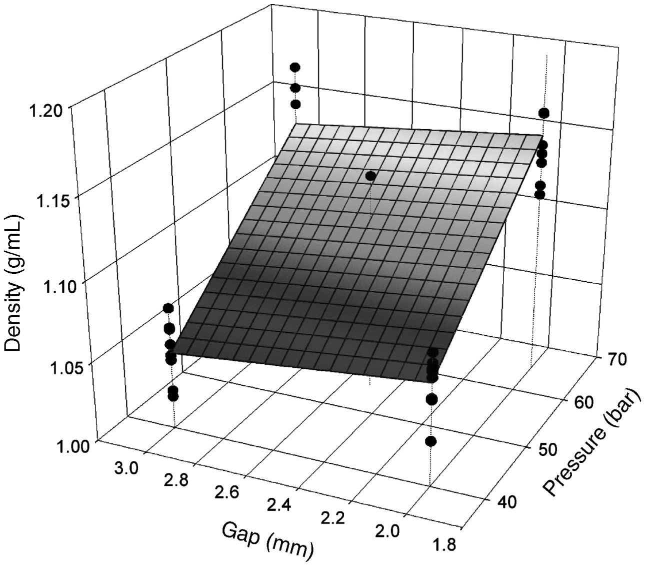


FIGURE 38.19 Effect of roller gap and roller pressure on ribbon density.

(mm), and P is the roll pressure (bar). The intercept accounts for the relaxation postcompaction.

$$h = 0.98 \times G - 0.002 \times P + 0.45 \qquad (38.10)$$

There was a marginal two-way interactive effect between gap and pressure on ribbon density (Figure 38.19). Equation 38.11 depicts this relationship, where ρ_a is the apparent ribbon density (g/mL), G is the gap setting (mm), and P is the roll pressure (bar). The intercept probably refers to the density in the powder bed just prior to significant consolidation.

$$\rho_a = 0.94 + 0.004 \times P - 0.008 \times G - 0.0001 \times P \times G \qquad (38.11)$$

Ribbon densification was more efficient at lower gap settings, which aligns with the common understanding of force transmission though a powder bed under load. The desired ribbon density could be obtained simply by setting the load to the necessary setting (under gap control).

Figure 38.20 shows that ribbon recovery is determined by roll pressure and roll gap. Equation 38.12 depicts this relationship, where R is the apparent ribbon relaxation (%), ε refers to the maximum elastic recovery (19.8%), G is the gap setting (mm), and P is the roll pressure (bar).

$$R = \varepsilon - 0.03 \times P - 3.298 \times G \qquad (38.12)$$

Both applied pressure and gap influenced the degree of recovery seen postcompaction, with gap being more dominant. The least recovery is seen with high pressure and wide gap, and most recovery is seen with low pressure and narrow gap. The effect of compression pressure on recovery is opposite that seen with tablets (Adolfsson and Nyström [81]). This is consistent with the view that weaker ribbons recover more.

38.5.3.2 Particle Size and Powder Flow Increasing roller speed reduced the powder flow. This reduction was mainly attributed to the change in particle size distribution; the mean particle size decreased while the fines increased. Potentially,

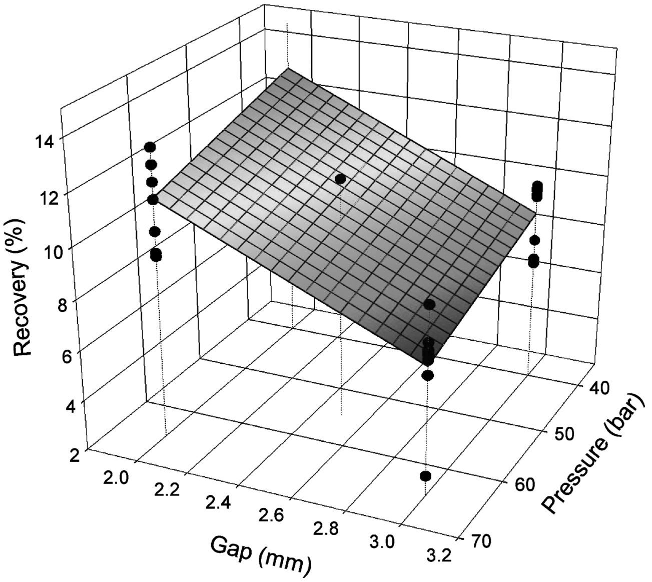


FIGURE 38.20 Effect of roller gap and roller pressure on ribbon recovery.

this can be the result of increased residence time in the milling chamber. Increasing the input rate into the milling chamber, while keeping the output constant, would increase the residence time. Increased residence time should produce a particle size distribution skewed to smaller sizes (see Case Study I).

Increasing the roller pressure used to produce the ribbons increased the powder flow. This increase is mainly attributed to the change in particle size distribution; the mean particle size increased while the fines decreased. This is consistent with the theory that stronger ribbon (produced at higher loads) would produce larger granules with fewer fines (Herting and Kleinebudde [26, 33]).

Increasing the roller gap used to produce the ribbons, decreased the powder flow. This reduction is mainly attributed to the change in particle size distribution; the mean particle decreased while the fines increased. This is consistent with the theory that ribbons have a density gradient decreasing from the surface to the center. The thicker the ribbon is the lower the density at the center. This low-density center will mimic ribbons made at lower loads and produce smaller particles during the milling process. Using principal component analysis, Soh et al. [16], showed that roller gap is an important predictor of granule properties. Figure 38.21 shows the interactive effect of roller pressure and roller gap on mass flow. The data shows that the ribbons made at opposite extremes of pressure and gap have minimum and maximum flow. Low pressure and large gap produced minimum flow; high pressure and narrow gap produced maximum flow. These powder properties are directly linked to the particle size distribution obtained from the ribbons. The data strongly suggests that pressure can be used with some degree of success to offset the effect of increased gap. This clearly illustrates the importance of control over ribbon quality as a scale-up metric.

The interaction between roller speed and roller gap is notable since it affects process efficiency (Figure 38.22). The best flow is seen with a small gap running at slow speed, which coincides with the largest mean particle size and lowest amount of fines. These conditions would be the least efficient. Efficiency gains could be obtained with wider roller gaps at faster speeds. However, this combination yielded the slowest flow, which coincides with the smallest mean particle size and the highest amount of fines.

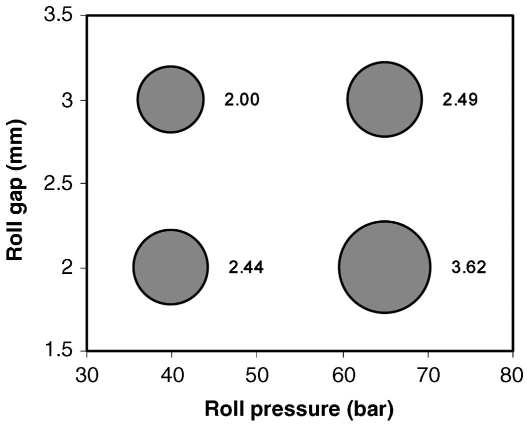


FIGURE 38.21 Effect of roller pressure and roller gap on granule mass (g/s).

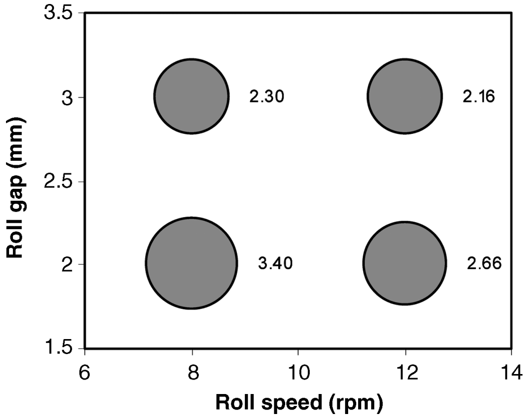


FIGURE 38.22 Effect of roller speed and roller gap on granule mass flow (g/s).

The effect of ribbon density and thickness on bulk mass flow is illustrated in Figure 38.23. Equation 38.13 depicts this relationship, where M is the mass flow (g/s), ρ_a is the apparent ribbon density (g/mL), h is the ribbon thickness (mm).

$$M = 9.49 \times \rho_a - 0.69 \times h - 0.582 \tag{38.13}$$

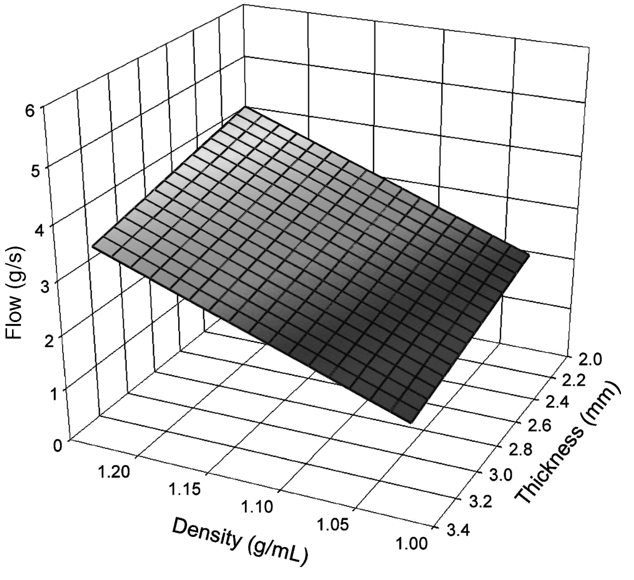


FIGURE 38.23 Effect of ribbon density and thickness on granule mass flow.

This coincided with their effect on granule mean size. Increased ribbon density produces larger granules with enhanced flow. Increased ribbon thickness leads to a smaller granules with reduced flow. The effect of ribbon thickness on the amount of fines produced after milling was marginal, but the effect of ribbon density was significant. Higher ribbon densities correlated with higher amounts of fines. This could be due to increased residence time in the mill leading to more attrition by shear. Herting and Kleinebudde [26, 33] reported a similar growth in particle size and improved flow with increased ribbon density.

Fragility of granules can be a main contributor to reduction on mass flow with processing postroller compaction. This was due to particle attrition during additional mixing of the granules with extragranular ingredients. To separate out the relative importance of changes in fines from changes in mean size on flow, the relative change in flow (final blend-granule) was evaluated against the relative change in mean size and fines (Figure 38.24). Equation 38.14 depicts this relationship, where ΔM is the change in mass flow (g/s), *ms* is the mean size and *f* is the amount of fines.

$$\Delta M = -0.24 - 0.04 \times \Delta ms + 0.004 \times \Delta t - 0.04 \times \Delta ms^2 + 0.0004 \times \Delta f^2 \tag{38.14}$$

Flow was relatively resistant to change mean size over the range observed. Flow was quite sensitive to changes in the amount of fines. This indicates that efforts to improve flow are better spent reducing the amount of fines rather than optimizing the mean size. The bulk powder property of interest for tablet compression is the mass flow. Powder mass flow is governed by the properties of the particles making up the bulk. The two particle properties controlled by the roller compaction process are mean particle size and amount of fines. These two particle properties have an opposite effect on mass flow. To maximize flow, the mean particle size would have to be increased to compensate for a higher amount of fines.

38.5.3.3 Powder Compactability The performance of the compression operation depends on the characteristics of the input final blend. There are two main metrics that describe the performance of the process: compactability (how hard the press has to work to make tablets) and process stability (how variable the product properties are).

Ribbon production variables affected compactability, whereas ribbon milling conditions did not affect compactability appreciably. There were two populations of ribbons analyzed for compactability, one set corresponding to low roller pressure and one corresponding to high roller pressure. The ribbons compressed at low pressure had a lower apparent density and a higher compactability compared to ribbons compressed at high pressure that had a higher apparent density and a lower compactability. Malkowska and Khan [40] reported a similar observation of increased compactability with a reduction in ribbon density.

In addition to density, ribbons also had a characteristic thickness. The effect of density and thickness on compactability was evaluated. Figure 38.25 suggests that ribbon thickness had only a small impact, while ribbon density had a substantial impact on compactability. Equation 38.15 depicts this relationship, where *K* is the compactability

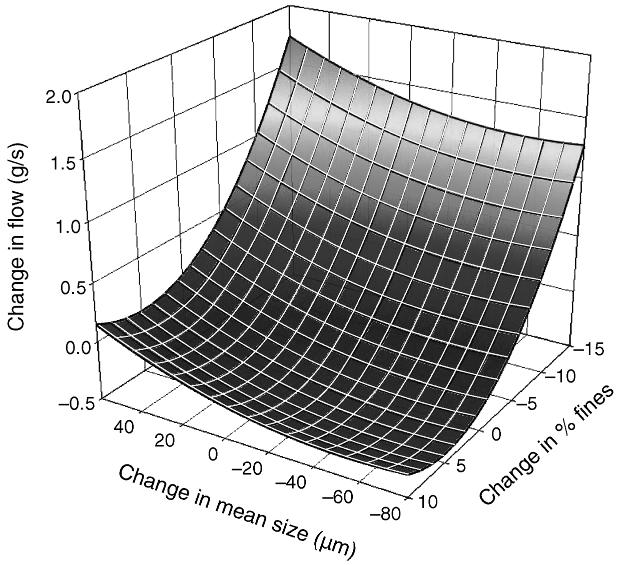


FIGURE 38.24 The interaction between change in mean diameter and fines on change in bulk mass flow.

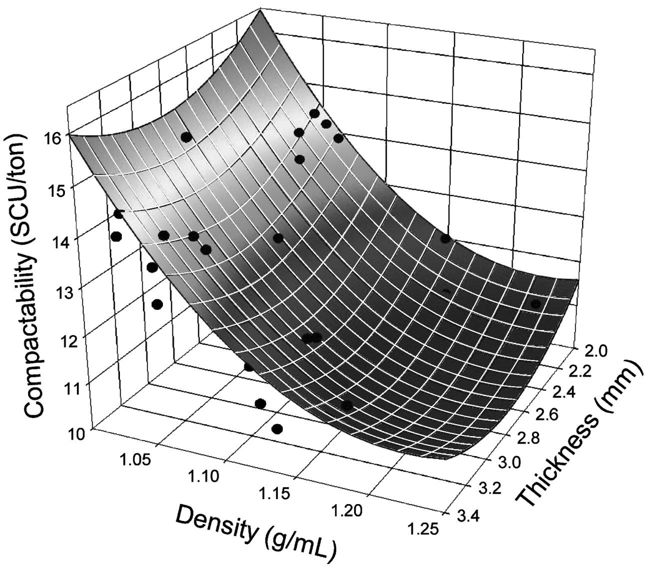


FIGURE 38.25 Effect of ribbon density and thickness on final blend compactability.

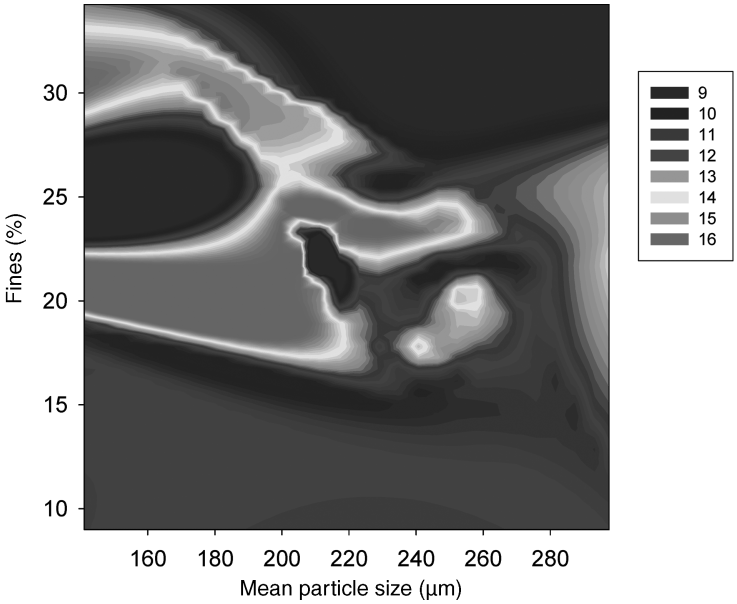


FIGURE 38.26 Effect of mean particle size and amount of fines on final blend compactability.

(SCU/ton), ρ_a is the apparent ribbon density (g/mL), and h is the ribbon thickness (mm).

$$K = 174 - 9.74 \times h - 245 \times \rho_a + 1.74 \times h^2 + 100 \times \rho_a \qquad (38.15)$$

In addition to the direct affect of density on compression, the link between density and compactability may also be mediated through particle size (Figure 38.26).

Blends with lower amounts of fines or a small mean particle size had on average higher compactability. There was a direct relationship between ribbon density and mean size, but an inverse relationship between the ribbon density and the amount of fines. The hypothesis explaining increased compactability with decreased ribbon density includes two parts. The ribbon density (and by extension the particle density) affects the particle strength and hence the force needed for deformation. Ribbon density affects the particle size distribution (mean size and fines) of the resulting final blend. A higher amount of fines and a smaller mean particle size promotes compactability.

38.5.3.4 Process Quality Process quality has two measurable quantities, that is, process stability and process repeatability. Process stability is defined as the variance in the metric of interest during a single batch run (within run variability). Process repeatability or capability is defined as the variance in the metric of interest across a study (between run variability), also as the capability of a process to meet its purpose. This analysis can be done on unit operations for which the parameters are not varied, or for upstream operation variables under evaluation.

Process repeatability is a metric for the downstream effect of the roller compaction unit operation. Based on the proposed target core tablet attributes (tablet weight, hardness, and thickness), the process capability indices (*Cp*) [82] were calculated. A *Cp* value of 2 is generally expected for a process under control (6σ).

The *Cp* analysis based on tablet weight showed a compression operation unaffected by the roller compaction settings. Process capability (*Cp*) based on tablet hardness was improved with a decrease in roller gap. A narrower roller gap correlated with a faster mass flow, higher recovery and lower amount of fines. Of these three coincidental facts, mass flow variations would have been reflected in the weight-based *Cp* analysis. In principle, variations in recovery and fines amount affect compactability, and, by reasoning, hardness-based *Cp*.

38.6 SUMMARY

Dry granulation is an effective means of improving the performance of powders. Improvements in flow and compaction for most pharmaceutical applications aid in the filling of capsules, and compression of tablets. Although several methods are available, roller compaction is the predominant method for the production of granules without solvent. The roller compaction unit operation is comprised of several subprocesses. Powder feeding and milling, the first and last of these subprocesses, have large bodies of knowledge which can be adapted to roller compaction. The compaction step itself is of most interest when designing the roller compaction process. Material properties, in-process and final product measurements, and their interaction with the feed rate, roller speed, roller pressure, and gap have been reviewed and examples given for process development and scale-up. This information confirms the utility of roller compaction and provides tools for designing the roller compaction process.

SYMBOLS

B	roller width
Cp	process capability index
D	roller diameter
F	compaction force per unit distance of roller width
M	mass flow (g/s)
G	roller gap
G	gap setting (mm)
h	thickness of compacted ribbon (mm)
K	compactability (SCU/ton)
n	roller speed
P	hydraulic pressure (roller pressure) (bar)
R	apparent ribbon relaxation (%)
S	gap
T	throughput
α	nip angle
χ	position
δ	angle of internal friction
δ_E	effective angle of internal friction
ε	maximum elastic recovery (%)
ϕ, ϕ_w	angle of wall stress
μ	friction coefficient
ϑ	angular roll position
ϑ_h	angular position at which feed pressure is applied
ρ	density
ρ_a	apparent ribbon density (g/mL)
τ	shear stress
υ	acute angle roller tangent to normal stress
ms	mean size
f	amount of fines

REFERENCES

1. Nishii K, Horio M. Dry granulation. In: Salmon AD, Hounslow MJ, Seville JPK,editors. *Granulation*, Vol. 11, Elsevier, Amsterdam, 2007, pp. 289–322.
2. Horio M. Binderless granulation—its potential, achievements and future issues. *Powder Technol.* 2003; 130:1–7.
3. Pietsch W. *Agglomeration in Industry* Volume 1. Wiley-VCH, Weinheim, 2004.
4. Johnson CE. Production of granular products by roll compaction. In: Beestman GB, Vander Hooven DIB, editors. *Pesticide Formulations and Application Systems: Seventh Volume*, ASTM Special Technical Publication 968. American Society for Testing and Materials, Philadelphia, 1987, pp. 199–206.
5. Bakele W. New developments in the production of heavy soda-ash via compacting method. *Powder Technol.* 2003;130: 253–256.
6. Kleinebudde P. Roll compaction/dry granulation: pharmaceutical applications. *Eur. J. Pharmaceut. Biopharmaceut.* 2004;58 (2):317–326.
7. Mouro D, Noack R, Musico B, King H, Shah U. *Enhancement of Xcelodose Capsule-Filling Capabilities Using Roller Compaction*, Pharmaceutical Technology, February 2006. Available at http://license.icopyright.net/3.74587?icx_id=301460 Accessed 2009 April 18
8. Miller RW. Advances in pharmaceutical roller compactor feed system designs. *Pharmaceut. Technol.* 1994; March:154–162.
9. Miller RW. Roller compaction technology. In: Parikh D, editor. *Handbook of Pharmaceutical Granulation Technology*, 2nd edition, Taylor & Francis, New York, 2005, pp. 159–172.
10. Daugherity PD, Chu JH. Investigation of serrated roll surface differences on ribbon thickness during roll compaction. *Pharmaceut. Dev. Technol.* 2007;12:603–608.
11. Rambali B, Baert L, Jans E, Massart DL. Influence of the roll compactor parameter settings and the compression pressure on the buccal bio-adhesive tablet properties. *Int. J. Pharmaceut.* 2001;220:129–140.
12. Pietsch W. Granulate dry particulate solids by compaction and retain key powder particle properties. *Chem. Eng. Prog.* 1997; April:24–46.
13. Guangsheng H, Lingyun W, Zhongwei Z, Guangjie H, Fuhseng P. Manufacturing technique of magnesium alloy sheets by powder rolling. *Mater. Sci. Forum* 2005;488–489:445–448.
14. Bacher C, Olsen PM, Bertelsen P, Sonnergaard JM. Granule fraction inhomogeneity of calcium carbonate/sorbitol in roller compacted granules. *Int. J. Pharmaceut.* 2008;349:19–23.
15. Johanson JR. A rolling theory for granular solids. *Trans. Am. Soc. Mech. Eng.* 1965; December:842–848.
16. Soh JLP, Boersen N, Carvajal TM, Morris KR, Peck GE, Pinal R. Importance of raw material attributes for modeling ribbon and granule properties in roller compaction: multivariate analysis on roll gap and NIR spectral slope as process critical control parameters. *J. Pharmaceut. Innov.* 2007;2:106–124.
17. Soh JLP, Wang F, Boersen N, Pinal R, Peck GE, Carvajal TM, Cheney J, Valthorsson H, Pazdan J. Utility of multivariate analysis in modeling the effects of raw material properties and operating parameters on granule and ribbon properties prepared in roller compaction. *Drug Dev. Ind. Pharmacy* 2008;34: 1022–1035.
18. Sheskey PJ, Dasbach TP. Evaluation of various polymers as dry binders in the preparation of an immediate-release tablet formulation by roller compaction. *Pharmaceut. Technol.* 1995;19 (10):98–112.
19. Falzone AM, Peck GE, McCabe GP. Effects of changes in roller compactor parameters on granulation produced by compaction. *Drug Dev. Ind. Pharmacy* 1992;18:469–489.
20. Inghelbrecht S, Remon JP. Roller compaction and tableting of microcrystalline cellulose/drug mixtures. *Int. J. Pharmaceut.* 1998;161:215–224.

21. Riepma KA, Vromans H, Zuurman K, Lerk CF. The effect of dry granulation on the consolidation and compaction of crystalline lactose. *Int. J. Pharmaceut.* 1993;97:29–38.
22. Inghelbrecht S, Remon JP. The roller compaction of different types of lactose. *J. Int. Pharmaceut.* 1998;166:135–144.
23. Sheskey PJ, Cabelka TD, Robb RT, Boyce BM. Use of roller compaction in the preparation of controlled-release hydrophilic matrix tablets containing methylcellulose and hydroxypropyl methylcellulose polymers. *Pharmaceut. Technol.* 1994;18 (9):132–150.
24. Freitag F, Kleinebudde P. How do roll compaction/dry granulation affect the tableting behavior of inorganic materials? Comparison of four magnesium carbonates. *Eur. J. Pharmaceut. Sci.* 2003;19:281–189.
25. Freitag F, Runge J, Kleinebudde P. Coprocessing of powdered cellulose and magnesium carbonate: direct tableting versus tableting after roll compaction/dry granulation. *Pharmaceut. Dev. Technol.* 2005;10:353–362.
26. Herting MG, Kleinebudde P. Roll compaction/dry granulation: effect of raw material particle size on granule and tablet properties. *Int. J. Pharmacuet.* 2007;338:110–118.
27. Bacher C, Olsen PM, Bertelsen P, Kirstensen J. Sonnergaard JM. Improving the compaction of roller compacted calcium carbonate. *Int. J. Pharmaceut.* 2007;342:115–123.
28. He X, Secreast PJ, Amidon GE. Mechanistic Study of the effect of roller compaction and lubricant on tablet mechanical strength. *J. Pharmaceut. Sci.* 2007;96 (5):1342–1355.
29. Gupta A, Peck GE, Miller RW, Morris KR. Influence of ambient moisture on the compaction behavior of microcrystalline cellulose powder undergoing uni-axial compression and roller compaction: a comparative study using near-infrared spectroscopy. *J. Pharmaceut. Sci.* 2005;94 (10): 2301–2313.
30. Inghelbrecht S, Remon JP. Reducing dust and improving granule and tablet quality in the roller compaction process. *Int. J. Pharmaceut.* 1998;171:195–206.
31. Bultmann JM. Multiple compaction of microcrystalline cellulose in a roller compactor. *Eur. J. Pharmaceut. Biopharmaceut.* 2002;54:59–64.
32. Miguelez-Moran AM, Wu CY, Seville JPK. The effect of lubrication on density distributions on roller compacted ribbons. *Int. J. Pharmaceut.* 2008;362:52–59.
33. Herting MG, Kleinebudde P. Reduction of tensile strength of tablets after roll compaction/dry granulation. *Int. J. Pharmaceut.* 2008;70:372–378.
34. Herting MG, Klose K, Kleinebudde P. Comparison of different dry binders for roll compaction/dry granulation. *Pharmaceut. Dev. Technol.* 2007;12 (5):525–532.
35. Sheskey PJ, Hendren J. The effects of roll compaction equipment variables, granulation technique, and HPMC polymer level on a controlled-release matrix model drug formulation. *Pharmaceut. Technol.* 1999;223:90–106.
36. Weyenberg W, Vermeire A, Vandervoort J, Remon JP, Ludwig A. Effects of roller compaction settings on the preparation of bioadhesive granules and ocular minitablets. *Eur. J. Pharmaceut. Biopharmaceut.* 2005;59:527–536.
37. Farber L, Hapgood KP, Michaels JN, Fu X-Y, Meyer R, Johnson M-A, Li F. Unified compaction curve model for tensile strength of tablets made by roller compaction and direct compression. *Int. J. Pharmaceut.* 2008;346:17–24.
38. Patel C, Kaushal AM, Bansal AK. Compaction behavior of roller compacted ibuprofen. *Eur. J. Pharmaceut. Biopharmaceut.* 2008;69:743–749.
39. Sun CC, Himmilspach MW. Reduced tabletability of roller compacted granules as a result of granule size enlargement. *Int. J. Pharmaceut.* 2006;95:200–206.
40. Malkowska S, Khan KA. Effect of recompression on the properties of tablets prepared by dry granulation. *Drug Dev. Ind. Pharmacy* 1983;9:331–347.
41. Sheskey PJ, Cabelka TD. Re-workability of sustained release tablet formulation containing HPMC polymers. *Pharmaceut. Technol.* 1992;7:60–74.
42. Zinchuk AV, Mullarney MP, Hancock B. Simulation of roller compaction using a laboratory scale compaction simulator. *Int. J. Pharmaceut.* 2004;269:403–415.
43. Miguelez-Moran AM, Wu CY, Dong H, Seville JPK. *Eur. J. Pharmaceut. Biopharmaceut.* 2009;72:173–182.
44. Guigon P, Simon O. Roll press design—influence of force feed systems on compaction. *Powder Technol.* 2003;130:41–48.
45. Funakoshi Y, Asogawa T, Satake E. The use of a novel roller compactor with a concavo-convex roller pair to obtain uniform compacting pressure. *Drug Dev. Ind. Pharmacy* 1977;3 (6): 555–573.
46. Parrott EL. Densification of powders by concavo-convex roller compactor. *J. Pharmaceut. Sci.* 1981;70:288–291.
47. Guigon P, Simon O. Interaction between feeding and compaction during lactose compaction in a laboratory roll press. *KONA* 2000;18:131–138.
48. Zhang JQ, Yan Y. On-line continuous measurement of particle size using electrostatic sensors. *Powder Technol.* 2003;135: 164–168.
49. Frake P, Greenhalg D, Grierson SM, Hempenstall JM, RuddJr., Process control and endpoint determination of a fluid bed granulation by application of near infra-red spectroscopy. *Int. J. Pharmaceut.* 1997;151:75–80.
50. Rantanen J, Yliruusi J. Determination of particle size in a fluidized bed granulator with a near infrared (NIR) set-up. *Pharmaceut. Pharmacol. Commun.* 1998;4:73–75.
51. Gupta A, Peck GE, Miller RW, Morris KR. Nondestructive measurements of the compact strength and the particle-size distribution after milling of roller compacted powders by near-infrared spectroscopy. *J. Pharmaceut. Sci.* 2004;93: 1047–1053.
52. Rantanen J, Rasanen E, Tenhunen J, Kansakoski M, Mannermaa JP, Yliruusi J. In-line moisture measurement during granulation with a four-wavelength near infrared sensor: an evaluation of particle size and binder effects. *Eur. J. Pharmaceut. Biopharmaceut.* 2000;50:271–276.
53. Bordes C, Garcia F, Snabre P, Frances C. On-line characterization of particle size during an ultrafine wet grinding process. *Powder Technol.* 2002;128:218–228.

54. Liao CW, Tarng YS. On-line automatic optical inspection system for coarse particle size distribution. *Powder Technol.* 2009;189:508–513.
55. Sprockel OL, Yang E, Jayawickrama D, Li L. Ultrasound Propagation in Porous Materials, *AIChE Annual Meeting*, 2008, p. 294.
56. Feng T, Feng W, Pinal R, Wassgren C, Carvajal MT. Investigation of the variability of NIR in-line monitoring of roller compaction process by using fast fourier transform (FFT) analysis. *Pharmaceut. Sci. Technol.* 2008;9:419–424.
57. Ghorab MK, Chatlapalli R, Hasan S, Nagi A. Application of thermal effusivity as a process analytical technology tool for monitoring and control of the roller compaction process. *Pharmaceut. Sci. Technol.* 2007;8:1–7.
58. Alexander AW, Muzzio FJ. Batch size increase in dry blending and mixing. In: Levin M,editor. *Pharmaceutical Process Scale Up*, Informa Health Care, New York, 2002, pp. 115–132.
59. Prescott JK. Powder handling. In: Levin M,editor. *Pharmaceutical Process Scale Up*, Informa Health Care, New York, 2002, pp. 133–150.
60. Yang S, Evans JRG. Metering and dispensing of powder; the quest for new solid freeforming techniques. *Powder Technol.* 2007;178:56–72.
61. Sander U, Schonert K. Operation conditions of a screw-feeder-equipped high-pressure roller mill. *Powder Technol.* 1999;105: 282–287.
62. Simon O, Guigon P. Correlation between powder-packing properties and roll press compact heterogeneity. *Powder Technol.* 2003;130:257–264.
63. Lecompte T, Doremus P, Thomas G, Perrier-Camby L, LeThiesse L-C, Masteau J-C, Debove L. Dry granulation of organic powders—dependence of pressure 2D distribution on different process parameters. *Chem. Eng. Sci.* 2005;60: 3933–3940.
64. Podczeck F. *Particle-Particle Adhesion in Pharmaceutical Powder Handling*, Imperial College Press, London, 1998.
65. Bindhumadhavan G, Seville JPK, Adams MJ, Greenwood RW, Fitzpatrick S. Roll compaction of a pharmaceutical excipient: experimental validation of rolling theory for granular solids. *Chem. Eng. Sci.* 2005;60:3891–3897.
66. Yusof YA, Smith AC, Briscoe BJ. Roll compaction of maize powder. *Chem. Eng. Sci.* 2005;60:3919–3931.
67. Sommer K, Hauser G. Flow and compression properties of feed solids for roll-type presses and extrusion presses. *Powder Technol.* 2003; 272–276.
68. Schonert K, Sander U. Shear stresses and material slip in high pressure roller mills. *Powder Technol.* 2002;122:136–144.
69. Yehia KA. Estimation of roll press design parameters based on the assessment of a particular nip region. *Powder Technol.* 2007;177:148–153.
70. Dec RT, Zavaliangos A, Cunningham JC. Comparison of various modeling methods for analysis of powder compaction in roller press. *Powder Technol.* 2003;130:265–271.
71. Hervieu P, Dehont F, Jerome E, Delacourte A, Guyot JC. Granulation of pharmaceutical powders by compaction an experimental study. *Drug Dev. Ind. Pharmacy* 1994;20 (1): 65–74.
72. am Ende MT, Moses SK, Carella AJ, Gadkari RA, Graul TW, Otano AL, Timpano RJ. Improving the content uniformity of a low-dose tablet formulation through roller compaction optimization. *Pharmaceut. Dev. Technol.* 2007;12:391–404.
73. Rekhi GS, Sidwell R. Sizing of granulation. In: Parikh D,editor. *Handbook of Pharmaceutical Granulation Technology*, 2nd edition, Taylor & Francis, New York, 2005, pp. 159–172.
74. Hein S, Picker-Freyer KM, Langridge J. Simulation of roller compaction with subsequent tableting and characterization of lactose and microcrystalline cellulose. *Pharmaceut. Dev. Technol.* 2008;13:523–532.
75. Inghelbrecht S, Remon J-P, Fernandes de Aguiar P, Walczak B, Luc Massart D, Van De Velde F, De Baets P, Vermeersch H, DeBacker P. Instrumentation of a roll compactor and the evaluation of the parameter setting by neural networks. *Int. J. Pharmaceut.* 1997;148:103–115.
76. Turkoglu M, Aydin I, Murray M, Sakr A. Modeling of a roller-compaction process using neural networks and genetic algorithms. *Eur. J. Pharmaceut. Biopharmaceut.* 1999;48: 239–245.
77. Mansa RF, Bridson RH, Greenwood RW, Barker H, Seville JPK. Using intelligent software to predict the effects of formulation and processing parameters on roller compaction. *Powder Technol.* 2008;181:217–225.
78. Campbell GM, Bunn PJ, Webb C, Hook SCW. On predicting roller milling performance: Part II. The breakage function. *Powder Technol.* 2001;115:243–255.
79. Morrison RD, Shi F, Whyte R. Modeling of incremental rock breakage by impact—for use in DEM models. *Miner. Eng.* 2007;20:303–309.
80. Kochhar SK, Rubinstein MH, Barnes D. The effects of slugging and recompression on pharmaceutical excipients. *Int. J. Pharmaceut.* 1995;115:35–43.
81. Adolfsson A, Nyström C. Tablet strength, porosity, elasticity and solid state structure of tablets compressed at high loads, *Int. J. Pharmaceut.* 1996;132:95–106.
82. *NIST/Semateche-Handbook of Statistical Methods,* http://www.itl.nist.gov/div898/handbook, accessed November 1 2009.