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RESEARCH ARTICLE

An investigation into the impact of magnesium stearate on powder feeding during roller compaction

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Abstract

A systematic evaluation on the effect of magnesium stearate on the transmission of a placebo formulation from the hopper to the rolls during screw fed roller compaction has been carried out. It is demonstrated that, for a system with two 'knurled' rollers, addition of 0.5% w/w magnesium stearate can lead to a significant increase in ribbon mass throughput, with a consequential increase in roll gap, compared to an unlubricated formulation (manufactured at equivalent process conditions). However, this effect is reduced if one of the rollers is smooth. Roller compaction of a lubricated formulation using two smooth rollers was found to be ineffective due to a reduction in friction at the powder/roll interface, i.e. powder was not drawn through the rollers leading to a blockage in the feeding system. An increase in ribbon mass throughput could also be achieved if the equipment surfaces were pre-lubricated. However this increase was found to be temporary suggesting that the residual magnesium stearate layer was removed from the equipment surfaces. Powder sticking to the equipment surfaces, which is common during pharmaceutical manufacturing, was prevented if magnesium stearate was present either in the blend, or at the roll surface. It is further demonstrated that the influence of the hopper stirrer, which is primarily used to prevent bridge formation in the hopper and help draw powder more evenly into the auger chamber, can lead to further mixing of the formulation, and could therefore affect a change in the lubricity of the carefully blended input material.

Keywords: Roller compaction, lubrication, magnesium stearate, powder flow

Introduction

Roller compaction is a dry granulation method in which a powder blend is compacted between two counter rotating rolls forming a ribbon compact, which is subsequently milled into granules of a desired size range. Unlike wet granulation, roll compaction does not require the use of a liquid binder and thus it is suitable for actives that are sensitive to moisture; additionally since there is no need for a drying stage, it is also more suitable for actives that are sensitive to heat,[1] whilst frictional affects will generate heat during roller compaction, the heating is less prolonged.

A typical roller compactor consists of a feeding system, either gravity fed or force fed, which can be mounted horizontally, vertically or at an incline. The purpose of the feeding system is to transfer powder blend from the hopper to the rolls. An additional function of the screw feeder is the removal of air and pre-densification of the powder blend; this can be assisted by the use of vacuum de-aeration.

Due to the resistance to volume decrease during compression, the powder forces the rolls to move apart. Roll separation is opposed by the application of a hydraulic force on the rollers. The steady-state roll gap (at a fixed roll speed) is an equilibrium between the amount of powder being fed to the rolls, i.e. feed auger rotational speed, and the hydraulic force applied to the rolls.

The roll compaction process is usually split into three distinct zones[2,3]:

(i) The slip region, where the rolls move faster than the powder and hence relative slip occurs; in this zone the pressure is relatively low and hence densification of the powder blend is due to particle rearrangement.

(ii) The nip region, where the powder is 'gripped' by the roll surface and drawn in between the rolls; as the

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powder is forced into a smaller volume the pressure greatly increases causing particle deformation and/or fracture, a compact is formed as particle bonding occurs.

(iii) The release region, where the ribbon slips on the roll surface causing it to accelerate as it is released from the rolls;[4] the pressure rapidly reduces and porosity expansion occurs due to elastic recovery.

Maximum compression during roll compaction occurs prior to the minimum roll gap and is usually referred to as the neutral angle. The nip angle (α), defined with reference to the neutral angle is the transition between the slip region and the nip region and is the point at which compaction begins.[5] Figure 1 shows a schematic representation of the roll compaction process, denoting the various regions and angles.

Lubricants, usually magnesium stearate, are added to granules prior to tabletting, in order to reduce friction at the die-walls, minimize wear on the tooling, prevent picking of tablets and to reduce the ejection force and scrape-off force.[6] Magnesium stearate is also frequently added to powder blends prior to roll compaction; however, this is an empirical process and is frequently based on a formulators experience rather than a mechanistic understanding. The reduction in friction that is evident from the addition of lubricants may not be advantageous during roll compaction as friction between the powder and the roll surface is necessary to enable powder to be drawn-in to the rolls. In addition to this, magnesium stearate has a number of adverse effects on the final quality of the tablet. Magnesium stearate is hydrophobic in nature and hence disintegration time of tablets is increased,[7,8] and tablet strength is reduced due to decreased bonding between particles.[9–13]

Mechanism of lubrication

Magnesium stearate has a number of hydrate forms; commercially available magnesium stearate will typically consist of the dihydrate form or a mixture of mono-, di-, and trihydrates, with various compositions of amorphous and crystalline materials.[6] Lack of strict control over material properties can cause problems with variability, particularly from one vendor to another.[14] Magnesium stearate is often envisaged as a 'deck of cards', with a remarkably low resistance to shear stress hence the mechanism of magnesium stearate mixing is usually referred to as the stack of cards theory.[15] The mixing process is considered to occur as a two step process. Initially magnesium stearate adheres to the surface of the excipient particles forming a uniform surface-adsorbed film similar to a Langmuir-type adsorption. During prolonged mixing the magnesium stearate 'spreads' over the surface of the particles due to delamination and deagglomeration of the primary magnesium

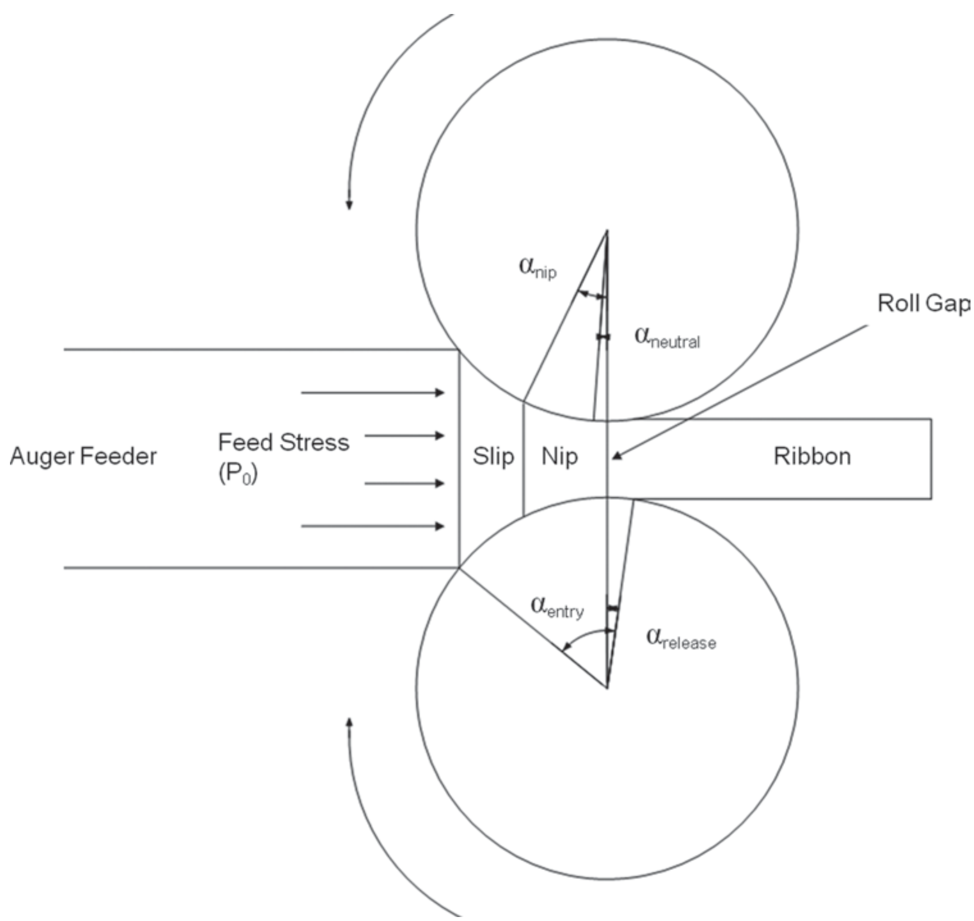

Figure 1. Schematic representation of the various regions of a roll compactor ($\alpha_{neutral}$ is the neutral angle, α_{nip} is the nip angle, α_{entry} is the entry angle and $\alpha_{release}$ is the release angle).

stearate particles. Once the magnesium stearate exists as individual 'cards' it is unable to spread over the surface further. The two stage process of lubricant mixing is supported experimentally by several authors.[7,15–17] Reduction in tablet hardness was found to follow two first-order processes; an initial rapid reduction in tablet hardness with increased mixing time, representing the initial introduction of magnesium stearate to the particle surface, followed by a slow decline in tablet hardness caused by spreading of the lubricant upon the surface. Tablet hardness eventually reaches a plateau at which point the magnesium stearate is considered to exist as individual 'cards' and no further spreading is possible. Similar trends have been observed for tablet dissolution and in-die ejection force with respect to magnesium stearate mixing time. Ragnarsson et al.,[18] found that it was possible to achieve good lubrication even when the lubricant is poorly distributed within a formulation. As such, the typical strategy employed during lubrication of pharmaceutical formulations is to blend the formulation to homogeneity prior to addition of the lubricant. Subsequently, upon the addition of the lubricant, a formulation is mixed for a small number of revolutions such that the lubricant is non-homogeneously distributed in order to maximise the beneficial attributes afforded by the presence of magnesium stearate within the formulation whilst attempting to minimise the adverse effects. As suggested by Kushner and Moore,[16] two zones can be identified during the mixing of a lubricant:

(1) A highly sensitive domain at the beginning where the extent of lubrication and product quality attributes can change significantly due to a small change in processing conditions.

(2) A domain where extent of lubrication and product quality attributes is affected only by a significant change in processing conditions.

Manufacturing of pharmaceutical formulations is typically conducted within the highly sensitive zone and as such additional mixing during downstream processes, which is often overlooked, could potentially have an impact on the overall product quality.

Most of the literature investigating the effects of magnesium stearate during roller compaction is limited to studying the effects on roll compacted ribbons and re-compressibility of the subsequent granules (e.g.[9,10,19–21]). However, only a handful of researchers have attempted to elucidate how magnesium stearate actually affects the feeding system of the roll compaction process. Miguelez-Moran et al.[22] found that without the addition of a lubricant the flow of microcrystalline cellulose (MCC) into a gravity fed roll compactor was slower at the equipment surface than at the centre, leading to ribbon compacts with loosely compacted edges. However, with the addition of magnesium stearate the flow of MCC into the roll compactor was more homogenous leading to ribbons with less variation in density. In a later study[23] they used X-ray tomography to characterize the density distribution of roll compacted ribbons which confirmed the effects of magnesium stearate on density distributions of roll compacted ribbons.

Figure 2 depicts the feeding system of the Alexanderwerk WP 120. The powder formulation is introduced into the feed hopper, which incorporates a hopper stirrer located at the bottom of the hopper which is used to prevent powder bridge formation and to ensure a consistent flow of powder into the feed auger chamber. Powder is transported forward by the action of the feed auger chamber to the nip region where it is drawn in between the rolls and compressed into a ribbon compact. The inclusion of the hopper stirrer will create a region of localised mixing which could theoretically impact the lubricity of a formulation.

One could suggest that due to its friction lowering properties, the addition of magnesium stearate prior to roller compaction is liable to increase slip at the roll surface. As a consequence, the nip angle would be expected to reduce, resulting in an undesirable decrease in both dwell time and maximum pressure between the rolls.[22] On the contrary, the reduction in friction at the cheek plate surface can be advantageous as seen from previous studies[22,23] given that flow is less impeded at the wall surface, resulting in a more homogenous density distribution along the width of the ribbon. Synonymous to tablet press surfaces, roll surfaces exhibit powder sticking in the absence of magnesium stearate.[1] However, due to the non-homogenous distribution of magnesium stearate throughout a powder blend, variability in the final blend could become a problem. Additionally further mixing during downstream processes could increase the lubricity of the formulation. Whilst in theory the presence of magnesium stearate could be beneficial during

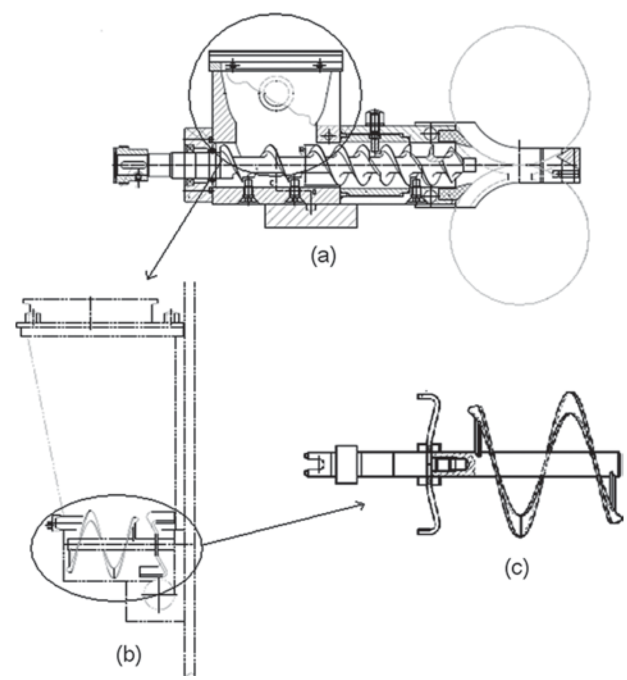

Figure 2. Schematic representation of the feeding system of the Alexanderwerk WP120 roller compactor (a) whole feeding system; (b) hopper; and (c) hopper stirrer.

roll compaction, there are a number of potential adverse effects, such as reducing the nip angle hence dwell time and limiting powder draw through the rollers.

The present study attempts to investigate the role of magnesium stearate during roll compaction. It involves a systematic evaluation of the behaviour of an unlubricated and lubricated placebo formulation during roller compaction. Particular attention will also be focused towards assessing the potential for further magnesium stearate mixing within the feed systems. This paper is focused on the events that occur prior to the actual compaction process, consequently characterization of ribbons and the subsequent granules is not considered.

Materials and methods

Materials

The placebo formulation consisted of microcrystalline cellulose (Avicel PH102) (batch numbers; P207818801, P208820081 and P209820621) and croscarmellose sodium (Ac-Di-Sol) (batch numbers; TN07818216 and 0E58972) both from FMC, Ireland; lactose anhydrous (batch numbers; 1320002859, 1320002502 and 1320009142) and lactose monohydrate (batch number 8507032861) (both from Kerry Bioscience, Norwich, NY); and magnesium stearate (batch number J11627) (Mallinckrodt Inc., Phillipsberg, NJ). Materials were screened prior to blending using a 1000 μm screen for microcrystalline cellulose, lactose anhydrous/monohydrate and croscarmellose sodium; magnesium stearate was pre-screened using a 500 μm screen.

Formulations

The composition of the formulations used is given in Table 1. Croscarmellose sodium was added to the formulations to represent a model disintegrant and was fixed at a representative concentration of 5% w/w.[14] Microcrystalline cellulose and lactose anhydrous were used as model binders and kept at a constant ratio of 3:2 microcrystalline cellulose:lactose anhydrous. As such the total mass of croscarmellose sodium was the same in both formulations (5% w/w), whilst the mass of microcrystalline cellulose and lactose anhydrous was reduced (maintaining the same ratio) to keep a total batch size of 2500 g following addition of magnesium stearate. Studies have shown that magnesium stearate (vegetal) acquired from Mallinckrodt is probably a dihydrate or a mixture of hydrates.'[24]

Blending

Blending was performed using a tumble blender (GEA Process Engineering Inc, Copenhagen, Denmark) with a 10 l intermediate bulk container (IBC). The unlubricated formulation was blended for 10 min at 15 rpm (150 revolutions) with all excipients except magnesium stearate added. The lubricated formulation was then blended for a further 7 min at 15 rpm (105 revolutions) after the addition of magnesium stearate.

Methods

True density

The true density of the powder blend (for each formulation) was determined using helium pycnometry (AccuPyc II 1340, Micromeritics Instrument Co., Norcross, GA). Samples were dried at 50°C for at least 12 h prior to analysis. Calibration of the AccuPyc was performed using two standard stainless steel balls of known mass and volume (Micromeritics Instrument Co.).

Roller compaction

Roller compaction was performed using an Alexanderwerk WP120 roller compactor (Alexanderwerk, Remscheid, Germany), which has a horizontal force fed screw feeder and vertically aligned rollers (using both knurled and smooth roll surfaces). The stages of roller compaction and the process routes for unlubricated and lubricated formulations are given in Figure 3.

The initial experiment was designed to obtain ribbons of varying porosity by altering the processing conditions. This was achieved by determining the minimum hydraulic pressure required to maintain a roll gap of 2.2 mm at a range of auger feeder rotational speeds for an unlubricated placebo formulation; the parameters are shown in Table 2. Vacuum deaeration was not used in this study. These process conditions were then repeated for a lubricated placebo formulation. In order

Table 1. Quantities of excipients used for each formulation on weight basis (%w/w).

Excipient	Unlubricated	Lubricated
Microcrystalline cellulose	57.00%	56.70%
Lactose Anhydrous	38.00%	37.80%
Croscarmellose sodium	5.00%	5.00%
Magnesium stearate	—	0.50%
Total	2500.00 g	2500.00 g

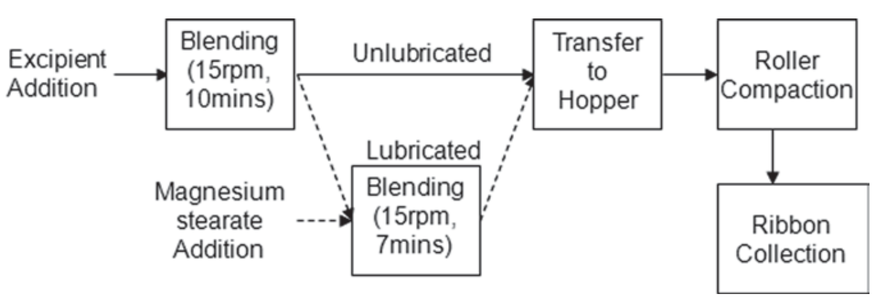

Figure 3. Flow diagram showing the stages of roller compaction and the process routes for the unlubricated and lubricated formulations.

Table 2. Roller compaction parameter settings for unlubricated formulation.

Screw speed (rpm)	Roll gap (mm)	Hydraulic pressure (bar)	Roll speed (rpm)
25	2.2	45	3.4
30	2.2	60	3.4
32	2.2	80	3.4
34	2.2	110	3.4
45	2.2	200	3.4

to monitor batch-to-batch variability, each condition was repeated six times.

Ribbon throughput

For each condition the roller compactor was considered to be operating under steady state conditions once the roll gap remained constant for at least 1 min. Ribbons were then collected for 1 min and the mass, M_{ribbon} (g), was measured using an analytical balance (Sartorious AG, Goettingen, Germany). In order to nullify the effect of mill retention time, the milling section was dismantled and thus ribbon was collected instead of granule.

In-Gap ribbon porosity

In-Gap ribbon porosity was calculated using a method described by Gamble et al.[25] Briefly; the volume of ribbon (in-die), V_{ribbon} (cm^3), produced in 1 min is theoretically determined using Equation 1:

$$V_{\text{ribbon}} = (\pi . d_r . w_r . v_r . S . t) + V_k \quad (1)$$

Where; d_r is the roll diameter (cm); w_r is the width of the rolls (cm), v_r is the roll speed (rpm), S is the roll separation (cm), t is the production time (minutes) and V_k (cm^3) is a correction factor to account for the volume of material within the knurling. In-gap ribbon density, $\rho_{\text{ribbon(in-gap)}}$ (g/cm^3), is then calculated using Equation 2:

$$\rho_{\text{ribbon(in-gap)}} = \frac{M_{\text{ribbon}}}{V_{\text{ribbon}}} \quad (2)$$

Ribbon true density, ρ_{true}, is measured using helium pycnometry therefore the in-gap ribbon porosity, $\varepsilon_{\text{ribbon}}$, can be calculated using Equation 3:

$$\varepsilon_{\text{ribbon}} = \left(1 - \frac{\rho_{\text{ribbon(in-gap)}}}{\rho_{\text{true}}}\right) \times 100\% \quad (3)$$

Near-infrared imaging

Near infrared (NIR) chemical imaging data was collected using a Sapphire® NIR chemical imaging system and processed using ISys® software (Malvern, Worcestershire, UK). Calibration scanning was conducted prior to data collection by first performing a background scan using a highly reflective white ceramic surface, followed by a dark scan using a mirrored surface. Spectra was taken between 1400 and 2400 nm with a 10 nm step size, and 16 co-adds. Analysis of the data was performed using a partial least squares (PLS) model based on 4 principle components.

Near-infrared spectroscopy

Diffuse reflection spectra were taken directly from the surface of the samples. NIR spectra were measured on an FT-NIR spectrometer (Thermo Antaris, Madison, WI). Diffuse reflection spectra using the integrating sphere were recorded from 1100–2300 nm using 64 scans at 8 cm^{-1} resolution.

Results and discussion

Roller compacted ribbons, produced with both lubricated (0.5% w/w magnesium stearate) and unlubricated placebo formulations, were manufactured at a range of solid fractions (0.7-0.95), as described previously, to assess the impact of the lubricant on the powder transmission. A comparison between the mass throughput (○,□) and corresponding roll gap (■,•) for the unlubricated (○,•) and lubricated (□,■) formulations is given in Figure 4. The results indicate that for a given set of conditions (auger speed and hydraulic roll pressure), the addition of magnesium stearate led to an increase in the mass throughput of material, which, since the in-gap porosity remained constant, is directly related to an increase in the roll gap. The mass throughput was seen to increase by ~80–90% due to the inclusion of 0.5% w/w magnesium stearate to the blend. Correspondingly, the original roll gap for the unlubricated blend was maintained at a constant 2.2 mm, however, the inclusion of 0.5% w/w magnesium stearate led to the roll gap increasing to a range between 3.8 and 4.5 mm. The in-gap ribbon porosity as calculated using the method outlined remained constant for a given set of conditions (i.e. hydraulic pressure and screw speed), between unlubricated and lubricated ribbons. As expected, ribbons manufactured using higher pressure and screw speed demonstrated a reduction in in-gap ribbon porosity.

An explanation of how magnesium stearate has led to this increased throughput requires an understanding of each section of the blend transmission through the roller compactor, namely: (a) hopper (and hopper stirrer), (b) feed auger and pre-nip chamber (including the cheek plates), and (c) roll surface.

Hopper

Transmission of powder through hopper

Flow from hoppers can often lead to variations in throughput, particularly for poor flowing or cohesive powders, due to issues such as bridging or funnel flow.[26] In order to investigate the effects of hopper discharge into the feed auger the roll compactor was operated without the rolls in place. A comparison between the hopper emptying of unlubricated and lubricated placebo blends indicated that presence of magnesium stearate resulted in minimal differences. The throughput was slightly increased for the lubricated blend (roughly a 9% increase in mass

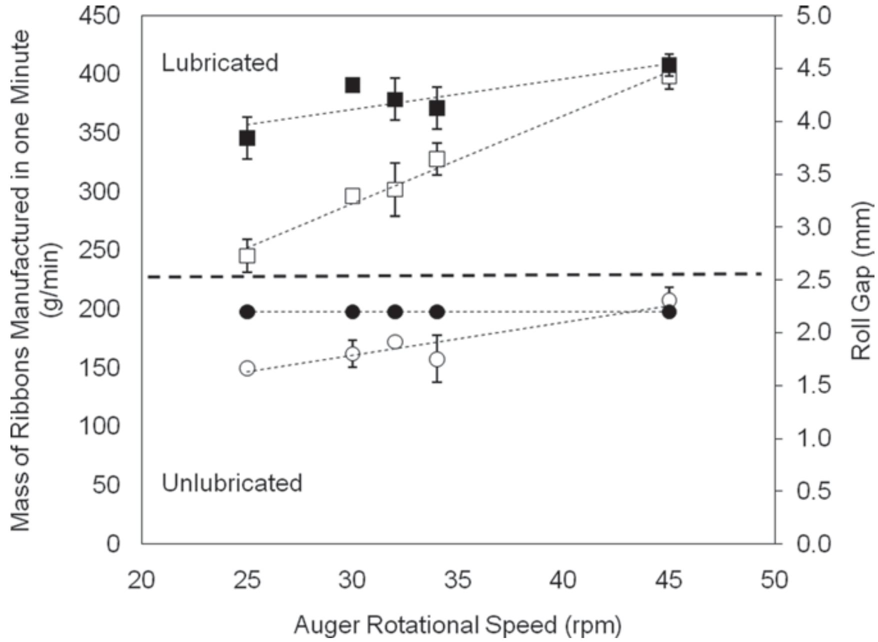

Figure 4. Comparison of mass throughput; unlubricated R2 = 0.87 (○), lubricated R2 = 0.99 (□), and roll gap; unlubricated R2 = 1.00 (●), lubricated R2 = 0.70 (■), for a given set of conditions (auger speed and hydraulic roll pressure).

throughput) but not to the same extent as when the rolls were in place (roughly an 80–90% increase in mass throughput). This lack of difference could be due to the action of the hopper stirrer which both disrupts bridge formation and helps draw the powder into the auger feed chamber.

The obvious limitation of this experiment is that there is no generation of back pressure resulting from the restriction to flow of powder into the pre-nip area by the rolls. The presence of back pressure leads to consolidation of the powder blend within the pre-nip area and hence an increase in the powder bed density. This in turn would be expected to result in an increase in the internal wall friction within the pre-nip area thus impacting the forward momentum of the powder bed. In this situation we may expect the presence of a lubricant to have an impact on the throughput, i.e. lubricated powder would exhibit lower frictional affects at the cheek plate surface and hence flow would be less restricted at the wall surface as found previously[22] leading to increased throughput through the roller compactor.

Mixing within the hopper

The action of the hopper stirrer may change the effect that the magnesium stearate has on the powder blend and hence the final properties of the ribbons and tablets. The effect of mixing time and its potential to cause over-lubrication are well characterized in the literature.[7,17,18] As mixing time increases, the negative effects of lubrication on granule compactability, such as reduced tensile strength,[10–13] are exacerbated. As such, the mixing of magnesium stearate is often carefully controlled to prevent over-lubrication. Despite this, further lubrication due to downstream processing is often over-looked. In an attempt to understand the degree of mixing inside the hopper, a 500 g layer of lubricated placebo blend was poured over a 500 g layer of unlubricated placebo blend within the hopper. The experiment was also done in reverse with lubricated blend transitioning to the unlubricated blend during the run. In the absence of mixing in the hopper one would expect a distinct shift in the throughput and roll gap as the two powders transition, i.e. for the case of lubricated powder on top of unlubricated powder one would expect the roll gap to increase from 2.2 mm to around 4 mm as the lubricated blend starts to pass through.

The data (Figure 5) shows that the roll gap for the unlubricated to lubricated formulation (□) starts at 2.5 mm but after 30–60 s increases to 3.8 mm and stays constant for the remainder of the experiment; the gap does reduce to ~3.4 mm at the end of the run but this is attributed to the low hopper fill which also leads to less powder being transmitted through the auger feeder. For the lubricated to unlubricated condition (○) the roll gap begins at 3.6 mm and after 210 s had reduced to 3.4 mm. Neither condition led to the same roll gap obtained for the lubricated control (■), but both had significantly larger roll gaps than the unlubricated control (•). This would suggest that mixing is occurring during powder conveyance from the hopper to the rollers, causing a dilution of magnesium stearate throughout the blend. This mixing, or the presence of magnesium stearate within the feed system, leads to the initially unlubricated blend behaving more like lubricated material.

In order to investigate the exact location of this mixing, a band of lactose monohydrate was sandwiched between layers of the placebo blend containing lactose anhydrous. Near infra red imaging (NIR) was used to monitor the presence of the two lactose species, which can be differentiated due to the presence of a water band

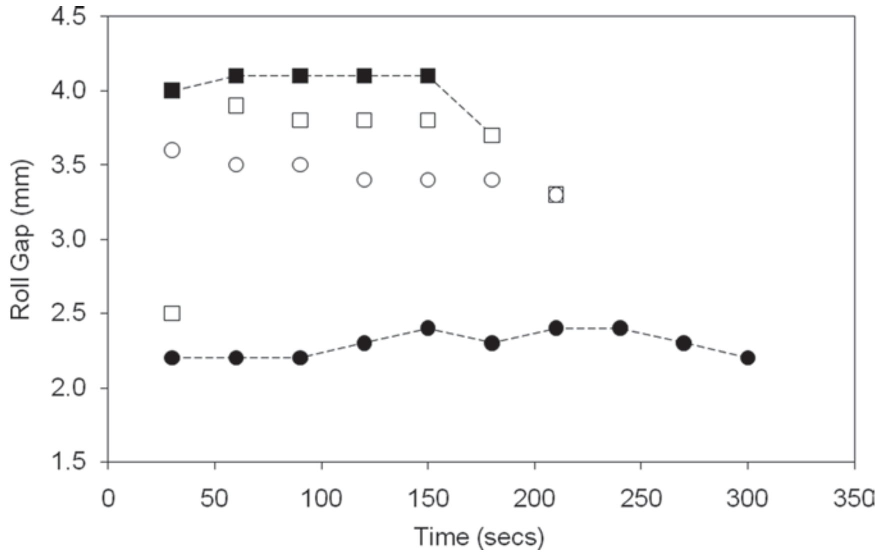

Figure 5. Change in roll gap over time, (1) unlubricated control (●); (2) lubricated control (■); (3) unlubricated – lubricated (□), and; (4) lubricated – unlubricated (○). (Process conditions; auger speed = 30 rpm, roll speed = 3.4 rpm and hydraulic roll pressure = 60 bar).

at around the 1900–1940 nm wavelengths in the monohydrate species. Three conditions were investigated;

Condition 1—a band of lactose monohydrate in the hopper above the stirrer (to investigate the occurrence of mixing in the hopper).

Condition 2—a band of lactose monohydrate in the hopper with the stirrer removed (to investigate the occurrence of mixing during the transmission from the hopper into the auger chamber).

Condition 3—a band of lactose monohydrate in the auger chamber below the stirrer (to investigate the occurrence of mixing within the auger chamber).

Figure 6 shows that when the lactose monohydrate is introduced above the hopper stirrer (a) it becomes mixed within the powder blend and there is no distinct transition from purely lactose anhydrous to lactose monohydrate. When the stirrer is removed (b), or the lactose monohydrate plug is located within the auger chamber (c), there is an absence of mixing between the lactose anhydrous and lactose monohydrate; as such the lactose monohydrate is seen to come out as a discrete band (although a degree of dilution is observed in condition b).

As previously discussed, the manufacture of pharmaceutical products is conducted in the highly sensitive zone for lubricant mixing. This means that product quality attributes can change significantly due to small changes in processing conditions.[16] As such the additional mixing that occurs within the feeding system is likely to alter the distribution of magnesium stearate throughout the blend and on the surfaces of the excipient particles. The consequence of this mixing is such that when the blend reaches the nip region it may have different properties to when it was first added to the feed hopper. This effect is likely to be intensified at large scale; whilst residence time may decrease due to increased mass throughput, due to the inclusion of a dual auger feeding system the intensity of mixing will increase, as suggested by Kushner and Moore[16] magnesium stearate mixing does not only depend upon the time of mixing but other processing conditions as well, i.e. mixing intensity. As such, two ribbons made from identical blends with equivalent solid fractions could exhibit different ribbon / granule properties (i.e. tensile strength, granule tablettability) depending on the degree of additional mixing within the feed system. This mechanism for potential further lubrication within the feeding system has previously been overlooked when modelling roller compaction using a compaction simulator. This method involves comparing the properties, i.e. tensile strength and granule size distribution, of ribbons with equivalent solid fractions produced from roller compaction and compaction simulators.[19,27]

Feed auger and pre-nip chamber

In order to investigate the effects of wall friction within the feeding chamber, roller compaction of an unlubricated formulation was performed using pre-lubricated equipment surfaces. To achieve this, a lubricated formulation was first passed through the roller compactor. The system was then emptied of any loose powder, but the instrument surfaces were not thoroughly cleaned in order to ensure that any residual magnesium stearate adhered to the walls remained. A Near infrared spectrum of magnesium stearate has characteristic peaks at 4325 and 4254 cm^{-1}. The presence of 0.5% w/w magnesium stearate within the formulation was identified by the observation of these peaks in the NIR spectrum of the blend. Analysis of the near infrared spectra acquired from the equipment surfaces (i.e. roll surface and cheek plate surface), following the lubricated run, showed that the material adhered to the equipment surfaces was consistent with that of the formulation composition including magnesium stearate. As a control 1000 g of unlubricated (•) and 1000 g of lubricated formulation (▪) were roller compacted using the following process conditions; auger speed 30 rpm, roll speed 3.4 rpm and hydraulic roll pressure 60 bar. The change in roll gap was

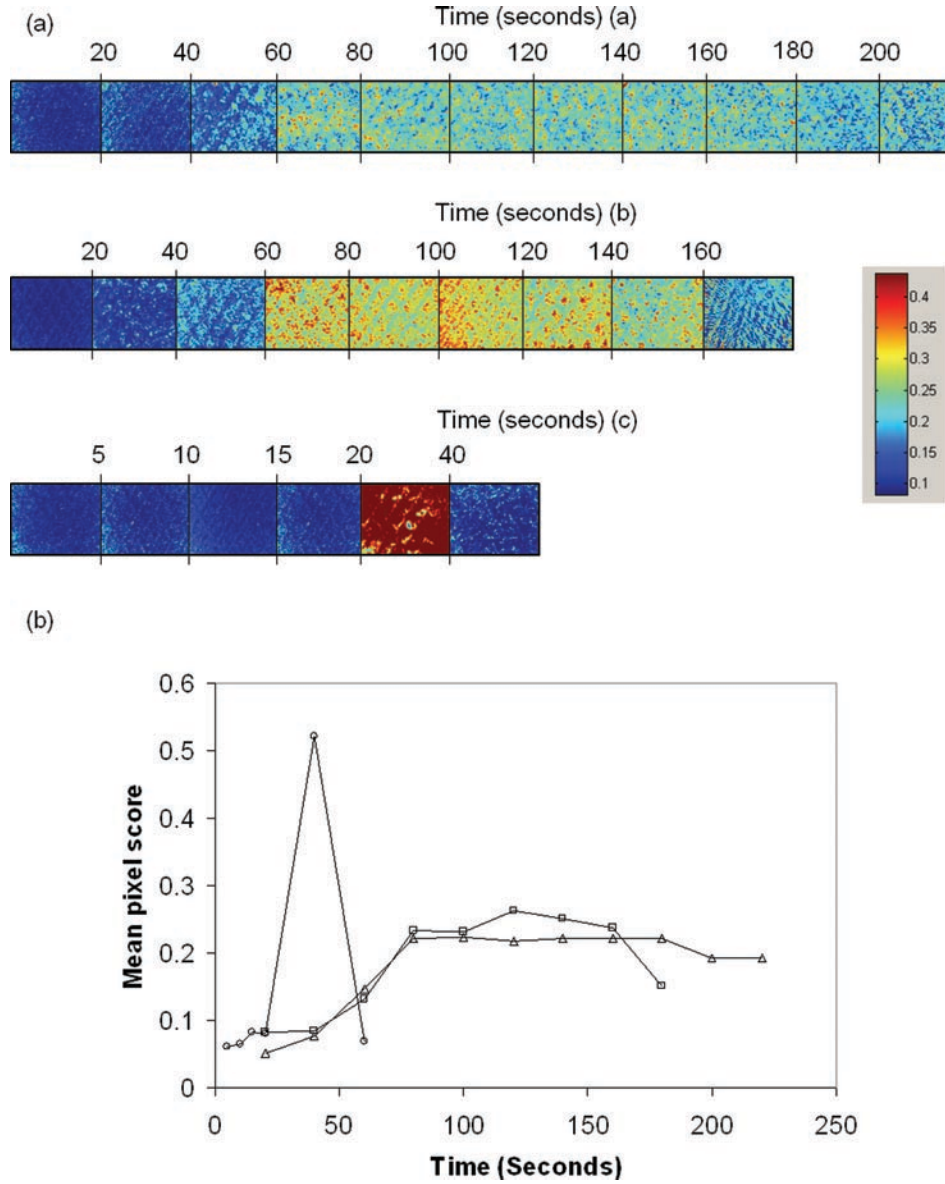

Figure 6. (6a) NIR images of pieces of ribbon representing the presence of lactose monohydrate for (a) condition 1; (b) condition 2, and; (c) condition 3 (6b) Graphical representation of mean pixel score (higher score represents larger proportion of lactose monohydrate present) from NIR image analysis. Condition 1 (Δ); condition 2 (□); condition 3 (○).

monitored every 30 s, until the all formulation was used (results shown in Figure 7). To determine the effect of the presence of lubrication at the equipment surface-powder interface, 1000 g of unlubricated powder blend was compacted using pre-lubricated equipment. The results (Figure 7—fully lubricated equipment surfaces—□, lubricated feeding system with clean rollers—○) indicated that the conveyance of the unlubricated blend is equivalent to that of the lubricated material, both in terms of mass throughput and corresponding roll gap, indicating that the effect of magnesium stearate on powder throughput is dependent upon its presence at the equipment surface. However, the effects were only temporary as the roll gap reduced to 2.5 mm after 180 s suggesting that the residual coating of magnesium stearate on the equipment surface was removed as the process continued. The results would however appear to indicate that the level of magnesium stearate required to achieve the more favourable flow behaviour within the roller compaction process could be significantly lower than the 0.5% used in the formulation, thus providing a potential means to minimise the detrimental impacts of the lubricant whilst retaining the beneficial ones.

The increase in the powder transmission observed for the lubricated material can be rationalised thus; the powder-wall friction dynamics within feed auger system can be described as two counter-opposing mechanisms. The reduction in friction due to the presence of magnesium stearate can be thought to lead to less efficient transmission due to reduced friction at the powder-auger interface, since the auger will glide more easily through the powder blend; alternatively the reduction in friction occurring at the powder/chamber wall interface would lead to more efficient powder transmission. The balance

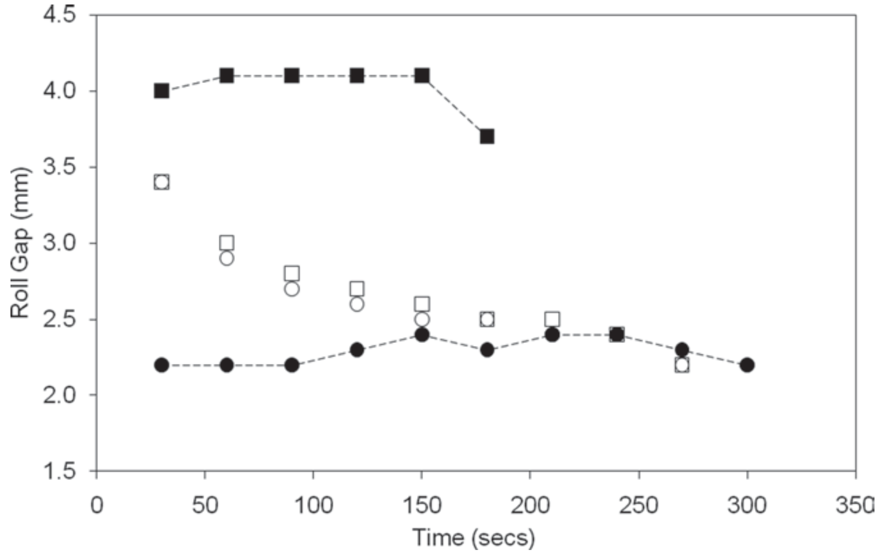

Figure 7. Change in roll gap over time for an unlubricated placebo blend using pre-lubricated equipment surfaces; (1) unlubricated control (●); (2) lubricated control (■); (3) unlubricated placebo blend with fully lubricated equipment surfaces (□), and; (4) unlubricated placebo blend with lubricated feeding system but clean rollers (○). (Process conditions; auger speed = 30 rpm, roll speed = 3.4 rpm and hydraulic roll pressure = 60 bar).

between these two opposing mechanisms will control the powder transmission rate through the auger; however, it would be logical to assume that as powder blend within the feed auger becomes more densely packed then the reduction in the friction at the auger chamber wall would become the more important factor.

Reduced magnesium stearate level

In order to investigate if a reduced level of lubricant would still deliver the positive powder flow attributes, the level of magnesium stearate was decreased 10-fold to 0.05% w/w and the blending time was increased to 60 min at 15 rpm (900 revolutions) to ensure homogeneous distribution of the lubricant. Furthermore, as the magnesium stearate surface coverage is limited by the amount available rather than the mixing conditions, the formulation should be less sensitive to any additional uncontrolled mixing that occurs within the feeding system of the roller compactor. Additionally, if blending a smaller amount of magnesium stearate to homogeneity is a viable option, it eliminates the need for a two step blending process, i.e. magnesium stearate can be added during the first blending stage. This would afford both a reduction in processing time and potentially a more practical approach toward continuous manufacturing. Roller compaction was performed using the conditions outlined previously. The results (Figure 8) indicated that even at very low lubricant levels an increase in mass throughput is still observed.

Roll surface

As previously discussed, the anti-frictional effects of magnesium stearate could be deleterious to the efficiency of roller compaction as it prevents the powder from being 'gripped' at the roll surface and thus could impede the draw of blend into the compaction zone. Knurled roll surfaces are typically used to increase friction at the powder/roll surface interface. A comparison of the roller compaction behaviour of unlubricated and lubricated formulations was performed using varied roll surface configurations, namely knurled-knurled, knurled (bottom roller)—smooth (top roller) and smooth-smooth. Roll surface configuration was found to have no significant impact on the roller compaction of the unlubricated formulation in terms of mass throughput and roll gap. However, for the lubricated formulation replacing one of the knurled rollers with a smooth roller led to a reduction in mass throughput and corresponding roll gap, and for one set of conditions (hydraulic roll pressure 200 bar, auger speed 45 rpm and roll speed 3.4 rpm) roller compaction was not possible. More-over, replacing both knurled rollers with smooth rollers caused powder to build up in the pre-nip region which was not drawn into the rolls resulting in a blockage in the feed system. These results confirm that the presence of magnesium stearate in the formulation leads to a reduction in friction at the roll surface; as the degree of mechanically induced friction is reduced, i.e. by changing knurled rollers for smooth rollers, less powder is 'gripped' at the roll surface when magnesium stearate is present in the formulation. Additionally the bulk powder at the surface of the rolls comes into contact with the powder trapped within the knurling of the roll surface, which even when lubricated has more surface roughness than the smooth roll surfaces, hence providing even more friction with which to draw powder. As a result of this reduction in friction between the powder and roll surface the nip angle will be reduced leading to less material being drawn through the rolls, and when the roll surfaces are entirely smooth the level

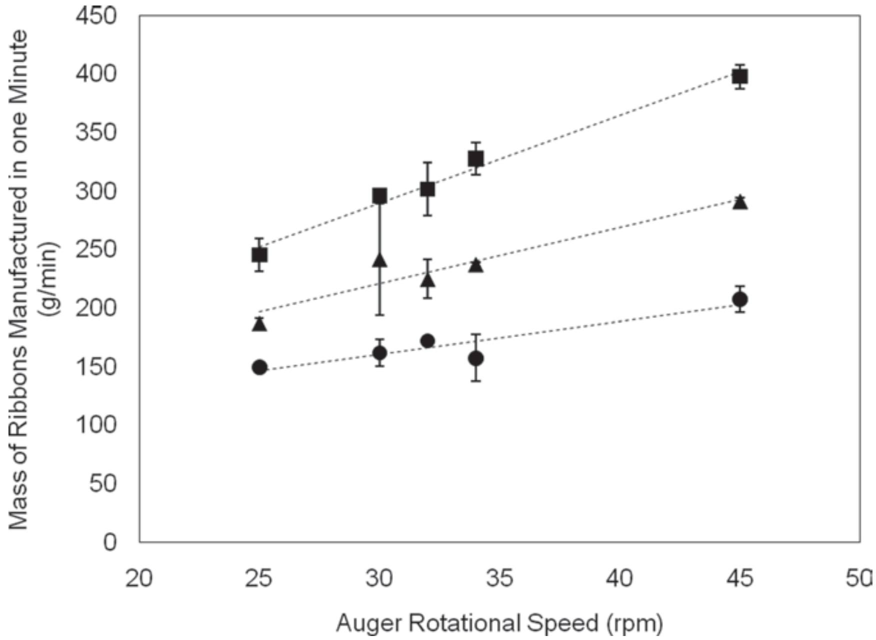

Figure 8. Comparison of mass throughput for unlubricated R2 = 0.87 (●), 0.5 % w/w lubricated R2 = 0.99 (■), and 0.05 % w/w lubricated R2 = 0.90 (▲), for a given set of conditions (auger speed and hydraulic roll pressure).

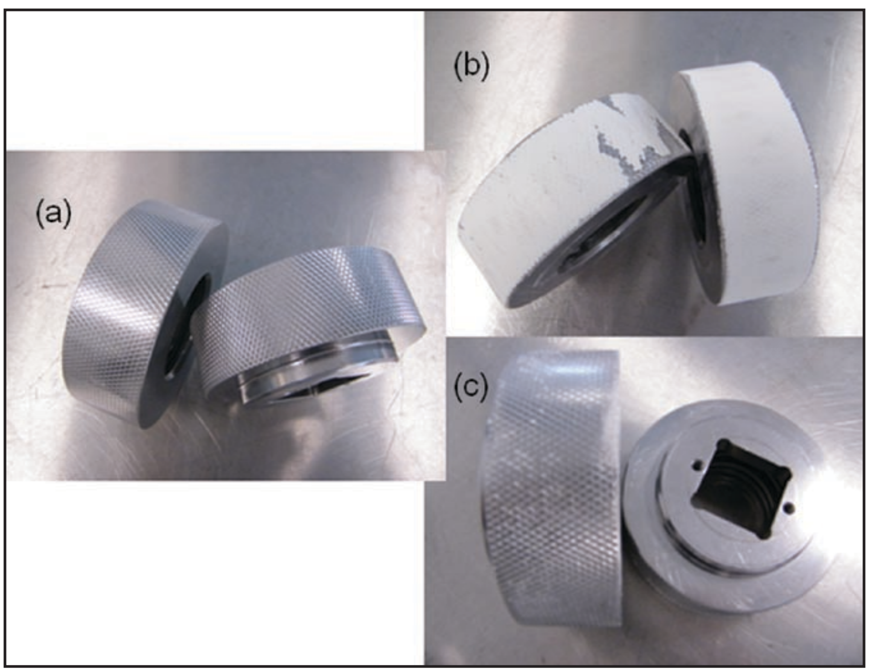

Figure 9. Effect of addition of magnesium stearate on powder sticking to rollers, (a) clean roller; (b) after RC of a powder blend without magnesium stearate, and; (c) after RC of a powder blend with 0.5% w/w magnesium stearate.

of friction at the roll surface/powder interface is insufficient to draw the lubricated blend into the roll gap.

In the absence of magnesium stearate sticking of the powder to the roll surfaces is a problem as shown in Figure 9. In such a case the condition of slip is likely to be governed by frictional affects between the adhered powder layer on the roll and powder present in the slip region, as opposed to the roll surface and the powder present in the slip region. Powder adhered to the roll surface is likely to cause problems when operating the roller compactor in an automated roll gap control mode. Roll gap control uses a set-point for the minimum roll separation; any deviation from this set point will cause an automatic adjustment of the auger feeder rotational speed, such that the roll separation returns to its original set-point. A layer of powder adhered to the surface of the roll will cause the roll gap to open wider, as such the auger rotational speed will automatically reduce to maintain the roll gap at the set-point. The extent of auger rotational speed reduction, and hence mass throughput, will depend on the thickness of the adhered powder layer. Additionally powder adhered to the roll surface will undergo multiple compaction cycles which could in turn affect the properties of the final granule.[28] In the unlubricated roller compaction experiments, roll sticking occurred shortly after the start-up (ca. 30–60 s), whilst sticking was not observed during roller compaction of formulations containing magnesium stearate (both 0.5 and 0.05% w/w). When the roll surface was pre-lubricated, sticking of the unlubricated blend was not observed until later in the run (ca. 180 s). Clearly, magnesium stearate is important in preventing adherence of powder to the roll surface.

Conclusions

The addition of magnesium stearate as a lubricant was observed to increase the throughput of material through the roller compactor, which lead to a subsequent increase in roll gap when knurled roll surfaces were used. Conversely, if two smooth rollers were used then the condition of friction at the roll/powder interface was insufficient to allow the powder to be gripped at the roll surface and hence drawn through the rollers. This caused powder to build up in the pre-nip region and ultimately a blockage within the feeding system. The effect of the magnesium stearate on powder conveyance was reproduced using unlubricated powder when the equipment surfaces were pre-lubricated. This demonstrates that the mechanism of this increase in powder transmission was due to the presence of the lubricant on instrument surfaces within the feed system, even at very low levels, which led to a reduction in frictional forces. This finding could indicate that the level of magnesium stearate within a blend could be significantly reduced, reducing the detrimental impacts of magnesium stearate on granule compactability, whilst maintaining the beneficial impact on the blend conveyance.

It was also found that mixing occurs within the feed system of the roller compactor, leading to the possibility of further, uncontrolled lubrication of the blend. This potential to cause over-lubrication of a powder blend could provide a challenge when attempting to scale up the process.

The observations from this study imply that presence of magnesium stearate can be beneficial during roller compaction. However, the feeding mechanism is likely to alter the distribution of magnesium stearate throughout the blend and upon the surfaces of the excipient particles.

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