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Improving liquid distribution by reducing dimensionless spray flux in wet granulation—A pharmaceutical manufacturing case study

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ABSTRACT

Controlling liquid distribution in a wet granulation process is critical to maintaining control of both nucleation and growth, as highly saturated patches created by uneven liquid distribution will have a much higher growth rate and may form large "balls". The size of these balls depends on the granulator scale, but in full-scale pharmaceutical manufacturing these lumps are commonly 2–3 cm in diameter, but may even be larger. The presence of a significant quantity of "balls" frequently results in downstream problems in drying, milling, compression and final product attributes.

This paper presents a case study of attempting to improve the liquid distribution during manufacturing of an existing wet-granulated product with a long history of "balls". The flowrate and spray area of the original nozzle were measured, and a simple estimation of the drop size was obtained by a high-speed photograph and image analysis. The powder surface velocity in a 400L Diosna was measured using a high-speed camera and a simple image analysis technique for several batches using different lots of the drug. Since the manufacturing process was validated and filed, the simplest process change that could be made to attempt to reduce the spray flux and improve liquid distribution was to find a new nozzle. A new nozzle was selected and implemented in a full-scale production batch and the results are compared with the original nozzle conditions. Reducing spray flux by changing the nozzle actually increased ball formation, contrary to what was expected. For products in the growth and/or induction regimes, increasing the efficiency of liquid distribution may mean that less total liquid is required to be added to achieve the same extent of granulation. Improving liquid distribution without also reducing the total volume will result in a shorter induction period and/or a higher growth rate and larger granule size. The study found that the major contribution to batch-to-batch variation in spray flux was the large variations in powder surface velocity for each batch, which is presumably caused by changes in the physical properties of each lot of drug. This has not been reported previously and has important implications for understanding the causes of variability in liquid distribution and granule/ball size in full-scale production of wet-granulated pharmaceutical products.

1. Introduction

Granulation is a processing technique commonly used in the pharmaceutical industry to creating porous, free-flowing granules from a mixture of dry powders. During wet granulation, all the dry powder ingredients – the drug and typically 3–8 other excipients – are mixed vigorously while a granulating fluid is added, which may be water or a volatile but non-toxic solvent, such as ethanol or isopropanol, or a mixture. These solvents can be used directly as a granulation liquid or as a delivery agent for a polymeric binder. Binders are a polymeric excipient used to ensure that the particles are still being held together after being dried and commonly come in several grades of varying molecular weights and physical properties.

The granulating liquid is typically sprayed onto to moving powder bed, provided that the fluid is not too viscous. This liquid will be gradually dispersed by wetting and capillary action combined with mechanical agitation from the impeller. The particles will then bond to each other either due to being immersed in a drop, or as a result of the distributed liquid films creating bridges between the particles. In either case, a distribution of nuclei granules will be created – this stage is called wetting and nucleation [1]. The granulation mechanism will then follow by consolidation and growth where the granules are colliding with each others, or with other powders, to form bigger granules [1]. The last stage is attrition and breakage. At this stage, the gran-

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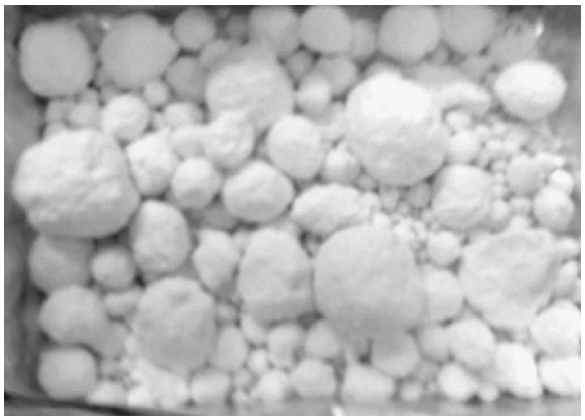

Fig. 1. Example of lumps or balls in a wet-granulated product (prior to milling). The largest balls are approx 2.5 cm in diameter.

ules break due to impact, wear or compaction in the granulator [1].

In current industrial practice, the granule is not directly controlled. Instead, the manufacturing proceeds according to a set batch "recipe", which commonly sets the total liquid quantity to be added, the liquid addition time (i.e. spray rate) and the impeller speed. There may also be an extra period of mixing after the end of the liquid addition step, which is often referred to as "wet massing". During product development, the granulation recipe is set to provide a process which is as robust as possible. However, it is common on scale-up, or over time during the 10–50-year life of a product, for the process conditions to drift, due to cumulative small changes in equipment (nozzles, pumps, excipient suppliers and grades) and/or variations are the physio-chemical properties of the incoming drug. This latter problem has become more prevalent recently, as the need to reduce manufacturing costs often requires that alternate cheaper sources of a drug be used. It is impossible to completely specify all of the properties of a powder and eliminate all variation, even if all the required properties were known. Although rarely seen in development, all full-scale pharmaceutical manufacturing sites struggle with batch-to-batch variation in raw materials, unit operation performance and subsequently the product performance. Most manufacturing sites have one variable product, and these products often (but not always) have relatively high drug loads. Since there is no on-line, real time control of granule size during manufacture, operators often find that the batch contains three broad types of granules – fine particles (say <100 μm), small to medium granules (100 μm to 1 mm) and "lumps" or "balls". The size of these balls depends on the granulator scale, but in full-scale pharmaceutical manufacturing these lumps are commonly 2–3 cm in diameter, and may be even be larger (see Fig. 1).

Lumps or balls are undesirable, and cause multiple downstream processing problems can arise. During pharmaceutical manufacturing of a wet-granulated product, the wet granules are dried in a fluidised bed and then passed through a size-selective mill. The drying time is proportional to granule size, and the large lumps are difficult to dry and make it difficult to accurately determine the average moisture content of the batch. Even when the moisture content is low enough to seem "dry" and the drying operation is ended, the large 0.5–1 in. balls often have dry exteriors surrounding a wet centre.

After drying, the granules are milled in a size-selective mill. A screen retains the granules in the milling chamber, where a high-speed impeller is rotating. Granules smaller than the screen hole size (around 0.5–1 mm) pass quickly through with little comminution, while larger granules are held in the milling chamber and subjected to impact and shearing from the impeller blades, until they are small enough to pass through the screen holes and exit the milling chamber. If there are too many large balls which need substantial milling, the milling chamber can become clogged or blocked, and heat build-up can adversely affect the product stability. The large balls experience substantial attrition, which generates new fine particles in the product, effectively "undoing" some of the granulation process. The milled granule flow and ability to form strong tablets are both adversely affected by fine particles. In addition, if the balls contain a wet centre, the moisture is released during milling and can smear the inside of the mill, or re-humidify the entire batch.

Once a batch is in process, there is currently no way to correct or adjust the processing conditions to fix these problems. The only place where adjustments can be made is during tablet compression, where the fine and/or damp powder results in variable tablet weights due to inconsistent flow and variations in tablet hardness and thickness data due to the small particle size or moist patches. Often these issues can be overcome by adjusting the compression force or slowing down the press, but at the very least this represents reduced manufacturing efficiency due to lost time and product while troubleshooting to find a new set of successful tabletting conditions. Ultimately, the failure to reach the specified tablet hardness or thickness may result in batch rejection, which is extremely expensive.

Clearly, it is desirable to minimise the presence of large lumps or balls in a wet-granulated product. There are two main ways that these large balls are thought to form during granulation:

1. Rapid formation and growth of granules due to the presence of highly saturated regions of powder within the granulator (i.e. wet patches).
2. Rapid uncontrolled coalescence of granules, often in the induction growth regime [2]. At the onset of growth, the granule porosity is at a minimum and the granule saturation reaches a maximum, producing surface-wet granules. The tendency for induction behaviour is set by the formulation and the process conditions affecting granule consolidation.

This paper summarises an industrial case study focusing on the first mechanism, where wet patches form large, wet nuclei which then grow rapidly due to their higher saturation. Controlling liquid distribution in a wet granulation process is beneficial to maintaining control of both nucleation and growth, as highly saturated patches created by uneven liquid distribution will have a much higher growth rate and form large balls. After a brief review of the literature on spray flux and liquid distribution, we present a real industrial case study calculating the dimensionless spray flux and using this information to improve the liquid distribution by selecting a new nozzle. The case study was performed on an existing wet-granulated product with a long history of "balls" and unwanted variation in granulation and tabletting performance.

2. Literature review

Liquid distribution during the nucleation stage of granulation can be described by the dimensionless spray flux parameter, Ψ_a, which is a measure of the drop density in the spray zone [3], and is calculated using the following formula:

$$\Psi_a = \frac{3\dot{V}}{2d_d v w} \quad (1)$$

where $\dot{V}$ is the volumetric flow rate (m^3/s); d_d is the drop size of the spray (m); v is the powder surface velocity beneath the nozzle (m/s); w is the width of the spray (90° to powder flow direction) (m).

Spray flux directly impacts the size and shape of the nuclei size distribution at nucleation stage and has been validated in several studies [3–7]. When Ψ_a is lower than 0.1, the nucleation in the drop controlled regime. In this regime, one drop of binding solution forms one nucleus. If the drop size distribution is narrow, the granule size distribution will also be narrow. At higher Ψ_a (>1.0), the drop of the binding solution will overlap each other and produce a broad particle size distribution [8]. It is recommended to have the spray flux value less than 0.1 to maintain a narrow particle distribution. However, it is often difficult to adjust the spray flux to be less than 0.1. Moreover, high-shear wet granulation process at production scale usually has a high spray flux value, well outside the drop controlled regime [5,9]. In general, the spray flux should be as low as possible and the drop penetration time should be as short as possible to maintain the best possible distribution of the binding solution and reduce the amount of the wet lumps formed.

The spray flux value can be decreased by increasing powder surface velocity or by decreasing the volumetric flow rate of the binding solution. However, changing the mixer speed or the powder surface velocity will alter the intensity of the shear force in granulator [9]. On the other hand, decreasing volumetric flow rate of the binding solution can increase the time needed for a full granulation process. Furthermore, changing these two parameters can lead to different kinetics of the granules in the granulation process [9]. Multiple spray nozzles in the granulator could be used to increase the area wetted by the spray drops and result in smaller spray flux value [5,10]. This change will alter only the spray flux and leave powder mixing unchanged. However, this approach may not sufficiently reduce the spray flux value to drop controlled regime [9,10] and may not be practical to implement in a production scale high-shear wet granulation process. In one case study, Plank et al. [9] calculated that 14 nozzles would be needed to reach the drop controlled regime. However, even in the mechanical dispersion regime, a reduction in spray flux is still expected to help improve liquid distribution, if changes to the mechanical mixing are not possible. In pharmaceutical production, the impeller speed, total fluid amount and either the flow rate or the total spray times are usually tightly specified. The only option usually available in a validated process is to use a new nozzle to achieve the best liquid dispersion possible.

Therefore, this project was initiated to develop a method to find all the critical parameters in calculating the dimensionless spray flux Ψ_a: the powder surface velocity, drop size of the spray, spray area, and the binder solution flow rate. The spray pattern of several potential replacement nozzles was characterised, particularly the spray width and drop size. The new nozzle was selected based on the smallest spray flux, with assumption that the binding solution delivery and powder properties do not change from batch to batch. The new nozzle was implemented in a live production batch and the process performance was analysed.

3. Experimental

3.1. Granulation procedure

This study was performed as part of a process improvement campaign for an existing, validated pharmaceutical dispersible product. The granulating step involves adding approximately 80 kg of milled drug X, 8.5 kg microcrystalline cellulose, 4 kg sodium starch glycolate, and 5 kg aluminium magnesium silicate to the P400A Diosna granulator. Fig. 2 shows a SEM image of a historical reference sample of the drug used, showing a mixture of rectangular crystals and agglomerated fines. The Diosna granulator was 108 cm in diameter with a three bladed impeller with reinforcing struts, and a chopper on the sidewall.

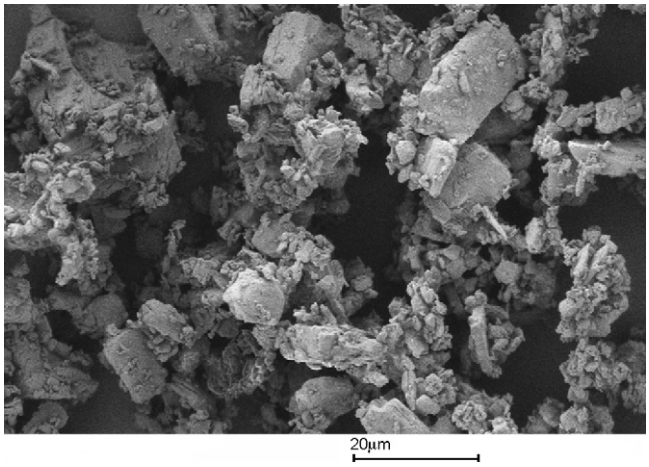

Fig. 2. SEM of a reference sample of the API.

The powders are dry mixed at a low impeller speed of 70 rpm (equivalent tip speed ~4 m/s) before adding the binder solution, a 4% polyvinyl pyrrolidine (K30) solution based on a 50:50 mixture of ethanol and RO water, at 4.1 kg/min. A small amount of blue Indigo Carmine was also added to the binder fluid. The nozzle port was located approximately 90° before the chopper and an observation port-hole was located approximately 45° after the chopper. A positive displacement pump was used to deliver the fluid to the nozzle, which results in some periodic pulsing or surging of the fluid at the nozzle tip as the displacement pump progresses through its cycle. After solution addition is completed, the impeller speed is switched to high speed (140 rpm) and wet massing continues for a further 2 min.

After the new nozzle had been selected, the nozzle was implemented during a trial validation batch. The manufacturing process was identical to the standard process and only the nozzle was changed. The performance of this new process was observed and compared to the performance data prior to the change. Some additional, non-standard measurements, such as recording manual impeller power current, and estimation of the "lumps" or "balls" prior to milling, were also performed.

During the dry mix stage, the powder surface velocity and the bed depth were recorded. The impeller current was manually recorded 30 s intervals throughout the liquid delivery and wet massing steps. At the end of granulation, the granules were discharged and transferred into a fluid bed dryer.

Once dry, the size range and the number of big "lumps" and "balls" produced during the granulation process was estimated before and after the implementation of the new nozzle. This was done during manual vacuum transfer of granules from fluid bed dryer bowl into the cone-mill. The bowl was lowered and an operator used a pneumatic vacuum to manually transfer the bowl contents to the blending bin via the cone-mills. Representative samples of the granules, including lumps, were taken by manually scooping from the Aeromatic bowl approximately every 2 min. Each sample was hand-sieved through a large 2 mm sieve shaker screen and the lumps retained on the screen were photographed using a camera. The sieved granules were placed temporarily in a plastic bucket lined with a clean plastic bag and weighed. The pictures of the large granules retained on the sieve were analysed using ImageJ software to obtain the particle distribution of the lumps. The diameter of the sieve (53.2 cm) was used as the reference scale. The number and area distribution of the granules was calculated by the ImageJ program. Due to restrictions on the camera that could be used in the presence of residual solvent, a lower resolution home camera taped inside a plastic bag was used.

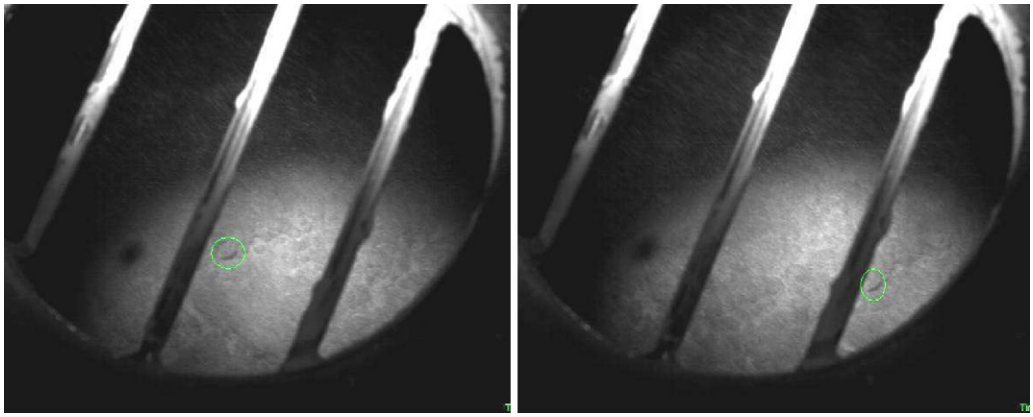

Fig. 3. Example of a feature (circled in green) as it moves across the powder surface used to measure powder surface velocity. Time between initial frame (left) and final frame (right) is 0.086 s.

Any particles smaller than 4 mm in diameter were too small to be measured accurately. This was an acceptable trade-off since this activity was intended to characterise the big lumps, mostly much larger than 4 mm. The amount and size of the "balls" before and after the new nozzle implementation were compared. At the end of the transfer, all sieved granules were put back into batch and transferred into the Comil.

Granule samples were taken before and after the milling process, as well as after the blending process. The milled granules were sieved using a Restch mechanical shaker and 8 sieve trays (850, 500, 355, 250, 150, 75 μm, 45 μm and pan). Sieving was performed on 25 g of each sample for 15 min at an amplitude setting of 10. The sieving data from the batch using the current nozzle was compared to the average sieve data for 6 batches made using the standard nozzle.

3.2. Measurement of surface velocity of the powder

When calculating spray flux, surface velocity is one of the most difficult parameters to estimate. The surface velocity is known to be much lower than the velocity of the impeller blades of the mixer [5,9,11–13]. In addition, surface stagnation can occur, where the powder surface is temporarily stops moving [9]. It is also a strong function of granulator design, loading and scale, and must be measured experimentally using the exact granulator and exact formulation.

Filming of powder surface velocity in the P400A Diosna was performed during dry mixing (prior to granulation solution addition) on three separate batches of the product to observe the variance of the powder surface velocity measured from batch to batch. Each batch contained a mixture of different lots of the drug. A high-speed camera (TroubleShooter by Fastec Imaging), with a wide angle lens was used to film the powder turbulence behaviour through an observation port-hole. The camera was mounted on a tripod which enabled the camera to look downwards through the observation hole. A 1000 W halogen spotlight was used in conjunction with a hand-held mirror to illuminate the interior of the Diosna. A reference shot was taken by placing a clean metal ruler just above the surface powder bed, in view of the camera.

Without changing the position of the camera, the viewing port was opened during the dry mix stage, and approximately 10 s of footage at 500 frames per second were recorded. Due to the very narrow field of view, all observations were approximately at the same radial distance, about halfway from the centre of the mixer. For safety reasons, the granulation solution was kept out of the room during filming to avoid any possible ignition of the ethanol solvent especially due to the heat generated by 1000 W lighting.

The distance between the nozzle tip and the powder bed surface was measured using a clean ruler after the dry mix step was complete. These experiments were performed on the same three batches containing different lots of drug prior to the nozzle change and one batch after the nozzle change.

The short video footage was downloaded and analysed manually using VirtualDubMod, Microsoft Excel and MS Paint software. VirtualDubMod was used to scroll frame-by-frame through the video until a clear feature on the surface of the powder was located. An example of a feature is shown in Fig. 3. Going forward frame-by-frame, the motion of this feature is followed until it disappears from view. The x, y coordinates (in pixels) of this feature was measured using MS Paint, and the start and end frame numbers were recorded.

Using this information, the straight-line velocity and instantaneous velocity were calculated assuming the feature was moving in an arc as illustrated schematically in Fig. 4. Fig. 4 is a physical representation of the powder surface as viewed from above. A feature starts its travel within the Diosna at point 1 and ends at point 2 after n frames. The distance actually travelled by the feature (shown as purple arc line d in Fig. 4) is longer than the straight-line distance between points 1 and 2 (straight green line c). To calculate the actual distance travelled by the feature, the radius of curvature of the arc, b, is calculated:

$$b = \frac{(c/2)^2 + a^2}{2a} \tag{2}$$

The height of the arc, a, was assumed as the midpoint between the start and end point travelled by the feature (point 1 to point 2) for purpose of the calculation. The distance travelled by the granule d is the circumference of this arc, d can then be calculated:

$$d = \left[\frac{2 \times \sin^{-1}((c/2)/b) \times (180/\pi)}{360}\right] \times 2\pi \times b \tag{3}$$

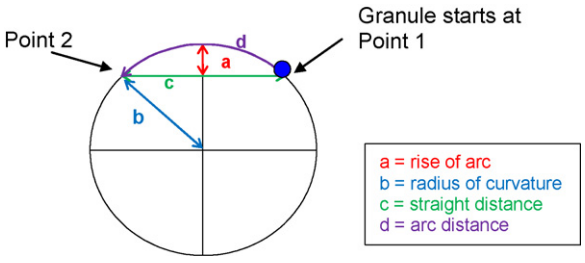

Fig. 4. Overhead view of the powder surface and coordinates showing the initial and final coordinates of a feature used to calculate powder surface velocity.

Table 1
Specifications of nozzles used.

Nozzle	Model number	Current/new
SS40	FullJet B1/2HH-SS40	Current
SS6.5	FullJet B1/4HH-SS6.5	New
SS14W	FullJet wide angle B1/4HH-SS14W	New
SS8W	FullJet wide angle B1/8HH-SS8W	New

The time taken to travel the distance d was calculated by multiplying the number of frames between points 1 and 2 by the frame speed (1/500th of a second). The powder surface velocity v could be found by dividing the arc distance d by the travel time. Features on the powder surface were followed for between 37 and 76 frames, although only one feature was located per batch, due to both the short footage and the relatively long duration each feature could be tracked.

3.3. Characterising the nozzle spray patterns

The spray pattern characterisation was performed while the Diosna P400A was not in production. A compact camera, sealed in a waterproof/sparkproof enclosure, was used to take pictures of the blue coloured ethanol-based binder solution sprayed through the nozzle tip against a contrasting background. Three new proposed nozzles were suggested by a consultant after an observation of the existing granulation process. The four nozzles investigated were listed in Table 1.

The spray pattern produced from current and new nozzles were captured on a camera against a clear and flat background. ImageJ software was used to analyse drop size distribution and spray width. The tip of the nozzle was used as the reference size to obtain the image scale. ImageJ calculates all drop sizes in a two-dimensional view and provided the area of each drop detected. Assuming that all drops are in circular shape, the drop size distribution is calculated. This is clearly a rough estimate of the drop size, as not all the drops can be seen by the camera. Laser diffraction would provide much more accurate drop size information, but was unavailable. We found that this rough method was sufficient for this study. Finally, the spray width of the nozzle was estimated by measuring the spray width at the point where the spray would have hit the powder surface.

The binder flow rate, powder surface velocity, nozzle spray width and drop size results were used to calculate the spray flux Ψ_a using Eq. (1). The calculations were slightly more complicated than anticipated since the calculation is very sensitive to the drop size value used and larger drop sizes result in a smaller calculated spray flux. Therefore, the largest and smallest drop sizes were used to calculate the *range* of spray flux for each nozzle. The new nozzle was chosen based on the smallest *range* of spray flux values and visual observations of nozzle performance.

4. Results

4.1. Measurement of powder surface velocity

Fig. 5 shows the sample frames from these footages. From the visual observation on site and the camera footage, the powder flow regime was in the "bumping" regime [5], as the surface of the powder showed no signs of turbulence or vigorous mixing, apart from dusting for one of the batches. Given the slow powder motion on the surface, the only effective agitation occurring within the mixer is at the base powder bed rather than through all levels of the powder. The lack of turbulence within the powder bed may be an important contributor to poor dispersion of larger size spray drops, causing large snow-ball sized granules to form.

Significant variance in the physio-chemical properties of the raw materials was demonstrated during the dry mix stage. The level of dust generated by the chopper during dry mixing varied significantly (see Fig. 5).

The measured surface velocities for batches 1, 2 and 3 were 0.64, 0.95 and 0.85 m/s, respectively. These velocities are much slower than the impeller tip speed of 4 m/s, supporting previous literature reports. These values are consistent with the range of 0.3–1.1 m/s reported by Plank et al. [9] in a similar sized 300L machine but a completely different formulation. However, the level of variation is significant – the third batch had a 50% higher surface velocity compared to the first batch. Since each batch was mostly composed of the active ingredient, the changes in the powder surface velocity and the level of dust are presumed to be due to changes in the properties of the drug particles, such as bulk density, particle size or moisture content. Unfortunately, these properties were not recorded prior to granulation and due to the mixed lots of drug within each batch, this data could not be reconstructed from quality assurance testing.

4.2. Spray pattern characterisation and nozzle selection

The spray patterns of the four nozzles are shown in Fig. 6 and ImageJ analysis results are summarised in Table 2. The spray pattern produced by the original nozzle SS40 showed an inconsistent spray width and a range of small to large drop sizes. Although well atomised at the highest flowrate of the positive displacement pump cycle (see Fig. 6a), the spray collapsed during the low flow section and dribbled out of the nozzle. The nozzle tip back pressure was found to be zero, which means that the spray pattern could not be maintained at all during the low flow stages of the pump cycle. The spray area produced by the original nozzle was inconsistent with finer drop sizes on the outer edges of the spray and a flow like a running tap in the centre of the spray. The uncontrolled flow pattern in conjunction with the lack of turbulent agitation under the bumping flow observed within the Diosna P400A means that the process would have significant trouble dispersing the liquid though the powder. The large spray drops produced by the current nozzle,

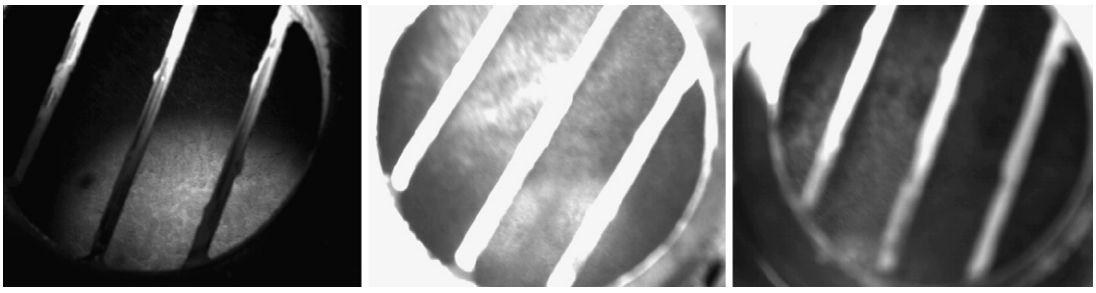

Fig. 5. View through the observation port of three different batches, showing visibly different powder flow and dust levels at identical impeller speed.

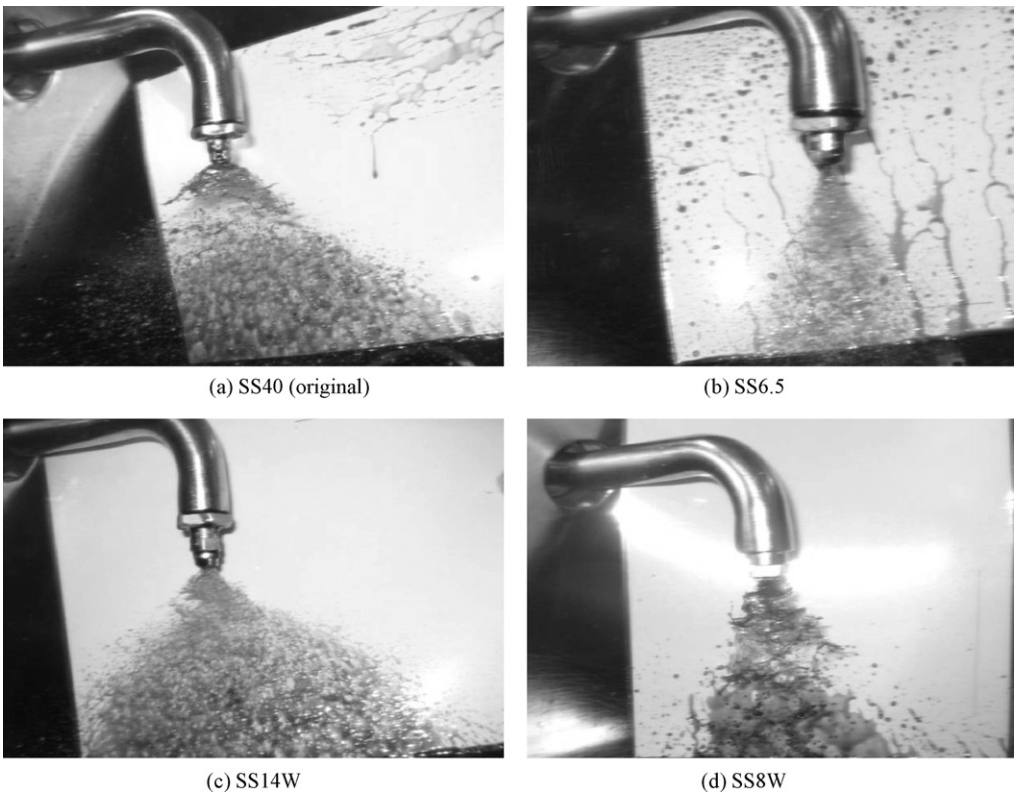

Fig. 6. Spray pattern photos for each of the four nozzles.

Table 2
Spray width and estimated drop size of each nozzle.

Nozzle	Drop size, d_d (mm)			Spray area, w (m)	Nozzle tip back pressure (bar g)
	Min	Max	Std dev		
A. SS40 (original)	0.59	4.72	2.22	0.15–0.2	0
B. SS6.5 (new)	0.592	2.13	0.99	0.1	1.4
C. SS14W (new)	0.592	2.40	1.14	0.26	0.4
D. SS8W (new)	0.564	1.77	0.89	0.25	1.2

especially during the low flow cycle of the pump, could easily have led to the formation of large, wet lumps.

The three proposed new nozzles showed much more consistent spray patterns (see Fig. 6b–d) with a smaller range of drop sizes and a more consistent spray area, due in part to the correct sizing of the nozzle orifice to increase the nozzle tip back pressure and maintain atomisation. Wide angle nozzles C&D had a noticeably larger spray area compared to nozzle number B, but estimated range of drop sizes was very consistent.

The dimensionless spray flux was calculated for each of the three nozzles, using the best and worst case measured powder velocities of 0.64 and 0.95 m/s and a flow rate of 4.1 kg/min (equivalent to 4.36 l/min). The remaining parameters in Eq. (1) are summarised for each nozzle are summarised in Table 2. The minimum and maximum spray flux values, calculated using the largest and smallest drop size, respectively, for each nozzle is reported in Table 3.

The spray flux for the current nozzle was found to be in the range of 0.18–1.92. This indicates that the maximum value of the spray flux falls within the mechanical dispersion regime. According to the spray flux theory and the nucleation regime map, large drops do not necessarily pose a problem for granulation provided that there is sufficient shear to disperse the droplets into the powder. However, from observations during filming of the current product at the current impeller speed, it was apparent that the shear within the Diosna is unlikely to be strong enough to disperse the spray drops and to break up agglomerates. The chopper was able to pro-

Table 3
Spray flux range calculations for each nozzle, based on $v = 0.65$ m/s.

Nozzle	Spray flux, Ψ_a			
	$v = 0.65$ m/s		$v = 0.95$ m/s	
	Max	Min	Max	Min
A. FullJet B1/2HH-SS40 (current)	1.92	0.18	1.29	0.12
B. FullJet B1/4HH-SS6.5 (new)	2.88	0.80	1.94	0.54
C. FullJet Wide Angle B1/4HH-SS14W (new)	1.11	0.27	0.75	0.18
D. FullJet Wide Angle B1/8HH-SS8W (new)	1.21	0.39	0.82	0.26

Fig. 7. Inside of the fluid bed dryer bowl mid-way through the vacuum transfer operation, showing both round balls and irregular lumps.

duce significant turbulence and shear, but only affects a relatively small section of the powder.

Among the three proposed new nozzles, nozzle C shows the smallest range of spray flux, and indicates that nucleation would occur mostly in the intermediate region, which is halfway between drop controlled regime and mechanical dispersion regime. The range of drop sizes of this nozzle is narrower compared to the present nozzle and hence will be better suited for the bumping powder flow conditions. Therefore, spray nozzle C, FullJet Wide Angle B1/4HH-SS14W, was selected as the nozzle for the granulation process.

4.3. Manufacturing experience with the new nozzle

Based on visual observation by the plant operators, the new spray pattern appeared to give a more uniformly dispersed blue colour in the wet-granulated powder, suggesting that the new nozzle was able to more evenly distribute the binder solution within the powder. However, a large number of balls were still observed at the end of the granulation process and during the manual discharge into the fluid bed dryer bowl. The balls appeared to be mostly 2–3 cm in diameter, and operator feedback suggested that there appeared to be more balls present, although they were more uniform in size than usual.

The drying time was approximately 45 min, which was longer than the usual process, although the drying recipe was also modified slightly during the trial and may have also contributed to the longer drying time. Anecdotally, the lumps and balls appeared to have grown in size during drying. Agglomerate formation during drying has recently been demonstrated [14]. A number of irregular shaped lumps were observed which may have been formed during scraping of the granulator bowl, or by compaction of wet material at the base of the dryer during loading. Fig. 7 shows a photo of the inside of the fluid bed dryer bowl mid-way through the transfer operation, showing both round balls and irregular lumps.

After drying was complete, the granules were vacuum transferred into the milling unit. Only a small quantity could be transferred before the dry lumps clogged up the transfer wand. Operators removed the slightly narrower wand end and transferred the granules using the plastic hose directly, although blockages still occurred. The total granule transfer time was three times longer than usual and represented a significant delay in the manufacturing schedule. The blending operation proceeded without incident.

The granules flowed into the inlet of the compression machine and compression was successful on the first day but a small

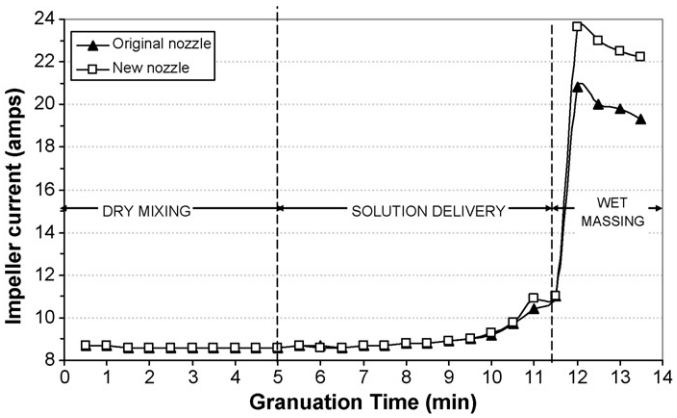

Fig. 8. Impeller current for batches made with the original and new spray nozzle.

equipment problem meant that compression was temporarily halted. When the compression process was eventually restarted approximately 48 h later, the particles did not flow at all into the compression machine as they were compacted into a cake in the blending bin and the vertical plastic connector. The delay in compression could also have allowed moisture released via milling from the wet interior of the "balls" to diffuse through the bed, increasing the overall moisture content and leading to inter-particle bonding and sintering. Alternatively, the heat generated during milling may have caused increased moisture sorption at the granule surface, again leading to inter-particle bonding in the blending bin. The granules were subsequently hand-scooped into the tablet press hopper while compression proceeded at a much lower production rate to compensate for the poor–flow behaviour of the granules. In process testing confirmed that the tablets were well within the weight, thickness and hardness specifications. It is not known whether the compaction of the granules and subsequent flow problems were caused by the process change or the delay in compaction. This extremely poor flow behaviour has happened in past batches with the original nozzle, but was considered unusual.

4.4. Comparison of process performance with new nozzle

4.4.1. Impeller current draw

Fig. 8 shows the current over time trend in for two granulated batches – one batch manufactured with the original nozzle, and the other batch manufactured with the new nozzle. The current reading is stable during the dry mix stage at 70 rpm and begins to climb slowly approximately 2.5 min after the beginning of solution addition. The two batches are almost identical up until the end of the solution delivery. The impeller speed is then switched to high speed (140 rpm) and this causes a sudden spike in the impeller current. The spike is 2–3 A higher for the new nozzle compared to the old, and this current differential is maintained until the end of the granulation process after 13.5 min. The current decreasing current during the wet massing stage might suggest that the process has reached an over-granulated state, where the saturation level is higher than 100% and the excess liquid acting as lubricant in the inter-particle movement [15]. Unfortunately, impeller current is not regularly recorded as part of the normal manufacturing procedure for this product, and no other impeller current data is available for comparison.

4.4.2. Size and extent of "balls"

Samples of the granules were scooped at regular intervals from the fluid bed dryer bowl, during vacuum transfer of the granules to the mill. The total weight of the large lumps and balls separated from the main batch was approximately 4% of the total batch weight

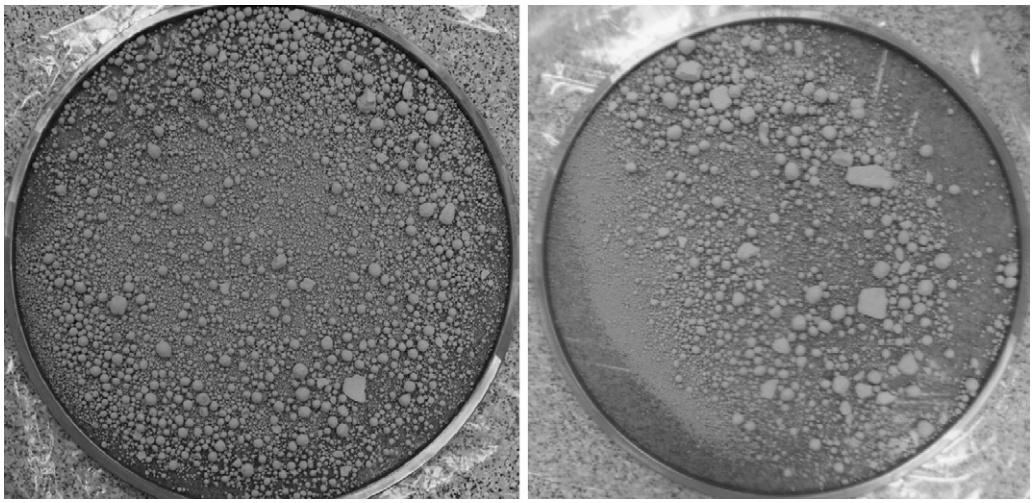

Fig. 9. Unmilled lumps or balls. Left: original nozzle; right: new nozzle. Screen diameter is 53.2 cm.

Table 4
Summary of the unmilled size distribution of large lumps and balls (>2 mm).

Nozzle used	Original	New
Average diameter (cm)	1.130	1.136
Max Diameter (cm)	5.4	4.5
Min Diameter (cm)	0.4	0.8
Total number of particles analysed	1031	1900

for both batches. Since only regular sub-samples were sieved, this means that at least 4% of the granules in both batches were larger than 2 mm. The true fraction of balls was much larger and probably closer to 10%, but hand-sieving 98 kg of granules was impractical in a live production batch. However, the mass data does give us confidence that sampling error had a minimal effect on the estimated size distribution of the lumps as measured by sieve separation and image analysis.

Fig. 9 compares pictures of a sample of sieved lumps for the original nozzle (left) and the new nozzle (right). Eight samples of lumps were photographed and analysed for the batch made with the original nozzle, while eleven images of lumps from the new nozzle batch were analysed. The average diameters of the large granules are summarised in Table 4 and Fig. 10 shows more detailed size distributions calculated by image analysis. For both batches, the image analysis shows that approximately 77% of the balls were between 0.4-2.5 cm. The original nozzle had a further 12% of granules between 2.5–3 cm and approximately 5% of granules were 4–5.5 cm in diameter. In comparison, the batch made with the new nozzle produced fewer granules between 2.5–3 cm and no granule greater than 4.5 cm. However, 17% of granules were sized between 3 and 4.5 cm. Thus the new nozzle had more balls between 1 and 2 in., but fewer really larger ones greater than 2 in., which supported the operators' observation that the new nozzle produced a narrower size range but were overall a bit larger.

The milled and blended granules size distribution data for 6 historical batches was compared with the corresponding size distribution data for the batch made with the new nozzle (see Fig. 11). The size distributions are qualitatively quite similar above approximately 250 μm, although the new nozzle generally produced larger granules. In particular, the new nozzle appears to have produced far more fine granules between 50–100 μm and no granules smaller than 50 μm. This difference in the finest granules has had a strong effect on the d_{10} and d_{50} statistics (refer to Fig. 11). In retrospect, it is possible that the sample from the new nozzle batch suffered from blinding on the 63 μm sieve but this possibility was not noticed at the time.

5. Discussion

The aim of the project was to reduce the level of balls or lumps in a wet-granulated product, as these frequently caused downstream processing issues. Our hypothesis was that the balls were forming due to inadequate liquid dispersion, caused by an underperforming nozzle. The new nozzle was selected to provide both a more consistent spray pattern and the lowest range of spray flux.

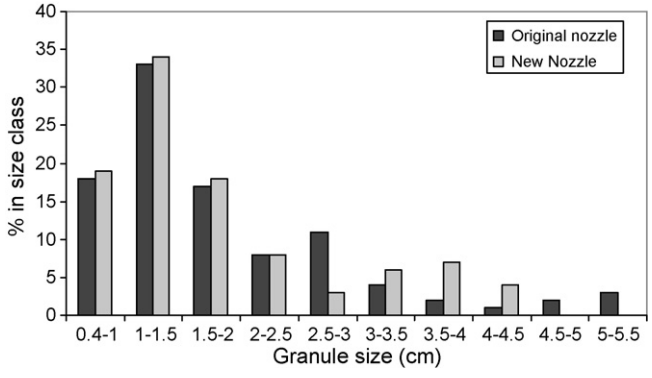

Fig. 10. Size distribution of lumps (granules >2 mm) measured by image analysis.

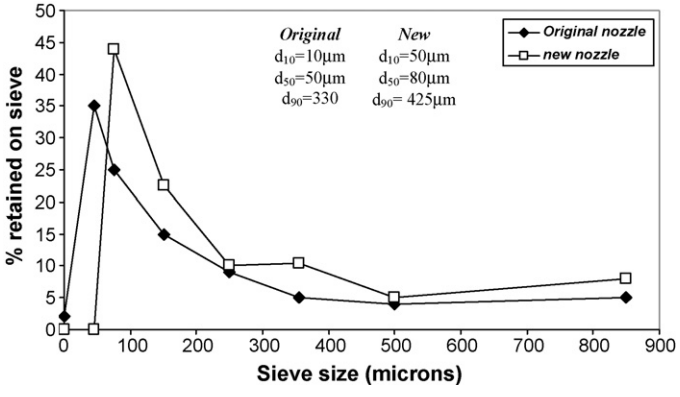

Fig. 11. Comparison of granule size distribution after milling and blending for original (average of $n = 6$) vs. new nozzle ($n = 1$).

However, during the trial batch for the new nozzle, ball formation was unchanged or actually increased, contrary to what was expected. There are three possible reasons for this result:

1. *The balls may be formed by rapid or induction growth of the granules, rather than by local over-wetting during nucleation*. The impeller power current (refer Fig. 8) shows some signs induction growth, as the current readings are flat and steady but begin to climb at the end of the solution delivery step. Unfortunately, the simultaneous increase in impeller speed at the end of solution delivery dominates the data. It is possible that the higher impeller speed and the sudden increase in force applied to the granules could initiate rapid growth of the granules, creating the balls in the final 2 min. However, sampling at the end of liquid addition requires deviating from the standard manufacturing instructions, and therefore was not conducted as part of this study.
2. Increasing the efficiency of liquid distribution may mean that less total liquid is required to be added to achieve the same extent of granulation. When the liquid binder is distributed inefficiently, the liquid is locally concentrated in very wet areas, while other sections of the powder are dry. During product development or transfer, the total amount of liquid is often increased slightly to achieve an acceptable level of granulation of all the powder. If the liquid distribution is suddenly improved and distributed equally, there will be more free fluid available to granulate the powders, and the batch will respond as if "extra" liquid had been added. Typically, for products in the growth regime [2,16], the response would be for the growth rate to increase which results in a larger granules. For products in the induction regime [2], improving liquid distribution without also reducing the total volume will result in a shorter induction period, so that the rapid growth rate will create larger granules at an earlier time that usual. If the granulation process runs for a fixed time, the final granules will be larger.
3. *The lot(s) of drug X used in the new nozzle batch were responsible for the lumps*. This project was performed on a "tricky" product prone to variation and a long history of producing balls during the granulation step. The cause of this variation has long been suspected to be variation in the properties of the drug, although the root-cause has not yet been established. We have shown in this paper that the flow behaviour of the formulation does vary, and the wide variation in surface powder velocity was large enough to be measured. It is possible that had a different lot of drug been selected for the batch, the new nozzle trial might have been successful. It is also possible that if a different lot of drug had been used, the trial would have appeared to be successful even if the nozzle had no effect! This is an occupational hazard of attempting process improvements in the pharmaceutical industry – the products most in need of process improvements are also the products that have the highest risk of batch problems or even failure, independent of the success or failure of the process change.

We are unable to conclusively determine why the improvement in liquid distribution was unsuccessful, and perhaps all three reasons outlined above are responsible. Never the less, we still consider the study to have been successful as we have been able to determine that the *major contribution to batch-to-batch variation is the large variations in powder surface velocity for each batch*. Variations in lot-to-lot powder flow have a direct effect on the spray flux via the powder surface velocity as shown in see Eq. (1). Table 4 shows sample calculations of how a 50% change in powder velocity causes a significant change in the value of spray flux Ψ_a. Thus, controlling the spray conditions alone is not always sufficient for controlling the liquid distribution and spray flux – the strong influence of the powder velocity also needs to be controlled in products where this varies significantly from batch to batch.

In addition to the effect on spray flux and liquid distribution, changes in batch-to-batch powder flow would also have a direct effect on all the other granulation mechanisms: granule growth, consolidation and breakage. Any one of these could change the granulation process outcome and cause large balls to form.

The variation is presumably caused by changes in the physical properties of each lot of drug, but preliminary reviews of the QA data did not reveal anything obvious. However, the manufacturing operators commonly report that different drug lots seem "different" although it is difficult to link these observations to any data. The measurable changes in powder surface velocity are a new discovery and represent an important conclusion from this work.

5.1. Future directions for pharmaceutical manufacturing

This paper has presented case study of attempting to improve the liquid distribution during manufacturing of an existing wet-granulated product with a long history of "ball" formation. Since the manufacturing process was validated and filed, changing the nozzle was the simplest change that could be made with minimal validation and potential regulatory impact. The change was implemented as part of a live trial batch, in a pharmaceutical production environment, and the Good Manufacturing Practice (GMP) regulations were not developed to be compatible with process research. Some compromises were required in the experimental methods (particularly measuring the size of the balls). This meant that the study was not as "neat" as a laboratory-based study, and has raised new questions about the sources of process variation. However, we believe that this paper is still a valuable case study of how advances in our scientific understanding of pharmaceutical processes can be applied to try to improve manufacturing performance. For established products, the permissible process improvements may be limited, but this paper demonstrates that developing stronger scientific knowledge leads towards identifying the root-cause(s) of process variation in each manufactured product.

As a result of this study, GSK Boronia have continued filming of the powder surface velocity of each batch during manufacture, with the intent of building a stronger knowledge of the level of surface velocity variation, and in the longer term attempting to identify the cause of the variation which is currently suspected to be changes in the physical properties of the drug.

The final step of the journey is to either eliminate the variation, or use a science-based rationale to re-engineer the process to be flexible enough to tolerate a wide variety of disturbances. This is the essence of quality by design, and we expect that it will revolutionise the manufacture of pharmaceutical products. For instance, we expect that the process would be more robust if the impeller speed could be adjusted in real time to achieve a pre-specified powder velocity and/or flow regime. This would mean that for some lots of the drug, the impeller would run slightly faster to compensate for the poorer flow properties. This could initially be done by measuring the key physical property (or properties) of the drug prior to the batch starting and setting a new (fixed) the impeller speed for the batch. This would be achievable within the current paradigm of pharmaceutical manufacturing, if the drug properties could be identified. Adding an extra step to the manufacturing process does lengthen the cycle time per batch, but the reduction in processing problems would most likely compensate for this. In the longer term, the powder surface velocity could be measured in real time using video or laser-doppler technology, and the impeller speed continuously adjusted in real time as each batch was processed, without any pre-testing step. The final granule size could be measured online using a FBRM-type laser probe, or a high-speed camera system, and the information could be used to control the amount of liquid

added, the addition rate, and/or the impeller speed to prevent the formation of large balls during granulation. These and other new manufacturing approaches in a similar vein have the potential to greatly reduce production costs and improve manufacturing efficiency, as a truly flexible process would be able to produce saleable product meeting all specifications each and every time, even if the drug supply source was new or changing rapidly based on the most competitive price.

6. Conclusion

A case study of applying dimensionless spray flux theory to improve liquid distribution and eliminate "balls" formation was conducted. The powder surface velocity and nozzle spray patterns were characterised, and a new nozzle was implemented. Reducing spray flux by changing the nozzle actually increased ball formation, contrary to what was expected. For products in the growth and/or induction regimes, increasing the efficiency of liquid distribution may mean that less total liquid is required to be added to achieve the same extent of granulation. A wide variation in surface powder velocity was measured, and this was found to be the major contribution to batch-to-batch variation in spray flux batch. Controlling the spray conditions alone is not always sufficient for controlling the liquid distribution and spray flux – the strong influence of the powder velocity also needs to be controlled in products where this varies significantly from batch to batch.

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