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Layered growth with bottom-spray granulation for spray deposition of drug

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ABSTRACT

The gap in scientific knowledge on bottom-spray fluidized bed granulation has emphasized the need for more studies in this area. This paper comparatively studied the applicability of a modified bottom-spray process and the conventional top-spray process for the spray deposition of a micronized drug during granulation. The differences in circulation pattern, mode of growth and resultant granule properties between the two processes were highlighted. The more ordered and consistent circulation pattern of particles in a bottom-spray fluidized bed was observed to give rise to layered granule growth. This resulted in better drug content uniformity among the granule batches and within a granule batch. The processes' sensitivities to wetting and feed material characteristics were also compared and found to differ markedly. Less robustness to differing process conditions was observed for the top-spray process. The resultant bottom-spray granules formed were observed to be less porous, more spherical and had good flow properties. The bottom-spray technique can thus be potentially applied for the spray deposition of drug during granulation and was observed to be a good alternative to the conventional technique for preparing granules.

1. Introduction

Fluidized bed technology has been widely employed to carry out coating, granulation and drying since its first reported use in the pharmaceutical industry by Wurster (1959). Granulation in the fluidized bed is efficient and convenient (Turton et al., 1999). Typically, the spray nozzle is directed downwards from the top of the product chamber onto the powder bed. This top-spray technique has generally been regarded as the method of choice to carry out granulation, and has been extensively studied over the years (Davies and Gloor, 1971; Lipps and Sakr, 1994; Kokubo and Sunada, 1997; Pont et al., 2001; Rambali et al., 2001; Gao et al., 2002). Fluidized bed granulation can also be carried out using the bottom-spray technique where the spray nozzle is positioned in an upward direction from the base of the product chamber into the powder bed. Even though it has been comparatively much less explored than the top-spray method, there is growing interest in this technique for granule preparation as can be seen from recent studies. For instance, the bottom-spray process was proposed to be capable of offering promising advantages such as good process control, facilitates on-line control of granule size and allows for one step processing of taste masking and controlled release preparations (Shelukar et al., 2005). Rajniak et al. (2007, 2009) examined the impact of binder properties on granule morphology and developed a methodology that combined theoretical and experimental techniques for analyzing the growth of granules. The bottom-spray technique was also studied by Wang et al. (2003), in which granules of good physical properties were obtained under optimized operating conditions that were determined using artificial neural network analysis.

There is a current need for more scientific knowledge to determine the advantages, limitations and potential applications of the bottom-spray technique. Achieving good drug content uniformity in dosage forms containing a low dose drug is a challenge. It would be valuable if a uniform mix of low dose drug with the rest of the excipients is attained during granulation together with the convenience and benefits brought about by particle size enlargement. The granules formed can then be made into tablet dosage forms. In a bottom-spray process, attributing to a highly organized circulation pattern during processing, particles undergo distinct phases of wetting, growth and drying. It was therefore hypothesized that the bottom-spray technique can be applied for precise deposition of a low dose, water insoluble drug (dispersed in the liquid binder) onto feed particles. The widely accepted top-spray fluidized bed granulation (TG) process was used as the standard for comparison in this study with precision granulation (PG), a modified Wurster process (Walter, 2002), for better comprehension of the less explored bottom-spray process. Various spray rates and mean sizes of starting feed material were employed to study the applicability of the processes to different processing conditions. The characteristics of resultant granules were examined as important objectives of granulation also include attaining specific size and shape to improve flow.

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Table 1
Composition of the various powder blends and their physical properties.

Powder blend	Lactose 200M (%, w/w)	Lactose 450M (%, w/w)	Mean particle size (μm)	Angle of repose (°)
1[a]	100	0	39.0 (1.1)	49.5 (1.2)
2	90	10	37.0 (1.1)	52.4 (0.4)
3	80	20	34.2 (0.3)	54.2 (0.5)
4	70	30	33.5 (0.0)	55.1 (0.2)
5	60	40	32.8 (3.7)	56.2 (0.4)
6	50	50	30.3 (1.7)	56.9 (0.5)
7	0	100	24.7 (0.4)	60.2 (0.4)

[a] Formulation used unless otherwise stated; values in parentheses denote standard deviations.

2. Materials and methods

2.1. Materials

Lactose monohydrate (Pharmatose 200M; Pharmatose 450M, DMV, The Netherlands) was used as the feed material for granulation. The aqueous binder dispersion comprised two grades of polyvinylpyrrolidone (Povidone K25; Povidone K90, ISP Technologies, USA), micronized drug hydrochlorothiazide (B.P. grade, Sinochem, Shenzhen, China) and deionized water.

2.2. Methods

2.2.1. Micronization of drug

Raw drug was milled using a fluidized bed hammer mill (50 ZPS, Hosokawa Alpine, Germany) at an inlet airflow rate of 90 m^3/h, beater rotational speed of 20,000 rpm, classifier speed of 10,000 rpm and with long grinding zones. The batch size was 1 kg.

2.2.1.1. Determination of drug particle size. The milled drug particles were examined at a magnification of 100×, using a light microscope (BH2, Olympus, Japan) connected to a monitor via a video camera (YS-W130P, Sony, Japan). The size of each batch of milled drug particles was determined from 625 projected images of different particles, across the longest diameter of the projected plane. The size at the 99th percentile (D_{99}) of the cumulative undersize distribution was employed to characterize the particle size of the drug to indicate the upper limit of the particle size distribution. D_{99} was reported as the mean of four batches.

2.2.2. Preparation of lactose powder blends

Lactose 200M was mixed with varying concentrations of lactose 450M to give a range of lactose powder blends, coded as 1–7 (Table 1). In blends 1 and 7, lactose 200M and 450M were present as 100%, respectively. The different grades of lactose powders were weighed out and blended in a double-cone mixer (AR 400E, Erweka, Germany) at 40 turns/min for 60 min prior to characterization and granulation.

2.2.2.1. Powder particle size. The mean particle sizes of the different lactose powder blends were determined using a laser diffraction particle sizer (LS 230, Coulter Corporation, USA). The dry powder module was employed. For each blend, three representative samples were randomly obtained and sized.

2.2.2.2. Powder flow. Powder flow was evaluated using a powder tester (PT-N, Hosokawa Micron, Japan), from which the flow parameter, angle of repose, was determined. The blended powder was manually fed through a funnel onto a fixed base, forming a cone, and an angle pointer was used to determine the angle of the formed cone, defined as angle of repose. Five measurements were obtained for each powder blend and results averaged.

2.2.3. Fluidized bed granulation

2.2.3.1. Equipment set-up of PG and TG. The PG and TG modules were fitted onto the same air handling system (MP-1 Multi-processor, GEA Aeromatic-Fielder, UK). For PG, a spray nozzle is positioned in the middle of a standard air distribution plate to spray upwardly (Fig. 1a). In the traditional Wurster process, a large proportion of the air flows up to the bed region peripheral to the column which is then fully fluidized, causing powder to flood into the spray granulation zone. On the contrary, much more of the air is directed into the partition column via a uniquely engineered air distribution plate and a swirl accelerator in the PG process. The plate has a graduated open area, defined as the area of the periphery of the perforated air distribution plate, from 2% at the peripheral edge to 1.5%, 1%, 0.5% and 0% at the center. The perforations are tapered with a diameter of 0.8–1.0 mm airside and 0.7 mm product side. The horizontal air distribution plate is attached to the swirl accelerator, which directs air passing through the partition column at a high volume and velocity. Air accelerator inserts, with central openings of different diameters can be selected for the middle of the plate to modulate the velocity of air flowing through the partition column (Heng et al., 2006). A larger insert opening would generate an air stream of lower velocity

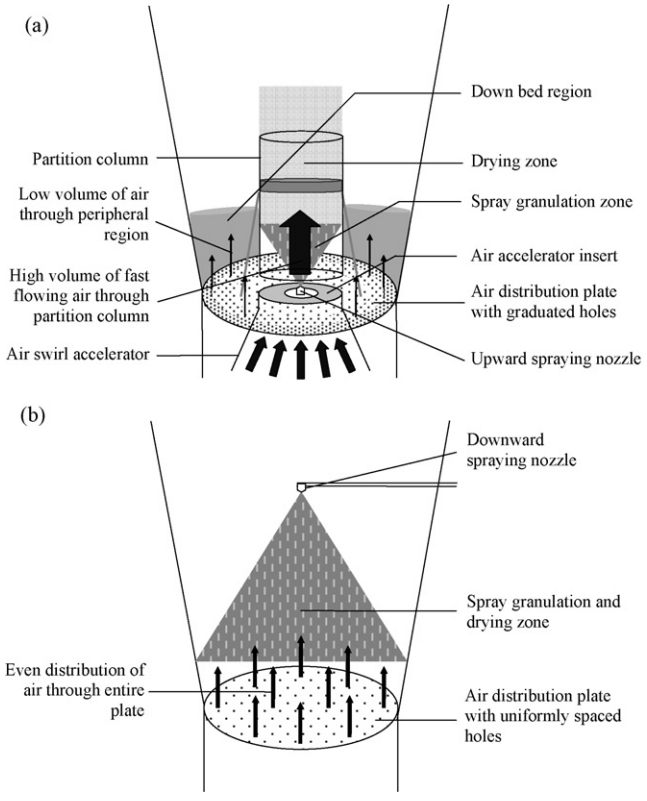

Fig. 1. Schematic diagrams of (a) precision granulator and (b) top-spray granulator (not drawn to scale) with (⟶) representing airflow.

Table 2
Operating conditions for PG and TG.

Process variables	Operating conditions	
	PG	TG
Binder spray rate (g/min)[a]	18, 21,[b] 24	18, 21,[b] 24
Fluidizing airflow rate (m^3/h)	50–110	70–110
Atomizing air pressure (bar)	0.8	0.8
Inlet air temperature (°C)	60	60
Drying time (min)	10	10
Drying airflow rate (m^3/h)	80	80
Nozzle tip diameter (mm)	1	1
Nozzle tip protruded level (mm)	1.2	1.2
Partition gap (mm)	26	N.A.
Diameter of air accelerator insert (mm)	35	N.A.
Nozzle height from base plate (mm)	N.A.	235

N.A.: not applicable.
[a] Specified by experimental design.
[b] Value used unless otherwise stated.

through the partition column and this can be explained by the law of conservation of mass (Batchelor, 2000) where the same volume of air flowing by in the same time through a narrower opening would have to move faster, resulting in an air stream of higher velocity and lower pressure. The partition column mounted above the air distribution plate creates a partition gap which regulates fluidization and powder entry into the spray granulation zone.

For TG, a spray nozzle is positioned to spray downwardly onto the powder bed (Fig. 1b). The air distribution plate used in TG has circular holes, 3 mm in diameter, uniformly spaced at a distance of 10 mm apart throughout the plate. Unlike the PG process, air passes evenly at the same volume and velocity across the air distribution plate.

2.2.3.2. Processing conditions. The granulation runs were carried out in triplicates under standardized conditions as shown in Table 2. For each run, 1 kg of lactose powder blend was used as the feed material and 500 g of liquid binder with 85 g total solid content comprising 9% (w/w) Povidone K25, 3% (w/w) Povidone K90 and 5% (w/w) micronized drug (D_{99} of 12.51 ± 0.59 μm) in deionized water was used. Prior to granulation, the drug was added to the aqueous dispersion of povidones and stirred using a high-shear homogenizer (L4RT, Silverson Machines, USA) for 10 min at 3500 rpm. During granulation, the binder dispersion was stirred continuously with a magnetic stirrer (Cb162, Bibby Sterlin, UK) to prevent sedimentation of drug particles.

2.2.3.3. Granule drug content. Drug contents within 10 size fractions of granules, ranging from the 1400 μm oversize fraction in a decreasing $\sqrt{2}$ progression to the 90 μm undersize fraction for each granule batch were determined. Approximately 600 mg of granules was randomly sampled from each size fraction and dissolved in 100 ml of deionized water. UV spectrometry (UV-1201, Shimadzu, Japan) was used to detect the amount of drug present at 273 nm. Triplicate analyses were carried out for each size fraction in each of the three granule batches. The readings were then summed up and averaged to obtain $Drug_x$ (%, w/w), the inter-batch drug content in a weighed amount of granules of the specific size fraction x. As a measure of drug content uniformity within the specific size fraction x, the relative standard deviation (R.S.D.) of $Drug_x$ was calculated to give RSD_x (%). A lower R.S.D. value signified better uniformity.

The granules were subsequently classified as small, medium and large for those belonging to the size fractions ≤250 μm, 250–710 μm, and ≥710 μm, respectively. The mean drug content and mean R.S.D. of drug content for small, medium and large granules were then calculated according to Eqs. (1) and (2):

$$\text{mean drug content} = \frac{1}{n}\sum_{i=1}^{n}(Drug_x) \quad (1)$$

$$\text{mean R.S.D. of drug content} = \frac{1}{n}\sum_{i=1}^{n}(RSD_x) \quad (2)$$

where n is the number of size fractions within the granule size classifications.

Taking into consideration the different proportions of the various size fractions within a granule batch and thus their relative contributions to the overall batch drug content uniformity, the overall weighted R.S.D. of drug content was calculated as shown in Eq. (3):

$$\text{overall weighted R.S.D. of drug content} = \sum_{i=1}^{n}(p_x)(RSD_x) \quad (3)$$

where p_x is the proportion of a specific size fraction x calculated from triplicate batches.

2.2.3.4. Granule size. The granules prepared were divided into random samples of approximately 120 g using a riffler (PT, Retsch, Germany), and samples subjected to size analysis using a nest of sieves (Endecotts, UK) with a series of aperture sizes 90, 125, 180, 250, 355, 500, 710, 1000 and 1400 μm vibrated at an amplitude of 1 mm for 15 min (VS1000, Retsch, Germany). Mass median diameter (MMD) and span were defined as D_{50} and as in Eq. (4), respectively. The fraction of granules larger than 1400 μm was defined as lumps:

$$\text{span} = \frac{D_{90} - D_{10}}{D_{50}} \quad (4)$$

where D_{10}, D_{50} and D_{90} are the particle sizes at the 10th, 50th and 90th percentiles of the cumulative undersize distribution, respectively. Sizing was carried out on each granule batch and results of triplicate granule batches were averaged.

2.2.3.5. Granule shape. The granules from the 355–500 μm size fraction were first gently sieved through a 500 μm aperture size sieve manually. Granules trapped at the sieve apertures were then carefully removed and subjected to analysis. Particle shapes of 60 randomly chosen granules from each of the triplicate granule batches were assessed using a stereomicroscope (SZH, Olympus, Japan) linked to an image analyzer (Micro Image, Media Cybernetics LP, USA). The captured images were digitalized and analyzed by the software. Sphericity was defined as:

$$\text{sphericity} = \frac{4\pi a}{P^2} \quad (5)$$

where a is the cross-sectional area and P is the perimeter of the granule.

The morphology of the granules was also assessed qualitatively using a scanning electron microscope (JSM-5200, JEOL, Japan) after pretreatment of samples by gold sputtering (JFC-1100, JEOL, Japan).

2.2.3.6. Granule flow. Evaluation of granule flowability was carried out by determination of angle of repose (Section 2.2.2.2), bulk and tapped densities. Bulk and tapped densities were determined according to the United States Pharmacopeia (USP) method, using a USP tap density tester (TD2, Sotax, Switzerland). Granules were filled up to 100 ml in a graduated cylinder and the weight (w) determined. The granules were subjected to tapping until a constant volume (v_c) was obtained. Duplicate analyses were carried out for

each granule batch and results from triplicate granule batches averaged. Bulk density, tapped density and Carr index were defined as follows:

$$\text{bulk density} = \frac{w}{100} \quad (6)$$

$$\text{tapped density} = \frac{w}{v_c} \quad (7)$$

$$\text{Carr index}\,(\%) = \left[1 - \frac{\text{bulk density}}{\text{tapped density}}\right] \times 100 \quad (8)$$

2.2.3.7. Granule porosity. The porosity of the granules was derived from tapped density and particle density determinations, as shown in Eq. (9). A helium pentapycnometer (PPY-14, Quantachrome, USA) was used to estimate the particle density of the granules. The samples were oven-dried at 105 °C for 2 h and cooled to room temperature in a dessicator prior to use. Triplicate tests were performed on each granule batch and results from triplicate batches averaged:

$$\text{porosity}\,(\%) = \left[1 - \frac{\text{tapped density}}{\text{particle density}}\right] \times 100 \quad (9)$$

2.2.4. Statistical analysis

The statistical analyses were carried out using MINITAB® Release 14 (Minitab Inc., USA). One-way ANOVA was used to compare more than two sample sets with Tukey's test as the post hoc analysis. The level of significance was defined as $p < 0.05$.

3. Results and discussion

3.1. Drug content and drug content uniformity

All granule batches prepared had process yields ranging from 80% to 95%. The theoretical loading of 25 g drug onto each granule batch was calculated to be 2.3% (w/w). From Figs. 2a and 3a, it could be observed that small granules had drug content lower than 2.3% (w/w) whereas medium and large granules generally had higher than expected drug content for both processes. Between medium and large granules, there was generally no difference in drug content, indicating that the drug content of granule within each batch did not vary much for granules larger than 250 μm. This observation was consistent for both PG and TG granules.

At the start of both granulation processes before the powder feed material was sufficiently moistened by the liquid binder spray, fine powder particles were easily lifted upwards from the base of the product chamber to the expansion chamber above the product chamber by the upward flowing air stream. Due to static caused by air friction, the relatively dry powder particles were initially trapped onto the sock filters located at the expansion chamber. As such, during the early stages of granulation, the lower than expected load of feed particles that remained at the product chamber region rapidly circulated through the spray granulation zone where liquid binder was sprayed onto the particles, effecting growth to form granules. Meanwhile, at the sock filters, trapped fines were gradually dislodged by the blow-back air that was programmed to activate at 10 s intervals throughout the processes. Over time, these fines rejoined the granulating load at the product chamber, increasing the total amount of feed material available for granulation. Nonetheless, their shortened duration at the product chamber meant that these fines had lesser opportunities to undergo circulation through the spray granulation zone and were less likely to grow and to have drug particles deposited on them. Consequently, they formed the bulk of the small granules, and had lower drug content than the calculated expected value of 2.3% (w/w). Likewise, this observation accounted for the higher drug content values obtained for medium and large granules, which mainly grew from feed particles that remained at the product chamber throughout

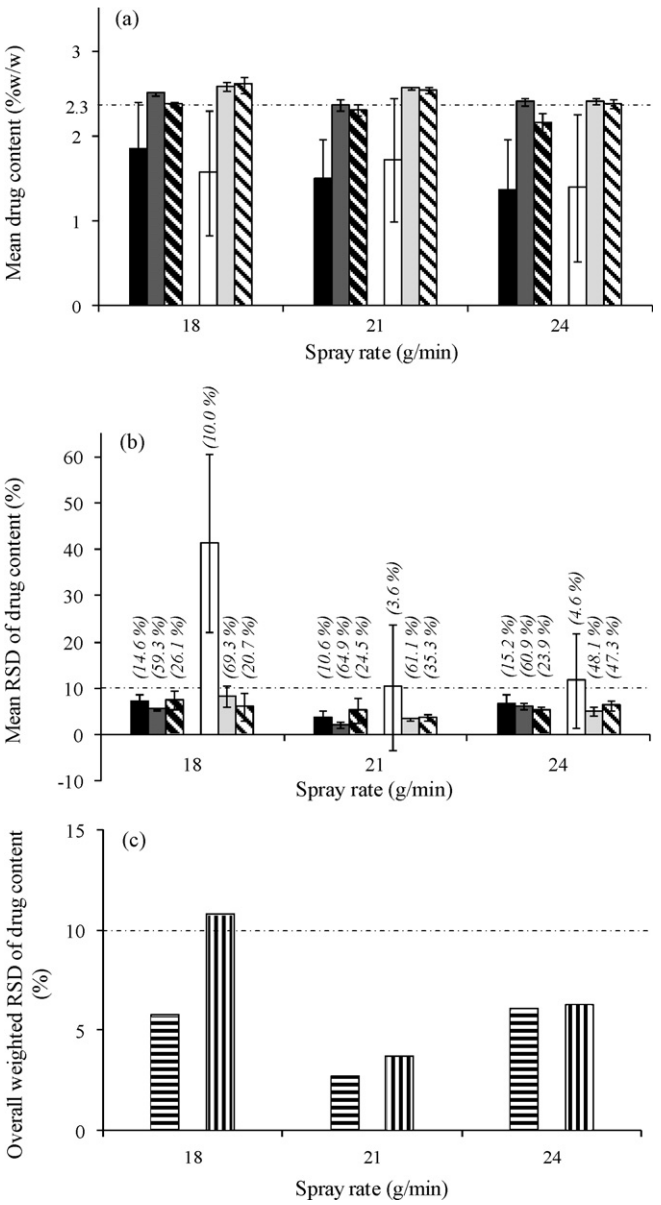

Fig. 2. Influence of binder spray rate on (a) mean drug content, (b) mean R.S.D. of drug content and (c) overall weighted R.S.D. of drug content of PG and TG granules: PG/small (■), PG/medium (▩), PG/large (▨), PG/batch (▤), TG/small (□), TG/medium (▨), TG/large (▨) and TG/batch (▥). Values in parentheses denote mean amounts of small, medium and large granules within the batches (%, w/w).

the entire duration of granulation. As these medium and large granules underwent comparatively more circulation cycles through the spray granulation zone, they had a greater amount of drug deposited on them.

In PG, the mean R.S.D. of drug content for the different classes of granules were found to be less than 10% (Figs. 2b and 3b) at the various investigated conditions. On the contrary, higher R.S.D.s of drug content were observed for small TG granules. This could be due to the nearly unavoidable higher extent of spray drying effect with the use of the top-spray technique (Jones, 1989). The poor drug content uniformity of small TG granules would be less of a concern at wetter bed conditions (21 and 24 g/min) and with uni-component feed material that flowed well (lactose powder blend 1), as they made up only less than 5% (w/w) of a granule batch. For batches prepared at the other investigated conditions, though small granules were not the representative class of granule size, they still made up 10–20% (w/w) of the batch and their poor drug content uniformity had a big-

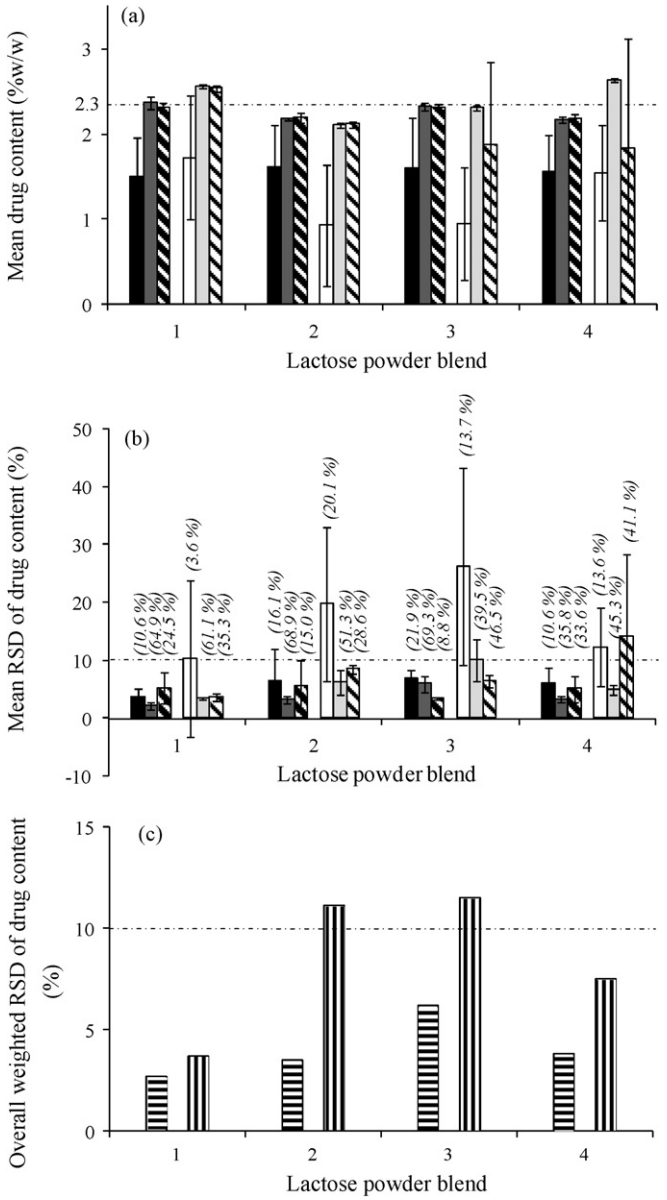

Fig. 3. Influence of lactose powder blend on (a) mean drug content, (b) mean R.S.D. of drug content and (c) overall weighted R.S.D. of drug content of PG and TG granules: PG/small (■), PG/medium (▩), PG/large (▨), PG/batch (☰), TG/small (□), TG/medium (▩), TG/large (▨) and TG/batch (▥). Values in parentheses denote mean amounts of small, medium and large granules within the batches (%, w/w).

ger impact on the overall batch drug content uniformity. As such, graphs of the overall weighted R.S.D. of drug content of these TG batches (Figs. 2c and 3c) had higher values. Conversely, the overall weighted R.S.D.s of drug content of PG batches were found to be less influenced by the changes in processing conditions. The observed differences between the two processes could be explained by their difference in the dominant mode of granule growth that resulted from dissimilar particle circulation patterns in the fluidized bed, as discussed in the section below.

3.2. Influence of circulation pattern

The partition column present in a bottom-spray process serves to regulate particle fluidization and flow into the spray granulation zone (Cheng and Turton, 2000; Christensen and Bertelsen, 1997). At the spray granulation zone (Fig. 1a), the atomized binder droplets were dispersed onto surfaces of the feed particles and the surface wetting rapidly formed a layer of liquid binder on the feed particles. Growth occurred via the layering of liquid binder onto the particles during each cyclic pass through the spray granulation zone (Fig. 4a). In addition, growth via agglomeration of binder-layered feed particles may also occur when the wet particles successfully coalesced with each other after collision. Consolidation of these coalesced particles was timely aided by the shear force of the high velocity air stream passing through the partition column (Fig. 1a). This stream of hot drying air not only imparted shear onto the particles, but also caused rapid solidification of the binder layer and lifted the particles into the drying zone almost instantaneously after wetting. After these binder-layered feed particles exited the partition column, they began to decelerate in the expansion chamber and dropped into the down bed (region between the column and the wall of the product chamber) when they could no longer be entrained, creating a fountain-like path. At the down bed, the almost dried particles awaited re-entry into the spray granulation zone through the partition gap and the cycle repeats. This circulation pattern was repeated throughout processing as the feed particles underwent distinct steps of wetting, growth, drying and queuing. Because of the orderly and consistent circulation pattern present in PG, layered growth of granules mainly resulted and made it a suitable technique to be employed for the spray deposition of drug onto feed particles during granulation.

As with the bottom-spray process, particles in TG were recycled through the spray granulation zone in a matter of seconds. In TG, the liquid binder was sprayed counter-currently into the randomly fluidizing particles and there was scattered and unpredictable spread of liquid binder onto the particle surfaces (Fig. 4b). As a consequence of the even distribution of air volume across the powder bed, air flowed upwards through the spray granulation zone at a relatively much lower velocity. This gave rise to a comparative lack of shear force from the air to aid coalescence and consolidation in the top-spray process, and TG granules thus grew mainly by the formation of liquid bridges between particles when they were brought together. As particles were lifted upwards, the decreasing air velocity decelerated the particles and they fell back onto the bubbling powder bed. However, in contrast to PG, the circulation pattern was much less organized, without clearly distinguishable spray granulation and drying zones. Wetting, growth and drying occurred within the same region in the fluidized bed and thus though the circulation pattern was repeated throughout the process, there were no distinct steps for wetting, growth and drying during the cycle. Particles may be wetted again before they were completely dried. Agglomeration of particles may occur immediately after wetting, or after partial drying. As wetting and spreading of liquid binder was more random in the TG process, some particles might have been wetted to a greater extent, resulting in a higher amount of deposited drug. This in turn led to the generally poorer drug content uniformity observed in TG granules. At the same time, the nearly unavoidable spray drying presented serious challenges to development personnel attempting to use this technique for layering.

3.3. Influence of binder spray rate

With the exception of a markedly high mean R.S.D. of drug content (≥40%) at the lowest binder spray rate employed for small TG granules, drug content and drug content uniformity of both PG and TG granules were relatively unaffected by changes in binder spray rate (Fig. 2). This observation was due to spray drying effect of the liquid binder, which became more significant and evident at dry bed conditions. Generally in a spray granulation process, an increase in wetness of the powder bed would result when the liquid binder was sprayed at a faster rate while the drying conditions remained unchanged. This was found to promote coalescence of

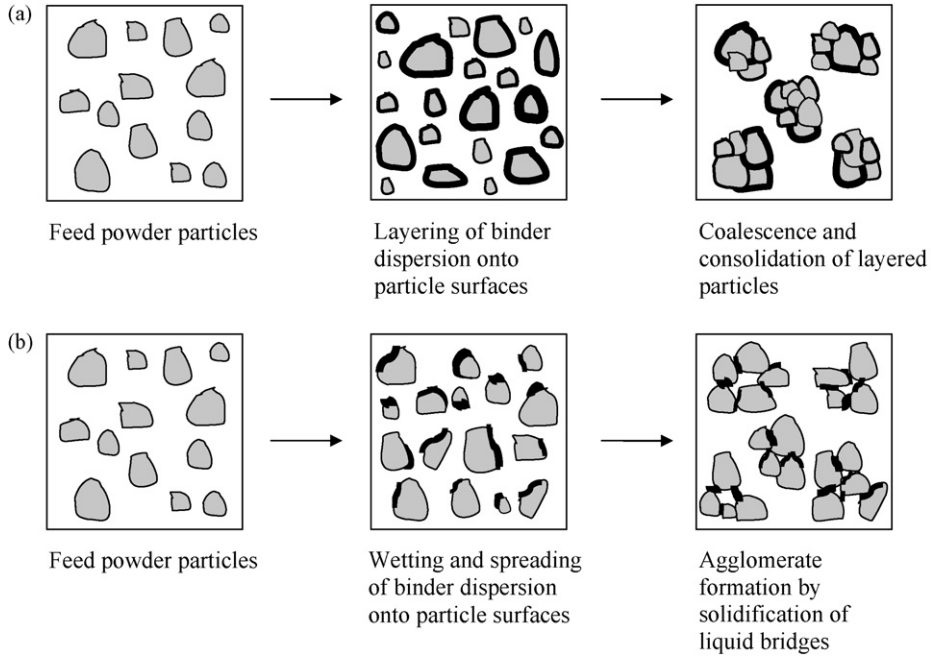

Fig. 4. Mode of wetting and granule growth in (a) PG and (b) TG.

particles, giving rise to granules that were more spherical and less porous in both processes (Table 3 and Fig. 5). Increasing binder spray rates would also lead to an increase in the moisture content of the powder bed and granule growth, as typically observed in conventional TG in this study and in others (Menon et al., 1996; Watano et al., 1997; Cryer and Scherer, 2003). However, interestingly, no significant differences in MMD, span and lump values were observed for the PG process (Table 3). The size characteristics of PG granule batches formed at the three investigated spray rates were similar, indicating that granule growth in PG was relatively robust to changes in binder spray rate.

Litster et al. (2001) suggested that an increase in binder spray rate would create an increase in dimensionless spray flux, defined as "the ratio of wetted area covered by the nozzle to the spray area in the nucleation zone". This would lead to more rampant overlapping of spray droplet footprints on the powder particles. As the spray area in PG was much smaller as compared to TG, the bottom-spray process already possessed a higher dimensionless spray flux. In addition to the further increase in dimensionless spray flux with increased binder spray rate within the same spray area, the resultant very rampant overlapping of spray droplets promoted layered growth by forming a thicker binder layer around the particles during each cycle. Though there was thicker and a more thorough surface spread of liquid binder on the powder particles as they grew, the number of particles that were wetted in each cycle remained unchanged as there was a limitation on the number of particles entering the spray granulation zone. The similar size characteristics of granule batches formed also indicated the process's ability to efficiently dry layered particles under different wetting conditions without causing undesirable growth. Attributing to the layered mode of growth in PG, it was also observed that the formed granules were generally less porous and had a higher degree of sphericity (Fig. 5). The rounder structures were a result of the slow and steady build-up of layers around the powder particles and strong impact of fluid dynamics on growth in the bottom-spray process. When collision and coalescence of two wetted particles occurred, the high velocity of the air stream through the spray granulation zone imparted shear force on the coalesced particles and encouraged consolidation of the particles. Increased consolidation prior to drying reduced structure porosity. As most of the particle surfaces were already wetted and softened by the liquid binder, it was easier for shaping and consolidation to occur.

In contrast to PG, a broader nuclei size distribution in the TG powder bed resulted with increased binder spray rate as the spray droplets overlapped more frequently. This led to granule batches with wider size distribution and larger granules. Increase in lump formation was also significant. A lack of shear force due to the relatively slower air velocity at the granulation zone in TG reduced shaping and consolidation of coalesced particles. Thus during the TG process, growth mainly occurred when wetted particles agglomerated upon solidification of liquid bridges that bonded them after drying. This potentially increased the possibility of the characteristic highly irregularly shaped and porous granule structures to form.

Table 3
Influence of binder spray rate on PG and TG granule properties.

Code	Spray rate (g/min)	MMD (μm)	Span	Lumps (%, w/w)	Sphericity	Porosity (%)	Angle of repose (°)	Bulk density (g/L)	Tapped density (g/L)	Carr index (%)
PG	18	365 (13)	1.30 (0.12)	2.24 (2.78)	0.71 (0.03)	61.8 (2.1)	38.3 (0.0)	465 (28)	500 (27)	12.2 (0.8)
PG	21	422 (16)	1.29 (0.13)	1.05 (1.21)	0.77 (0.03)	59.9 (1.9)	37.1 (0.3)	489 (16)	523 (32)	13.5 (1.3)
PG	24	418 (73)	1.42 (0.02)	1.56 (1.51)	0.81 (0.02)	57.3 (1.2)	35.3 (0.2)	531 (27)	567 (9)	12.2 (1.0)
TG	18	440 (20)	0.96 (0.07)	0.27 (0.30)	0.57 (0.01)	68.8 (2.0)	45.1 (0.5)	393 (19)	568 (32)	15.5 (1.3)
TG	21	525 (55)	1.33 (0.18)	4.07 (4.08)	0.66 (0.03)	67.4 (1.1)	40.1 (0.1)	429 (18)	604 (28)	12.3 (1.0)
TG	24	585 (54)	1.52 (0.08)	9.55 (2.00)	0.70 (0.08)	64.8 (1.6)	39.8 (0.1)	473 (28)	646 (17)	11.0 (1.0)

Values in parentheses denote inter-batch standard deviations.

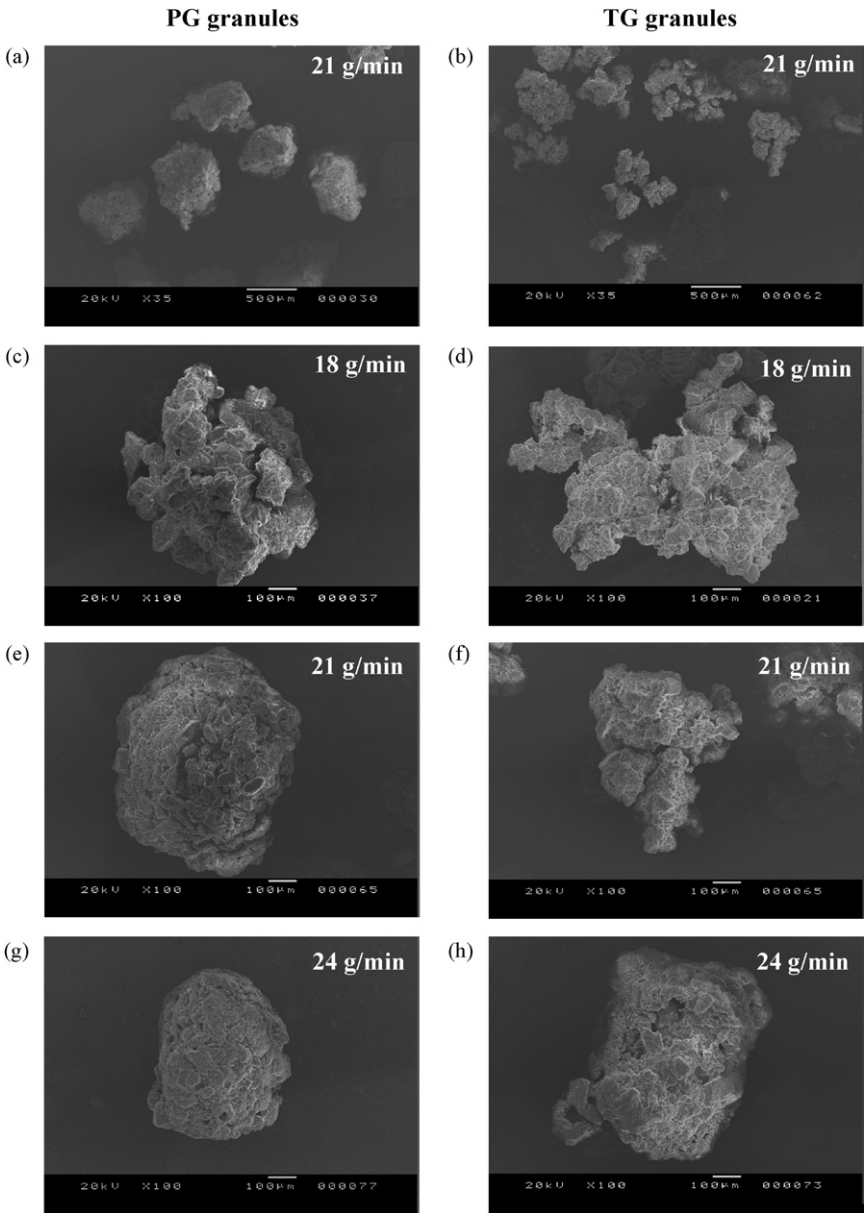

Fig. 5. Scanning electron micrographs of granules granulated using various spray rates: (a) and (b) taken at 35× magnification, (c)–(h) taken at 100× magnification.

Therefore even at high spray rates, TG granules that formed were still less spherical and more porous than PG granules.

3.4. Influence of mean particle size of feed powder

The angle of repose and mean particle size and values of the various powder blends are shown in Table 1. Increasing amounts of lactose 450M mixed with lactose 200M resulted in smaller mean particle sizes. This produced a more cohesive powder blend resulting in poorer flow. For PG, it was found that granulation of blends 5–7 could not be successfully carried out and a reduction in ease of fluidization during the start of granulation for blends 1–4 was visually observed. For PG, the fluidizing air was distributed between the partition column and the peripheral powder bed, with most of the air directed through the column. Peripheral fluidization was comparatively weaker in this bottom-spray process and the drawing in of particles into the spray granulation zone depended on a strong suction. This made the process less suitable for use with cohesive powders. Though PG faced a decreasing ease in fluidizing blends 1–4 at the start of processing, the suction force was still sufficient to break up the smaller lactose 450M particles that cohered strongly to one another and to draw them into the spray granulation zone for growth to take place. Thus physical characteristics such as size, shape and porosity of PG batches obtained did not vary significantly as the mean particle size and flow of feed material decreased from blends 1 to 4 (Fig. 6 and Table 4). Drug content and drug content uniformity of PG granules were also found not to be influenced (Fig. 3). This clearly suggested with sufficient suction force to draw particles into the partition column, the flow of feed powder had little influence on granule growth in the PG process.

In TG, all investigated powder blends could be granulated. This was mainly due to the differences in fluid dynamics between the two processes. The fluidizing air in TG was distributed evenly across the powder bed as air passed upwards from the plenum and transport of particles into the spray granulation zone depended greatly on the success of bed fluidization and gravity. Unlike in PG, no suction pressure was required and thus the process was able to granulate a wider range of cohesive powders. Across blends 1–4,

Table 4
Influence of various lactose powder blends on PG and TG granule properties.

Code	Powder blend	Sphericity	Porosity (%)	Angle of repose (°)	Bulk density (g/L)	Tapped density (g/L)	Carr index (%)
PG	1	0.77 (0.03)	59.9 (1.9)	37.1 (0.3)	523 (32)	604 (28)	13.5 (1.3)
PG	2	0.77 (0.03)	59.5 (1.1)	40.6 (0.7)	528 (4)	609 (18)	15.5 (3.0)
PG	3	0.73 (0.03)	61.0 (2.4)	40.5 (0.3)	505 (47)	586 (32)	16.2 (4.8)
PG	4	0.75 (0.03)	60.3 (1.2)	41.0 (0.7)	528 (26)	599 (15)	13.4 (2.5)
TG	1	0.66 (0.02)	67.4 (1.1)	40.1 (0.1)	429 (18)	489 (16)	12.3 (1.0)
TG	2	0.59 (0.03)	63.2 (1.9)	44.3 (1.0)	465 (14)	554 (30)	19.2 (4.3)
TG	3	0.64 (0.02)	65.6 (3.0)	44.2 (0.9)	447 (36)	518 (48)	15.7 (1.4)
TG	4	0.59 (0.01)	65.7 (2.2)	45.5 (1.7)	436 (35)	516 (35)	18.4 (2.4)

Values in parentheses denote inter-batch standard deviations.

MMD, span, sphericity and porosity of TG granules formed were found not to differ significantly (Fig. 6 and Table 4). However, higher proportions of small granules were observed to be formed when powder blends 2–4 were granulated, as compared to powder blend 1 (Fig. 3b). This was because the smaller lactose 450M particles present in these blends required a lower fluidization velocity and these particles were easily lifted by the incoming air to the expansion chamber above the spray nozzle. Being physically smaller, they were also lighter and it was more difficult for them to fall back onto the powder bed by gravitational force. In comparison to the larger lactose 200M particles, they spent less time at the powder bed and were largely suspended in the air or trapped at the sock filters. Upon end of granulation, these particles fell back onto the powder bed and thus made up a higher proportion of small granules within the batch, resulting in low drug content and poor drug content uniformity among the small granules in powder blends 2–4.

3.5. Resultant flow characteristics of granules

From Tables 3 and 4, the granule batches prepared by both processes had good flow properties (angles of repose $\leq 45^\circ$ and Carr indices $\leq 20\%$). As granule flow can be influenced by an array of factors such as bulk density, size, shape, surface area roughness, moisture content and cohesiveness of materials, the methods of flow assessment employed did not show the same indications when binder spray rate and feed material were varied. This discrepancy was not unexpected as current techniques for determining powder flow are based on different principles and have their own advantages and limitations, as shown in other studies (Velasco Antequera et al., 1994; Amidon, 1995; Lee et al., 2000). Nonetheless, the assessment methods showed some apparent trends. A decrease in flow of TG batches was observed for powder blends 2–4 as compared to powder blend 1. This was attributed to the higher proportions of small TG granules in these batches as discussed. The presence of higher amount of small granules increased cohesion between granules in these batches. Between the two processes, lower angles of repose, higher bulk densities and lower Carr indices were observed for PG batches. This was because compared to TG granules, the rounder structures made PG granules less likely to interlock with one another, leading to lower inter-granular frictional force and better flow. Being rounder, PG granules were also able to pack more closely in a powder column and this resulted in the higher bulk densities seen.

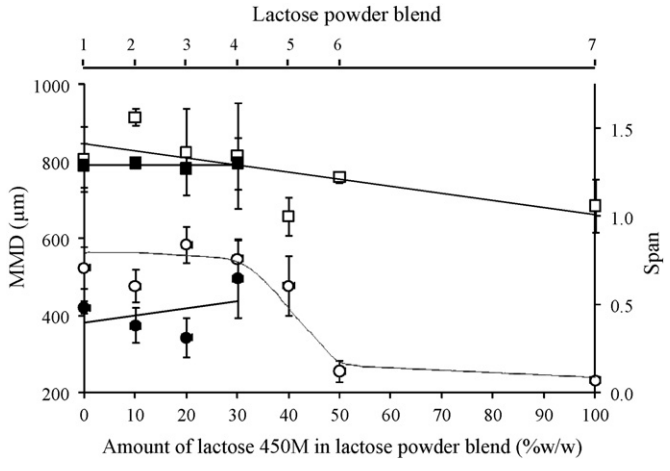

Fig. 6. Influence of feed material on MMD in PG (●) and TG (○); and span in PG (■) and TG (□).

4. Conclusion

Owing to the controlled and ordered particle circulation pattern in a bottom-spray process, distinct stages of wetting, growth, drying and queuing were present in the cycle during processing. This led to layered growth as liquid binder layers formed and solidified around particle surfaces. The precise surface wetting of the process coupled with the dominating role of air flow at the spray granulation zone aided particle coalescence and consolidation. PG granules that were less porous and more spherical than TG granules were thus formed, resulting in better flow of the resultant granule batches. In comparison, particle circulation pattern in TG was more random with no distinct stages of wetting, growth and drying. Additionally, the lack of shear force at the spray granulation zone contributed to preferential growth by formation of liquid bridges between particles. This mode of growth in TG gave rise to poorer drug content uniformity in small TG granules, and thus poorer overall weighted batch uniformity. The binder spray rate and feed material characteristics had a more pronounced effect on granule properties in TG, but the ability of the PG process to granulate showed a higher dependency on the flow of feed material. Within the PG process's ability to granulate, good robustness and little influence on granule properties was observed under the conditions investigated. Generally, the bottom-spray process was found to be a good alternative to conventional fluid bed granulation, especially for spray deposition of a low dose drug.

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