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ORIGINAL ARTICLE

Air-dictated bottom spray process: impact of fluid dynamics on granule growth and morphology

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Abstract
Background: Growing interest in the use of the less-explored bottom spray technique for fluidized bed granulation provided impetus for this study. *Aim*: The impact of fluid dynamics (air accelerator insert diameter; partition gap) and wetting (binder spray rate) on granule properties were investigated. *Method*: In this 3^3 full factorial study, the results were fitted to a quadratic model using response surface methodology. The air velocity at the spray granulation zone for the investigated conditions was measured using a pitot tube. *Results*: Air accelerator insert diameter correlated to measured air velocity at the spray granulation zone and was found to not only dictate growth but also influence granule morphology. The partition gap was found to play important roles in regulating particle movement into the spray granulation zone and optimizing process yields, whereas binder spray rate significantly affected granule morphology but not granule size. *Conclusions*: Unlike conventional fluidized bed granulation, ease of modulation of fluid dynamics and insensitivity of the bottom spray process to wetting allow flexible control of granule size, shape, and flow. Its good drying ability also indicated potential use in granulating moisture-sensitive materials.

Key words: *Bottom spray; fluid dynamics; fluidized bed granulation; granule growth; granule shape*

Introduction

Granulation is an important processing step in the manufacture of many pharmaceutical dosage forms. It is a size-enlargement process whereby small particles are agglomerated into larger masses while maintaining good control of the size and microstructure of the end product. Granules show more advantageous properties than fine powders, and hence, powders were granulated to improve flow, resistance to segregation, handling, strength, compaction characteristics, and appearance[1,2].

Since its first reported use in the pharmaceutical industry by Wurster[3], the fluidized bed technology has been widely employed for coating, granulating, and drying purposes. With regards to the purpose of fluidized bed granulation, the importance of physicochemical parameters has been widely investigated by many researchers. The types of binder[4,5], powder properties[6,7], and powder load[8] were shown to affect the process. Increasing the concentration and viscosity of the liquid binder was generally reported to result in increased mean granule size and decreased granule strength[9–12]. The mechanical and morphological properties of granules were also shown to be influenced by binder concentration[13], and growth kinetics in the fluid bed was found to have a strong dependence on the surface roughness of the particles[14]. Additionally, processing parameters such as binder spray rate and atomizing air volume have been extensively shown to influence granule formation and attributes[15–17]. For instance, it was reported that the liquid binder droplet size had a direct relationship to granule growth[18,19], and atomizing air pressure was found to be a prevailing factor for controlling growth[20]. The rate of the atomizing air was identified as the major parameter causing granule breakage[21]. Wang et al.[22] suggested that the use of a suitable fluidizing airflow rate can produce a high product yield while atomizing air volume had little influence on the yield. Lower inlet air temperatures were also reported to encourage the agglomeration of powders[23,24].

Notwithstanding it being a well-studied area, there is still keen interest in recent years in fluidized bed

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granulation[25–27]. Conventionally, fluidized bed granulation is carried out using the top spray technique, where the nozzle is at the top of the product container and the liquid binder is sprayed counter-current to the air flow. It is commonly accepted that granulation is carried out using the top spray technique, whereas the Wurster/bottom spray technique is generally used for coating purposes. However, with recent advances in fluidized bed equipment and the growing importance of process understanding in the pharmaceutical industry, there is increasing attention on bottom spray granulation[13,22,28,29]. Promising advantages such as good process control, ease of scale up, and production of granule batches with highly uniform drug and binder distribution with the Wurster granulation process have been proposed. Precision granulation, a modified Wurster process by Walter[30], was developed in recent years. The equipment setup of the precision granulator is shown in Figure 1. It consists of an adjustable partition column mounted in the center of the product chamber, above the air distribution plate. The partition gap is defined by the vertical distance between the bottom of the partition column and the air distribution plate. There are three unique features of this granulator that differentiate it from other bottom spray granulators. The first feature is an air distribution plate with a graduated open area, with more perforations at the periphery than at the center, which results in a higher central air velocity. Second, air accelerator inserts (AAIs) of different opening diameters can be selected for the middle of the air distribution plate to modulate the airflow rate through the partition column. The last feature is a swirl accelerator that imparts swirl to the upward flowing central air stream.

Despite the great potential that could be offered by the bottom spray technique, it has not been as widely studied by pharmaceutical scientists as the top spray technique, and a gap in the fundamental knowledge on bottom spray fluidized bed granulation still exists today. Thus, the intent of this study was to enhance the understanding on granule growth control in the bottom spray precision granulation process and to provide further insight into potential applications of this process. Three processing parameters (AAI diameter, partition gap, and binder spray rate) were hypothesized to affect granule growth. The postulation of their significance stems from the important roles they have played in studies on other bottom spray processes. In detail, it was of interest to study the influences of AAI diameter and partition gap because of their potential influences on the system's fluid dynamics. For instance, the important role of the partition gap in regulating particle movement in bottom spray systems had been identified[31,32], and it was reported that the agglomeration of coated pellets can be minimized with the use of an optimal AAI diameter and partition gap[33,34]. Liquid binder spray was chosen as the third parameter for investigation in this study because of the wide recognition of the sensitivity of fluidized bed granulation processes to changes in wetting and resultant moisture content in the powder bed[35–37]. During investigations, a factorial design was

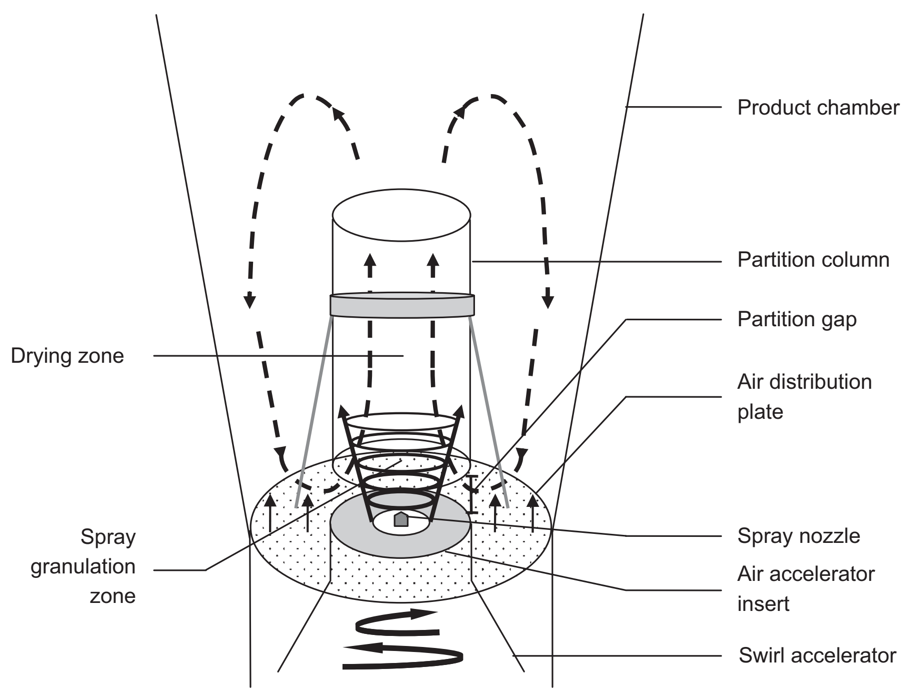

Figure 1. Schematic diagram of the precision granulator with (---) representing powder flow and (→) representing airflow.

carried out to determine the main effects of these three variables on granule batch properties and their interdependence, if any, over the wide range of wetting/drying conditions selected.

Materials and methods

Materials

Lactose monohydrate (Pharmatose 200M; DMV, Veghel, the Netherlands) was used as a feed material for fluidized bed granulation. The aqueous liquid binder consisted of two grades of polyvinylpyrrolidone (Povidone K25 and Povidone K90; ISP Technologies, Wayne, NJ, USA) and a micronized drug (hydrochlorothiazide BP; Sinochem, Zhejiang, China).

Methods

Granulation process

The precision granulation module was fitted onto an air handling system (MP-1 Multi-processor; GEA Aeromatic-Fielder, Eastleigh, UK). One kilogram of lactose (W_l) was used as the feed material for each granulation run in a conical acrylic product chamber. During granulation, 500 g of liquid binder with 85 g total solid content (W_b) comprising 9% (w/w) Povidone K25, 3% (w/w) Povidone K90, and 5% (w/w) micronized drug (mean size 6.75 ± 0.17 μm) in deionized water was used. The operating conditions employed are shown in Table 1. At the end of each run, all the granules were carefully collected from the product chamber and weighed (W_g). The process yield was then calculated as follows:

$$\text{Process yield (\%)} = \frac{W_g}{W_l + W_b} \times 100. \quad (1)$$

Table 1. Operating conditions in precision granulation.

Variables	Operating conditions Low level	Intermediate level	High level
X_1: AAI diameter (mm)*	24	30	35
X_2: Partition gap (mm)*	20	26	32
X_3: Binder spray rate (g/min)*	18	21	24
Fluidizing airflow rate (m^3/h)	50–110		
Atomizing air pressure (bar)	0.8		
Inlet air temperature (°C)	60		
Drying time (minutes)	10		
Drying airflow rate (m^3/h)	80		
Nozzle tip diameter (mm)	1		
Nozzle tip protruded level (mm)	1.2		

*Specified for each batch by factorial experimental design.

Factorial design

A randomized full factorial design (3^3) was carried out and all experimental batches were run in triplicates to increase the confidence in the resultant empirical relationships derived. Attempts were made to fit the responses to a quadratic model using response surface methodology. Before the application of the design, a number of preliminary trials were conducted to determine the conditions at which the process resulted in the formation of granules. The low, intermediate, and high levels of the variables used in the factorial design as defined in Table 1 were also determined by this procedure.

Measurement of air velocity within partition column

A Pitot tube (160–12; Dwyer Instruments, Michigan City, IN, USA) was used to measure the air velocity within the partition column of the granulator. The measurements were taken under nine different conditions when the AAI diameter and partition gap were varied at the defined low, intermediate, and high levels. Airflow rate was increased from 50 to 110 m^3/h, in intervals of 10 m^3/h, whereas the atomizing air pressure and inlet air temperature were set at 0.8 bar and 60°C. The Pitot tube was positioned 12.5 cm above the air distribution plate during the measurements. The air velocity at each different condition was investigated in three independent runs, with triplicate readings for each run.

Granule size analysis

The granules prepared were divided into random samples of approximately 120 g using a riffler (PT; Retsch, Haan, Germany) and sized using a nest of sieves (Endecotts, London, UK) of aperture sizes 90, 125, 180, 250, 355, 500, 710, 1000, and 1400 μm, vibrated at an amplitude of 1 mm for 15 minutes (VS1000; Retsch). From the data obtained, size parameters, mass median diameter (MMD), and span were determined and defined as follows:

$$\text{MMD} = D_{50} \quad (2)$$

$$\text{Span} = \frac{D_{90} - D_{10}}{D_{50}}, \quad (3)$$

where D_{10}, D_{50}, and D_{90} were the particle sizes at the 10th, 50th, and 90th percentiles of the cumulative undersize distribution, respectively. The fraction of 90 μm cumulative undersized granules was defined as fines, and the fraction of granules larger than 1400 μm was defined as lumps.

Granule flow analysis

Evaluation of powder flowability was carried out using a powder tester (PT-N; Hosokawa Micron, Osaka, Japan), from which the flow parameter was determined. The granules were 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 replicated measurements were carried out for each batch and the average values reported.

Granule shape analysis

The granules from the 355–500 µm size fraction were first gently sieved through a 500-µm aperture size sieve manually. Granules retained on the apertures of the 500-µm sieve were then carefully removed and collected for shape analysis. Image analysis was carried out on 60 randomly chosen granules using a stereomicroscope (SZH; Olympus, Tokyo, Japan) connected with a camera (DXC-390P; Sony, Tokyo, Japan) linked to an image analysis program (Olympus Micro Image; Media Cybernetics, Silver Spring, MD, USA). The derived shape factors, aspect ratio, and sphericity were defined as follows:

$$\text{Aspect ratio} = \frac{l}{b} \tag{4}$$

$$\text{Sphericity} = \frac{4\pi a}{P^2}, \tag{5}$$

where l was the length, b was the breadth, a was the cross-sectional area, and P was the perimeter of the granule.

Statistical analysis

The statistical analysis was carried out using MINITAB® Release 14 (Minitab Inc., State College, PA, USA). The quadratic equation used for response surface modeling of the three independent variables was as follows:

$$\begin{aligned} Y = {} & \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_2 X_3 + \beta_{11} X_1^2 + \beta_{22} X_2^2 \\ & + \beta_{33} X_3^2 + \beta_{12} X_1 X_2 + \beta_{23} X_2 X_3 + \beta_{13} X_1 X_3, \end{aligned} \tag{6}$$

where β_0 was the constant; β_1, β_2, and β_3 were the coefficients of the linear terms X_1, X_2, and X_3; β_{11}, β_{22}, and β_{33} were the coefficients of the squared terms X_1^2, X_2^2, and X_3^2; and β_{12}, β_{23}, and β_{13} were the coefficients of the interaction terms X_1X_2, X_2X_3, and X_1X_3. Regression analysis was carried out using coded units, with the low, intermediate, and high levels coded as 1, 2, and 3 respectively. The level of significance was defined as $P < 0.05$.

Results and discussion

In precision granulation, powder in the product chamber entered the spray granulation zone within the partition column via the partition gap. The gap setting determined the physical clearance, that is, cylindrical lateral surface area formed by the gap, and served as a 'doorway' for powder to enter the partition column. A higher partition gap would result in increased physical clearance and thus a bigger 'doorway' for powder to enter. After entry through the partition gap to the spray granulation zone, the atomized binder droplets were dispersed onto surfaces of the powder particles. The surface wetting promoted nucleation and coalescence in the powder and brought about granulation[38]. Drying of the agglomerated powder began almost instantaneously by the upward flowing air after wetting. The agglomerates rose beyond the partition column, then fall outward freely in an inverted U-shaped trajectory back to the staging periphery powder bed to await re-entry into the partition column. This fountain-like cyclic flow was repeated for the powder/granules until the process run was terminated.

In the traditional Wurster process, a large proportion of the air flowed up to the bed region peripheral to the column, which was then fully fluidized and caused powder to flood into the spray granulation zone. In contrast, much more of the air is directed into the partition column via the insert plate and the swirl accelerator in the precision granulator. As the upward flowing air jet passed through the swirl accelerator at the plenum, it was first compressed and directed through a narrowed passage by the AAI, before expanding in the partition column. This design created a much higher air velocity at the spray granulation zone (above the spray nozzle) and generated a local low pressure zone that aided in drawing particles into the core of the partition column. At a fixed partition gap, a faster flowing air stream would create a zone of lower pressure immediately above the spray nozzle. This would result in a stronger suction effect being experienced by the powder peripheral to the column. As the air velocity within the partition column not only influences the strength of the suction effect but also impacted wetting and drying by affecting residence time in the partition column and overall drying ability of the process, information about it would be extremely useful for process understanding.

Factors influencing air velocity within the partition column

From Figure 2a and b, it could be observed that an increase in airflow rate led to an increase in air velocity within the partition column. Linear regression was performed on airflow rate and air velocity within the partition column (at an AAI diameter of 30 mm and partition gap of 26 mm). The results obtained indicated a proportional relationship between the two variables ($y = 0.249x + 7.95$; $R^2 = 0.998$). The extent of

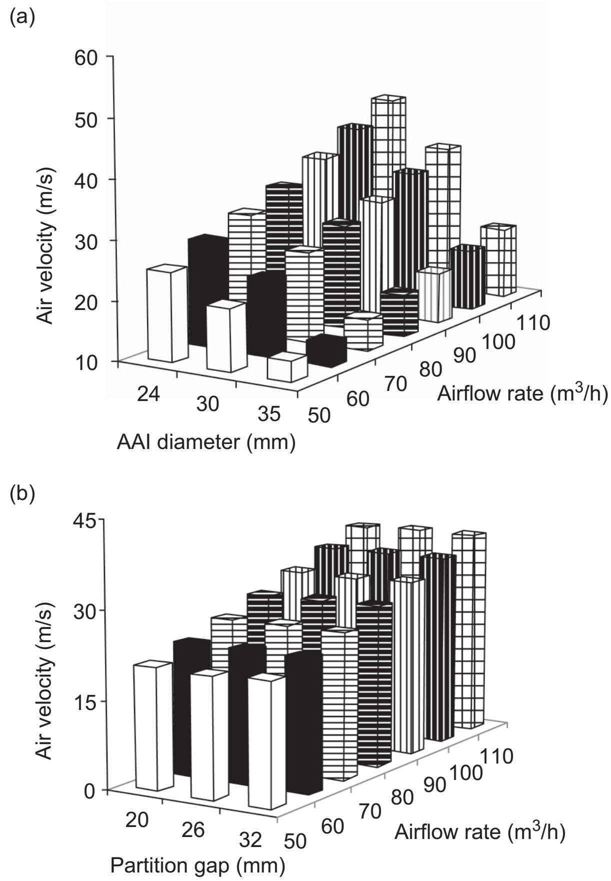

Figure 2. Influence of (a) AAI diameter (partition gap of 26 mm; n=3) and (b) partition gap (AAI diameter of 30 mm; n=3) on air velocity within the partition column at airflow rates of 50 (□), 60 (■), 70 (▤), 80 (▤), 90 (▥), 100 (▥), and 110 (▦) m^3/h.

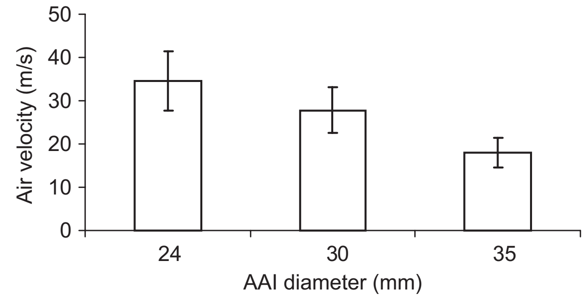

Figure 3. Influence of AAI diameter on air velocity within the partition column (averaged across partition gaps of 20, 26, and 32 mm; airflow rate of 80 m^3/h; n = 9).

increments in air velocity with airflow rate appeared to be consistent for the investigated partition gaps (Figure 2b), whereas the same increments in airflow rate led to steeper increases in air velocity for AAI of smaller diameters (Figure 2a). Therefore, when the 35 mm AAI was used, the air velocity within the partition column was comparatively less influenced by different airflow rates as compared to when smaller AAIs of 30 or 24 mm were used. From Figure 3, the relationship between AAI diameter and air velocity (averaged across partition gaps of 20, 26, and 32 mm) was established statistically using linear regression (y=−8.28x+43.3; R^2=0.988). Regression was carried out at an airflow rate of 80 m^3/h. It was shown that AAIs of larger diameters generated a lower air velocity within the partition column, and this could be explained by the law of conservation of mass[39], where the same volume of air flowing by in the same time through a narrower opening would have to move faster, giving rise to an air stream of higher velocity and lower pressure.

Factors influencing characteristics of granule batches

The various response parameters (process yield, size, shape, and flow) of the granule batches were obtained and first analyzed by factorial analyses to determine the main effects of the variables and interactions, if any. Subsequently, response surface modeling was carried out on the parameters, and the equations derived were discussed after insignificant lack-of-fit values were obtained (Table 2). Equations were successfully derived for fines, lumps, and aspect ratio.

Influence of variables on process yield

At the start of the granulation process, fine powder that was sucked into the partition column through the partition gap became trapped at the sock filters because of the static claused by the air friction. A higher binder spray rate increased the wetting rate of the lactose powder, bringing about reduced powder loss to the sock filters and avail more powder for granulation. Throughout the granulation run, sock filters positioned at the expansion chamber (above the product chamber) had a blow back air to dislodge the fines back into the product chamber after every 10 seconds. The granule batches prepared had good process yields ranging from 79.6% to 94.7%, w/w (Table 3). Among the three investigated variables, it was found that partition gap and binder spray rate had significant influences on the process yield of the granule batches (Table 4). The results advocated the usage of an optimal partition gap (at the intermediate setting) and a high binder spray rate to improve process yields. Significant interactions were found between AAI diameter and partition gap, as well as between partition gap and binder spray rate.

As mentioned above, the partition gap functioned as the ‘doorway’ for entry of powder into the partition column. The cylindrically shaped lateral physical clearances formed between the column itself and the air distribution plate were calculated to be 5027, 6535, and 8044 mm^2 at partition gaps of 20, 26, and 32 mm, respectively. As the physical clearance increased with increasing gaps, it allowed more particles to enter the

Table 2. Response surface modeling: regression coefficients of effect of variables on characteristics of the granule batches.

Coefficient	Process yield	Fines	Lumps	Modal size fraction	MMD	Span	Aspect ratio	Sphericity	Angle of repose
B_0	92.4[a]	3.65[a]	0.439	27.6[a]	342[a]	1.36[a]	1.29[a]	0.785[a]	39.4[a]
B_1	−0.281	−0.802[b]	0.199	1.55[a]	25.5[a]	−0.0820[a]	0.0169[c]	−0.0160[a]	−0.814[a]
B_2	1.18[b]	0.208	−0.209	0.421	−6.00	−0.00704	−0.00423	0.000824	−0.134
B_3	3.22[a]	−3.08[a]	−0.131	0.112	6.91	−0.0638[a]	−0.0250[a]	0.0540[a]	−0.869[a]
B_{11}	−1.34	−1.11	0.473[b]	−1.77[a]	32.5[c]	0.0305	0.00222	−0.0229[a]	−1.04[a]
B_{22}	−3.27[c]	0.0985	−0.380[b]	1.68[c]	8.52	−0.0886[c]	−0.0319[a]	−0.0433[a]	1.66[a]
B_{33}	−1.46	1.83[c]	0.221	−1.10[b]	3.52	0.118[a]	0.0115	−0.00302	0.0337
B_{12}	0.512	−0.107	0.0160	0.419	−3.63	−0.0171	0.00634	−0.00521	−0.105
B_{13}	−0.790	0.676	−0.195	−0.505	−1.87	0.0276	0.00245	0.00900[b]	0.100
B_{23}	−0.638	−0.397	−0.101	0.427	6.67	−0.0213	0.000360	−0.00328	0.159
R^2	0.422	0.631	0.244	0.493	0.290	0.538	0.459	0.830	0.706
Significance	0.000	0.000	0.014	0.000	0.002	0.000	0.000	0.000	0.000
F	5.82	13.50	2.54	7.68	3.22	9.17	6.71	38.59	18.99
Lack-of-fit significance	0.010	0.089	0.456	0.027	0.000	0.000	0.120	0.006	0.000

[a]Denotes statistical significance at 0.001 level, [b]at 0.05 level, and [c]at 0.01 level.

Table 3. Effect of variables on characteristics of granule batches.

AAI diameter (mm)	Partition gap (mm)	Spray rate (g/min)	Process yield (%)	Fines (% w/w)	Lumps (% w/w)	Modal size fraction (% w/w)	MMD (μm)	Span	Aspect ratio	Sphericity	Angle of repose (°)
24	20	18	79.6 (2.7)	7.46 (0.53)	0.72 (0.55)	24.6 (0.7)	373 (25)	1.55 (0.04)	1.28 (0.02)	0.67 (0.03)	40.9 (0.2)
24	20	21	83.0 (0.4)	2.78 (1.47)	0.78 (0.47)	25.5 (1.0)	418 (40)	1.40 (0.06)	1.26 (0.01)	0.72 (0.02)	40.0 (0.4)
24	20	24	90.9 (5.3)	1.82 (0.79)	1.68 (1.11)	25.6 (1.2)	383 (15)	1.44 (0.06)	1.24 (0.01)	0.80 (0.01)	39.1 (0.3)
24	26	18	90.1 (2.0)	8.83 (4.50)	0.32 (0.29)	22.7 (0.9)	308 (10)	1.78 (0.14)	1.33 (0.04)	0.75 (0.03)	41.6 (0.7)
24	26	21	93.7 (3.6)	4.75 (1.58)	0.07 (0.10)	25.2 (1.9)	272 (26)	1.29 (0.08)	1.27 (0.03)	0.78 (0.01)	40.1 (0.2)
24	26	24	93.6 (1.9)	1.76 (0.49)	0.67 (0.61)	23.8 (1.6)	335 (44)	1.51 (0.07)	1.27 (0.08)	0.81 (0.01)	39.3 (0.2)
24	32	18	81.8 (2.3)	8.76 (5.26)	0.27 (0.17)	24.8 (1.2)	367 (43)	1.56 (0.15)	1.24 (0.03)	0.69 (0.03)	41.8 (0.2)
24	32	21	92.3 (3.5)	3.70 (1.00)	0.42 (0.12)	23.7 (0.4)	367 (15)	1.51 (0.03)	1.23 (0.00)	0.73 (0.00)	40.4 (0.2)
24	32	24	88.5 (4.2)	1.80 (0.82)	0.53 (0.07)	25.7 (1.1)	387 (21)	1.41 (0.11)	1.20 (0.02)	0.79 (0.04)	39.3 (0.6)
30	20	18	84.0 (1.6)	7.21 (6.04)	0.11 (0.09)	27.1 (5.6)	323 (50)	1.38 (0.19)	1.28 (0.01)	0.69 (0.01)	42.6 (0.3)
30	20	21	89.8 (2.9)	4.60 (0.19)	0.08 (0.03)	29.4 (0.6)	315 (5)	1.31 (0.03)	1.25 (0.03)	0.74 (0.02)	42.6 (0.4)
30	20	24	94.7 (1.2)	1.45 (0.47)	0.23 (0.04)	27.2 (1.0)	332 (3)	1.28 (0.10)	1.24 (0.01)	0.80 (0.01)	40.8 (0.8)
30	26	18	84.8 (2.2)	12.0 (0.94)	0.13 (0.02)	27.6 (1.3)	388 (13)	1.67 (0.03)	1.38 (0.03)	0.71 (0.03)	39.1 (1.5)
30	26	21	94.5 (5.8)	3.53 (1.68)	0.71 (0.31)	25.6 (1.0)	375 (26)	1.42 (0.05)	1.27 (0.03)	0.77 (0.02)	39.0 (0.5)
30	26	24	90.0 (5.4)	1.22 (0.29)	1.43 (1.17)	26.0 (1.4)	415 (48)	1.48 (0.01)	1.25 (0.02)	0.80 (0.01)	38.4 (0.6)
30	32	18	85.1 (0.8)	9.94 (3.88)	0.09 (0.05)	26.5 (3.9)	335 (46)	1.44 (0.07)	1.31 (0.01)	0.71 (0.01)	41.0 (0.2)
30	32	21	86.7 (5.5)	1.77 (0.66)	0.19 (0.08)	33.3 (0.9)	355 (5)	1.18 (0.02)	1.27 (0.03)	0.76 (0.01)	40.4 (0.4)
30	32	24	93.5 (2.5)	2.06 (0.99)	0.22 (0.31)	30.0 (1.1)	332 (26)	1.28 (0.04)	1.24 (0.02)	0.79 (0.02)	40.0 (0.2)
35	20	18	79.8 (1.8)	6.47 (0.86)	0.95 (0.55)	28.1 (2.0)	455 (44)	1.39 (0.04)	1.31 (0.03)	0.63 (0.02)	40.7 (0.2)
35	20	21	85.9 (2.4)	2.13 (0.43)	0.97 (0.61)	27.5 (1.5)	425 (25)	1.34 (0.09)	1.31 (0.07)	0.70 (0.02)	39.0 (0.1)
35	20	24	86.9 (4.7)	2.07 (0.59)	1.12 (0.79)	27.4 (0.6)	405 (18)	1.31 (0.05)	1.26 (0.02)	0.77 (0.01)	38.6 (0.3)
35	26	18	89.8 (6.3)	2.51 (1.21)	2.24 (2.78)	28.5 (2.3)	365 (13)	1.30 (0.12)	1.33 (0.02)	0.71 (0.01)	38.3 (0.0)
35	26	21	89.8 (4.3)	0.76 (0.13)	1.05 (1.21)	27.0 (2.5)	422 (16)	1.29 (0.13)	1.28 (0.06)	0.77 (0.03)	37.1 (0.3)
35	26	24	88.3 (7.8)	1.64 (0.43)	1.56 (1.51)	24.9 (1.8)	418 (73)	1.42 (0.02)	1.30 (0.01)	0.81 (0.00)	35.3 (0.2)
35	32	18	86.7 (3.9)	7.43 (2.90)	0.60 (0.31)	27.3 (0.1)	383 (64)	1.49 (0.09)	1.29 (0.05)	0.60 (0.03)	40.0 (0.5)
35	32	21	88.0 (0.6)	2.52 (0.75)	0.30 (0.08)	30.6 (2.2)	380 (33)	1.17 (0.14)	1.28 (0.03)	0.69 (0.04)	39.2 (0.1)
35	32	24	93.1 (0.7)	1.71 (0.60)	0.25 (0.17)	28.3 (1.3)	415 (13)	1.26 (0.09)	1.27 (0.03)	0.76 (0.03)	39.7 (0.1)

Reported as mean of three batches, values in parentheses denote SD.

Table 4. Analysis of variance of effect of variables on characteristics of the granule batches.

Source	Process yield	Fines	Lumps	Modal size fraction	MMD	Span	Aspect ratio	Sphericity	Angle of repose
X_1	—	b	c	a	a	a	b	a	a
X_2	a	—	c	b	—	a	a	a	a
X_3	a	a	—	—	—	a	a	a	a
$X_1 X_2$	c	—	c	—	a	b	—	a	a
$X_1 X_3$	—	c	—	—	—	—	—	c	b
$X_2 X_3$	c	—	—	—	—	c	—	—	—
$X_1 X_2 X_3$	—	—	—	c	—	b	—	—	a

[a]Denotes statistical significance at 0.001 level, [b]at 0.01 level, and [c]at 0.05 level and (—) denotes statistical insignificance.

column. However, this increment in gap might weaken and undermine the suction effect on the peripheral powder particles. Therefore, when the physical clearance was low (20 mm), it limited the amount of powder entering the column. At 32 mm, the high physical clearance might have allowed a greater amount of powder to enter the column, but it also weakened the suction effect. Hence, an optimal gap setting was found at 26 mm where a maximal amount of powder was drawn into the column. As it was more difficult for the upward flowing air stream to transport the particles upward with the presence of more powder in the column, the particles were lifted to a comparatively lower height before falling freely outward onto the periphery bed. This resulted in less of the static-charged powder trapped onto the sock filters during the initial phase of the process and improved the process yields as observed. The diameter of the AAI was found to have a significant interaction with partition gap and played a less direct role in influencing process yield. A more humid environment in the product chamber brought about by high binder spray rates promoted agglomeration, especially of fines onto larger aggregates when they were dislodged from the sock filters, resulting in the observation of better process yields with increasing binder spray rates. Higher process yields were seen in batches under processing conditions with intermediate partition gap and high binder spray rates because of a synergistic interaction between the two variables (Table 4). Lewis et al.[40] explained that an interaction is the failure of a factor to produce the same effect at the same response for the different levels of the other factor. Hence, it implied that with intermediate partition gap and high binder spray rate, the increase in process yield would be more than with intermediate partition gap and intermediate level of binder spray rate.

Influence of variables on granule size and size distribution

The amount of fines seen in the granule batches ranged from 12.0% to 0.76% (w/w). The analysis of variance indicated that a significantly higher amount of fines were seen in batches under processing conditions with AAI of small diameters and low binder spray rates, with synergistic interaction between the two variables (Table 4). To reduce the amount of fines, usage of an AAI of large diameter with high binder spray rate would be recommended. Within the conditions investigated, a relatively small amount of lumps, ranging from 0.11% to 2.24 % (w/w), were seen in the batches prepared. Significantly, more lumps were observed when small or large AAI diameters were used, and there was also a higher amount of lumps produced at the intermediate level of partition gap as compared to other gap settings. This could have been attributed to the higher amount of powder drawn into the column at this optimal clearance gap compared to the other two gap settings, which resulted in more opportunities for agglomeration at the spray granulation zone.

An interaction between AAI diameter and partition gap for lumps was also observed. The regression equations after adequate fit by the quadratic model [Equation (6)] for fines (Y_{fines}) and lumps (Y_{lumps}) were

$$Y_{\text{fines}} = 3.65 - 0.802X_1 - 3.80X_3 - 1.83{X_3}^2 \quad (7)$$

$$Y_{\text{lumps}} = 0.473{X_1}^2 - 0.380{X_2}^2. \quad (8)$$

In Equation (7), the coefficients of the binder spray rate terms (linear and squared) were higher than that of the AAI linear term and could be due to the wetter conditions in the powder bed when high binder spray rates were employed. More wetting also occurred when medium and large diameters of AAIs were used, because of the longer residence time of the powder particles at the spray granulation zone resulting from the lower air velocity within. This allowed greater opportunities for agglomeration in the spray granulation zone, thus decreasing the amount of fines (Figure 4a) but

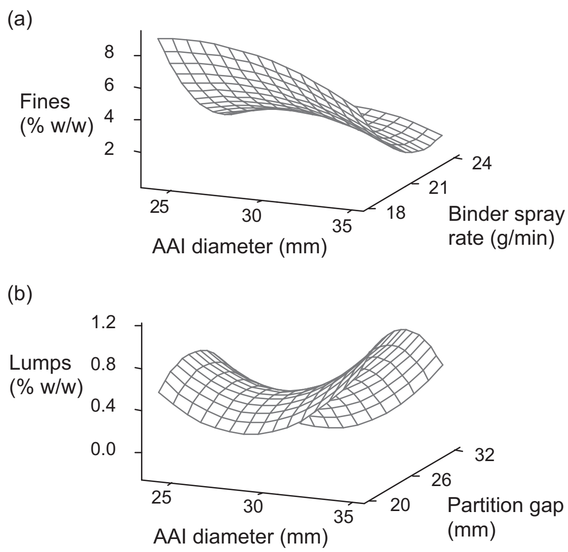

Figure 4. Response surface graphs of the effect of (a) AAI diameter and binder spray rate on fines (hold values at partition gap = 26 mm) and (b) AAI diameter and partition gap on lumps (hold values at binder spray rate = 21 g/min).

increasing the amount of lumps generated (Figure 4b) at large AAI diameter of 35 mm. When AAIs of small diameter (24 mm) were used, powder mass was rapidly transferred out of the partition column onto the staging peripheral powder bed, and the strong air velocity could have caused a lot of the fine powder to be trapped on the sock filters at the early phase of the process. This resulted in an initial lower load of actively granulating powder in the product chamber, and, consequently, larger granules were produced as the cyclic flow of powder into the spray granulation zone was more frequent as compared to a process with a higher load of actively granulating powder. As the process progressed, fines from the sock filters were gradually blown down into the product chamber to be granulated and thus did not affect the eventual process yield. This explained the large amounts of fines and lumps found when AAI of small diameter was used (Figure 4a and b). The amounts of resultant fines and lumps under different conditions correspondingly determined the proportion of the granule modal size fraction of granules. The high amounts of fines and lumps in batches when AAI of small diameters were used significantly decreased the proportion of the modal size fraction (Table 3). Slightly lower amounts of modal size fraction were obtained at the intermediate level of partition gap, where comparatively higher amount of lumps were formed. An interaction between the three variables was also observed (Table 4).

AAI diameter was the only significant variable found to influence MMD, an increase from small to medium AAI diameter led to a very slight decrease, whereas a marked increase was observed from an increase from medium to large AAI diameter (Table 3). This could be explained by the initial lower effective powder loads for granulation as discussed in the previous section for usage of AAI with small diameter, which led to the formation of comparatively more large granules within the size distribution, resulting in higher MMDs at this setting. Correlation analyses between the air velocity within the partition column and MMDs of granule batches when AAI diameter was increased from 30 to 35 mm were significant (Pearson correlation = −0.553, $P = 0.000$). A decrease in air velocity within the partition column corresponded to larger granule size within the batch. This meant that the air velocity within the partition column indeed led to wetter conditions at the spray granulation zone and helped to promote granule growth. Even though a slight increase in MMD values was observed as binder spray rate increased, this variable was insignificant. This finding was in contrast to earlier reports, in which binder spray rate was found to result in significant increase in granule size[17,21,23]. This interestingly pointed out that in this process, control of the AAI diameter was more important than binder spray rate in controlling granule growth. The relative insensitivity of the process to binder spray rate due to its good drying efficiency suggested that it may be possible to granulate moisture-sensitive drugs using precision granulation. A shortening in processing and thus exposure time of the moisture-sensitive drugs to water may also be achieved by employing high binder spray rates, with further usage of high inlet air temperature to enhance process drying efficiency. In addition, a significant interaction was observed between AAI diameter and partition gap. Even though granule growth was shown to be dictated by the air velocity at the spray granulation zone, usage of a partition gap at the intermediate setting could generally promote growth.

The results indicated that all variables studied affected the span with significant interactions (Table 4). The wider size distributions with maximal mean span of 1.78 were obtained for batches using small AAI diameter, low binder spray rate, and intermediate partition gap (Table 3). This was because of the large amounts of fines and lumps formed under these conditions. AAI diameter accounted for the production of lower amounts of fines when AAIs of medium and large diameters were used, resulting in narrow size distributions. The larger amount of lumps produced at the intermediate level of partition gap also consistently led to wider size distributions across all conditions investigated. There appeared to be an optimal decrease in span with increasing binder spray rates. This was attributed to the high amount of fines produced at the dry conditions created at low binder spray rate of 18 g/min and the formation of more lumps during wetter conditions at high binder spray rate of 24 g/min. Therefore, a decrease in span values was observed at the intermediate binder spray rate.

Influence of variables on granule shape

Becher and Schlunder[41] suggested that formation of a drying zone above a spouting powder bed employing bottom spray encouraged spherical granule growth by surface layering. Growth by surface layering would occur when evaporation of the solvent from a binder suspension or solution leaves behind the deposited solid materials on particles as layers. The authors proposed that in precision granulation, surface layering occurred during the early stages of granulation. At the later stages, size-enlargement took place either by coalescence of fines onto larger particles (that had grown via surface layering) or by coalescence of these larger particles with one another. High presence of fines and drier conditions would encourage coalescence of fines onto larger particles, giving rise to granules that are more spherical.

The main effects of the three variables on aspect ratio and sphericity were found to be statistically significant (Table 4). Significant interactions among the investigated variables were also observed. The quadratic model [Equation (6)] was able to fit the data obtained for aspect ratio (Y_{asp}):

$$Y_{asp} = 1.29 + 0.0169X_1 - 0.0249X_3 - 0.0319X_2^2. \quad (9)$$

An increase in AAI diameter led to granules that were less spherical with higher aspect ratios (Figure 5a). Less spherical granules were also observed at the intermediate level of partition gap. The model suggested that to obtain granules that were more spherical, the air velocity at the spray granulation zone should be fast. This setting generated batches with comparatively higher amount of small particles and fines, which subsequently coalesce onto the larger particles. The layering of these fines onto the larger particles helped to produce a more spherical structure. Additionally, the faster air through the spray granulation zone would give rise to a stronger shear action on the coalesced particles and help to shape them. When slower air velocities were generated from usage of larger AAI diameters, they allowed particles longer residence times at the spray granulation zone and generated batches with large particles and less fines. Thus, coalescence of these large particles with one another predominated. On top of the weaker shear action of the slower air passing through the spray granulation zone, granules that were less spherical were thus observed. At the intermediate partition gap, a higher amount of powder was able to enter the column as it was the optimal physical clearance observed. The presence of more powder within the partition column and more lumps at this gap setting gave rise to the formation of less spherical granules. The findings emphasized the important role of fluid dynamics at the spray granulation zone in influencing the mode of granule growth and thus granule morphology, highlighting the difference of the bottom spray process from conventional top spray.

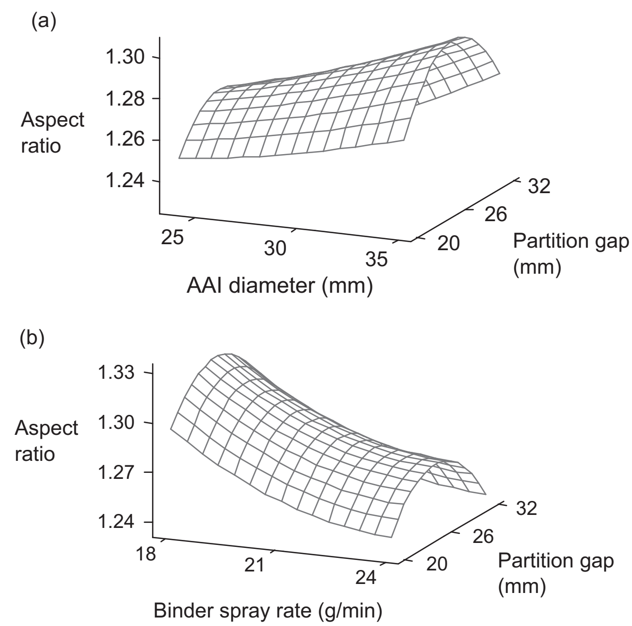

Figure 5. Response surface graphs of the effect of (a) AAI diameter and partition gap (hold values at binder spray rate = 21 g/min) and (b) binder spray rate and partition gap (hold values at AAI diameter=29.5 mm) on aspect ratio.

The influence of wetting on granule morphology too cannot be neglected. A general decrease in aspect ratio and increase in sphericity values were observed as binder spray rate increased and granules with the highest degree of sphericity were obtained at high binder spray rate level (Table 3). When the binder spray rate increased, surfaces of these particles were wetted more thoroughly, thus the particles deformed and coalesced evenly in all directions, resulting in structures that were more spherical. In comparison, agglomeration was observed to take place in a less uniform manner under drier conditions when lower spray rates were used. As suggested by the model, high binder spray rate along with small AAI diameter and intermediate partition gap should be employed if granules with higher degree of sphericity are desired (Figure 5b).

Influence of variables on granule flow

The batches produced had good general flow with angle of repose ranging from 35.3° to 42.6° (Table 3). The results indicated that batches with larger granules flowed better with lower angles of repose. The lowest mean angle of repose was observed when large AAI diameter, intermediate partition gap, and high spray rate were employed. Flow of the batches was dependent on granule size and shape. The improvement in bulk granule flow with usage of large AAI diameter was mainly due to the larger granules that were formed, and being less cohesive, large granules flowed better than smaller granules. The lesser amount of fines that resulted at this setting also contributed to improve the flow. The high binder spray rate resulted in structures that were comparatively more spherical and thus flowed better.

Conclusion

AAI diameter and partition gap were shown to strongly affect granule size and morphology in the bottom spray precision granulation process, through their influences on the fluid dynamics at the spray granulation zone. The AAI diameter was shown to determine the velocity of the air passing through the spray granulation zone, whereas the partition gap regulated particle movement into the zone. Generally, with the usage of a large AAI diameter, a comparatively slower air velocity resulted, which increased the residence time at the spray granulation zone and produced batches with larger size, narrower size distributions, and granules of less spherical structures. An intermediate level of partition gap was found to be necessary to optimally transport particles into the spray granulation zone to increase process yields. Because of the process's good drying ability, binder spray rate was found to affect granule morphology but not granule size. This indicated that better flowing granules with more spherical structures could be obtained with the use of high binder spray rates, and this could be achieved without an increase in the resultant granule size of the batch. In comparison to the conventional fluidized bed granulation, this dependence of growth on the fluid dynamics at the spray granulation zone makes this process more robust to changes in wetting conditions and allows the user flexible control of granule size and morphology. More important are the implied capabilities for potential development for on-line control of granule size and adaptation for granulation of moisture-sensitive materials.

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