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RESEARCH PAPER

Role of Base Plate Rotational Speed in Controlling Spheroid Size Distribution and Minimizing Oversize Particle Formation During Spheroid Production by Rotary Processing

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ABSTRACT

The occurrence of material adhesion and formation of oversize particles in the product yield during one-pot spheroid production by rotary processing leads to a less predictable process and a decrease in the usable portion of the total product yield obtained from each production run. The use of variable speeds of the rotating frictional base plate during the spheronization run was investigated for achieving optimal spheroid production. When the base plate speed was increased during liquid addition, the greater centrifugal forces generated improved liquid distribution and the mixing of the moist powder mass, resulting in a decrease in the amount of oversize particles formed. When the base plate was maintained at a high speed throughout the run, the amount of oversize particles and mean spheroid size increased, and a greater ''between batch'' mean spheroid size variability was also observed. The findings showed that, when higher speeds were used, the residence time must be adjusted accordingly to avoid excessive coalescence and growth while maintaining even liquid distribution. A ''low-high-low'' speed variation during rotary processing may be used to produce spheroids with a narrow size distribution and with a minimal amount of oversize particles in the total product yield.

Key Words: *Base plate rotational speed; Oversize particles; Rotary processing; Rotary processor; Spheroids; Spheronization.*

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INTRODUCTION

During spheroid production by rotary processing, part of the moistened mass may occasionally be deposited on the chamber wall and/or onto the rotating frictional base plate (1). Previously, Robinson and Hollenbeck (2) also noted the occurrence of a buildup of nonspherical moist material on the wall and the formation of oversize spherical material that had agglomerated at a faster rate than the rest of the product yield. Due to material adhesion and the formation of oversize particles, the usable portion of the total yield obtained from each production run was decreased. This led to a less predictable process, wastage of starting material, and higher production cost. Moreover, a high yield of spheroids in the desired size range is a prerequisite if the rotary processor is to be used for a one-pot spheroid production and coating operation.

Material adhesion to the chamber wall is minimized by lining the wall of the product chamber with polytetrafluoroethylene (PTFE) (3–6). In our laboratory, attempts were made to reduce material adhesion by applying a layer of PTFE lining onto the surface of the inner chamber wall just above the base plate. Efforts were also directed at coating the base plate with a layer of nonstick silicon (Silikophen Non-Stick 50, Tego Chemie, Essen, Germany) to reduce material adhesion. Despite these efforts, oversize particles were still found in the batches of spheroids produced.

In higher shear mixers in which material adhesion (7–9) was also encountered during wet pelletization, specialized impellers and choppers may be used to narrow the size distribution of the pellets by breaking up agglomerated or caked masses (7,8,10). A scraper has also been used to reduce material adhesion at the bottom of the mixer bowl (11). The rotary processor did not have such specialized tools with direct comminuting and/or scraping actions to counteract problems arising from the adhesion of moist material as such tools may interfere with the later spheroid rounding process. It was reported that baffles can be installed in the rotary processor to direct the upper part of the powder mass downward on to the base plate and toward the center of the inner chamber to ensure that the powder mass travels in a tumbling rope-like motion on the base plate (4,5). According to these researchers, the application of a wall coating of PTFE and the use of baffles are prerequisites for process reproducibility.

This paper describes an alternative approach of using variable speeds of the rotating frictional base plate during the course of the production run for achieving optimal spheroid production. Qualitative visual studies using water-soluble dyes were first conducted to investigate the distribution pattern of the moistening liquid, the mixing pattern of the powder mass during liquid addition, and the occurrence of material adhesion and oversize particle formation during rotary processing (12).

EXPERIMENTAL

Materials

Microcrystalline cellulose (MCC; Avicel® PH-101, Asahi Chemical, Osaka, Japan) and lactose monohydrate (Pharmatose® 200M, De Melkindustrie Veghel, Veghel, The Netherlands) were used as supplied. Distilled water was used as the moistening liquid. Chlorpheniramine maleate (BP grade) was used as a model drug. It was added either by dry mixing with the MCC and lactose powders or by dissolving in the amount of distilled water used as the moistening liquid for spheroid production.

Preparation of Spheroids by Rotary Processing

MCC and lactose powders in a weight ratio of 1 : 3 were premixed in a laboratory double-cone mixer (JEL, J. Engelsmann, Ludwigshafen, Germany) for 30 min. A weighed amount (500 g) of the mixed MCC : lactose powder was poured into the inner chamber of the rotary processor (MP-1 with rotoprocessor accessories, Niro Aeromatic, Bubendorf, Switzerland). The 30-cm diameter frictional base plate had a crosshatch design comprised of square studs with rounded edges (diameter 9 mm, height 2 mm) arranged in a 10-mm square grid pattern at alternate intersections. The base plate was set into motion while the moistening liquid was sprayed onto the rotating powder mix at a constant liquid spray rate (20 ml/min unless other otherwise stated) using a peristaltic pump (503S1, Watson Marlow, Falmouth, UK). Unless otherwise stated, moistening liquid amounting to 200 ml (i.e., 40% w/w of the total weight of MCC : lactose powder mass) and a rotational speed of 480 rpm were used. The inlet air temperature was set at 30°C during the liquid addition and tumbling stages. The gap air pressure and atomizing air pressure settings were both fixed at 0.8 bar.

After liquid addition, the spheroids were allowed to tumble for 20 min before proceeding to the drying stage. During drying, the inlet air temperature was increased to 60°C, and the rotational speed was reduced to 145 rpm. The upper wall of the inner chamber was raised to allow spheroids to travel out of the inner chamber into the fluidization zone located between the inner and outer chambers and where heated fluidizing air was introduced for drying the spheroids. Drying was continued for about 20 min until a constant raised outlet air temperature of 45°C was attained.

Distribution of Moistening Liquid and Mixing of Powder Mass During the Liquid Addition Stage

Dye (3 ml) was injected rapidly into the spray tubing at two different times during the liquid addition stage. A red dye was used for the first injection at 2.5 min after the start of liquid addition, and a blue dye was employed at 8 min. High-speed photographs (1/4000 sec) were taken at various times during the liquid addition stage to monitor the spread of the dyes into the powder mass.

Occurrence of Material Adhesion and Formation of Oversize Particles

Three bolus doses of water-soluble dyes, in order of increasing color intensity, were injected into the spray tubing at three different times during the liquid addition stage. The colors of the dyes added after 2.5, 4.5, and 8 min were green, red, and blue, respectively. The agglomeration-spheronization process was terminated immediately after completion of liquid addition without proceeding to the tumbling and drying phases. The discrete moist agglomerates were collected. Moist material that remained as layers or cakes adhering on the base plate and chamber wall was noted. The base plate was then removed carefully such that the residue on the plate could be examined.

Investigations on Influence of Base Plate Rotational Speed

Agglomeration-spheronization runs were conducted with the rotational speed of the base plate set at 480 and 700 rpm throughout the liquid addition and tumbling stages. In another series of runs, the base plate was rotated at 480 or 700 rpm during the liquid addition stage and at 480 rpm during the tumbling stage using liquid spray rates of 15, 20, and 30 ml/min. Runs were also carried out with 38%, 40, and 45% water while varying the rotational speed during the liquid addition and tumbling stages using various ‘‘low-high-low’’ speed conditions.

The powder masses undergoing agglomeration-spheronization were also photographed at various time intervals during the liquid addition and tumbling stages to evaluate the influence of base plate rotational speed on spheroid formation and growth. High-speed photographs were taken during the early part of the liquid addition stage when a red dye was injected into the spray tubing at 2.5 min after beginning liquid addition. The various rotational speeds used during the liquid addition stage were 480, 700, and 1150 rpm. Runs were also carried out with 45% water using single speeds of 480 and 700 rpm as well as a low-high-low speed variation (480 rpm for 20 min, 1150 rpm for 6 min, then 480 rpm for the rest of the liquid addition stage and during the tumbling stage).

Size Analysis

After rotary processing, the total yield obtained was sieved using a 2-mm aperture size sieve (Endecotts, London, UK). The amount retained on the sieve represented the amount of oversize particles with a diameter greater than 2 mm. These were considered oversize in comparison with the rest of the spheroids and were defined as ‘‘lumps.’’

The lengths of 50 of the largest oversize particles were measured using a micrometer screw gauge (7305, Mitutoyo, Tokyo, Japan) to determine their average length. The fraction greater than 2 mm size was then recombined with the rest of the yield, and the total yield was randomly divided into 8 samples using a spinning riffler (Retsch, Haan, Germany). For size analysis, a sample about 60 g was accurately weighed, and a nest of sieves (Endecotts) was used to separate the weighed amount of spheroids into various size fractions. The geometric weight mean diameter and geometric standard deviation of the spheroids were calculated (13).

Image Analysis

At least 60 particles were randomly selected for image analysis. The spheroids were selected from the modal class fraction obtained from size analysis by sieving. The image analyzer (Imageplus, Dapple System, Sunnyvale, CA) consisted of a computer system connected to a video camera (WV-1500 E/C, National, Osaka, Japan). The average area, perimeter, length, and breadth of the spheroids were determined from their digitized images. The elongation index, aspect ratio, is expressed as the quotient of the average length and breadth of the particle. Form factor, a measure of the degree of particle sphericity and a value of unity, describes a perfect circle, and is found by

$$\text{Form factor} = \frac{4\pi(\text{Area})}{(\text{Perimeter})^2}$$

RESULTS AND DISCUSSION

Distribution of Moistening Liquid and Mixing of Powder Mass During the Liquid Addition Stage

During the liquid addition stage of spheroid production by rotary processing, the moistening liquid was sprayed onto the rotating powder mass in the form of atomized droplets through a spray nozzle located at the lower wall of the inner product chamber. The powder mass became increasingly moistened as it moved repeatedly across the path of the spray droplets. When a bolus of red dye was injected at 2.5 min after the start of liquid addition, the dye diffused out quickly to form a colored band around the powder mass at the lower part of the chamber. The colored portion then gradually, within 0.5 min, moved upward and mixed with the rest of the powder mass until the whole mass was colored.

The distribution of the moistening liquid began from the lower part of the product chamber, spreading upward from the spray zone eventually to the whole powder mass. After picking up moisture, the wetted portion of the powder mass was forced by the centrifugal forces generated by the rotating base plate to move upward along the chamber wall. Due to the mixing action effected by the tumbling motion of the powder mass, as the wetter portion encountered the less wet regions of the powder mass, moisture tended to distribute out from the wetter portion to the less wet regions, equilibrating the moisture content of the powder mass. The attempt at equilibrating the moisture content of the powder mass by liquid distribution was in accordance with the findings of Njikam and Spring (14). They reported that, when a binding liquid was added to dry powder during wet granulation, the liquid from an overwetted region tended to distribute to the rest of the powder bed by drainage as well as by the action of a mixer-granulator.

During the initial part of the liquid addition phase (about 2.5 min), the powder particles tended to clump together and seemed to move collectively as moisture-quenched chunks (Fig. 1). With time and on the addition of more moistening liquid, the shearing action set up by the rotating base plate effected the mixing of the powder mass with the moistening liquid and gradually transformed the moisture-quenched chunks into discrete aggregates that were visibly larger than the original powder particles. The moist aggregates, on random collision or adhesion with one another, undergo coalescence, fusing to form larger units. The deformation and coalescence process between agglomerates was enhanced by the augmentation of agglomerate plasticity in the presence of increasing amounts of surface moisture. The agglomerates continued to grow in size during liquid addition when moistening liquid was continually added.

(a)
(b)
(c)

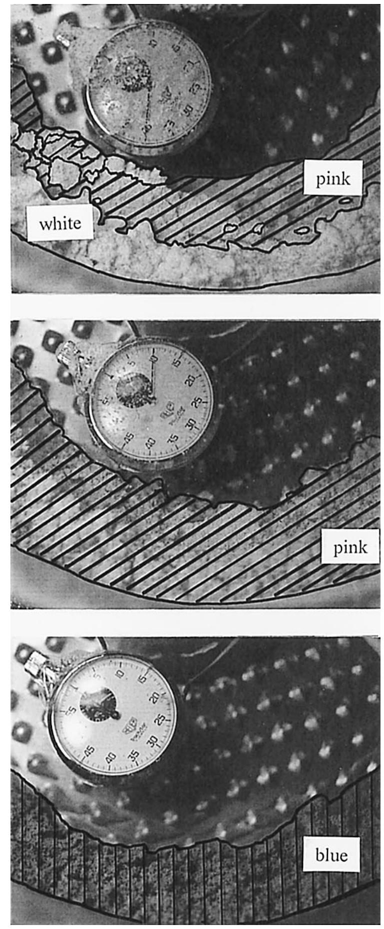

Figure 1. High-speed photographs (aerial view) taken at (a) 2 min 40 sec, (b) 3 min 10 sec, and (c) 9 min after the commencement of liquid addition showing the spread of a dye to the powder mix when the base plate was rotated at 480 rpm (0.6×).

When a blue dye was injected at a later stage (8 min) during the run, discrete agglomerates could be seen moving on the rotating plate in a tumbling ropelike motion typically associated with spheroids during the spheronization stage in extrusion-spheronization (Fig. 1).

Occurrence of Material Adhesion and Formation of Oversize Particles

Dyes of different colors were injected at three different times (2.5, 4.5, and 8 min) during liquid addition for monitoring the liquid addition process to elucidate how, where, and when material adhesion occurred. The powder mass was first colored green, then pink, and last blue during the course of liquid addition.

In an ideal situation in which there was homogeneous distribution of the moistening liquid into the powder mass, the entire mass should be colored blue after liquid addition, and there should be no traces of green or pink material as the blue dye was the last to be injected. The mass should also consist of discrete agglomerates that, after liquid addition, would be relatively round in shape.

From the product collected at the end of the liquid addition phase, it was observed that most of the powder mass was indeed converted into discrete agglomerates that were colored blue. However, some of the moist material was also found to remain as a cake on the base plate and on the lower wall, which could not be lined with the PTFE tape due to its proximity to the rotating base plate.

When the residual moist cake was sliced perpendicular to the base plate, different colored patches and layers were observed (Table 1). Traces of green patches were found at the bottom on the base plate, indicating that material adhesion on the plate had already begun in the early stages of liquid addition as the green dye was the first to be injected. The absence of white moist powder indicated that some degree of wetting must precede the process of material adhesion. The initial adhesion of material to the base plate was attributed to an increase in the cohesiveness of the powder mass following the addition of the moistening liquid. Moist material continued to be deposited with time as the powder mass was progressively wetted, as shown by the pink and blue layers on the base plate. Material adhesion to the lower wall occurred at a relatively later stage in time, as demonstrated by the presence of mostly blue cakes with some pink patches adhering to the chamber wall. The distribution of the dye to the tumbling nonadhering powder mass was rapid. The tumbling powder mass was likely to be evenly colored very soon after dye addition. The presence of patches and cakes with different colors indicated that adhesion occurred continuously during liquid addition. It was inferred that since wetting commenced from the bottom portion of the chamber, adhesion and caking on the plate and lower wall were due to localized overwetting in this vicinity.

Table 1

Observations Made of the Moistened Powder Mass Immediately After the Liquid Addition Stage

Dye Color	Dye Injection Time During the Liquid Addition Stage (min)	Observations Made Immediately After the Liquid Addition Stage
Green	2.5	Green patches found on base plate, usually found below pink layer
Red	4.5	Substantial amount of pink caking below blue layer on base plate and at lower wall
Blue	8.0	Largest amount of caking forming blue topmost layer on base plate and at lower wall Aside from caking, most of powder mass in the form of moist blue discrete agglomerates

Forty percent water delivered at 20 ml/min.
Rotational speed of base plate during the liquid addition stage 480 rpm.

In a complete run, the moistened mass was allowed to tumble on the rotating base plate for some time after liquid addition and before drying was carried out. Depending on the prevailing conditions, the residual moist material adhering onto the base plate and wall may have several possible outcomes after the liquid addition stage.

The moist material could remain wedged between the studs on the base plate or be stuck onto the wall and not participate in the agglomeration-spheronization process. This would lead to a decrease in the spheroid yield with the buildup of moist material on the plate and wall. As spheroids enter in a tumbling ropelike motion on the rotating base plate, some of the adhered moist material may be dislodged and added onto the tumbling spheroids by a mass transfer process. Moist residues may also detach from the base plate and lower wall. When broken up into smaller units, these caked residue units could eventually be rounded into spheroids such that they blended in with the rest of the yield. As for larger break-off pieces, these were the likely precursors of the unwanted lumps found interspersed among the relatively smaller spheroids in the yield. Even if the break-off pieces were smaller, the eventual spheroids produced were of a different population and tended to produce a wider size distribution.

The forces set up in the rotary processor were generally of lower intensity than those encountered in the high-shear mixer. The continued tumbling after the liquid addition stage may not be as effective in equilibrating moisture in a nonhomogeneously wetted powder mass as they would be if higher intensity forces were involved. Moreover, it has been reported that the nonhomogeneous distribution of the moistening liquid in the powder mass after liquid addition could complicate the growth of granules in the massing stage in high-shear pelletization as both moisture equilibration and growth of granules had to take place at the same time (15,16). As it was difficult to reverse the effects of a nonhomogeneously wetted mass by attempting moisture equilibration during the tumbling stage, it was important to ensure that the powder mass was homogeneously wetted right from the start of the liquid addition stage. A uniformly moistened mass was essential for producing well-formed nuclei such that spheroid formation and growth can proceed in a controlled manner to give spheroids with a narrow size distribution.

In the absence of specialized tools for mixing and breaking up adhered masses, the rotary processor would rely largely on the kinetic forces set up by the rotating base plate to bring about liquid distribution and mixing during the liquid addition stage. Consequently, in rotary processing, the rotational speed of the base plate may be used as a variable for effecting an improvement in mixing and in liquid distribution to minimize material adhesion and the subsequent formation of unwanted oversize particles. The use of baffles may be effective in aiding the breaking up of adhered masses or moisture-quenched powder chunks at the early stages of liquid addition. For the baffles to be effective, they have to be inserted in sufficient depth into the tumbling powder mass. These baffles can interfere with the subsequent spheroid-rounding stage by becoming an attritive barrier unless they are raised or removed.

Influence of Base Plate Rotational Speed

The tangential acceleration and the peripheral velocity of the rotating base plate were usually maintained during spheronization on scaling-up from a small scale to a larger scale system (17,18). From previous studies (19) using a small-scale spheronizer, rotational speeds of 1000 to 2000 rpm were found to be favorable for spheroid production. Based on these assumptions, rotational speeds of 400 to 800 rpm were used in rotary processing as the diameter of the frictional base plate in the rotary processor was 2.5 times larger.

A rotational speed of 480 rpm was first chosen for use in the investigations of spheroid production by rotary processing. This speed was maintained throughout the liquid addition and tumbling phases. The rationale for this choice of a speed at the lower end of the predicted speed range was to minimize loss of dry powder from the inner product chamber at the start of each run when the base plate was first set into motion. However, large oversize particles were found among the product yield (Table 2).

When a higher rotational speed was used during liquid addition, the powder mass was able to make a faster pass through the spray zone, and at each pass, less liquid was

Table 2

Effect of Base Plate Rotational Speed on the Mean Size and Size Distribution of the Spheroids

Rotational Speed (rpm)	Liquid Spray Rate (ml/min)	Geometric Weight Mean Diameter (mm)	Geometric Standard Deviation	Fraction of Yield > 2 mm size (% w/w)	Average Length of Oversize Particles (mm)
480 during liquid addition and tumbling stages	15	0.59	2.05	6.62	10.59
	20	0.73 (0.06)	1.74 (0.06)	8.10 (0.78)	12.30
	30	1.15	1.61	11.01	10.95
700 during liquid addition stage; 480 during tumbling stage	15	0.47	1.35	1.52	4.69
	20	0.63	1.51	2.67	8.89
	30	1.09	1.51	9.93	8.53
700 during liquid addition and tumbling stages	20	1.04 (0.26)	1.53 (0.08)	9.29 (4.83)	6.99

Standard deviation values of $n = 3$ runs given in parentheses.

sprayed onto the moving mass per unit distance moved. The increased rotational speed correspondingly increased the number of such passes through the spray zone. Consequently, the moistening liquid may be distributed more evenly into the powder mass. The higher centrifugal forces generated by the rotating base plate also enhanced material motion and intensified the mixing action of the powder mass. During the initial liquid addition stage, the powder mass was forced to move higher on the chamber wall, and there was also less clumping such that it appeared as a narrow band when viewed from the top (Fig. 2). Although spheroid geometric weight mean diameters remained relatively constant, the geometric size distributions of spheroids narrowed, as indicated by the smaller geometric standard deviation values when base plate rotational speed was increased from 480 to 700 rpm during the liquid addition stage (Table 2). A decrease in both the amount and average length of oversize particles were noted for formulations with a similar amount of moistening liquid delivered at liquid spray rates of 15 and 20 ml/min. However, these observations were less obvious at a higher spray rate. This was attributed to an increased rate of wetting, which resulted in greater spheroid growth and the formation of larger agglomerates with an overall increase in spheroid mean size.

(a)

(b)

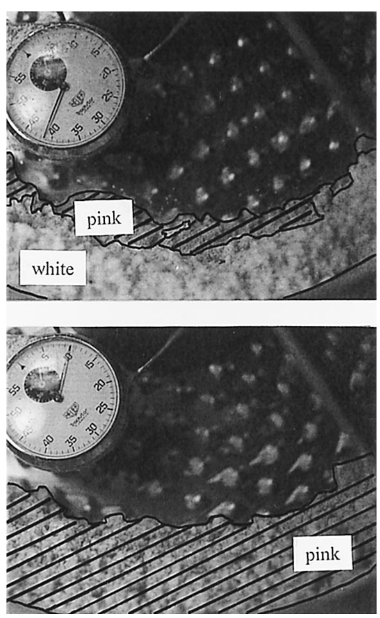

Figure 2. High-speed photograps (aerial view) taken at (a) 2 min 41 sec and (b) 3 min 10 sec during the liquid addition stage when the base plate was rotated at 700 rpm (0.6×).

When the rotational speed was increased to 700 rpm during both the liquid addition and tumbling stages, larger spheroids were produced (Table 2). Besides influencing liquid distribution, base plate rotational speed can also influence the extent of spheroid growth. With higher rotational speeds, the stronger forces involved increased the tendency for coalescence of moist nuclei when they collided and adhered together, forming larger agglomerates. In rotary processing, if the base plate is rotated at a different rotational speed during the liquid addition stage, the agglomerates obtained immediately after liquid addition may not have equivalent characteristics even though a similar formulation and amount of moistening liquid, delivered at a constant liquid spray rate, were used. The degrees of liquid distribution, mixing, and coalescence vary depending on growth in the preceding liquid addition stage. As a higher growth rate was generally associated with the use of a higher rotational speed, high-speed photographs taken at similar processing times showed that larger agglomerates were formed at each time frame during rotary processing at a higher rotational speed.

Agglomerate surface moisture may be increased by liquid addition and by the squeezing out of moisture from the agglomerate interior during densification, when the agglomerates travel in a tumbling ropelike motion on the rotating base plate. An increase in surface moisture augmented agglomerate surface plasticity and facilitated agglomerate surface remodeling. An excess of surface moisture heightened the chance for coalescence to take place when particles collided. If a high speed was maintained throughout the run, the stronger forces involved might have given rise to excessive coalescence and growth, particularly when the powder mass was adequately moistened. Therefore, the combined effects of a high rotational speed and high agglomerate plasticity resulted in the production of spheroids with a wider ''between-batch'' geometric weight mean diameter variation, as shown by the comparatively higher standard deviation value (Table 2) when a rotational speed of 700 rpm was maintained throughout the liquid addition and tumbling stages. However, the average length of the oversize particles was shorter than that obtained when the rotational speed was kept at 480 rpm throughout the run. The higher rotational speed during the liquid addition stage enhanced the break up of loose chunks of moist aggregates, improved liquid distribution, and reduced material adhesion. There was also an augmentation of the rounding/spheronizing and densification processes with reduced length of oversize particles. Due to the high rotational speed during the tumbling stage, oversize agglomerates found in these runs may also be the result of increased coalescence.

These findings showed that the base plate rotational speed had different roles to play at different times during the course of a single continuous run. Each run can be divided into three consecutive stages: liquid addition, tumbling, and drying. Aside from the conventional roles of enhancing agglomerate coalescence, densification, and rounding/spheronizing, the base plate rotational speed also has an additional role of ensuring that the moistening liquid is well distributed into the powder mass during liquid addition by imparting kinetic energy to the powder mass and acting as an attritive force to break up large chunks of moist powder aggregates.

Use of Low-High-Low Speed Variation

Base plate rotational speed may be varied accordingly at appropriate times during the course of a single continuous run to optimize liquid distribution and at the same time to promote spheroid growth. At the start of a run, some of the powder mass would be blown up and out of the inner chamber when the powder mass was first set into motion on the rotating base plate before the commencement of wetting. As the MCC:lactose powder mass was comparatively light in the dry form, a relatively low rotational speed was preferable at this initial period to minimize powder loss. After the mass was slightly moistened, it became more cohesive and less susceptible to being blown up and out of the chamber. The rotational speed then could be increased to improve liquid distribution and mixing, thereby reducing localized overwetting and caking while the moistening liquid was continually added to the powder mass.

As the mass became increasingly wet, the liquid saturation of the agglomerates was correspondingly increased. After the agglomerates are sufficiently moistened, the speed may have to be reduced accordingly to allow the agglomerates to grow and to be rounded into spheroids at a slower pace while avoiding excessive agglomeration. The use of a low-high-low speed variation during rotary processing led to a marked decrease in the amount, as well as in the average length, of the oversize particles (Table 3).

With 38% and 40% water, the high speed could be maintained for some time (about 5 min) after the end of liquid addition without excessive agglomeration, although some spheroids were observed to have started vaulting out of the uniformly tumbling band about 1 to 2 min after completing liquid addition. With a longer period at a high base plate rotational speed, there was a decrease in the average length of oversize particles (Table 3). Agglomerates also appeared to be more spherical when the high speed was maintained until 5 min after liquid addition, as shown by an increase in the form factor values on comparing conditions B and D with C and E, respectively (Table 4). This was ascribed to the greater

Table 3

Effect of Varying Base Plate Rotational Speed During Rotary Processing on the Size and Size Distribution of Spheroids Produced Using Different Amounts of Water as the Moistening Liquid

Processing Conditions[a]	Geometric Weight Mean Diameter (mm)	Geometric Standard Deviation	Fraction of Yield > 2 mm Size (% w/w)	Average Length of Oversize Particles (mm)
40% water				
A	0.54	1.32	0.48	5.40
B	0.62	1.34	0.88	3.69
45% water				
A	0.98	1.21	0.50	4.88
C	2.63	1.25	95.96	N.D.

N.D. = Not determined.

[a]A = 480 rpm for 2 min, 1150 rpm for 6 min, then 480 rpm for the rest of the liquid addition stage and during the tumbling stage; B = 480 rpm for 2 min, 1150 rpm until 5 min after liquid addition, then 480 rpm during the rest of the tumbling stage; C = 480 rpm for 2 min, 1150 rpm until the end of liquid addition, then 480 rpm during the tumbling stage.

Table 4

Effect of Varying Base Plate Rotational Speed During Rotary Processing on the Size and Shape Characteristics of MCC : Lactose Spheroids With and Without 2% w/w Chlorpheniramine Maleate with 38% w/w Water as the Moistening Liquid

Processing Conditions[a]	Geometric Weight Mean Diameter (mm)	Geometric Standard Deviation	Fraction of Yield > 2 mm size (% w/w)	Form Factor	Aspect Ratio
Without drug					
B	0.73	1.50	2.11	0.961	1.176
C	0.48	1.37	0.48	0.906	1.272
E	0.53	1.27	0	0.892	1.240
F	1.31	2.04	26.73	0.874	1.223
G	0.61	1.52	2.05	0.971	1.124
Drug loaded (dry mixed)					
D	0.95	1.70	14.88	0.945	1.173
E	0.56	1.36	0.77	0.916	1.251

[a]B = 480 rpm for 2 min, 1150 rpm until 5 min after liquid addition, then 480 rpm during the rest of the tumbling stage; C = 480 rpm for 2 min, 1150 rpm until the end of liquid addition, then 480 rpm during the tumbling stage; D = 480 rpm for 5 min, 1150 rpm until 5 min after liquid addition, then 480 rpm during the rest of the tumbling stage; E = 480 rpm for 5 min, 1150 rpm until the end of liquid addition, then 480 rpm during the tumbling stage; F = 480 rpm until the end of liquid addition, then 1150 rpm during the tumbling stage; G = 480 rpm for 2 min, then 1150 rpm until the end of the tumbling stage.

densification and rounding/spheronizing effects associated with a longer processing time at a higher speed as the spheroids had a longer opportunity to tumble on the rotating base plate. The observation of some spheroids starting to vault out of the uniformly tumbling band could be taken as an approximate indication for reducing the rotational speed to allow the agglomerates to attain their optimal size and sphericity while maintaining the uniform tumbling pattern.

If the rotational speed was kept at a low level during liquid addition and increased during the tumbling stage (condition F), an end product with a wider geometric size distribution was obtained (Table 4). The obtained yield had an overall large mean size and a much larger amount of oversize particles. As a low speed was used during the liquid addition stage, the mass was more susceptible to nonhomogeneous liquid distribution and mixing, leading to a greater tendency for material adhesion and lump formation to occur. The situation was further aggravated by the use of a high rotational speed after the mass had been moistened as the strong forces generated prompted an increase in the agglomeration rate. Overwetted agglomerates obtained from the liquid addition phase could then agglomerate at much faster rates during the tumbling stage. Under these conditions, the agglomeration process was uncontrollable. It was also reported by other investigators that the combination of a low impeller speed during liquid addition and a high speed in the kneading stage in high-shear pelletization was found to give rise to uncontrollable growth (16,20).

As the size of spheroids was related to both base plate rotational speed and the amount of moistening liquid supplied to the powder mass, the length of time over which the high speed was maintained had to be adjusted and shortened accordingly when the amount of moistening liquid was increased. When the amount of moistening liquid delivered was increased from 40% to 45%, the high rotational speed was reduced at an earlier time toward the end of liquid addition to enable the moist particles to grow and to spheronize at a slower, but controlled, rate. This was done to obtain spheroids with a suitable mean size and to avoid the production of oversize particles as attributed to excessive and uncontrollable agglomeration (Table 3). With 45% water, a high yield of spheroids within the desired size range with a minimal amount of oversize particles could be obtained by varying the speed of the rotating base plate using a low-high-low speed variation during the run.

The need for reducing the rotational speed corresponding to a shorter residence time at high speed was more critical when a larger amount of moistening liquid was used. For example, larger spheroids with a wide geometric size distribution were formed when the base plate was rotated at a high speed until the end of the liquid addition stage (condition C) when 45% water was employed (Table 3). With 38% water, differences in the form factor and mean size of spheroids were less obvious when the period at the high speed was lengthened from 5 min after the end of liquid addition to the end of the tumbling stage as it was less likely for uncontrollable agglomeration to occur with this relatively lower amount of moistening liquid (Table 4). Since spheroids with similar characteristics were already obtained when a high speed was maintained up to 5 min after the end of liquid addition, the period at high speed did need not to be extended further.

The phenomenon of spheroid vaulting when tumbling at a high speed could be seen when the spheroids were left to tumble for a period after the end of liquid addition. It was likely that, as moisture was lost during tumbling, the drying of spheroid surfaces reduced surface plasticity and increased friction between the tumbling spheroids. This increased friction between the spheroids would cause the spheroids to vault as fast-moving spheroids impinged onto slower moving counterparts on the upper surfaces. The spheroid-spheroid impacts without adequate lubrication caused random deflections, vaulting spheroids out of the tumbling, twisted, ropelike path of the spheronizing mass. Thus, as more and more spheroids began to exhibit the vaulting phenomenon, it was indicative that the surface moisture had largely been removed.

In the course of drying, the loss of moisture from spheroids due to evaporation decreased spheroid plasticity. This made the spheroids more liable to fragmentation and chipping. Base plate rotational speed was reduced to a minimum level to maintain the tumbling motion of spheroids in the inner chamber and the random movement of spheroids between the inner chamber and the outer fluidization zone. A slower rotational speed was preferable during the drying period so that spheroids were fluidized in a gentle bubbling pattern and were dried without experiencing excessive breakdown.

Previously, Robinson and Hollenbeck (2) postulated that a load size of 500 g might not be as suitable as a larger batch size 1 kg for spheroid production in the rotary processor. They reported that the yield and the size and shape characteristics of spheroids produced were improved with the larger load. However, for our study, it was found that, on optimizing the formulation and process conditions, a load of 500 g could produce spheroids with comparatively high yield and satisfactory size and shape characteristics (Table 5).

Scaling up the load to 800 g required the liquid spray rate to be increased proportionally to match the increase in load size and amount of moistening liquid when a similar rotational speed and process time variation was to be maintained as for the 500 g load. Due to the increase in load size and higher spray rate, the mixing process might not have been as efficient. The atomizing air pressure was increased from 0.8 to 1.0 bar to improve the distribution of the moistening liquid into the powder mass. During the early stages of liquid addition (2 min 40 sec), the initial clumping of the moist powder particles was apparently more prominent with the heavier load. The moist material also occupied a larger volume in the chamber and tended to move up to a relatively higher point on the chamber wall. A PTFE-lined sluglike baffle was attached

Table 5

Properties of MCC:Lactose Spheroids Containing 2% w/w Chlorpheniramine Maleate Prepared Using Different Load Sizes and Spray Rates

Load Size (g)	Liquid Spray Rate (ml/min)	Geometric Weight Mean Diameter (mm)	Geometric Standard Deviation	Fraction of Yield in 0.71–1.40 mm Size Range (% w/w)	Fraction of Yield > 2 mm (% w/w)	Form Factor	Aspect Ratio
500	20	1.05 (0.12)	1.16 (0.01)	95.19 (3.30)	0.10	0.959	1.130
800	32	1.19 (0.11)	1.13 (0.01)	94.93 (3.11)	0.00	0.965	1.096

Standard deviation values of $n = 3$ runs given in parentheses.
Processing condition: 480 rpm for 2 min, 1150 rpm for 6 min, then 480 rpm for the rest of the liquid addition stage and during the tumbling stage; 45% water used.

onto the upper wall of the chamber just before the spray zone to improve material motion further by aiding moist material that had moved up on the chamber wall in its downward fall from its highest point back inward onto the rotating base plate. The geometric weight mean diameter obtained with the larger load was close to that of the 500 g load (Table 5). High yields of over 90% in the size range 0.71 to 1.4 mm were obtained for both load sizes. With the optimization of the rotational speed and processing time, the fraction of oversize particles was much reduced and may be considered negligible in comparison to the usable yield obtained. A small geometric standard deviation was also noted as the overall geometric size distribution of the end product was narrow. The comparatively high form factor values and aspect ratios, which were close to unity, indicated that highly spherical granules were produced.

CONCLUSION

This study showed that base plate rotational speed may be varied accordingly using a low-high-low speed variation during the single-step continuous spheroid production run to produce spheroids within a narrow size distribution with a minimal amount of oversize particles in the yield. It was important to ensure that a suitable speed was chosen at the appropriate times as the base plate rotational speed had different effects during the course of the run. The usefulness of a low-high-low speed variation in obtaining high yields of spheroids with the desired mean size and within a narrow size distribution has been verified in an optimization study in which a many rotary processing runs were conducted (21).

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