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Spheronization conditions on spheroid shape and size

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Summary

The effects of spheronization speed and residence time on the size and sphericity of microcrystalline cellulose (MCC)-lactose spheroids were investigated. Generally, spheroids became larger and more spherical with an increase in the residence time and spheronization speed. With very high speeds or long residence times, small spheroids resulted. It was found that a combination of speeds ranging from 1000 to 2000 rpm and residence times between 5 and 15 min may be used to produce spheroids with a modal fraction in a size range of 0.7–1.0 mm. The effects of varying MCC content and amount of water required for spheronization were also studied. The addition of a larger amount of water produced spheroids with larger mass median diameters. A higher proportion of MCC required correspondingly a greater amount of water to form spheroids of a certain mean size. An equation could be used to predict the quantity of water needed to produce spheroids of a required size range. Variation in the particle size of the lactose used also affected the size of spheroids formed. The coarser lactose grade produced larger spheroids. Granule size distribution and sphericity were found to be dependent on the operating conditions. Therefore, with a particular formulation, the variable parameters must be suitably adjusted to complement each other for successful spheronization.

Introduction

The use of spherical granules has advantages in the pharmaceutical industry (Reynolds, 1970). The low surface to volume ratio and good flow characteristics of spheroids aid the transfer of materials and are useful in processes which require an exact metering of granules such as in tabletting and capsule filling. Spheroids are ideal for coating as their shape allows for the application of a uniform layer of coating material. The quality of spherical granules has been shown to be governed by the choice of starting materials. Formulations with microcrystalline cellulose (MCC) were generally observed to be favourable for spheronization (Miyake et al., 1973a; O'Connor and Schwartz, 1989). Besides the choice of materials, operating variables also affect the physical characteristics of spheroids. Spheronization speed, residence time and moisture content of the granulated mass have been found to have a significant influence on spheroid characteristics (Miyake et al., 1973b; Bains et al., 1991; Hasznos et al., 1992). The amount of liquid required for

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spheronization depended on the type and proportion of starting materials.

This paper aims to study the effects of spheronization speed, residence time and amount of liquid required for spheronization on the size and shape characteristics of spheroids in order to optimize the conditions for producing spherical granules with a narrow size distribution in the size range ideal for further coating. The influence of varying the proportion of MCC and the particle size of lactose were also investigated.

Materials and Methods

Two grades of lactose monohydrate (Pharmatose, 200 and 50 Mesh, De Melkindustrie Veghel, The Netherlands) and microcrystalline cellulose (MCC; Avicel PH-101, Asahi Chemical, Japan) were used as supplied.

A total weight of 30 g MCC and lactose in a ratio of 1:3 was mixed using geometric dilution. Water was sprayed onto the powder mix. The moistening process was carried out over 15 min. After granulation, the wetted mass was extruded through a 1.0 mm aperture size sieve and the extrudates were then transferred to a spheronizer (Caleva, Model 120, England) with a friction plate of 12 cm diameter. The plate had a fine cross-hatch pattern with studs (0.12 cm width) which were 0.20 cm apart. After a period of spheronization, the spheroids obtained were oven-dried at 60°C for 6 h.

Different amounts of water were initially used to determine a suitable quantity for spheronization. Unless otherwise stated, spheronization was carried out at 500 rpm for 10 min and then at 1000 rpm for a further 10 min.

Size analysis

The spheroids were sieved through a nest of sieves (Endecotts test sieves, U.K.) to separate them into various size fractions. Sieves of aperture sizes, 3.35, 2.80, 2.00, 1.40, 1.00, 0.850, 0.710 and 0.355 mm, were used. The mass median diameter of the spheroids is the spheroid diameter at the 50 percentile mark on the respective cumulative percent oversize plot.

Image analysis

60 granules from the modal class obtained from size analysis by sieving were analyzed using an image analyzer (Imageplus, Dapple System, U.S.A.). The image analyzer consists of a computer system linked to a video camera and a stereomicroscope. The average area, perimeter, length and breadth of the spheroids were determined from the digitized images. Spheroid size and form factor may be derived from these four basic parameters. Spheroid size is the average of the length and breadth of the spheroids. Form factor values give a measure of the degree of spheroid sphericity. A value of unity describes a perfect circle.

$$\text{Form factor} = \frac{4\pi[\text{area}]}{[\text{perimeter}]^2}$$

TABLE 1

Effect of amount of water on microcrystalline cellulose-lactose (1:3) spheroids

Water (% w/w)	Form factor	Size (mm)	Largest fraction sieve size [a] (mm)	Appearance
25	–	–	–	powder, spheroids not formed
30	0.945	0.622	0.355 (55.1)	small-sized granules
35	0.960	1.038	0.850 (36.7)	spherical granules
40	0.949	1.981	1.400 (62.0)	spherical granules
45	0.943	2.699	2.000 (71.9)	spherical granules
50	0.935	5.387	3.350 (100.0)	spherical granules

[a] Values in parentheses represent the % weight of spheroids in the modal fraction.

Results and Discussion

From preliminary investigations (Table 1), it was found that spheroids did not form in formulations moistened with 30% w/w water (calculated as a percentage of the total weight of MCC and lactose) or less. Spherical granules were formed only when the amount of water added exceeded 30% w/w. Further addition of water resulted in an increase in the mass median diameter and size of the spheroids. For formulations of MCC-lactose (1 : 3), 35% w/w water was sufficient to produce a suitably wetted and plastic mass for the formation of spheroids with a modal fraction in the size range of 0.7–1.0 mm.

Spheroids of MCC-lactose (1 : 3) with 35% w/w water were prepared for investigating the effects of speed and time of spheronization. Spheronization speeds of 500, 1000, 1500, 2000, 2500 and 3000 rpm were employed and residence time was varied from 1 to 20 min. During the spheronization process, the relatively long and fluffy extrudates may be broken up into shorter lengths. They may also coalesce to form granules which then agglomerate and densify. Moisture is forced out from the interior to the outer surfaces as they were spun on the rotating plate. This available moisture plasticizes the surfaces and aids the formation of spheroids (Ghebre-Sellassie, 1989).

When the spheroids were spun at a relatively low speed, the forces set up in the spheronizer were insufficient to round them off. Therefore, low form factor values were obtained at a speed of 500 rpm (Fig. 1). Generally, spheroids were more spherical after 5 min at speeds of 1000 rpm and above. At higher speeds, the stronger centrifugal and rotational forces contribute to the rounding off of granules to form spheroids.

Changes in spheroid mass median diameter and size followed similar patterns (Figs 2 and 3). Spheroid size increased progressively with higher spheronization speeds and residence times. This was observed up to 1500 rpm and 10 min, respectively. The growth in size was attributed to agglomeration. Further increase in spheronization speed and residence time resulted in a size decrease. The spinning motion of the friction plate generated forces which caused collisions between

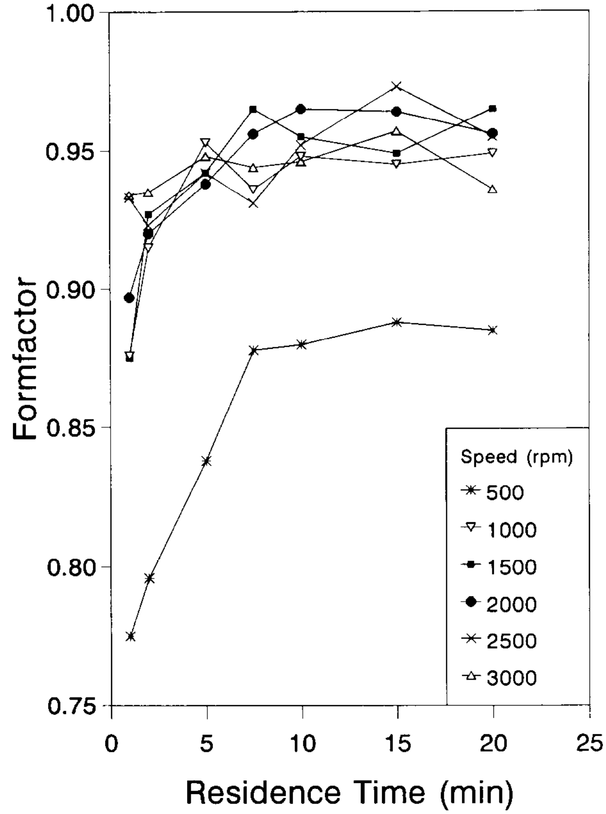

Fig. 1. Effect of spheronization speed and residence time on the sphericity of spheroids with MCC-lactose, 1 : 3.

the particles. Cohesive forces responsible for the formation of spheroids must withstand the destructive forces in order to promote growth (Wan and Jeyabalan, 1985). At the extreme high end of the speed range studied, the forces acting may be far too great to be conductive to agglomeration. Instead, the high speeds encouraged the formation of smaller spheroids.

With short runs of 1–2 min, higher spheronization speeds of 2500–3000 rpm favoured the production of round but small spheroids. These had relatively higher form factor values (Fig. 1) than those spun at lower speeds with these residence times.

The amount of fines produced during a run may be represented by the percentage weight of the less than 0.355 mm size fraction. During spheronization, the amount of fines decreased with longer residence times (Fig. 4). This observation could be attributed to a longer opportunity for agglomeration. With shorter residence times, spheronization at very high speeds produced less fines than at lower speeds.

The above findings showed that for the formulation studied, speeds ranging from 1000 to 2000 rpm and residence times of 5–15 min may be used to form spherical granules with a modal class in the size range of 0.7–1.0 mm.

Formulations of MCC and lactose in weight ratios of 1:3, 1:5 and 1:9 were prepared. For all the formulations studied, it was observed that a minimum amount of granulating liquid was necessary before spheroids could be formed. This quantity was needed to form a moist, cohesive and plastic mass for spheronization. The granules grew in size with further additions of water (Table 2). The form factor values generally showed

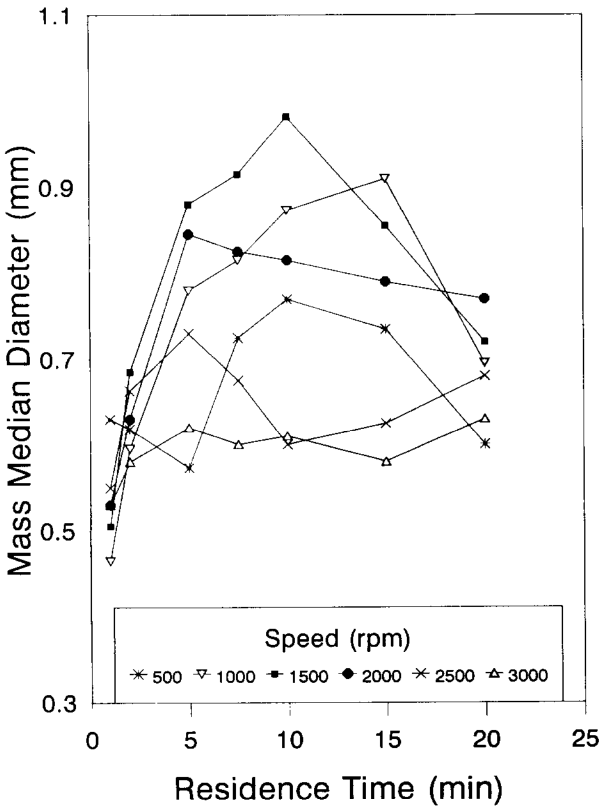

Fig. 2. Influence of spheronization speed and residence time on the mass median diameter of spheroids with MCC-lactose, 1:3.

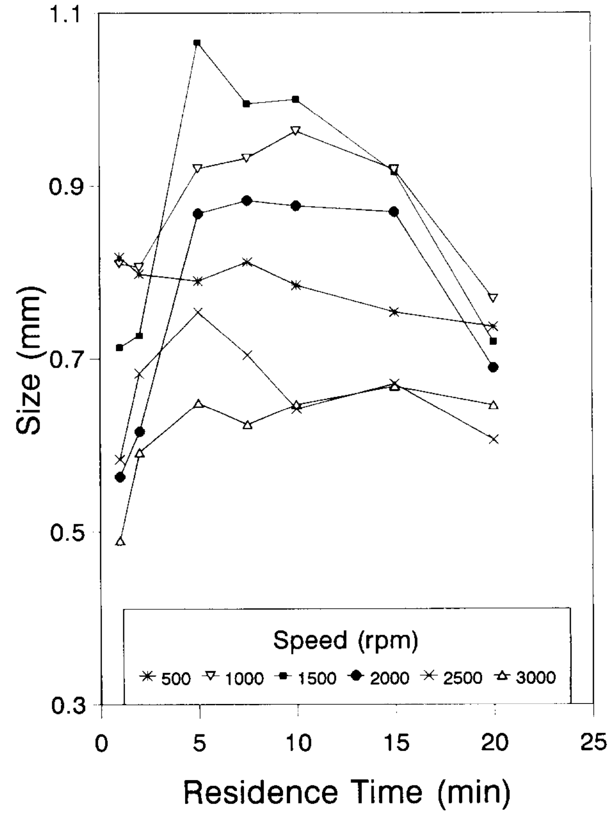

Fig. 3. Change of size of MCC-lactose (1:3) spheroids with different spheronization speed and residence time.

an initial rising trend which was later followed by a slight decline. Water has two major roles in the granulation and spheronization process. It is required to bind the powder mix during granulation. Its plasticizing and lubricating properties also aid the extrusion process (O'Connor and Schwartz, 1989). A slight excess of moisture on the surface enhances deformation and promotes coalescence and spheroid growth (Ghebre-Sellassie, 1989). The surface plasticity together with the tumbling action of the granules in the spheronizer gave rise to the formation of spheroids. The results showed that each weight ratio of MCC and lactose had a range of amount of water suitable for spheroid production. This range was rather narrow and was dependent on the proportion of MCC. A small change in the quantity of water may cause the mass median diameter, size and formfactor values to differ considerably. Below the range, there was insufficient moisture to form spheroids. With overwetting, there was excessive moisture on the surfaces, forming granules and aggregates with irregular shapes and sizes.

The amount of water required to form spheroids of a certain size range was found to increase with a higher proportion of MCC in the formulations (Table 2). The form factor values were generally lower when the spheroids were either very small or very large as the amount of water may be insufficient or in excess for a particular formulation. An increase in the proportion of MCC, which takes up water, led to a greater uptake of water. MCC is used widely as a spheronization enhancer (Harris and Ghebre-Sellassie, 1989). It has binding and plasticizing properties. An augmentation of these properties may account for the slightly higher form factor values

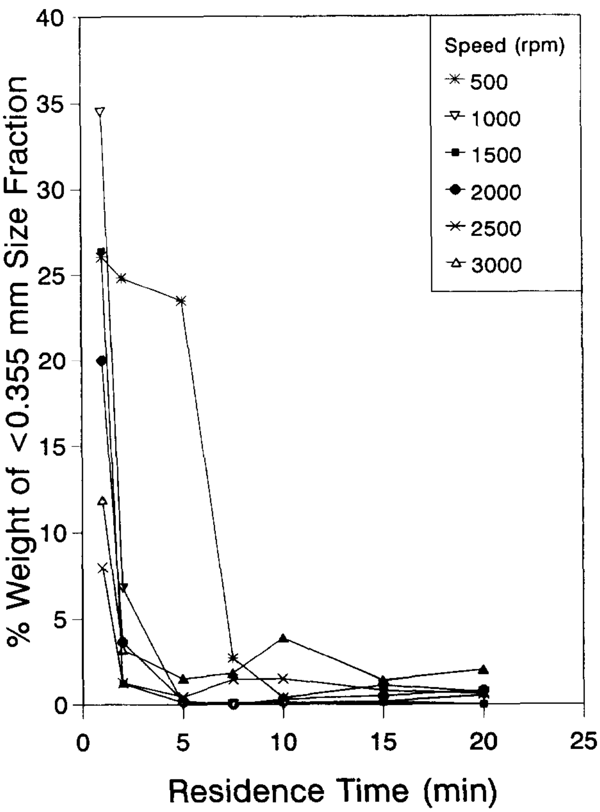

Fig. 4. Amount of fines obtained with variation of spheronization speed and residence time of formulations with MCC-lactose, 1:3.

TABLE 2

Effect of amount of water on the sphericity and size distribution of spheroids prepared with varying proportions of microcrystalline cellulose and two grades of lactose (200 and 50 mesh)

Ratio of MCC: lactose (200 mesh)				
1:3 W	30.0	35.4	40.1	45.0
FF	0.901	0.942	0.898	0.904
MMD	0.520	0.880	1.640	2.470
S	0.622	1.066	1.765	2.604
1:5 W	24.9	28.4	30.6	34.9
FF	0.852	0.922	0.914	0.909
MMD	0.390	0.600	1.290	1.890
S	0.615	0.626	1.345	1.801
1:9 W	20.0	25.7	27.4	29.9
FF	0.791	0.869	0.903	0.899
MMD	0.370	0.740	1.120	1.575
S	0.313	0.707	1.222	1.667
Ratio of MCC: lactose (50 mesh)				
1:3 W	25.0	29.4	33.2	35.0
FF	0.866	0.900	0.913	0.911
MMD	0.510	0.910	1.830	1.770
S	0.608	1.042	1.862	1.880
1:5 W	18.4	21.8	25.1	28.9
FF	0.824	0.895	0.902	0.875
MMD	0.500	0.950	1.665	2.80 < M < 3.35
S	0.583	1.033	1.789	2.827
1:9 W	15.1	18.0	20.1	25.0
FF	0.886	0.906	0.899	0.867
MMD	0.610	1.070	1.585	2.490
S	0.739	1.195	1.684	2.633

W, water for spheronization (% w/w); FF, form factor; MMD, mass median diameter (mm); S, size (mm).

of spheroids containing higher proportions of MCC with appropriate amounts of water for spheronization.

A comparison between the use of small (200 mesh) and large (50 mesh) size lactose particles showed that less water was required for the formation of spheroids of a specified size range with the larger size lactose (Table 2). When a similar quantity of water was used for spheronization, formulations containing 50 mesh lactose produced larger spheroids. With a greater content of MCC and a corresponding amount of water sufficient for producing spheroids of the required mean size, spheroids containing smaller lactose particles appeared to be more spherical than those formed with the larger size lactose. This may be attributed to large crystals in the 50 mesh lactose which resulted in the formation of spheroids with rougher surfaces.

A linear relationship was obtained between mass median diameter and amount of water used for spheronization within the range of amount of water investigated (Figs. 5 and 6). The theoretical amount of water required for spheronization may be calculated using the following general equation:

$$L_i a + M_i b = c$$

where L_i is the weight of lactose (g), M_i the weight of MCC (g), a the amount of water (g) required by 1 g of lactose, b the amount of water (g) required by 1 g of MCC, and c the amount of water (g) required to form spheroids with a modal fraction in the size range of 0.7–1.0 mm.

The amounts of water required for spheronization to produce spheroids with mass median diameters of 0.7 and 1.0 mm, c, were determined by regression analysis. These were then used to form two sets of equations for deriving factors a and b.

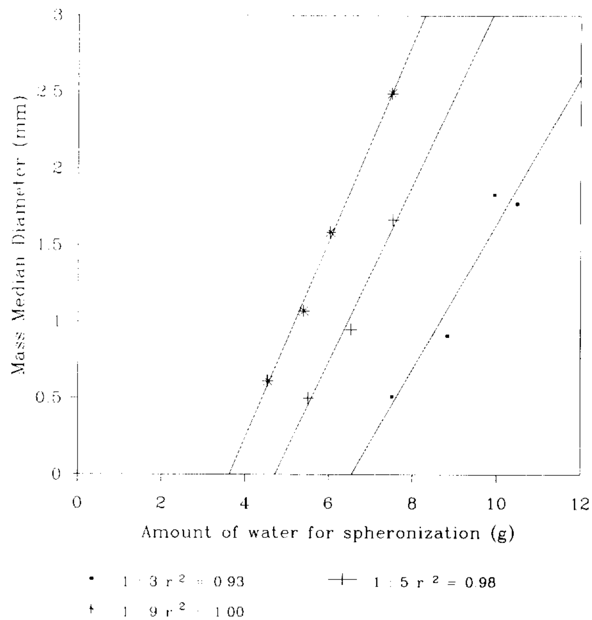

Fig. 6. Effect of amount of water for spheronization on the mass median diameter of spheroids with varying proportions of MCC and lactose of 50 mesh.

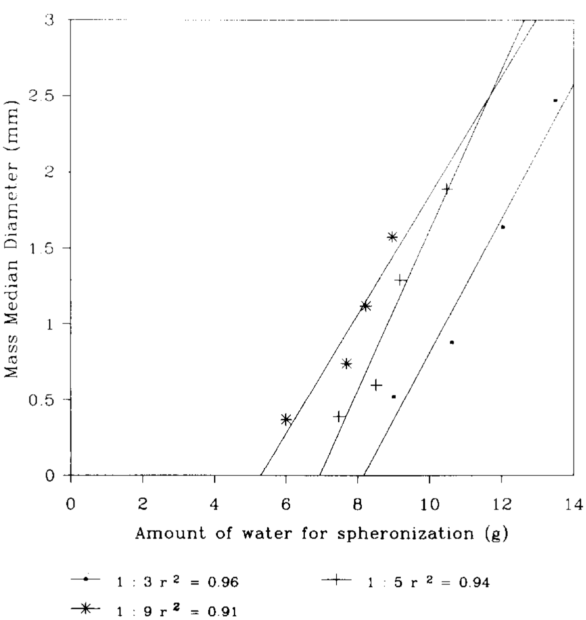

Fig. 5. Effect of amount of water for spheronization on the mass median diameter of spheroids with varying proportions of MCC and lactose of 200 mesh.

For formulations of MCC and lactose 200 Mesh, when mass median diameter = 0.7 mm:

$$[\mathrm{MCC:L} = 1:3]\ 22.5a + 7.5b = 9.75,$$

$$[\mathrm{MCC:L} = 1:5]\ 25a + 5b = 8.26,$$

$$[\mathrm{MCC:L} = 1:9]\ 27a + 3b = 7.08.$$

When mass median diameter = 1.0 mm,

$$[\mathrm{MCC:L} = 1:3]\ 22.5a + 7.5b = 10.43,$$

$$[\mathrm{MCC:L} = 1:5]\ 25a + 5b = 8.83,$$

$$[\mathrm{MCC:L} = 1:9]\ 27a + 3b = 7.85.$$

On solving any two of the equations in either set, the averaged values of a and b were found to be 0.2 and 0.8, respectively. For MCC and lactose

TABLE 3

Comparison of predicted and experimentally determined values of amounts of water required to form spheroids within a size range of 0.7 – 1.0 mm

Ratio of MCC:lactose	Amount of water required for spheronization [a] (g)		Mass median diameter [b] (mm)
	Predicted	Experimentally determined	
1:3	10.5 (35.0%)	10.254 (34.18%)	0.850
1:4	9.6 (32.0%)	9.423 (31.41%)	0.950
1:5	9.0 (30.0%)	8.469 (28.23%)	0.750

[a] Values in parentheses represent the amount of water calculated as a percentage of the total weight of microcrystalline cellulose and lactose 200 mesh.
[b] Experimentally determined mass median diameter values.

50 mesh formulations, the respective values of *a* and *b* were 0.1 and 0.8.

The predicted values of amount of water required for spheronization were close to those obtained experimentally (Table 3). Therefore, the proposed general equation may be used to predict the amount of water used for producing spheroids with the required size characteristics.

The results from this study showed that operating variables such as spheronization speed, residence time and amount of granulating liquid affect the nature of spheronized products. The operating variables must be suitably adjusted to complement one another. Depending on the proportion of the starting materials, a protocol which takes all these variables into account is required for the successful production of spheroids with a certain size range and degree of sphericity.

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