The Influence of Microcrystalline Cellulose Grade on Shape and Shape Distributions of Pellets Produced by Extrusion-Spheronization

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In this study, five microcrystalline cellulose (MCC) grades were physically characterized and their extrusion-spheronization behaviours were characterized in terms of water requirements and pellet shape profiles. It was found that the MCC grades differed significantly in the physical properties investigated. Physical properties of MCC were found to influence the water requirement for extrusion-spheronization. MCC grades of higher bulk densities, lower porosities and water retentive capacities required less water to produce pellets of equivalent size. These MCC grades were also found to produce pellets of lower sphericity and wider shape distributions. Packing of MCC particles within the agglomerate played a role in determining amount of water retention and pellet rounding during spheronization. However, there was a limit to the influence of packing density on the rate of pellet rounding because poor packing resulted in higher water retentive capacity, which also limited the rate of rounding.

Key words microcrystalline cellulose; extrusion-spheronization; physical characterization; pellet shape

There has been strong interest in the production of spherical pellets due to an increasing use of multi-particulate controlled-release oral dosage forms. Spherical pellets possess many advantages, including a low surface area to volume ratio, good flow properties and uniform packing. The ideal shape of pellets also make them excellent substrates for coating as desired for aesthetic purposes or controlled release of actives.[1,2]

Extrusion-spheronization is the most commonly used method to produce pellets. Many authors have investigated the influence of extrusion-spheronization process variables on pellet shape characteristics.[3—5] The essential excipient for extrusion-spheronization is microcrystalline cellulose (MCC). MCC has been reported to aid the spheronization process by absorbing water like a molecular sponge and helps in the binding and lubrication of the moistened powder mass during extrusion.[6,7] During spheronization, the moisture entrapped in the MCC microfibrils adds plasticity to the extrudate and helps to round short extrudates into spherical pellets.

This paper reports a study on the influence of the MCC on the pellet forming process in terms of its water requirement and shape changes during extrusion-spheronization. Certain critical physical properties of MCC could be identified for their influences on the extrusion-spheronization and pellet rounding behaviour of MCC.

Experimental

Materials Lactose α-monohydrate (Pharmatose 200M, DMV, the Netherlands) was used as the bulk material for preparing pellets. The MCC grades used were Avicel PH 101, Avicel PH 102, Avicel PH 301, Avicel PH 302 and Ceolus KG 801 (Asahi Chemical Industry, Japan).

Particle Size and Size Distribution Particle size data for each MCC grade was determined using a laser light scattering system (Malvern 2600C, U.K.) equipped with a dry powder feeder. All measurements were carried out in triplicate and results averaged to obtain mean particle diameter ($\bar{X}$) and particle size span ($S_{\bar{X}}$). $S_{\bar{X}}$ is calculated as:

$$S_{\bar{X}}=\frac{X_{90}-X_{10}}{\bar{X}} \quad (1)$$

where X_{90} and X_{10} are the diameters of the 90th and 10th percentiles of the cumulative particle size distribution respectively.

Crystallinity An X-ray diffractometer (Shimadzu 6000, Japan) was used to obtain the X-ray diffraction pattern of the MCC powder under the following conditions; a monochromatic Cu$K\alpha$ radiation source was operated at 40 kV and 30 mA, scanning rate 1° (2θ)/min over the range of 5—45° (2θ). The classical method of Hermans and Weidinger, based on the two-phase concept was used to evaluate the percent crystallinity.[8] Percent crystallinity (X_{cr}) is calculated as follows,

$$X_{cr}=\frac{I_{cr}}{I_{cr}+I_a}\times 100\% \quad (2)$$

where I_{cr} and I_a are the crystalline and amorphous intensities respectively. The demarcation of the crystalline (I_{cr}) and amorphous (I_a) intensities was traced with the help of a computer program (Shimadzu XRD-6000 Version 2.5, Japan). X-ray diffraction patterns of 4 samples from each grade of MCC were measured and the calculated crystallinity results averaged.

Micromeritic Properties Micromeritic measurements were determined using a mercury intrusion porosimeter (Micromeritics 9320, U.S.A.). Mercury contact angle, surface tension and density were taken as 130°, 485 dyn/cm and 13.53 g/ml respectively. Samples were carefully poured into the bulb of a 5 ml penetrometer and subjected to slow vacuum evacuation. Mercury was allowed to fill the penetrometer at the beginning of the test at a pressure of 0 MPa. Mercury intrusion into pores between 250—10 μm occurred between 0—0.172 MPa.[9] $V_{low\ P}$ is the specific cumulative intruded mercury volume into the pores as pressure was increased from 0—0.172 MPa. High pressures of 0.172—207 MPa were used for mercury intrusion into intraparticulate pores between 10—0.006 μm. The specific cumulative intruded mercury volume for the high pressure intrusion was denoted as $V_{high\ P}$. Total specific intrusion volume for each MCC sample pores in the entire pressure range of 0—207 MPa, V_{total}, was also recorded, where

$$V_{total}=V_{low\ P}+V_{high\ P} \quad (3)$$

V_{total} represented the total pore volume per unit weight of sample and could also be used to calculate percent porosity, ε

$$\varepsilon=\left(1-\frac{\rho_e}{\rho_a}\right)\times 100\% \quad (4)$$

where, bulk density of sample, ρ_e is $W_{sample}/(V_{penetrometer}-V_{Hg})$, absolute density of sample, ρ_a is $W_{sample}/[(V_{penetrometer}-V_{Hg})-V_{total}]$, W_{sample} is weight of powder sample, $V_{penetrometer}$ is volume of empty penetrometer and V_{Hg} is volume of mercury filled into the penetrometer at 0 MPa.

Micromeritic measurements for each grade of MCC were carried out in triplicates and the results averaged.

Tapping Studies Both MCC powder and MCC : lactose=3 : 7 binary powder mixes were subjected to tapping studies. The powder sample was lightly sieved into a graduated cylinder, cut exactly at 100 ml, and leveled. The powder was tapped until no further change in volume was recorded.

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Bulk density (ρ_b) was calculated as the quotient of the weight of powder to the volume of the cylinder before tapping. Tapped density (ρ_t) was calculated as the quotient of the weight of the powder to its volume after tapping. The volume reduction of the powder mass due to tapping is determined using Kawakita's equation.[10]

$$\frac{N}{C}=\frac{l}{ab}+\frac{N}{a} \tag{5}$$

where N is the number of taps, C is the degree of volume reduction and calculated as,

$$C=\frac{V_o-V_n}{V_o} \tag{6}$$

where V_o is the initial volume and V_n is the bulk volume of the powder after N tappings. The constants, a and $1/b$, are related to compressibility and cohesion respectively. The tapping experiments were replicated five times and results averaged.

Water Retentive Capacity An accurately weighed amount of MCC, W_1, was suspended in distilled water and allowed to stand for 2 h before subjecting to centrifugation at 2800 rpm for 10 min. The weight of the sedimented MCC powder, W_2, was determined after centrifugation and decanting the liquid away. The water retentive capacity (ω) was the weight of water retained per unit weight MCC powder and calculated as,

$$\omega=\frac{W_2-W_1}{W_1} \tag{7}$$

This measurement was repeated 5 times using fresh samples for each MCC grade and results averaged.

Preparation of Pellets MCC–lactose dry powder blends in the ratio of 3 : 7 were mixed using a double cone tumbler mixer (Erweka AR 401, Germany) at load sizes of 2 kg for 1 h at 40 rpm. One kg of MCC–lactose powder was transferred to a planetary mixer (Kenwood Major, U.K.) and the required amount of water was gradually added and mixed over a period of 5 min. Water contents added were varied from 27.5 to 45% (w/w). The resultant wet powder mass was extruded using a radial screw extruder (Niro E140, U.K.) fitted with a screen of 1 mm thickness with 1 mm diameter circular dies. One kg of the extrudate formed was transferred to a spheronizer (Niro S320, U.K.) with a 300 mm diameter plate, and spheronized for 10 min. Spheronization was carried out at 600 rpm. The pellets formed were oven dried at 60 °C for 8 h.

Size Analysis of Pellets The pellet batches produced were sub-divided by a rotary sampler (Retsch PT, Germany). About 200 g of pellet sample was used in the sieve size analysis. The pellets were sieved through a nest of sieves of aperture sizes to give a $\sqrt[4]{2}$ progression from 250 to 2800 μm. Sieving was carried out on a mechanical sieve shaker (Retsch VS 1000, Germany) for 10 min. Geometric mean pellet size and size distribution were calculated using the equations described by Heng *et al.*[11] Linear regression analysis was done to assess the relationship between logarithm geometric mean pellet size and percent water content used for extrusion-spheronization. Logarithm geometric mean pellet size increased linearly with increasing water content, r^2 values ranged from 0.908 (Avicel PH 301) to 0.994 (Ceolus KG 801). A r^2 value close to 1 between logarithm geometric mean pellet size and water content indicates good linearity from linear regression analysis. From the plot of logarithm geometric mean pellet size obtained against the amount of water used (Fig. 1), the predicted percent water content required to produce pellets of 710 μm ($W_{710\,\mu m}$) was determined. Figure 1 shows the derivation of $W_{710\,\mu m}$ for each MCC grade. $W_{710\,\mu m}$ is an indication of the relative water requirement of each MCC grade for extrusion-spheronization.

Shape Analysis of Pellets Shape analysis of pellet samples collected at fixed time intervals of the spheronization process was performed to investigate the pellet shape changes during spheronization. Shape analysis of pellets was carried out on pellets prepared using 40% (w/w) water content for Avicel PH 101, Avicel PH 102 and Ceolus KG 801; 25% (w/w) water content for Avicel PH 301 and Avicel PH 302. This was to ensure that shape profiles were determined from pellets formed from formulations with water contents close to $W_{710\,\mu m}$. Randomly selected 100 pellets from each time interval, 0.5, 1, 2.5, 5, 7.5 and 10 min of spheronization were used for shape characterization. Pellets were placed under a stereomicroscope (Olympus, SZH, Japan) and the images produced were digitized and analyzed using a computer program (Foster Findlay Synoptics System, PC-Image, Version 2.2.03, U.K.). Various shape parameters were calculated as follows,

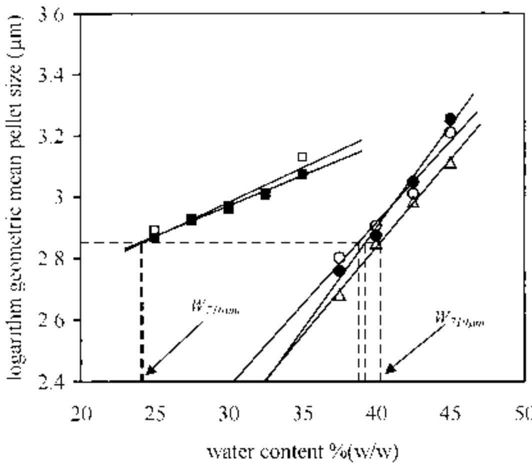

Fig. 1. Relationship between Logarithm Geometric Mean Pellet Size and Added Water Content for Extrusion-Spheronization Using Avicel PH 101 (○), Avicel PH 102 (●), Avicel PH 301 (□), Avicel PH 302 (■) and Ceolus KG 801 (△)

$$\text{roundness}=\frac{\text{area}}{\pi\times\text{max radius}^2} \tag{8}$$

$$\text{elongation}=\frac{\text{max radius}}{\text{min radius}} \tag{9}$$

$$\text{pellips}=\frac{\text{perimeter}}{2\times\pi\times\text{max radius}} \tag{10}$$

$$\text{rectang}=\frac{\text{area}}{4\times\text{max radius}\times\text{min radius}} \tag{11}$$

Roundness measures the spherical, elongation measures the oblongated, pellips measures the elliptical and rectang measures the rectangular shape of pellets respectively.[3] Span for the various shape parameter distributions is calculated as follows,

$$\text{span}=\frac{\text{90th percentile}-\text{10th percentile}}{\text{50th percentile}} \tag{12}$$

Statistical Analysis Pearson correlation was carried out on all data for the MCC physical properties and extrusion-spheronization parameters to determine the relationship between the MCC properties and extrusion-spheronization parameters. A significant correlation was indicated when the p value for the Pearson correlation test is less than 0.05 (*i.e.* $p<0.05$).

Results and Discussion

Physical Properties of MCC Grades and Their Influence on Water Requirement for Extrusion-Spheronization Tables 1 and 2 show the physical and tapping properties of the five MCC grades respectively. Avicel PH 301, Avicel PH 302 and Ceolus KG 801 are specially designed MCC grades, whilst Avicel PH 101 and Avicel 102 are the standard grades. It was observed that the physical and tapping properties of MCC were not significantly correlated to the MCC particle size and crystallinity (Pearson correlation, $p>0.05$). Avicel PH 301 and Avicel PH 302 had lower mercury intrusion volumes ($V_{\text{low P}}$, $V_{\text{high P}}$, V_{total}) and ε values. This meant that they possessed relatively smaller inter and intra-particulate void volumes. This was further confirmed by their high ρ_b and ρ_t values that were also related to smaller void vol-

Table 1. Physical Properties and Water Requirements for Extrusion-Spheronization of the Various MCC Grades[a)]

	Physical properties								Water requirement for extrusion-spheronization
MCC grades	$\bar{X}$ (μm)	$S_{\bar{X}}$	X_{cr} (%)	ϕ (%w/w)	$V_{low\ P}$ (ml/g)	$V_{high\ P}$ (ml/g)	V_{total} (ml/g)	ε (%)	$W_{710\,\mu m}$ (%w/w)
Avicel PH 101	76.53 (0.53)	1.91 (0.01)	36.72 (2.57)	4.6470 (0.1700)	1.1867 (0.0335)	0.3543 (0.0068)	1.5410 (0.0267)	65.45 (2.46)	38.77
Avicel PH 102	132.81 (1.95)	1.47 (0.04)	35.58 (3.48)	4.1800 (0.1372)	1.2236 (0.0580)	0.4436 (0.0436)	1.6672 (0.0842)	69.65 (1.53)	39.25
Avicel PH 301	73.55 (0.54)	1.65 (0.01)	43.38 (0.80)	4.4830 (0.2675)	0.8584 (0.0597)	0.2853 (0.0185)	1.1437 (0.0728)	61.15 (2.88)	24.15
Avicel PH 302	139.41 (1.36)	1.41 (0.02)	34.14 (4.45)	4.0282 (0.0619)	0.7520 (0.0615)	0.3026 (0.0283)	1.0546 (0.0799)	60.11 (2.76)	24.04
Ceolus KG 801	66.65 (0.39)	3.00 (0.07)	46.42 (1.96)	4.2631 (0.1700)	2.0358 (0.0516)	0.5693 (0.0191)	2.6051 (0.0701)	76.95 (2.55)	40.26

a) Values in parenthesis represent standard deviations.

Table 2. Results of the Tapping Studies[a)]

	MCC powder				MCC : lactose=3 : 7			
	ρ_b	ρ_t	a	$1/b$	ρ_b	ρ_t	a	$1/b$
Avicel PH 101	0.313 (0.003)	0.432 (0.002)	0.282 (0.010)	8.37 (0.65)	0.404 (0.002)	0.694 (0.005)	0.424 (0.005)	17.68 (1.18)
Avicel PH 102	0.309 (0.002)	0.421 (0.002)	0.268 (0.004)	9.33 (0.83)	0.405 (0.002)	0.687 (0.001)	0.415 (0.004)	17.29 (0.53)
Avicel PH 301	0.430 (0.004)	0.561 (0.001)	0.236 (0.006)	8.56 (0.21)	0.433 (0.002)	0.753 (0.004)	0.432 (0.003)	19.30 (1.00)
Avicel PH 302	0.456 (0.003)	0.589 (0.001)	0.226 (0.005)	7.85 (0.17)	0.454 (0.002)	0.775 (0.003)	0.420 (0.003)	17.90 (0.90)
Ceolus KG 801	0.194 (0.002)	0.297 (0.001)	0.355 (0.007)	15.92 (0.73)	0.323 (0.001)	0.556 (0.003)	0.425 (0.002)	18.72 (0.48)

a) Values in parenthesis represent standard deviations.

umes. On the other hand, Ceolus KG 801 displayed a greater void capacity and lower density than the standard MCC grades, Avicel PH 101 and Avicel PH 102. Tapping studies were performed on both MCC and MCC–lactose binary powders for all the MCC grades. The latter was a typical powder formulation used for pellet formation in extrusion-spheronization. There was significant correlation between the tapping behaviours of MCC powders and MCC–lactose binary powders (Pearson correlation, $p<0.05$). Thus, MCC grades with high bulk densities also imparted high densities to their MCC–lactose binary powders.

From Table 1, MCC grades with lower void volumes and porosities had low water retentive capacities and required less water for extrusion-spheronization. Therefore, the rank orders of the MCC grades for $W_{710\,\mu m}$, mercury intrusion volumes, porosities and water retentive capacities were similar. During extrusion and subsequent spheronization, the agglomerated particles underwent densification and volume reduction resulting in increased agglomerate surface liquid and plasticity. This condition was necessary for the formation of liquid bridges between the agglomerated particles that were responsible for the bonding forces between them. Increased surface plasticity allowed further pellet growth. High bulk and tapped densities of MCC implied better packing with smaller void volumes and resulting in lower capacities to accommodate water, thus making water more available on the agglomerate surface. As a result, MCC grades like Avicel PH 301 and Avicel PH 302, with high packing densities required less water (lower $W_{710\,\mu m}$) to form pellets of equivalent size when compared to those of lower packing densities. At equivalent water contents, the high density MCC grades (Avicel PH 301, Avicel PH 302) also formed pellets of higher densities compared to the lower density MCC grades.[12)]

Influence of MCC Physical Properties on Pellet Shape and Shape Distributions during Spheronization Figure 2 shows the shape changes during pellet formation with increasing spheronization duration for Avicel PH 101, Avicel PH 301 and Ceolus KG 801. Shape changes during pellet formation for Avicel PH 102 and Avicel PH 302 were similar to their corresponding small particle size grades, Avicel PH 101 and Avicel PH 301 respectively. It was observed that the high packing density, low porosity MCC grades such as Avicel PH 301 and Avicel PH 302 produced less spherical, more elongated pellets after 10 min of spheronization compared to the other three MCC grades. Shape profiles of pellets containing different MCC grades at various spheronization durations for roundness, elongation, pellips and rectang are shown in Fig. 3. Roundness and pellips parameters increase, whilst elongation and rectang decrease with higher sphericity. Avicel PH 301 and Avicel PH 302 were found to form less spherical pellets besides having a lower water requirement for extrusion-spheronization. Pellets containing Avicel

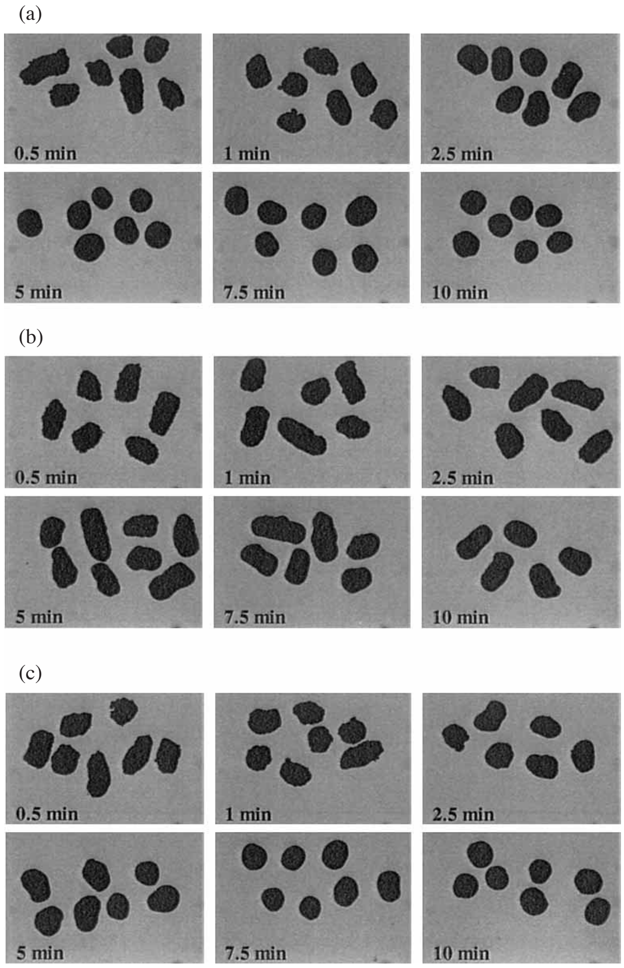

Fig. 2. Spheroids Formed at Various Spheronization Durations
(a) Avicel PH 101, (b) Avicel PH 301, (c) Ceolus KG 801.

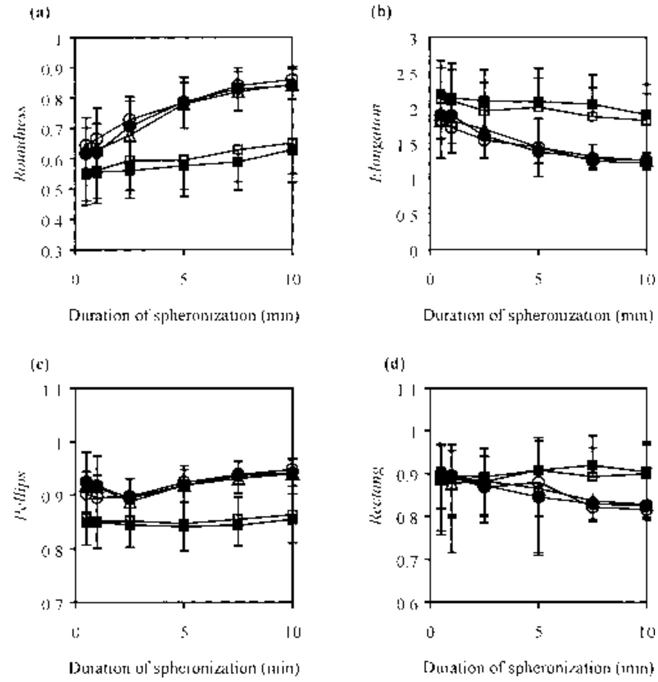

Fig. 3. Shape Descriptors, Roundness (a), Elongation (b), Pellips (c), Rectang (d) of Pellets at Various Spheronization Durations Containing Avicel PH 101 (○), Avicel PH 102 (●), Avicel PH 301 (□), Avicel PH 302 (■) and Ceolus KG 801 (△)

PH 301 or Avicel PH 302 were observed to have lower roundness and pellips values while elongation and rectang values were higher when compared to the other three MCC grades. From the micromeritics and tapping studies data, high density MCC grades had low void volumes and were poorly compressible. Therefore, when subjected to the compressive and rounding forces during extrusion-spheronization, these MCC grade formulations were inherently more resistant to deformation and spheronization. Thus, MCC grades with high packing densities formed agglomerates that were less deformable at water contents close to $W_{710\,\mu m}$. These MCC grades formed less porous agglomerates that were more densely packed and less able to deform for rounding of the agglomerates during the spheronization process. The other MCC grades with lower densities allowed pellets to deform more quickly and easily into more spherical pellets.

Figure 4 shows changes in the span of the various shape parameter distributions with spheronization duration for the various MCC grades. Generally, pellets produced using Avicel PH 301 and Avicel PH 302 as spheronising aid showed wider shape distributions with higher span values. High density MCC grades had less allowance for the control of water movement to the agglomerate surface for surface remoulding, leading to a less uniform change in shape for the agglomerates. Thus, a wide variation in sphericity of the pellets formed. Avicel PH 101, Avicel PH 102 and Ceolus KG 801, being more porous, would enable better water accommodation and water movement control during the pellet rounding process in the spheronizer. However, low density Ceolus KG 801 did not display a faster decrease in roundness compared to Avicel PH 101 and Avicel PH 102. This implied that packing density of the MCC grade used may have a limiting effect in encouraging the rounding of agglomerates. Ceolus KG 801 possessed the highest water retentive capacity that would compromise the rate release of water from Ceolus KG 801 when compared to the standard MCC grade, Avicel PH 101.

Conclusion

Five MCC grades were physically characterized and used as spheronizing aid to form pellets by extrusion-spheronization. MCC grades with higher packing densities required lower water contents for extrusion-spheronization. They also form pellets that were less plastic and deformable because of better packing of MCC particles within the agglomerates. The span values of the shape distributions of pellets containing higher bulk density MCC were also higher. This implied a less uniform pellet formation process. However, there was a limit to the influence of packing density on the rate of pellet rounding because poor packing also endowed Ceolus KG 801 with a higher water retentive capacity. Therefore, low bulk density Ceolus KG 801 did not exhibit significantly faster pellet rounding during spheronization when compared to Avicel PH 101 or Avicel PH 102.

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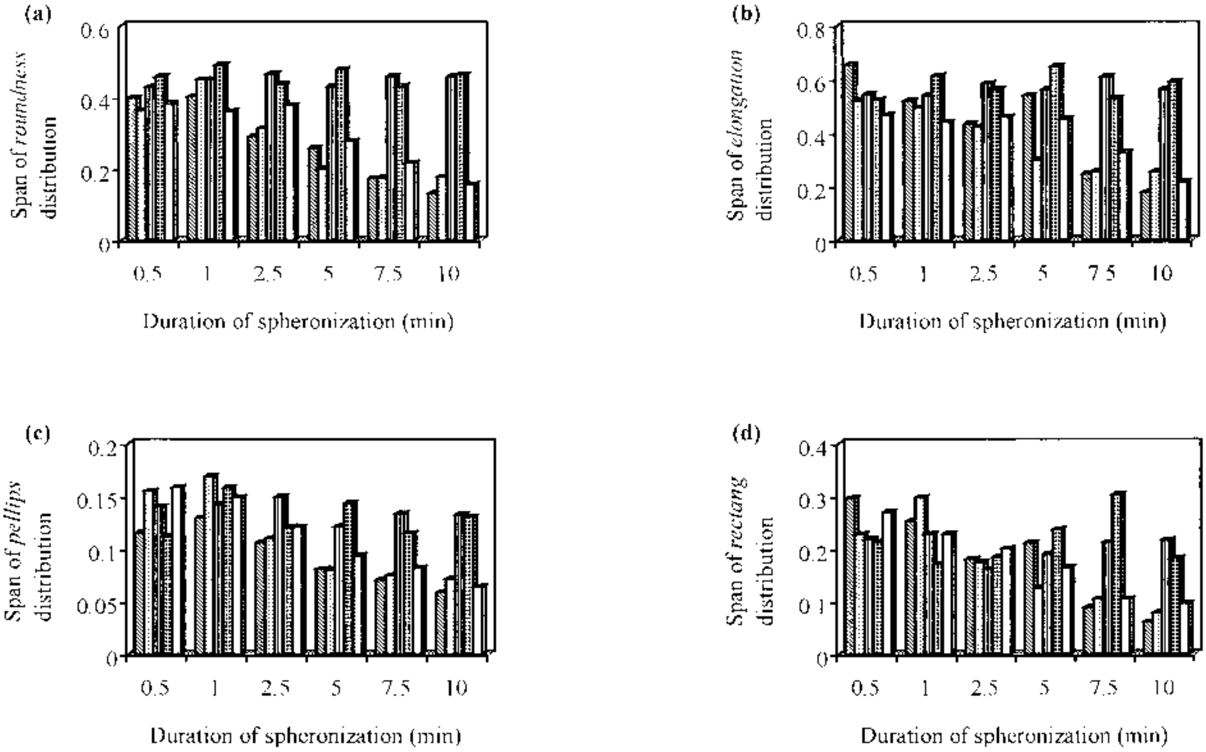

Fig. 4. Spans of Shape Descriptors, Roundness (a), Elongation (b), Pellips (c), Rectang (d) of Pellets at Various Spheronization Durations Containing Avicel PH 101 ( ), Avicel PH 102 ( ), Avicel PH 301 ( ), Avicel PH 302 ( ) and Ceolus KG 801 ( )

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