A Study of the Effects of the Physical Characteristics of Microcrystalline Cellulose on Performance in Extrusion Spheronization

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Purpose. Physical characterization and extrusion–spheronization profiles of 11 microcrystalline cellulose (MCC) grades were performed. Correlation between the physical characteristics and extrusion–spheronization behavior and pellet quality was performed to determine critical MCC characteristics that influence the water requirement and spheronization water sensitivity for extrusion–spheronization.

Methods. Extrusion–spheronization of MCC–lactose at varying water contents was performed to determine water requirement, spheronization water sensitivity, and the effect of increasing water content on some pellet qualities (pellet flow rate, friability, bulk, and tapped densities) of each MCC grade. MCC physical properties and tapping characteristics were assessed. Correlation between MCC physical properties and its spheronization behavior parameters was performed.

Results. MCC characteristics, such as powder particle size, size distribution, and porosity, were found to have little influence on the extrusion–spheronization process. However, significant correlation was found between void volumes or packing properties of MCC and the water requirement for extrusion–spheronization and pellet qualities.

Conclusions. A new insight into the action of MCC as a spheronizing aid was discovered. MCC void volume and packing properties play an important role in determining water retention and release during extrusion–spheronization.

KEY WORDS: extrusion–spheronization; microcrystalline cellulose; water requirement; physical characterization.

INTRODUCTION

The essential excipient for extrusion–spheronization is microcrystalline cellulose (MCC). MCC is reported to aid the spheronization process by absorbing water like a molecular sponge and help the binding and lubrication of the moistened powder mass during extrusion. During spheronization, MCC adds plasticity to the extrudate, helping to round short extrudates into spherical pellets (1,2).

There have been many reports on the inherent variability in physical properties that exist between MCCs of different batches and from different manufacturers (3–6). The causes of variability arise mainly from differences in raw material and manufacturing process.

Many authors have investigated the influence of process variables during extrusion spheronization on final pellet characteristics (7,8). However, limited work has been performed to assess the water requirement of MCC on pellet formation by extrusion–spheronization with respect to its physical properties. In this study, the physical properties of 11 different MCC grades were characterized, and their extrusion–spheronization profiles were examined. Certain critical physical properties of MCC could be identified to influence the water requirements during extrusion-spheronization and subsequent pellet qualities.

MATERIAL AND METHODS

Materials

Lactose α-monohydrate (Pharmatose 200M, DMV, Vaghel, 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, Ceolus KG 801 (Asahi, Osaka, Japan), Pharmacel 101, and 102 (DMV, Vaghel, The Netherlands), Celex 101 (ISP, Wayne, NJ, USA), Viva Pur 101 (J. Rettenmaier & Sohne, Ell Wangen, Holzmulle, Germany), Emcocel 50 M, and Prosolv 50 M (Mendell, Patterson, NJ, USA). Prosolv 50 M is a silicified MCC grade.

Preparation of Pellets

Pellets were prepared by extrusion-spheronization from the method described by Wan *et al.* (7). MCC: lactose blends (30 g) in the ratio of 3:7 were prepared using geometric dilution mixing. Water was added by spraying onto the powder blends. The mixing and wetting processes were completed within 10 minutes. Water content added was calculated as a percentage to the total dry powder weight. The amount of water added was varied from 25 to 45% (w/w). In order that loosely compacted extrudates were formed to elicit the influence of spheronization, extrudates were formed by manual extrusion of the moistened mass through a 1-mm aperture size mesh. Spheronization was carried out in a spheronizer (Caleva 120, Sturminster, Dorset, UK) with a friction plate of 120 mm diameter. The plate had a cross-hatch pattern with studs, which were 1.2-mm wide and 2-mm apart. The extrudate was spheronized at 1500 rpm for 5 minutes. Pellets prepared were oven dried at 60°C for 4 hours to moisture contents of below 1% (w/w). The moisture contents of the different dried pellet batches were not significantly different (ANOVA, $P > 0.05$).

Characterization of Pellets

Size Analysis of Pellets

The pellets were sieved through a nest of sieves of aperture sizes to give a $\sqrt{2}$ progression from 250 to 2,800 μm. Sieving was performed on a mechanical sieve shaker (Retsch VS 1000, Haan, Germany) for 10 minutes. The geometric mean pellet size was calculated using the equations described by Heng *et al.* (10). From the linear plot of logarithm geometric mean pellet size obtained against the amount of water used, the predicted percent water content required to produce pellets of 710 μm, $W_{710\,\mu m}$, was determined. Slope value, W_s, of the linear relationship between logarithm geometric mean pellet size, and amount of water used was used to evaluate the spheronization water sensitivity of each MCC grade. Figure 1A shows a typical relationship between logarithm

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geometric mean pellet size and amount of water used for Avicel PH 101, and the determination of $W_{710\,\mu m}$.

Pellet Flow Rate

Pellet flow time through an orifice was measured using a granulate flow tester (Erweka GDT-E, Heusenstamm, Germany) as described by Heng and Wan (11). Pellet flow rate was calculated by dividing the weight of pellets used with the orifice flow time.

Pellet Friability

A Roche friabilator (Erweka TA 20, Heusenstamm, Germany) was used to tumble 10 g of pellets for 200 rpm with 25 6-mm steel balls using the method described by Heng and Wan (11). After tumbling, the pellets were subjected to sieve size analysis and friability index was evaluated as the quotient, of the geometric mean pellet size after testing and that before the test. A friability index of 1 indicated that the size distribution of pellets was the same after and before testing.

Pellet Bulk and Tapped Density

Pellets were poured lightly into a graduated 10-ml cylinder and leveled. The pellets were tapped until no further change in volume was observed. Pellet bulk density, ρ_{pb}, was calculated as the quotient of the weight of the pellets to the volume of the cylinder before tapping. Pellet tapped density, ρ_{pp}, was calculated as the quotient of the weight of the pellets to its volume after tapping.

Physical Properties of the MCC Grades

Particle Size and Size Distribution

Particle size data for each MCC grade were determined using a laser light scattering system (Malvern 2600C, Malvern, Worcs., UK) equipped with a dry powder feeder. Mean particle diameter, $\overline{X}$ and particle size span, $S_{\overline{X}}$ were measured. $S_{\overline{X}}$ is calculated as:

$$S_{\overline{X}} = \frac{X_{90} - X_{10}}{\overline{X}} \tag{1}$$

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, Kyoto, Japan) was used to obtain the X-ray diffraction pattern of the MCC powder under the following conditions; a monochromatic CuKα 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 (12). Percent crystallinity, X_{cr}, is calculated as follows,

$$X_{cr} = \frac{I_{cr}}{I_{cr} + I_a} \times 100\% \tag{2}$$

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, Kyoto, Japan).

Moisture Content

Moisture content, ϕ (%w/w), was determined by oven drying samples of 5 g of MCC, accurately weighed, at 105°C for 3 hours (13). The dried samples were cooled under vacuum before weighing to determine their dry weights. Moisture content for each MCC grade was the quotient of the weight loss on drying over the original weight of the sample, expressed as a percentage.

Micromeritic Properties

Micromeritic measurements were determined using a mercury intrusion porosimeter (Micromeritics 9320, USA). Mercury contact angle, surface tension, and density were taken as 130°, 485 dyne/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. On achieving very high vacuum, mercury was intruded into pores between 250–10 μm, occurring between 0–0.172 MPa (14). $V_{low\,P}$ is the specific cumulative intruded mercury volume into the pores as pressure was increased from 0–0.172 MPa. Higher pressures of 0.172–207 MPa were used for intrusion into pores between 10–0.006 μm. The specific cumulative intruded mercury volume for 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} is:

$$V_{total} = V_{low\,P} + V_{high\,P} \tag{3}$$

where V_{total} represented the total pore volume per unit weight of sample and could also be used to calculate granular porosity, ε, as follows:

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

where granular 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.

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. 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.

Statistical Analysis

All data for the MCC physical properties and extrusion–spheronization parameters were normalized according to the following equation,

$$X_{normalized} = \frac{X_i - X_{min}}{X_{max} - X_{min}} \quad (7)$$

where $X_{normalized}$ is the normalized value for the MCC grade, X_i is the actual value being transformed, and X_{max} and X_{min} are the maximum and minimum values of each property respectively. Pearson correlation was carried out on the normalized values to determine the relationship between the MCC properties.

RESULTS AND DISCUSSION

Extrusion–Spheronization Profiles and Pellet Quality of the MCC Grades

Extrusion–spheronization of each MCC grade at MCC:lactose = 3:7 over various amounts of water in the range of 25–45% (w/w) was studied. Logarithm geometric mean pellet size increased linearly with amount of water added for all the MCC grades studied, r^2 ranged from 0.929 ± 0.012 (Avicel PH 302) to 0.993 ± 0.012 (Ceolus 101). Figure 1A shows this relationship for Avicel PH 101 (r^2 = 0.973 ± 0.009). Therefore, it was possible to calculate the predicted water content required to produce pellets of mean size 710 μm, $W_{710\,\mu m}$, which is a useful parameter to compare across the MCC grades, the relative water requirements to produce pellets of equivalent size. MCC grades that need less water to achieve the required liquid saturation for successful spheronization have lower $W_{710\,\mu m}$ values. The MCC grades were found to possess significantly different $W_{710\,\mu m}$ (ANOVA, $P < 0.05$) and this indicated that they have significantly different water requirements to produce pellets of 710 μm.

Spheronization water sensitivity, W_s, is the slope value of the linear relationship between logarithm geometric mean pellet size and amount of water added. W_s is derived to indicate the relative water sensitivity of each MCC grade. It is known that MCC is able to retain a large volume of water and control water movement during extrusion-spheronization (1,7). Thus, W_s is a measure of the tolerance of the MCC to the added moisture and could be associated with the ability of the MCC to control the extrusion–spheronization process. A lower value of W_s is desirable because the formulation will be less prone to respond to variability in amount of water added. ANOVA tests performed on the W_s values showed that the MCC grades possessed significantly different W_s (ANOVA, $P < 0.05$).

Pellet flow rate, friability, bulk, and tapped densities were used to evaluate pellet quality produced by the various MCC grades with increasing amount of water added for extrusion-spheronization. Figure 1, B and C show the effect of increasing water content on pellet flow rate, friability and densities for Avicel PH 101. Generally, the trends of pellet flow rate, friability and packing densities with increasing water content were similar for all the MCC grades. Pellet flow rate decreased with pellets made with increasing water content. As pellets produced with increasing water content were larger, their flow through the orifice became poorer. Pellets produced using 45% (w/w) water content were too large for flow measurements. Pellets were less friable when the water content was higher. As can be seen from Table I, at water contents of 40% (w/w) and above, friability indices of pellets produced from different MCC grades did not differ significantly (ANOVA, $P > 0.05$) as compared to those produced at lower water contents. Higher water contents ensured more dissolved lactose for solid bridge formation on drying and formed strong pellets. Water contents of around 35 to 40% (w/w) produced pellets of the highest bulk and tapped densities (Fig. 1C). Beyond this, increasing water contents pro-

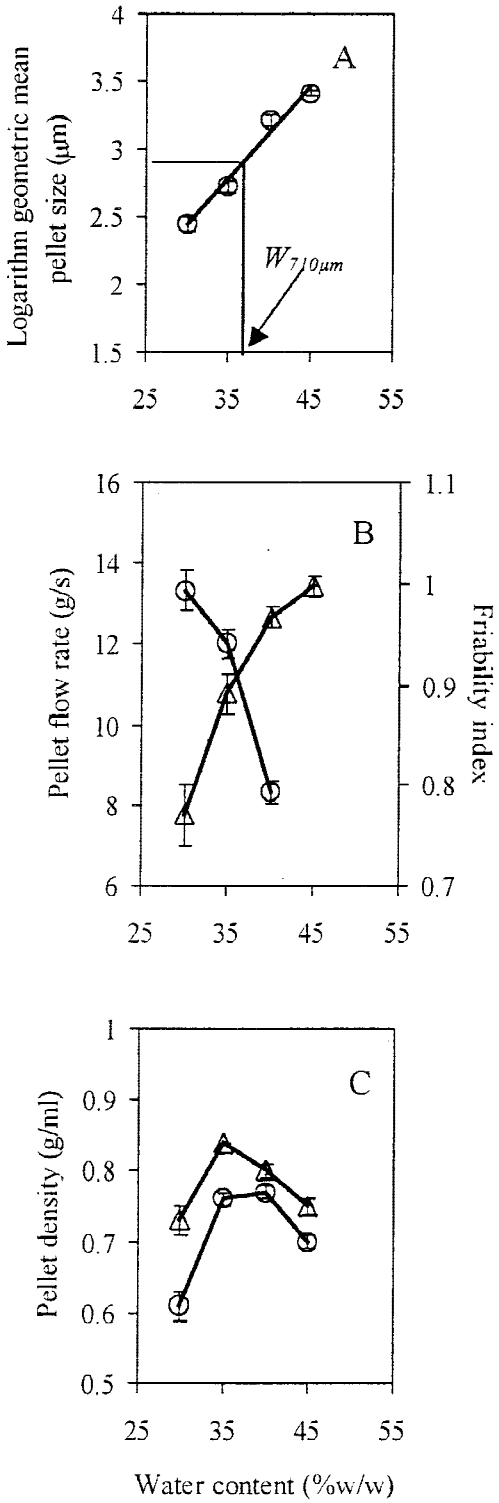

Fig. 1. Effect of varying water content on pellet properties like (A) pellet size; (B) pellet flow rate (○) and friability index (△); and (C) pellet bulk (○) and tapped (△) densities.

Table I. Extrusion–Spheronization Parameters and Pellet Characteristics of the Various MCC Grades[a]

MCC grades	Extrusion–spheronization parameters (n = 3)		Pellet flow rate (g/s) (n = 3)			Pellet friability index (n = 2)				Pellet densities (g/ml) (n = 3)							
			Water content % (w/w)			Water content % (w/w)				Water content % (w/w)							
			30[b]	35[b]	40[b]	30[b]	35[b]	40	45	30		35		40		45	
	$W_{710\mu m}$[b] (%w/w)	W_s[b]								ρ_{pb}[b]	ρ_{pt}[b]	ρ_{pb}[b]	ρ_{pt}[b]	ρ_{pb}[b]	ρ_{pt}[b]	ρ_{pb}[b]	ρ_{pt}[b]
Avicel PH 101	36.10	0.068	13.3	12.0	8.3	0.77	0.89	0.97	1.00	0.61	0.73	0.76	0.84	0.77	0.80	0.70	0.75
	(0.33)	(0.004)	(0.5)	(0.4)	(0.3)	(0.03)	(0.02)	(0.01)	(0.01)	(0.02)	(0.02)	(0.01)	(0.00)	(0.01)	(0.01)	(0.01)	(0.01)
Avicel PH 102	36.19	0.071	13.0	11.4	8.2	0.76	0.88	0.98	0.99	0.58	0.71	0.74	0.81	0.76	0.81	0.70	0.74
	(0.34)	(0.002)	(0.5)	(0.7)	(0.1)	(0.06)	(0.05)	(0.03)	(0.01)	(0.02)	(0.02)	(0.01)	(0.01)	(0.02)	(0.01)	(0.02)	(0.01)
Avicel PH 301	30.27	0.078	10.4	7.7	—	0.92	0.93	—	—	0.70	0.79	0.80	0.84	—	—	—	—
	(0.24)	(0.002)	(0.1)	(0.3)		(0.02)	(0.03)			(0.01)	(0.01)	(0.01)	(0.01)				
Avicel PH 302	29.82	0.076	10.5	6.8	—	0.90	0.93	—	—	0.71	0.81	0.78	0.82	—	—	—	—
	(0.85)	(0.006)	(0.0)	(0.7)		(0.05)	(0.04)			(0.01)	(0.01)	(0.01)	(0.01)				
Ceolus KG 801	37.17	0.064	13.6	11.4	9.5	0.77	0.92	0.95	1.00	0.59	0.71	0.75	0.82	0.79	0.84	0.72	0.76
	(0.75)	(0.003)	(0.8)	(0.1)	(0.1)	(0.03)	(0.03)	(0.04)	(0.00)	(0.01)	(0.01)	(0.03)	(0.01)	(0.02)	(0.02)	(0.01)	(0.01)
Pharmacel 101	37.64	0.062	13.7	11.9	10.1	0.69	0.84	0.92	0.97	0.50	0.65	0.72	0.81	0.76	0.82	0.75	0.79
	(0.92)	(0.001)	(1.1)	(0.7)	(1.0)	(0.02)	(0.03)	(0.06)	(0.02)	(0.01)	(0.01)	(0.04)	(0.04)	(0.03)	(0.04)	(0.03)	(0.03)
Pharmacel 102	37.50	0.065	13.0	11.5	9.1	0.70	0.84	0.95	0.98	0.52	0.65	0.70	0.78	0.73	0.78	0.72	0.76
	(0.62)	(0.001)	(0.3)	(1.7)	(0.3)	(0.04)	(0.01)	(0.08)	(0.02)	(0.03)	(0.03)	(0.05)	(0.05)	(0.02)	(0.02)	(0.01)	(0.01)
Celex 101	38.79	0.062	14.4	11.6	10.0	0.72	0.89	0.95	0.99	0.54	0.68	0.71	0.80	0.76	0.82	0.75	0.80
	(1.02)	(0.005)	(0.6)	(1.1)	(0.2)	(0.03)	(0.02)	(0.03)	(0.02)	(0.03)	(0.03)	(0.03)	(0.03)	(0.02)	(0.01)	(0.04)	(0.04)
Viva Pur 101	36.53	0.065	13.0	10.9	8.4	0.73	0.88	0.96	0.98	0.61	0.74	0.71	0.79	0.72	0.77	0.69	0.74
	(0.83)	(0.003)	(1.5)	(0.2)	(0.5)	(0.05)	(0.03)	(0.02)	(0.01)	(0.02)	(0.02)	(0.03)	(0.02)	(0.01)	(0.01)	(0.01)	(0.00)
Emcocel 50 M	38.10	0.059	13.4	10.8	11.2	0.71	0.88	0.94	1.00	0.58	0.72	0.69	0.77	0.80	0.84	0.72	0.76
	(0.29)	(0.002)	(0.8)	(0.4)	(0.2)	(0.03)	(0.03)	(0.01)	(0.00)	(0.01)	(0.01)	(0.01)	(0.00)	(0.02)	(0.01)	(0.01)	(0.01)
Prosolv 50 M	38.25	0.058	13.0	10.5	10.8	0.68	0.86	0.99	0.98	0.55	0.69	0.69	0.78	0.80	0.84	0.79	0.83
	(1.01)	(0.004)	(0.5)	(0.2)	(1.2)	(0.07)	(0.03)	(0.09)	(0.02)	(0.01)	(0.01)	(0.02)	(0.02)	(0.03)	(0.03)	(0.01)	(0.01)

[a] Values in parenthesis represent SDs.
[b] Significant difference among the MCC grades for this property (ANOVA, $P < 0.05$).

duced bigger pellets that packed less well and showed lower densities. Table 1 gives the extrusion-spheronization parameters and pellet characteristics mentioned above for the various MCC grades.

Correlation Between the Spheronization Behavior and Physical Properties of the MCC Grades

Table II shows physical properties of the various MCC grades. The MCC grades varied significantly in these properties (ANOVA, $P < 0.05$). Pearson correlation values between the normalized spheronization behavior parameters and physical properties of the MCC grades are given in Table III. It was observed that the mean particle size and span of size distribution of the MCC grades had no significant influence on $W_{710\,\mu m}$ and W_s. Particle size and span of the MCC did not affect the porosity and total mercury intrusion volume of MCC (Table 2). During spheronization, under the influence of centrifugal forces, size and span of MCC particles appear not to have any major influence on the amount of water required for agglomerate formation.

The X_{cr} of the MCC grades was found to be significantly different between grades (ANOVA, $P < 0.05$) and there was correlation (Table 3) between X_{cr} and $W_{710\,\mu m}$. The influence of crystallinity on granulation has been studied (15) in high shear granulation and it was found that differences in crystallinity were closely related to the capacity for bridge formation. MCC with higher amorphous content absorbed much more water and exhibited greater granule growth. Similarly, in this study, it was found that MCC grades of higher crystallinity values required smaller amounts of water for extrusion–spheronization.

The granular porosity of MCC was not significantly correlated to the water requirement for extrusion–spheronization (Table 3). MCC is made up of agglomerated particles of the microfibril bundles. Both inter and intraparticulate pores contribute to MCC porosity. There was comparatively better correlation between $W_{710\,\mu m}$ with $V_{low\,P}$ than $V_{high\,P}$ (Table 3). MCC grades with greater $V_{low\,P}$ had higher $W_{710\,\mu m}$, indicating that they possessed greater water requirements for extrusion-spheronization (Fig. 2A). During extrusion–spheronization, the voids comprising of the larger pores thus play a greater role in determining the amount of water to be held within the agglomerates. MCC grades with high void volumes could thus entrap more water for the process of pellet growth. MCC grades with higher quantities of large size pore volumes as indicated by greater $V_{low\,P}$ values also demonstrated lower W_s values and exhibited greater tolerance towards more water added during extrusion-spheronization (Fig. 2A).

Correlation Between Tapping Behavior and Extrusion–Spheronization Behavior of MCC

Generally, MCC powder has lower bulk (ρ_b) and tapped (ρ_t) densities compared to MCC-lactose binary powder mixes due to the higher densities of lactose (ρ_b and ρ_t of lactose was 0.487 ± 0.014 g/ml and 0.899 ± 0.008 g/ml, respectively). The correlation between the bulk and tapped densities of MCC powder with corresponding MCC–lactose binary powder mixes was found to be significant (Table 3). It could be seen that the rank order for densities of MCC and MCC-lactose powders were similar. Thus, MCC grades with high densities

Table II. Physical Properties of the Various MCC Grades[a]

	Physical properties											
					Micromeritics (n = 3)				MCC powder (n = 5)		MCC:lactose = 3:7 (n = 5)	
MCC grades	$\overline{X}^b$ (μm) (n = 3)	$S\,\overline{x}^b$ (n = 3)	$X_{cr}{}^b$ (%) (n = 4)	ϕ^b (%w/w) (n = 4)	$V_{low\ P}{}^b$ (ml/g)	$V_{high\ P}{}^b$ (ml/g)	$V_{total}{}^b$ (ml/g)	ε^b (%)	$\rho_b{}^b$ (g/ml)	$\rho_t{}^b$ (g/ml)	$\rho_b{}^b$ (g/ml)	$\rho_t{}^b$ (g/ml)
Avicel PH 101	76.5	1.91	69.6	4.65	1.19	0.35	1.54	65.45	0.313	0.432	0.404	0.694
	(0.5)	(0.01)	(1.0)	(0.17)	(0.03)	(0.01)	(0.03)	(2.46)	(0.003)	(0.002)	(0.002)	(0.005)
Avicel PH 102	132.8	1.47	69.5	4.18	1.22	0.44	1.67	69.65	0.309	0.421	0.405	0.687
	(2.0)	(0.04)	(0.3)	(0.14)	(0.06)	(0.04)	(0.08)	(1.53)	(0.002)	(0.002)	(0.002)	(0.001)
Avicel PH 301	73.6	1.65	76.4	4.48	0.86	0.29	1.14	61.15	0.430	0.561	0.433	0.753
	(0.5)	(0.01)	(8.0)	(0.27)	(0.06)	(0.02)	(0.07)	(2.88)	(0.004)	(0.001)	(0.002)	(0.004)
Avicel PH 302	139.4	1.41	84.8	4.03	0.75	0.30	1.05	60.11	0.456	0.589	0.454	0.775
	(1.4)	(0.02)	(7.0)	(0.06)	(0.06)	(0.03)	(0.08)	(2.76)	(0.003)	(0.001)	(0.002)	(0.003)
Ceolus KG 801	66.7	3.00	78.6	4.26	2.04	0.57	2.61	76.95	0.194	0.297	0.323	0.556
	(0.4)	(0.07)	(8.9)	(0.17)	(0.05)	(0.02)	(0.07)	(2.55)	(0.002)	(0.001)	(0.001)	(0.003)
Pharmacel 101	62.2	2.17	72.4	4.63	1.11	0.49	1.60	62.29	0.304	0.438	0.392	0.660
	(0.2)	(0.06)	(2.5)	(0.33)	(0.02)	(0.03)	(0.00)	(1.16)	(0.004)	(0.001)	(0.006)	(0.008)
Pharmacel 102	143.4	1.30	73.1	4.24	1.22	0.30	1.52	61.55	0.335	0.441	0.424	0.699
	(0.7)	(0.01)	(4.1)	(0.174)	(0.02)	(0.01)	(0.01)	(0.33)	(0.004)	(0.002)	(0.003)	(0.006)
Celex 101	57.2	1.74	72.9	3.92	1.38	0.45	1.83	68.28	0.282	0.397	0.375	0.639
	(0.2)	(0.02)	(7.3)	(0.07)	(0.03)	(0.05)	(0.05)	(1.16)	(0.003)	(0.001)	(0.004)	(0.004)
Viva Pur 101	68.0	1.58	73.5	4.63	1.22	0.30	1.52	65.35	0.315	0.447	0.398	0.675
	(0.3)	(0.01)	(3.2)	(0.14)	(0.07)	(0.01)	(0.08)	(1.93)	(0.002)	(0.001)	(0.003)	(0.003)
Emcocel 50 M	70.9	1.84	70.4	4.65	1.30	0.36	1.66	65.72	0.270	0.377	0.372	0.645
	(0.2)	(0.01)	(1.6)	(0.17)	(0.10)	(0.01)	(0.11)	(0.86)	(0.003)	(0.002)	(0.004)	(0.004)
Prosolv 50 M	81.4	1.70	70.7	4.29	1.45	0.35	1.81	70.00	0.301	0.406	0.402	0.666
	(0.5)	(0.01)	(1.6)	(0.12)	(0.04)	(0.04)	(0.07)	(3.60)	(0.003)	(0.002)	(0.001)	(0.001)

[a] Values in parenthesis represent SDs.
[b] Significant difference among the MCC grades for this property (ANOVA, $P < 0.05$).

imparted higher densities to the MCC-lactose binary powder used for extrusion–spheronization.

The ρ_b and ρ_t of MCC and MCC-lactose powders were found to have good correlations with $W_{710\,\mu m}$ *and* W_S (Table III, Fig. 2B). Therefore, packing densities of MCC play an important role in determining the extrusion-spheronization properties of MCC. MCC grades with higher packing densities require less water for extrusion-spheronization and were more sensitive to increases in water content for extrusion-spheronization. In the wet granulation process, the bonding forces that exist between particles depend on the formation of liquid bridges between. The different states of liquid saturation and bridging depend on the amount of binder liquid and the interparticulate porosity within the agglomerate. Increasing liquid saturation can be achieved either by continuous liquid addition or by densification of agglomerates. In extru-

Table III. Pearson Correlation Values Between the Various Normalized Parameters[a]

	Extrusion–spheronization parameters		MCC powder		MCC:lactose = 3:7	
Physical properties	$W_{0.71\,\mu m}$	W_s	ρ_b	ρ_t	ρ_b	ρ_t
$\overline{X}$	–0.35	0.44	0.47	0.41	0.61*	0.54
$S_{\overline{x}}$	0.28	–0.32	–0.68*	–0.65*	–0.83*	–0.78*
X_{cr}	–0.69*	0.53	0.46	0.47	0.24	0.29
ϕ	0.10	–0.14	–0.12	–0.06	–0.09	–0.05
$V_{low\ P}$	0.67*	–0.64*	–0.92*	–0.93*	–0.91*	–0.94*
$V_{high\ P}$	0.47	–0.38	–0.73*	–0.71*	–0.79*	–0.79*
V_{total}	0.66*	–0.61*	–0.93*	–0.93*	–0.93*	–0.96*
ε	0.53	–0.50	–0.83*	–0.84*	–0.86*	–0.86*
MCC powder						
ρ_b	–0.85*	0.77*		0.99*	0.94*	0.97*
ρ_t	–0.85*	0.78*	0.99*		0.92*	0.96*
MCC:lactose = 3:7						
ρ_b	–0.67*	0.64*	0.94*	0.92*		0.98*
ρ_t	–0.77*	0.73*	0.97*	0.96*	0.98*	

[a] Significant correlation at $p = 0.05$ level is marked with *.

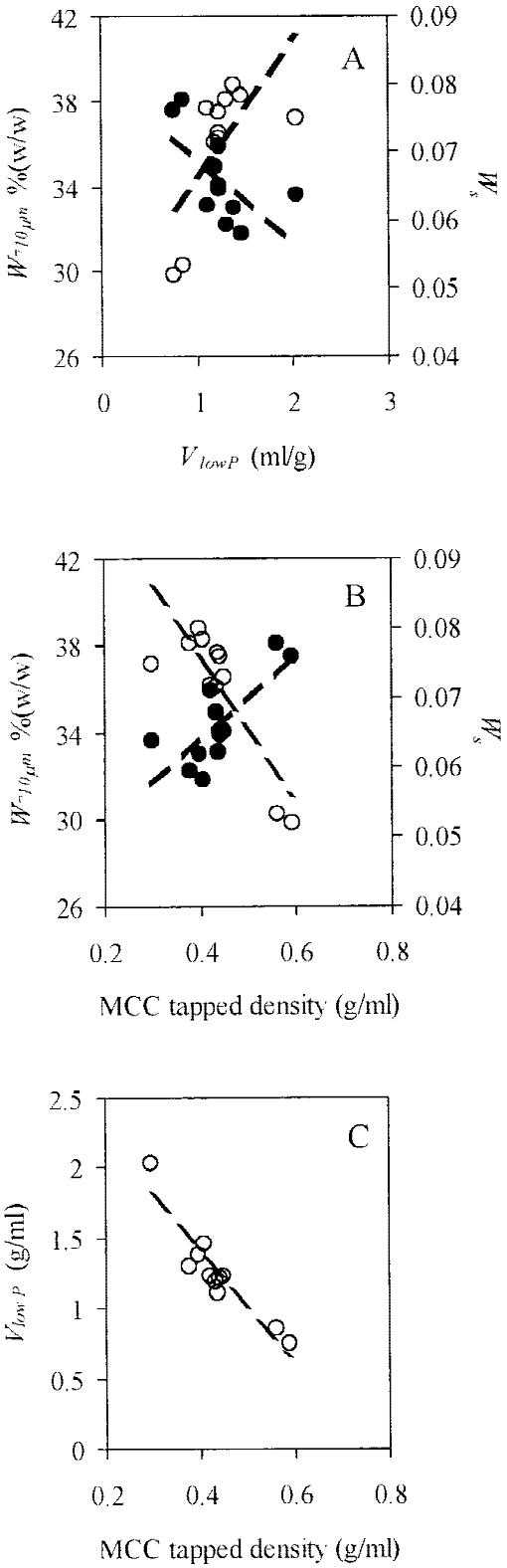

Fig. 2. Correlations of (A) $W_{710\,\mu m}$ (○) and W_S (●) with $V_{low\,P}$, (B) $W_{710\,\mu m}$ (○) and W_s (●) with MCC tapped density, and (C) $V_{low\,P}$ with MCC tapped density.

sion–spheronization, a fixed amount of water is added during the wetting phase and densification is more important for the agglomeration behavior. The extrusion process produces partially agglomerated extruded short rods which are converted into spheroids by the spheronization process. During spheronization, agglomerates undergo further densification resulting in increased availability of surface water and in increased surface plasticity. Increased surface plasticity will allow for faster rounding of spheroids but excessive surface water will result in further pellet growth. High bulk and tapped densities of MCC implied a better packing with smaller void volume and in turn a lower ability to accommodate water. As a result, MCC grades with high packing densities will require less water to form pellets of equivalent size, compared to those of lower packing densities.

No significant relationship was observed between MCC particle size and the ρ_b or ρ_t of MCC and MCC-lactose powder (Table III). This explains why there was little influence of MCC particle size on the extrusion-spheronization profiles of the MCC grades. MCC particle size within the agglomerate has little effect on the amount of water available on the surface upon densification. There was a significant correlation between $V_{low\,P}$ and ρ_b and ρ_t for both MCC and MCC-lactose powder (Table III). Figure 2C shows the relationship between $V_{low\,P}$ and ρ_t of MCC. $V_{low\,P}$, ρ_b and ρ_t are related to the void volume of MCC. The void volume, in turn, is correlated to the water retentive capacity of the MCC and determines the amount of water necessary for reaching the desired liquid saturation for pellet formation during extrusion-spheronization. Although both MCC crystallinity and packing properties could be related to its water requirements for extrusion-spheronization, they were not significantly related to each other (Table III).

Correlation Between Properties of the MCC Grades with Pellet Quality

Figure 3 shows the effect of the properties of MCC on pellet quality. Pellet qualities were characterized using pellets of size fractions 90–425 μm, 250–710 μm and 500–1000 μm for pellet batches produced using 30, 35, and 40 %(w/w) water contents respectively. MCC grades with higher tapped densities gave pellets showing poorer flow properties (Fig. 3A). This was explained by the lower water retentive capacities of these MCC grades resulting in formation of denser pellets and with poorer flow properties. Pellet friability was closely related to $W_{710\,\mu m}$ values (Fig. 3B). MCC grades with higher $W_{710\,\mu m}$ values produced more friable pellets at water contents of 30 and 35% (w/w). However, at water contents of 40% (w/w) and higher, the MCC grades had achieved the desired water saturation for extrusion and produced pellets that did not differ in friability (ANOVA, $P > 0.05$). MCC grades with high packing densities produced pellets of higher bulk and tapped densities at lower water contents (Fig. 3C). Thus, at low water contents, MCC packing and void volumes play a role in determining pellet packing densities. However, as pellet size increased at higher water content, the influence of MCC tapped densities on packing properties of the pellets diminished as pellets become larger.

The physical characteristics of MCC explain its action as a spheronizing aid. MCC is considered a crystalline sponge that is both a water repository and conduit. It also functions as a packing aid for volume reduction experienced in extrusion-spheronization. Under low stress, MCC is able to absorb excess water. When subjected to higher stress, MCC is able to

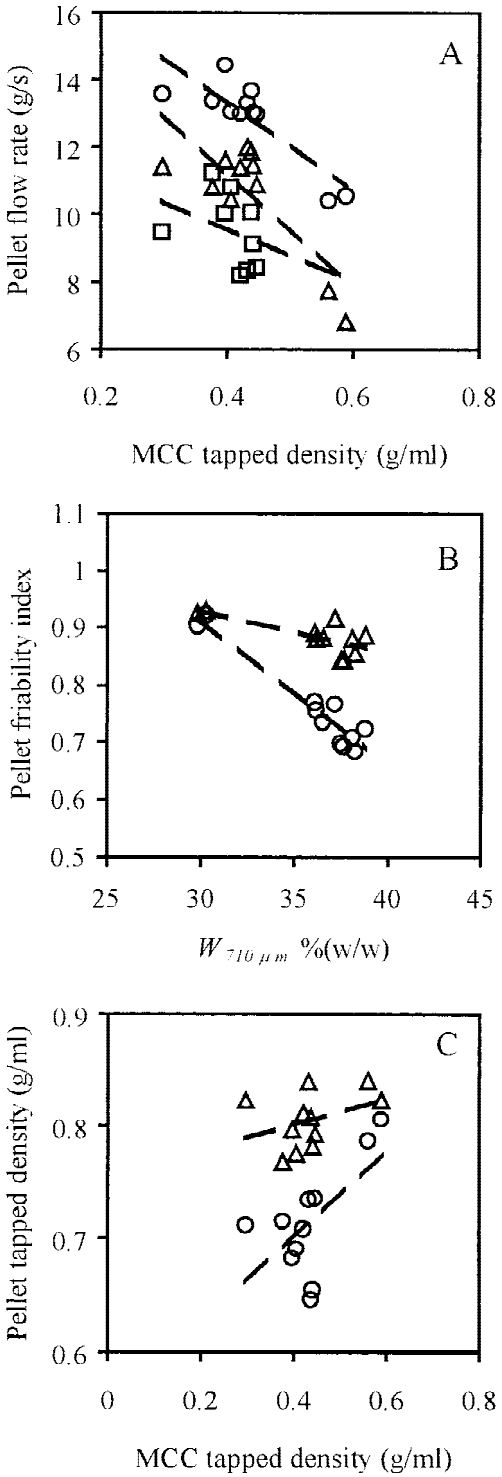

Fig. 3. Correlations of (A) pellet flow rates with MCC tapped density; (B) pellet friability indices with $W_{710\,\mu m}$; and (C) pellet tapped densities with MCC tapped density. Pellets produced using water contents of 30%(w/w), characterisation using pellets of size fraction 90–425 μm (○), 35% (w/w); pellets of size fraction 250–710 μm (△), 40% (w/w); and pellets of size fraction, 500–1000 μm (□).

liberate and distribute water for lubrication and surface plasticity. MCC packing characteristics also determine the ability of wetted powder mixtures containing MCC to deform and densify during spheroid forming process.

CONCLUSIONS

Eleven MCC grades were physically characterized. The extrusion-spheronization behavior and pellet quality using each MCC grade were also determined. The predicted water content required to produce pellets of 710 μm was found to correlate well with void volumes of pores greater than 10 μm and packing densities of MCC. Thus, it is concluded that interparticulate and intraparticulate voids greater than 10 μm play an important role in determining the amount of water retained within the agglomerate during extrusion-spheronization. A smaller void volume and better packing will allow less water to be held and greater migration of water to the agglomerate surface for bonding and pellet growth, and thus less water required for extrusion-spheronization. This study clearly demonstrated that MCC acted as a spheronizing aid by its ability to be a water repository with properties of a crystalline sponge.

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