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The change in characteristics of microcrystalline cellulose during wet granulation using a high-shear mixer

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Abstract

The objective of this study was to investigate the mechanism of hard granule formation and to demonstrate the applicability of X-ray diffraction methods for studying the polymeric pharmaceutical excipients. Using a high-shear mixer, microcrystalline cellulose (MCC) was granulated with water as the granulating liquid. The hardness of the MCC granules increased with granulation time and the amount of water added. The specific surface area measured by the N₂ adsorption method was reduced during the process. Crystallite size of cellulose, calculated by Scherrer's equation adapted for wide angle X-ray diffraction method, decreased with granulation time and with increasing amounts of water added. Debye plots for X-ray small scattering patterns suggested that the average magnitude of the continuous solid region in MCC granules became significantly greater, whereas the specific surface area of the MCC granules, calculated from Debye plots, became smaller in comparison with that of intact MCC. These findings suggested that the long-chain structures in MCC were disrupted, resulting in smaller units with shorter chain lengths due to the strong shear force of the impeller. These smaller units then form a network within the granules. Thus, MCC granules are strengthened with longer granulation time and greater amounts of water, resulting in a more intricate network. The change in MCC chain length and physical structure can be experimentally detected using the small-angle X-ray scattering and wide-angle powder X-ray diffraction methods.

Introduction

In an earlier study (Suzuki et al 1994), we reported that differences in the degree of crystallinity of microcrystalline cellulose (MCC) are closely related to the capacity for bridge formation, and result in different mechanisms of granulation. MCC in which a large proportion is amorphous can easily be divided by the force of an impeller, and can bond other homogenous particles together. In contrast, MCC in which a large proportion is crystalline may be more resistant to being divided by the impeller, so that many other ungranulated particles may remain in the small-size fraction. As a result of this behaviour, MCC with a low degree of crystallinity improves the content uniformity of the small-size fraction.

In the processes of wet granulation, extrusion and spheronization, MCC is frequently used as an extrusion aid. Fielden et al (1988) suggested a sponge model to explain the behaviour of MCC during extrusion. They regarded MCC as a

porous sponge, which can absorb a large quantity of water. During the extrusion process, water would be partly squeezed out due to mechanical pressure; the water squeezed out from the MCC acts as a lubricant, and thus induces smooth mobility in the powder in an extruder. MCC can then reabsorb water again after the pressure is released. In this model, MCC retains its original shape and size after granulation.

A new model for the wet granulation, extrusion and spheronization processes was proposed by Kleinebudde (1997), which he named the crystallite-gel model. According to this model, MCC is thought to be broken down into smaller particles due to the strong shear force of the impellers and possibly, ultimately, to single crystallites in the presence of water. Then the crystallites would form a network (gel) with characteristics which depend on the nature of single crystallites and the granulating conditions. No consensus has been reached regarding these contradictory models for explaining MCC's behaviour during granulation (Ek & Newton 1998).

Although our granulation method was wet granulation using a high-shear mixer, this can be regarded as essentially the same process as wet granulation, extrusion and spheronization, since both granulating methods use mechanical stress in the presence of water. In general, MCC contributes to the hardness of granules during wet granulation using a high-shear mixer. However, there are no studies which clarify the mechanism for this phenomenon. In this study, we examined the relationships between granulation time, quantities of water added to MCC and the mechanical strength of MCC granules using a mercury porosimeter, a helium-air pycnometer, an N₂ gas adsorption surface area analyser and a wide-angle powder X-ray diffractometer. In addition, we attempted to examine the applicability of the X-ray small-angle scattering method to understand quantitatively the change in the characteristics of MCC. Scattering occurred in the region of small angle ($2\theta \leq 5^\circ$, in general) which corresponds to the dimension of about 20–1000 Å. Since most micelles, polymers, colloids, etc., have this dimension, they are too large to be examined by wide-angle X-ray diffraction methods and too small to be examined by a microscope. Therefore the X-ray small-angle scattering method is useful to investigate the structural properties of MCC.

Materials and Methods

Materials

MCC (Avicel PH101) was obtained from Asahi Chemi-

cal Industry Co. Ltd. Mean particle diameter of MCC, measured by a laser beam particle analyser (Heros & Rodos, Japan Laser Corporation), was about 60 μm . Purified water was used as the granulating liquid.

Preparation of samples

The High Speed Mixer FS-GS-1 (Fukae Powtec, Japan), which was equipped with a 3-blade main impeller, was used as the granulating machine with a rotating speed of 500 rev min⁻¹, with no chopper used. Granulation was carried out using 100 g of MCC and 80 mL, 90 mL or 100 mL of water. Samples were removed at 1, 5 and 10 min after water was added. The damp mass sample was dried in a tray dryer at 50°C for 8 h, and then stored at 25°C and 60% r.h. to maintain the moisture content at 4–5%. Dried samples were sieved through 30-mesh and 42-mesh screens, and the fraction between 30-mesh and 42-mesh was used for evaluation.

Measurements

The mechanical strength of each granule was measured by GRANO (Okada Seiko Co. Ltd), which detects the strength of the granule's break point using a load cell. Loading speed was set at 100 $\mu\text{m s}^{-1}$. The average strength for each granule was determined from twenty consecutive measurements.

Apparent particle density (d_{ap}) was measured using a mercury porosimeter (Pore Sizer 9320, Shimadzu Corporation, Japan). True density (d_t) was determined using a helium-air pycnometer (Multivolume Pycnometer 1305, Shimadzu Corporation, Japan). The specific surface area was measured using the N₂ gas adsorption surface area analyser (SA-9603, HORIBA Ltd, Japan), and was calculated using the BET equation. Wide-angle powder X-ray diffraction patterns were measured using a powder X-ray diffractometer (MPX-3, Mac Science, Japan). Samples were milled using mortar and pestle and sieved through a 140-mesh screen before application. The measuring conditions were as follows: filter, Ni; target, CuK α ; voltage, 40 kV; current, 35 mA; scan range, $2\theta = 5\text{--}30^\circ$. X-ray small-angle scattering measurements were recorded using an X-ray diffractometer (RINT-2500, Rigaku Corporation, Japan). Scattering due to the apparatus and air was corrected by a measurement using only the sample holder as the blank test. The measuring conditions were as follows: filter, K β ; target, CuK α ; voltage, 50 kV; current, 150 mA; scan range, $2\theta = 0.100\text{--}3.000^\circ$ in steps of 0.005°; width of first slit, 0.04 mm; second slit, 0.06 mm; received slit, 0.1 mm.

Results and Discussion

Mechanical strength of granules

The mechanical strength of granules increased with increasing granulation time, without altering the volume of water added (Figure 1), and also increased with increasing quantity of water added to MCC with a constant granulation time of 10 min (Figure 2). Millili &

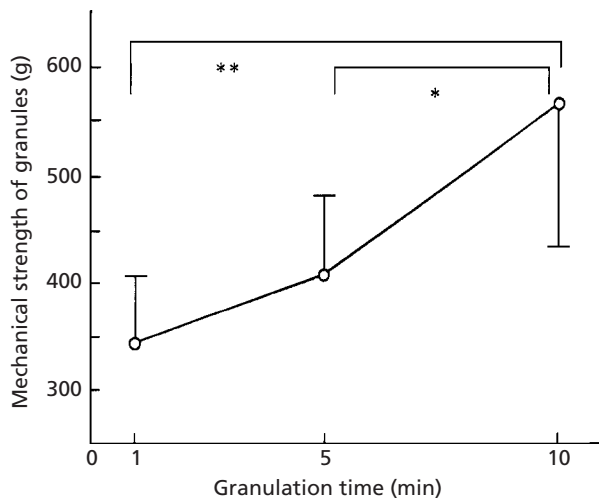


Figure 1 Change in the mechanical strength of MCC granules during wet granulation using a high-shear mixer with 100 mL of water added. Vertical bars represent s.d., $n = 20$. * $P < 0.05$; ** $P < 0.01$.

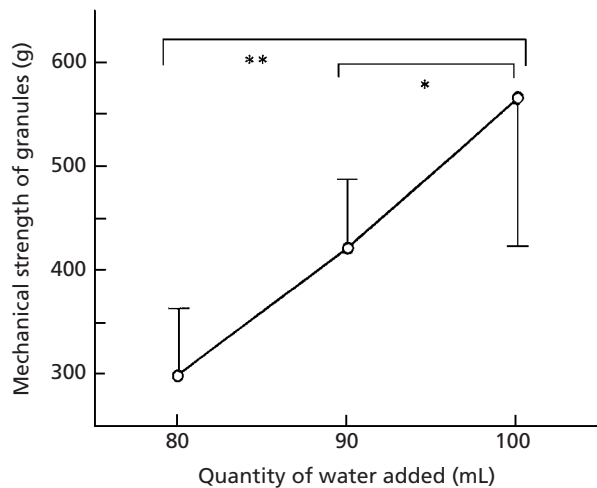


Figure 2 Change in the mechanical strength of MCC granules with 80 mL, 90 mL or 100 mL of water added during wet granulation using a high-shear mixer with 10 min of granulation time. Vertical bars represent s.d., $n = 20$. * $P < 0.05$; ** $P < 0.01$.

Schwartz (1990) reported that the mechanical strength of MCC pellets produced using water alone was greater than those produced using a mixture of ethanol and water (70:30), which is consistent with our findings. This suggested that certain changes in the characteristics of MCC may be induced during granulation, and water may be a relevant factor.

Measurements of density and specific surface area

Table 1 shows density measurements of intact MCC and MCC granules. Nakai et al (1977) reported that the effective surface area of MCC was mainly composed of pores up to 300 Å in diameter, and it is the relatively small pores, up to 100 Å in diameter, that play an important role. Zografis et al (1984) reported that mercury cannot access the small pores in MCC. Since the mercury porosimeter measures the total volume and the pores of MCC, the d_{ap} of each MCC sample is calculated by dividing the total volume by sample weight.

Although d_t values were almost constant among all samples, the d_{ap} values of the MCC granules were significantly greater in comparison with that of intact MCC. This suggested that the intact MCC has many smaller pores where the diameters were too small to be accessed by mercury (Zografis et al 1984). The number of small pores in the MCC granules may also be reduced during wet granulation, because the difference between d_{ap} and d_t decreased after granulation (Table 1). The results showed that increasing the volume of water added affected the d_{ap} of MCC granules with a constant granulation time of 10 min but the d_{ap} was hardly affected by increased granulation time in 100 mL of water. The specific surface area measured by the N_2 adsorption method is shown in Table 2. The specific surface area of MCC decreased during wet granulation from 0.93 m²

Table 1 Densities of intact MCC and MCC granules manufactured by wet granulation using a high-shear mixer.

Granulation time (min)	Quantity of water added (mL)	d_{ap} (g cm ⁻³)	d_t (g cm ⁻³)	Φ_p
Intact		1.360	1.568	0.133
1	100	1.533	1.568	0.022
5	100	1.532	1.564	0.020
10	100	1.536	1.567	0.020
10	90	1.521	1.570	0.031
10	80	1.505	1.566	0.039

d_{ap} , Apparent density; d_t , true density; Φ_p , void fraction of sample. The quantity of MCC used was 100 g.

Table 2 Specific surface area of intact MCC and MCC granules measured using the N₂ adsorption method.

Granulation time (min)	Quantity of water added (mL)	Specific surface area (m ² g ⁻¹)
Intact		0.93
1	100	0.25
5	100	0.24
10	100	0.29
10	90	0.14
10	80	0.13

The quantity of MCC used was 100 g

g⁻¹ to approximately 0.1–0.3 m² g⁻¹. Nakai et al (1977) determined the surface area of MCC using the BET equation by gas adsorption methods. They reported that the surface area was 1.0 m² g⁻¹ and 149 m² g⁻¹ using the N₂ gas and H₂O adsorption methods, respectively. Hollenbeck et al (1978) reported that the specific surface area of MCC was 138 m² g⁻¹ using the H₂O adsorption method. Zografis et al (1984) reported surface areas of 1.31 m² g⁻¹, and 1.44 m² g⁻¹ when using the N₂ gas and Kr gas adsorption methods at 100°C, respectively. The results for intact MCC in this study agreed well with those reported previously.

The reduction of the specific surface area of MCC during wet granulation may be due to two possible reasons: the reduction of the number of pores in MCC

and the formation of continuous regions in MCC granules. The results of mercury porosimeter measurements support the former explanation.

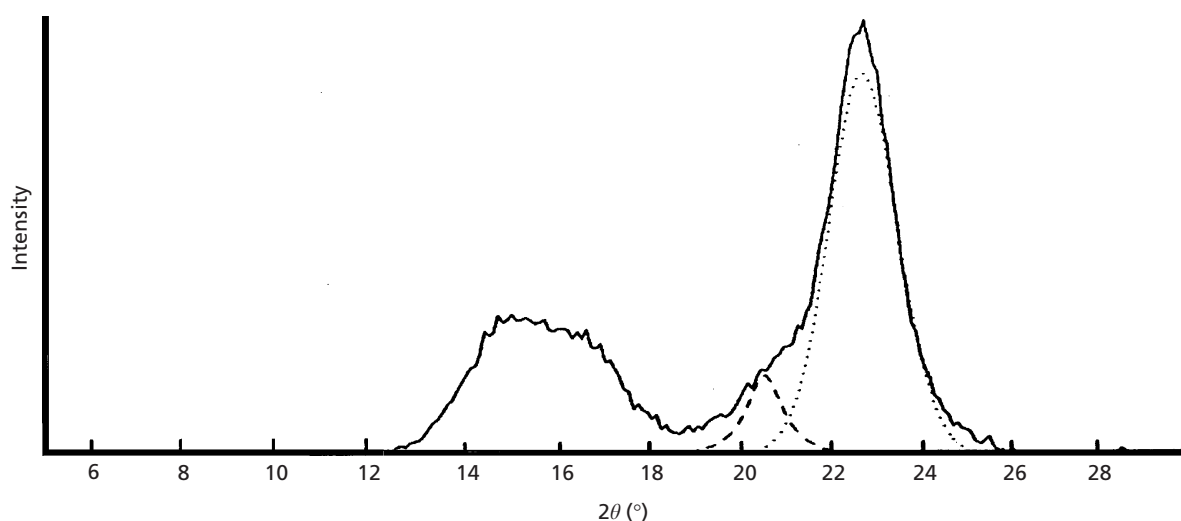
Wide-angle X-ray diffraction pattern

Wide-angle X-ray diffraction measurement was performed to examine the change of crystallite size of cellulose. Half-width of the peak at $2\theta = \text{approx. } 22^\circ$ for each sample was determined after subtracting the background from the original peak and separating the overlapping peaks. A typical X-ray diffraction pattern for intact MCC is shown in Figure 3. Scherrer's equation was used to calculate the size of crystallites of the MCC samples. The results are shown in Table 3. Our findings

Table 3 Change of crystallite size of MCC during wet granulation using a high-shear mixer.

Granulation time (min)	Quantity of water added (mL)	Half-width (°)	Crystallite size of MCC (nm)
Intact		1.79	4.54
1	100	2.22	3.65
5	100	2.41	3.36
10	100	2.45	3.30
10	90	2.32	3.50
10	80	2.09	3.87

Crystallite size was calculated by Scherrer's equation. The quantity of MCC used was 100 g

**Figure 3** A typical example of wide-angle diffraction pattern of intact MCC.

showed that the size of MCC crystallites decreased gradually with granulation time and also with increasing quantity of water added.

X-ray small-angle scattering measurement

X-ray small-angle scattering measurement was carried out to investigate the change in chain structure of MCC. Scattering intensities were observed in the range of $2\theta = 0.1-0.5^\circ$ for intact MCC and MCC granules. Scattering patterns are shown in Figures 4 and 5.

Debye plots were used to analyse scattering intensities, because they not depend on the sample system. Debye et al (1957) introduced equation 1 for calculating scattering intensity:

$$I(s) = I_c (\Delta\rho)^2 \Phi_p (1 - \Phi_p) V \int_0^\infty \gamma(r) (\sin sr/sr) 4\pi r^2 dr \tag{1}$$

$$s = 4\pi \sin\theta / \lambda \tag{2}$$

$$\Phi_p = 1 - (d_{ap}/d_i) \tag{3}$$

Where Φ_p represents the void fraction of samples, $I(s)$ is scattering intensities, I_c is a constant and $\Delta\rho$ is the

difference in electron density between particles and external media.

If pores are distributed randomly in a solid, equation 1 is integrated as follows:

$$I(s) = I_c 8\pi a^3 (\Delta\rho)^2 \Phi_p (1 - \Phi_p) V / (1 + a^2 s^2)^2 \tag{4}$$

From equation 4, a plot of $I(s)^{-\frac{1}{2}}$ against s^2 should yield a straight line, where a is the correlation distance, which expresses the characteristic dimension of a sample. This parameter, a , can be calculated from the value of the slope and intercept of regression lines obtained from Debye plots.

$$a = (\text{slope}/\text{intercept})^{\frac{1}{2}} \tag{5}$$

The average size of the solid part (a_{solid}), average pore size (a_{pore}) and the specific surface area of a sample (S_x), can be calculated from the following equations:

$$a_{\text{solid}} = a / \Phi_p \tag{6}$$

$$a_{\text{pore}} = a / (1 - \Phi_p) \tag{7}$$

$$S_x = [4 \times 10^3 \Phi_p (1 - \Phi_p) / d_{ap}] (1/a) \tag{8}$$

Figures 6 and 7 show Debye plots of samples. Various

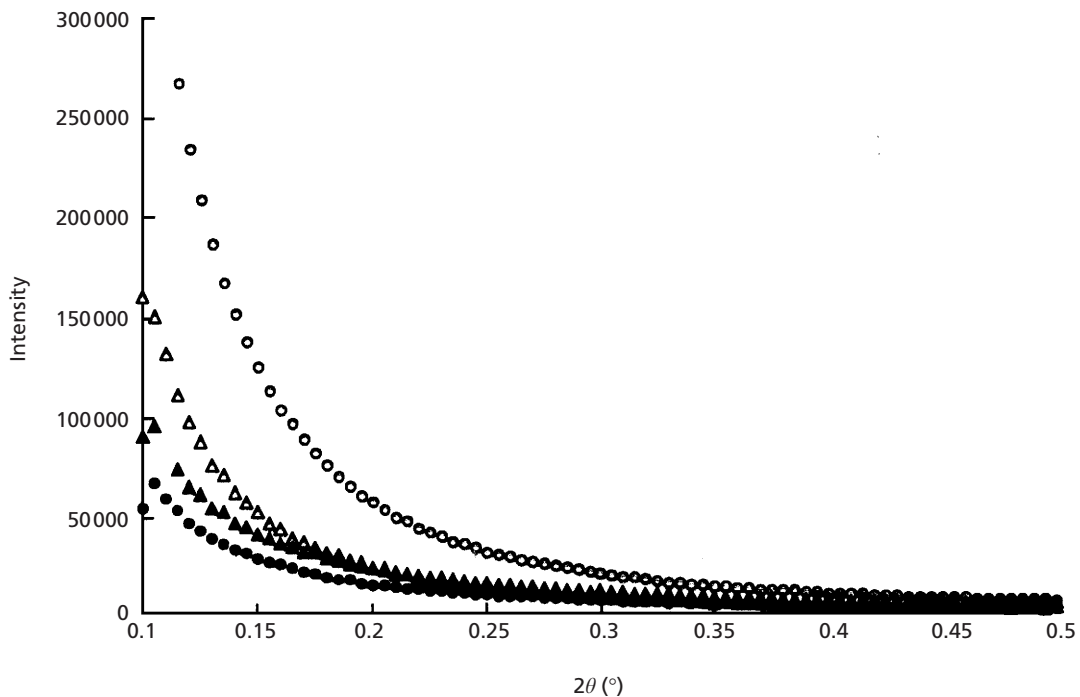


Figure 4 Small-angle scattering patterns of intact MCC and MCC granules of various granulation times during wet granulation using a high-shear mixer in 100mL of water. ○, Intact MCC; △, 1-min granulation; ●, 5-min granulation; ▲, 10-min granulation.

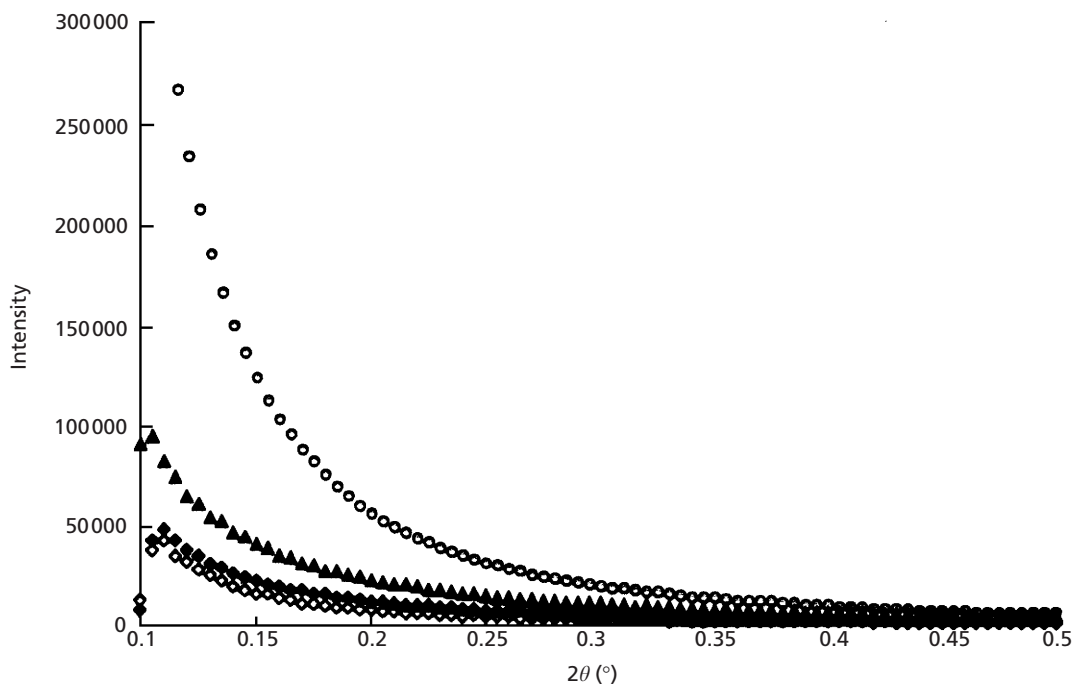


Figure 5 Small-angle scattering patterns of intact MCC and MCC granules produced with various amounts of water using a high-shear mixer with 10 min of granulation time. ○, Intact MCC; ◇, 80 mL water added during granulation; ◆, 90 mL water added; ▲, 100 mL water added.

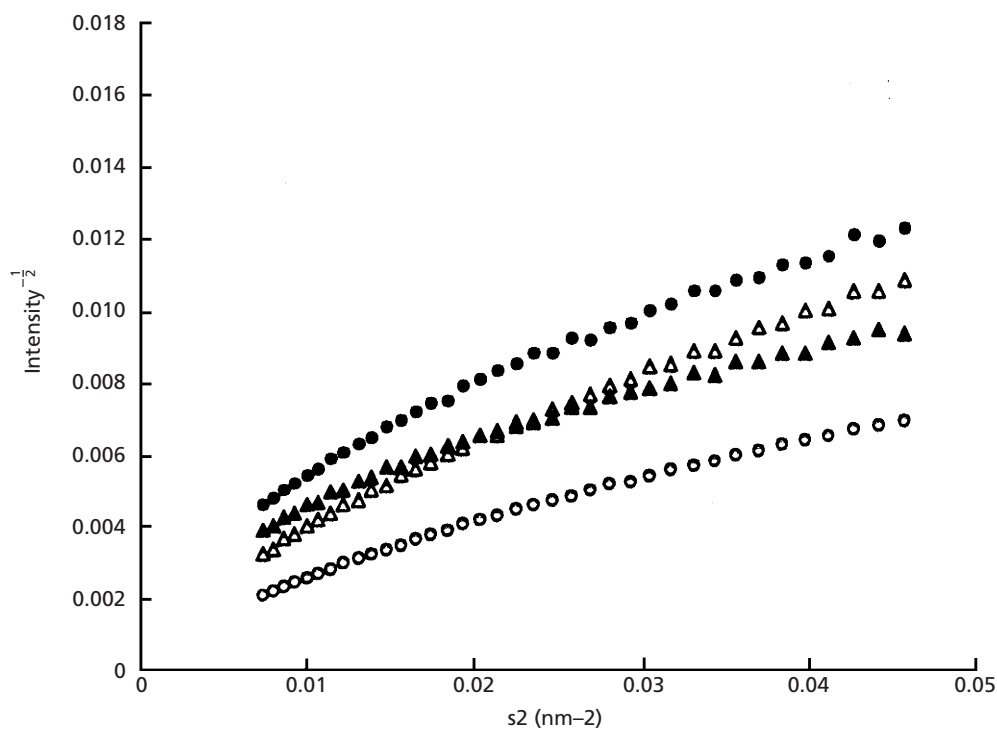


Figure 6 Debye plots for small-angle scattering patterns of intact MCC and MCC granules removed at various granulation times during wet granulation using a high-shear mixer in 100 mL of water. ○, Intact MCC; △, 1-min granulation; ●, 5-min granulation; ▲, 10-min granulation.

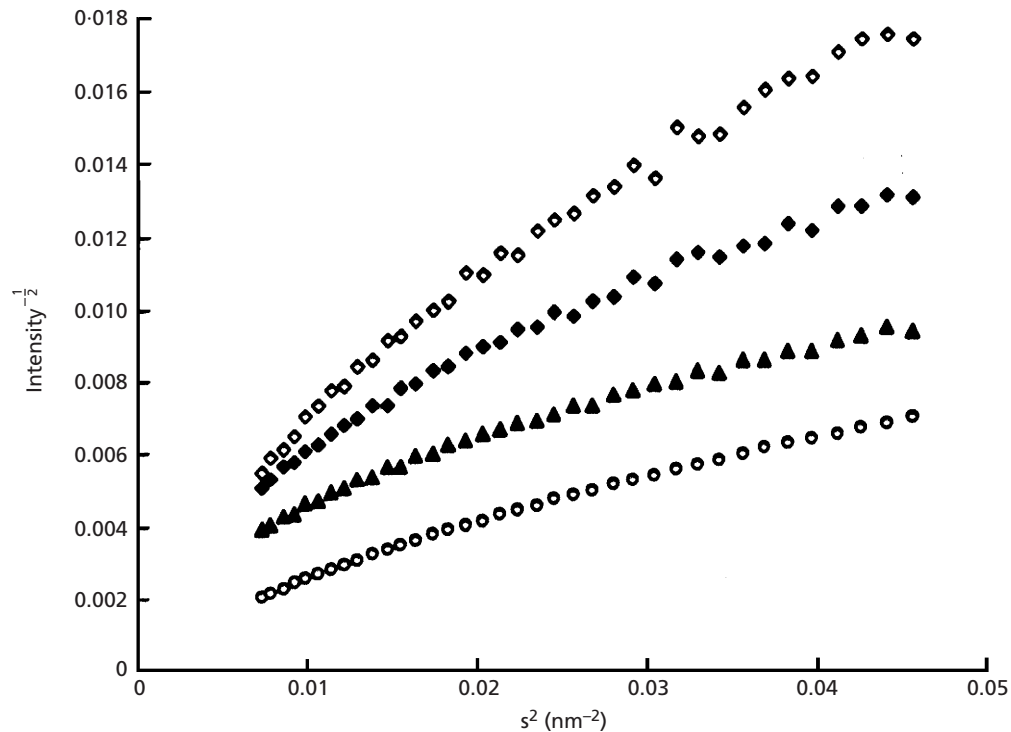


Figure 7 Debye plots for small angle scattering patterns of intact MCC and MCC granules produced with various amounts of water using a high-shear mixer with 10 min of granulation time. ○, Intact MCC; ◇, 80 mL water added; ◆, 90 mL water added; ▲, 100 mL water added.

Table 4 Parameters obtained from Debye plots for X-ray small-angle scattering patterns of intact MCC and MCC granules.

Granulation time (min)	Quantity of water added (mL)	a (nm)	a _{solid} (nm)	a _{pore} (nm)	S _x (m ² g ⁻¹)
Intact		9.59	72.3	11.1	35.3
1	100	9.51	429	9.73	5.95
5	100	7.23	354	7.38	7.21
10	100	6.52	323	6.66	7.91
10	90	6.98	225	7.20	11.3
10	80	8.68	224	9.03	11.4

a, Correlation distance; a_{solid}, average size of solid parts; a_{pore}, average pore size; S_x, specific surface area.

parameters obtained from analysis by Debye plots are listed in Table 4.

The correlation distance, *a*, decreased with granulation time and with increased amount of water added to the MCC. However, *a*_{solid} significantly increased from 72.3 nm for intact MCC to approximately 220–430 nm for MCC granules. The average size in solid parts calculated from Debye plots is different from the crystal

size calculated using the wide-angle X-ray diffraction method, because the latter expresses the size of crystallites but the former expresses the size of the continuous region. That is to say, wide-angle X-ray patterns are due to the diffractive phenomenon of X-rays due to the cyclic structure of solids, and, in contrast, X-ray small-angle scattering patterns are ascribable to the scattering phenomenon due to the difference in electron density

between the solid region and the pores (Ruike et al 1999).

The crystallite size of MCC calculated by Scherrer's equation was reduced and the size of the continuous solid region in MCC granules, a_{solid} , was increased during the wet granulation process. The reasons elicited were as follows: the fibril in MCC may be broken by the strong shear force of the impeller, and, divided, the MCC may form a network of gel on a macro scale. It was thought that this mechanism may contribute to the increasing hardness of MCC granules. However, not only the strong shear force of the impeller affects the change in characteristics of MCC granules but also the participation of water in the granulation process; characteristics such as the apparent density, specific surface area and so forth differed to a greater extent between intact MCC and MCC granules granulated for only 1 min, than between MCC granules formed with various granulation times.

In the case of the wet granulation, extrusion and spheronization process, there was a similar discussion (Ek & Newton 1998). It is possible to form MCC pellets without any extrusion process, simply by adding water, mixing and placing them on a spheronizer plate. However, there is little information regarding such pellets. Further work is needed to investigate the relevance of water and the change in characteristics of MCC.

A specific surface area, S_x , of $35.3 \text{ m}^2 \text{ g}^{-1}$ was obtained for intact MCC, compared with $5.95\text{--}11.4 \text{ m}^2 \text{ g}^{-1}$ for MCC granules. These values obtained using the X-ray small-angle scattering method were similar to those obtained using the N_2 adsorption method. Gas adsorption methods use gases as probes, which access the pores and get adsorbed there. However, the specific surface area calculated from the X-ray small-angle scattering method is derived from the difference in electron density between the solid region and the pores. That may be the reason why the present findings using the X-ray small-angle scattering method differed from those measured by the gas adsorption method. Although the precision of surface-area measurement by the X-ray small-angle scattering method is inferior to that achieved using the gas adsorption method, the X-ray small-angle scattering method can determine the average size of the continuous solid region.

Conclusions

From density and specific surface-area measurements, we can conclude that the number of pores in MCC were reduced during the wet granulation process. Moreover, the MCC fibrils may be broken by the strong shear forces of the impeller during wet granulation and the shorter-chain-length MCC structures may form a network that is the continuous solid phase. Consequently, the hardness of the MCC granules may increase.

The X-ray small-angle scattering method was useful in the investigation of the change of characteristics of polymeric pharmaceutical excipients.

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