

Research Article

Moistening Liquid-Dependent De-aggregation of Microcrystalline Cellulose and Its Impact on Pellet Formation by Extrusion–Spheronization

Srimanta Sarkar¹ and Celine Valeria Liew^{1,2}

Received 29 October 2013; accepted 28 January 2014; published online 20 February 2014

Abstract. The wet-state particle size of microcrystalline cellulose (MCC) dispersed in different moistening liquids was characterized to elucidate the effect of moistening liquid type on the extent of MCC particle de-aggregation. Cohesive strength of moistened MCC masses was also assessed and pellet production by extrusion–spheronization attempted. MCC dispersed in alcohol or water–alcohol mixtures with higher alcohol proportions generally had larger particle sizes. Moistened mass cohesive strength decreased and poorer quality pellets were obtained when water–alcohol mixtures with higher alcohol proportions were used as the moistening liquid. MCC comprise aggregates of small sub-units held together by hydrogen bonds. As MCC particle de-aggregation involves hydrogen bond breaking, moistening liquids with lower polarity, such as water–alcohol mixtures with higher alcohol proportions, induced lesser de-aggregation and yielded MCC with larger particle sizes. When such water–alcohol mixtures were employed during extrusion–spheronization with MCC, the larger particle size of MCC and lower surface tension of the moistening liquid gave rise to moistened masses with lower cohesive strength. During pelletization, agglomerate growth by coalescence and closer packing of components by particle rearrangement would be limited. Thus, weaker, less spherical pellets with smaller size and wider size distribution were produced.

KEY WORDS: extrusion–spheronization; microcrystalline cellulose; moistening liquid; particle size; pellets.

INTRODUCTION

Microcrystalline cellulose (MCC) is the most commonly employed pelletization aid for pellet production by extrusion–spheronization (1). With water as the moistening liquid, MCC yields highly spherical and uniform size pellets (2–6). Besides water, ethyl alcohol and isopropyl alcohol (IPA) had been tried as the moistening liquid for pelletization with MCC. While pellets could not be produced with alcohol alone as moistening liquid (7,8), successful pellet production was reported with liquid mixtures (water–alcohol mixtures) containing ethyl alcohol or IPA below a certain proportion (7,9). However, the properties of the resultant pellets were found to be dependent on the proportion of alcohol in the liquid mixture used as moistening liquid. In general, pellet hardness, sphericity (7), and disintegration time (9) decreased as the proportion of alcohol increased in the water–alcohol liquid mixtures. The observed differences in pellet properties were attributed to changes in the extent of both intra- and inter-molecular hydrogen bonding within the hydroxyl groups of the MCC (10) and in the extent of inter-particulate bonding (9). Microstructure of freeze-dried MCC pastes, prepared using different liquids, was analyzed by Mascia *et al.* (11).

The sizes of pores in the freeze-dried MCC–water paste ranged from 0.1 to 10 μm with a peak at around 1 μm . On the other hand, the freeze-dried MCC–ethyl alcohol paste exhibited bimodal pore size distribution with a dominant peak at around 20 μm . These findings suggested that MCC particles in the freeze-dried MCC–ethyl alcohol paste were packed more loosely than those in the MCC–water paste. Pellet formation by extrusion–spheronization was found to be mainly controlled by the inter-particulate forces and packing of the component materials which, in turn, are dependent on the size of the component particles during wet processing (12). It was observed that when water was used as the moistening liquid, MCC de-aggregated into smaller particles during wet processing (3). The cellulose fibers in MCC consist of a huge number of microcrystals or microfibrils of small size. The cohesion of the cellulose microcrystals is postulated to be largely due to van der Waals attraction between hydrogen-bonded sheets (13,14) which are susceptible to break up in the presence of water (15). Better wet packability of smaller particles resulted in moistened masses with high cohesive strength which subsequently produced good-quality pellets (3–5).

It is, thus, hypothesized that the type of moistening liquid employed can influence the extent of MCC particle de-aggregation. The resultant particle size of MCC could affect the packing of components and the subsequent cohesive strength and extrusion–spheronization performance of the moistened mass. This study aimed to characterize the wet-state particle size of MCC in different liquids (water, ethyl alcohol, or IPA) or water–alcohol

¹GEA-NUS Pharmaceutical Processing Research Laboratory, Department of Pharmacy, National University of Singapore, 18 Science Drive, Singapore, 117543, Singapore.

²To whom correspondence should be addressed. (e-mail: phalcv@nus.edu.sg)

mixtures with or without sonication treatment to elucidate the effect of moistening liquid type on the extent of particle deaggregation. In addition, cohesive strength of moistened masses prepared with the different liquids or liquid mixtures as moistening liquid was characterized by mixer torque rheometry and pelletization by extrusion–spheronization attempted. Preformulation characterization of the wet-state particle size of MCC dispersions and cohesive strength of MCC moistened masses could thus provide a better understanding of the influence of moistening liquid on the extent of MCC particle deaggregation and its impact on pellet formation by extrusion–spheronization. This, in turn, could be useful to formulation scientists in the selection of suitable moistening liquid and component material properties to produce pellets of the desired quality.

MATERIALS AND METHODS

Materials

Three commercial grades of MCC, Avicel PH 101 (PH101), Avicel PH 102 (PH102), and Avicel PH 105 (PH105), were obtained from FMC Biopolymer, Cork, Ireland. Ethyl alcohol (absolute alcohol, Hayman Ltd., England, UK), IPA (Aik Moh Paints & Chemicals Pte Ltd., Singapore), and filtered water (Milli-Q, Millipore Corporation, Billerica, MA, USA) were used as the dispersion media for wet-state particle size analysis. The alcohols used for particle size measurement were first passed through 0.45- μm pore-size filter (Sartorius Stedim Biotech GmbH, Göttingen, Germany). Distilled water, ethyl alcohol, IPA, and liquid mixtures were used as the moistening liquids in the rheological studies and for the preparation of MCC pellets by extrusion–spheronization.

Liquid and Liquid Mixture Surface Tension Measurements

Surface tension measurements were carried out on the different liquids and liquid mixtures at 25°C using a platinum ring tension balance (White Elec. Inst. Co. Ltd, England, UK). Approximately 50 mL of liquid was used, and the platform was raised gradually until the platinum ring was in contact with the liquid. The force required to detach the platinum ring from the liquid/liquid mixture, i.e., surface tension of the liquid/liquid mixture, was noted. For each liquid/liquid mixture, the average surface tension value was calculated from three repeats. Surface tension values of the different liquids and liquid mixtures are presented in Table I.

MCC Particle Size Analysis

Particle size analysis of MCC was carried out by laser diffraction using dry powder and wet powder modules (LS230, Coulter Corporation, Brea, CA, USA). The particle size and size distribution of the MCC were characterized by median particle diameter (X_{50}) and span, respectively. Span was calculated according to Eq. (1).

$$\text{Span} = \frac{X_{90} - X_{10}}{X_{50}} \quad (1)$$

where X_{10} , X_{50} , and X_{90} are diameters of particles at the 10, 50, and 90 percentiles of the cumulative percent undersize plot, respectively. For each MCC grade, the average value was calculated from three repeats.

Dry-State Particle Size Analysis

Size and size distribution determination of dry MCC powder was carried out by laser diffraction using the dry powder module at an obscuration of 4–11%. Sampling time was fixed at 100 s. The median particle diameter obtained from particle size analysis of a dry powder sample was termed as dry-state particle size.

Wet-State Particle Size Analysis

Wet-state particle size analysis of MCC in the different liquids (water, ethyl alcohol, and IPA) was conducted using three MCC grades, PH102, PH101, and PH105. In addition, the PH102 grade was employed to investigate the influence of liquid mixtures and liquid addition order on MCC particle size in the wet state. Approximately 0.2 g powder sample was added to 50 mL filtered water, ethyl alcohol, IPA, or liquid mixture and dispersed by sonication treatment (Sonorex, Erlangen, Germany) at 35 kHz frequency for different time periods. The median particle diameters of the sonicated powder dispersions were measured after predefined time periods. The dispersed sample was added drop by drop until polarization intensity differential scattering reached 45–55%. Sampling time was fixed at 100 s. The median particle diameter obtained after 30 min sonication treatment of the dispersion was termed as individual or unit particle size (15).

To study the impact of liquid addition order, powder samples (PH102) were either dispersed by 30 min sonication

Table I. Surface Tension Values of the Different Liquids and Liquid Mixtures at 25°C

Liquid	Liquid mixture				
	Water–ethyl alcohol		Water–IPA		
Type	Surface tension (dynes/cm)	Ethyl alcohol (% v/v)	Surface tension (dynes/cm)	IPA (% v/v)	Surface tension (dynes/cm)
Water	72.05±0.24	20	42.9±0.25	20	34.9±0.25
Ethyl alcohol	21.40±0.25	40	33.4±0.20	40	28.1±0.37
		60	30.0±0.16	60	26.5±0.32
IPA	22.30±0.19	80	25.0±0.16	80	24.8±0.19

IPA isopropyl alcohol

in IPA with subsequent addition of water to adjust to different IPA proportions and sonicated for an additional 5 min or dispersed by 30 min sonication in water with subsequent addition of IPA to adjust to different IPA proportions and sonicated for an additional 5 min. A magnetic stirrer was used to mix the liquids and disperse the powder particles during the addition of water or IPA to adjust to different IPA proportions. Particle sizes of the powder dispersions were measured before and after the adjustment of IPA proportion and after the additional sonication.

Scanning Electron Microscopy of Dry MCC Powders

Dry MCC powders were sprinkled onto a double-sided carbon tape mounted on studs and sputter-coated (JFC-1100, Jeol, Tokyo, Japan) with gold. Photomicrographs of gold-coated MCC powders were obtained using a scanning electron microscope (SEM; Phenom, FEI, Hillsboro, OR, USA). The SEM photomicrographs of the different MCC powder grades are shown in Fig. 1.

Photography of Sonicated Powder Dispersions

A drop of the powder dispersion sample after 30 min sonication was placed on a glass slide and shaken gently to spread the dispersion uniformly. Photographs were taken using a digital camera (DSP 3CCD, Sony, Tokyo, Japan) mounted on a light microscope (BX61, Olympus, Tokyo, Japan).

MCC Moistened Mass Rheological Studies

Rheological profiles of the MCC grades were determined using a mixer torque rheometer (Caleva Process Solutions, Dorset, UK). Water, ethyl alcohol, IPA, and liquid mixtures were used as moistening liquids. Dry powder sample (15 g) was then introduced into the mixer bowl and mixed for 30 s. Torque generated by the dry powder was recorded for another 20 s. Moistening liquid, corresponding to an increment of 15% (*v/w*), was added to the powder in the mixer bowl with continuous mixing. After each mixing phase, the torque value was recorded for another 20 s prior to the next liquid addition, and mean torque values were calculated. The mean torque describes the mean resistance of the mass to mixing, i.e., the cohesive strength of

moistened mass. The mean torque values generated for a total of 19 liquid additions were plotted against the amount of moistening liquid added. The plotted curve represents different states of liquid saturation. The peak region in the curve corresponds to the capillary state of liquid saturation (16).

Preparation of MCC Pellets by Extrusion–Spheronization

Pelletization by extrusion–spheronization was carried out with the PH102 grade using the different liquids or liquid mixtures. Thirty grams of powder was moistened with 28.5 mL of water, alcohol, or liquid mixture. The resultant wet mass was extruded through a 1-mm aperture size mesh. The wet massing and extrusion steps were completed in 7 min. The extrudates were transferred to a spheronizer (Model 120, Caleva Process Solutions, Dorset, UK) fitted with a cross-hatched 12-cm-diameter frictional base plate and spheronized at 1,250 rpm for 5 min. The pellets were collected and dried at room temperature.

Characterization of MCC Pellets

Size and Size Distribution

Pellets were sieved through a nest of sieves with aperture sizes chosen in $\sqrt{2}$ progression from 2,800 to 125 μm . Sieving was carried out on a mechanical sieve shaker (VS 1000, Retsch, Haan, Germany) vibrating at 1 mm amplitude for 10 min. The fraction of pellets retained on each sieve was weighed. D_{10} , D_{50} , and D_{90} , pellet diameters at the 10, 50, and 90 percentiles of the cumulative undersize plot, respectively, were determined. Size distribution was characterized by SP_{pel} calculated using Eq. (2).

$$SP_{\text{pel}} = \frac{D_{90} - D_{10}}{D_{50}} \quad (2)$$

Shape Characterization

The shape of at least 200 pellets from each formulation was characterized using the methodology reported earlier (12). The images of pellets captured using an image analyzer connected to a digital camera (DSP 3CCD, Sony, Tokyo,

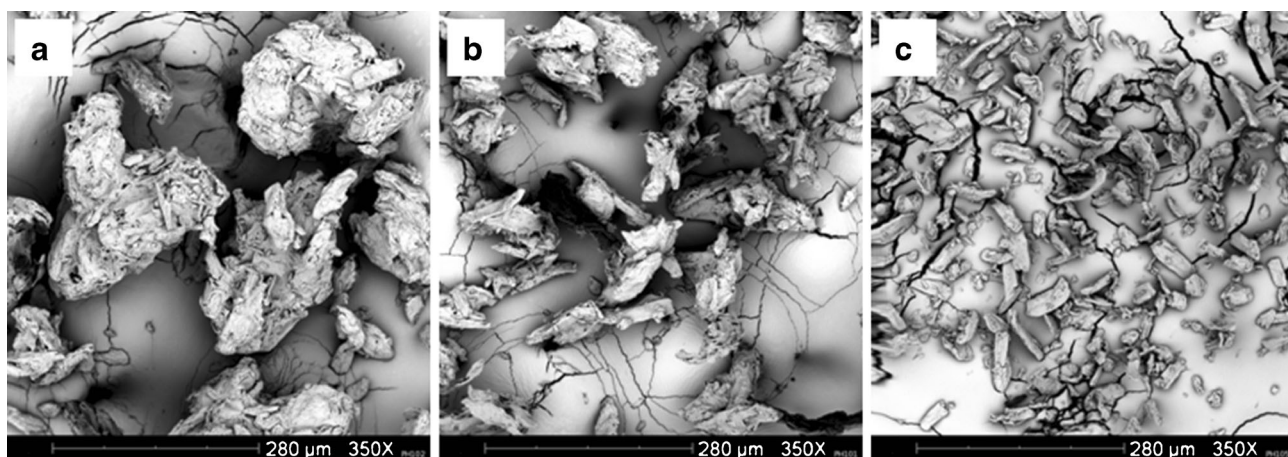


Fig. 1. SEM photomicrographs of the dry MCC particles; a PH102, b PH101, and c PH105

Japan) mounted on a stereomicroscope (SZH, Olympus, Tokyo, Japan) were analyzed (Image-Pro, Version 6.3, Media Cybernetics, Bethesda, MD, USA) for circularity. Circularity describes the sphericity of pellets. The circularity value of a perfectly round pellet is 1.

$$\text{Circularity} = \frac{4\pi R}{M^2} \quad (3)$$

where R and M are the area and perimeter of the two-dimensional pellet image, respectively.

Crushing Strength

Crushing force (F) of at least 20 pellets from each formulation was determined by a compression tester (EZ-Tester-100N, Shimadzu Corporation, Kyoto, Japan) at 1 mm/min loading rate. Crushing strength of each pellet was computed using the following equation, proposed by Dyer *et al.* (17) and results averaged.

$$\text{Crushing strength} = \frac{4F}{\pi\Phi^2} \quad (4)$$

where Φ is the pellet diameter.

RESULTS

MCC Particle Size in the Wet State

Influence of Liquid Type

Particle sizes as well as span values and sample photograph of individual or unit particles of the investigated MCC grades, obtained after 30 min sonication treatment of the powder dispersion in the different liquids, are presented in Table II and Fig. 2, respectively. Reduction in particle size and wider size distribution of all the MCC grades was observed with the sonicated MCC dispersions in the different liquids. When dispersed in water, all the investigated MCC grades, irrespective of their dry-state particle sizes, exhibited more or less similar individual or unit particle sizes ranging from 14 to 16 μm (Table II). When dispersed in ethyl alcohol or IPA, the different MCC grades exhibited different individual or unit particle sizes that increased following the rank order observed for their dry-state particle sizes, i.e., PH105 < PH101 < PH102. Overall, each MCC grade exhibited the smallest individual or unit particle size when water was used as the dispersion medium followed by ethyl alcohol

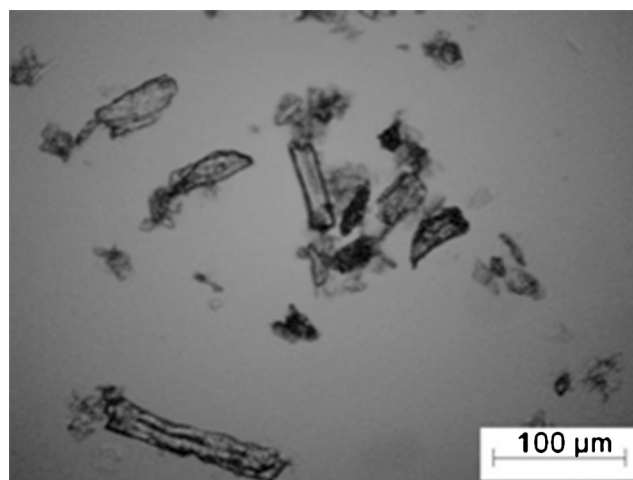


Fig. 2. Sample photograph of individual or unit particles of MCC (PH102) dispersed in water ($\times 400$ magnification)

and then by IPA. On the other hand, when liquid mixtures were used as the dispersion medium, the individual or unit particle size gradually decreased with a decrease in the ethyl alcohol or IPA proportion (Fig. 3).

Influence of Sonication Time

Figure 4 shows the influence of sonication time on the particle size of MCC powder (PH102) dispersed in the different liquids. Prior to sonication, the particle size of MCC dispersed in water was observed to be smaller than that of MCC dispersed in ethyl alcohol or IPA. Upon sonication, the particle size of MCC dispersed in the different liquids decreased steeply initially. With further sonication, MCC particle size continued to decrease albeit more gradually as shown in the particle size against sonication time plots. When MCC was dispersed either in water or in ethyl alcohol, the particle size of MCC reached a plateau state after the initial few minutes of sonication time. It was observed that compared to ethyl alcohol, MCC dispersions in water needed shorter sonication time to reach the plateau state. The rank order of the liquids based on the particle size of MCC at the end of the investigated sonication time period was water < ethyl alcohol < IPA.

Influence of Liquid Addition Order

The individual or unit particle size of MCC PH102 dispersed in IPA was 57.4 μm (Table II). When different amounts

Table II. Particle Size and Size Distribution of MCC Grades in Dry State and Dispersed in the Different Liquids

MCC grade	Dry state		Dispersed in water		Dispersed in ethyl alcohol		Dispersed in IPA	
	Particle size (μm)	Span	Individual particle size (μm)	Span	Individual particle size (μm)	Span	Individual particle size (μm)	Span
PH102	131.3 \pm 3.9	1.78 \pm 0.09	15.0 \pm 3.8	2.72 \pm 0.21	30.4 \pm 2.0	2.61 \pm 0.03	57.4 \pm 3.9	2.82 \pm 0.11
PH101	74.4 \pm 3.9	1.82 \pm 0.04	13.9 \pm 1.2	2.63 \pm 0.08	27.2 \pm 1.2	2.43 \pm 0.04	46.4 \pm 1.3	2.39 \pm 0.05
PH105	32.2 \pm 1.8	1.57 \pm 0.37	16.1 \pm 0.3	2.29 \pm 0.01	22.4 \pm 0.6	2.04 \pm 0.06	21.8 \pm 0.5	2.11 \pm 0.02

MCC microcrystalline cellulose, IPA isopropyl alcohol

of water were added to dispersions of MCC in IPA, the particle size of MCC gradually decreased with a decrease in the proportion of IPA in the water–IPA mixtures (Fig. 5). Further reduction in the particle size of MCC was observed with additional sonication treatment. The resultant particle sizes of MCC dispersed in the various water–IPA mixtures were comparable to the individual or unit particle sizes of MCC directly dispersed in water–IPA mixtures with the corresponding IPA proportions (Fig. 3).

However, no significant effect (ANOVA, $p > 0.05$) of IPA proportion on particle size of MCC was observed when different amounts of IPA were added to dispersions of MCC in water to achieve water–IPA mixtures with different IPA proportions (Fig. 5). The particle sizes of MCC were between 15 and 18 μm irrespective of the IPA proportion in the final water–IPA dispersions. Further change in particle size was not detected even after additional sonication of the final dispersions.

Influence of Liquid Type on Rheological Properties of MCC

Figure 6a shows the rheological profiles of all three investigated MCC grades using water as moistening liquid. Despite their different dry-state particle sizes, they were shown to have similar rheological profiles. Figure 6b, c shows the rheological profiles of MCC grade, PH102, using water–ethyl alcohol and water–IPA mixtures as moistening liquid, respectively. Torque decreased with increasing proportion of alcohol in the liquid mixtures. The lowest torque value was observed when 100% alcohol was employed.

Properties of MCC Pellets

Properties of the MCC pellets prepared using the different liquids and liquid mixtures as moistening liquid are summarized in Table III. As expected and as reported previously (2,3,6,12,18), wet masses containing MCC prepared using water as the moistening liquid were successfully processed through all the stages of extrusion–spheronization and produced pellets with narrow size distribution, as indicated by low SP_{pel} and median diameter close to the aperture size of the

extrusion screen. When water–alcohol mixtures were used as the moistening liquid, pellet median diameter, circularity, and crushing strength decreased while SP_{pel} increased with an increase in the alcohol proportion. Nonetheless, pellets could not be produced with ethyl alcohol alone or with water–IPA mixtures containing $\geq 80\%$ IPA.

DISCUSSION

Extent of MCC Particle De-aggregation Based on Liquid Type and Sonication Time

The different MCC grades with different dry-state particle sizes comprise aggregates with different numbers of small sub-units, held together by hydrogen bonds between their amorphous ends (15). MCC particles dispersed in an appropriate liquid or liquid mixture de-aggregate into smaller sub-units due to breaking of hydrogen bonds. The type of moistening liquid employed influenced the extent of MCC particle de-aggregation, and the sonication treatment assisted in dispersing MCC sub-units resulting from the de-aggregation of MCC in the presence of the moistening liquid.

The particle sizes of MCC dispersed in liquids (ethyl alcohol and IPA) or liquid mixtures (water–ethyl alcohol and water–IPA mixtures with 80% alcohol) with similar surface tension differed remarkably (Tables I and II; Fig. 3). Therefore, surface tension of the moistening liquid is not likely to be a major factor contributing to the effect of moistening liquid type on the extent of MCC particle de-aggregation.

Water is a more polar liquid compared to ethyl alcohol and IPA. Dielectric constant values indicating the polarity of water–ethyl alcohol and water–IPA mixtures containing different proportions of ethyl alcohol and IPA have been reported by Åkerlöf (19). The trend of the reported dielectric constants of water–alcohol mixtures showed that polarity of water–alcohol mixtures increased with a decrease in the proportion of alcohol in the liquid mixtures. In this study, the different MCC grades were observed to exhibit smaller particle sizes when dispersed in water, the moistening liquid with higher polarity (Table II). Particle size of MCC dispersed in water–alcohol mixtures decreased with a decrease in the

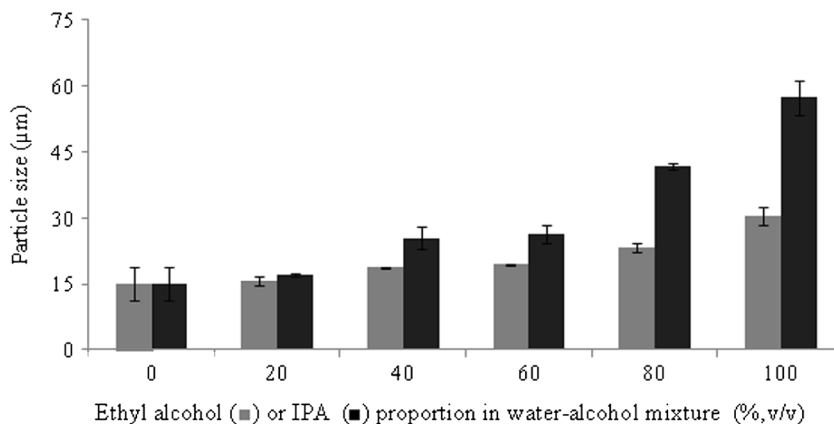


Fig. 3. Particle sizes of PH102 dispersed in liquid mixtures; powder samples dispersed by 30 min sonication in (gray square) water–ethyl alcohol mixtures and (black square) water–IPA mixtures. Error bars represent the standard deviations

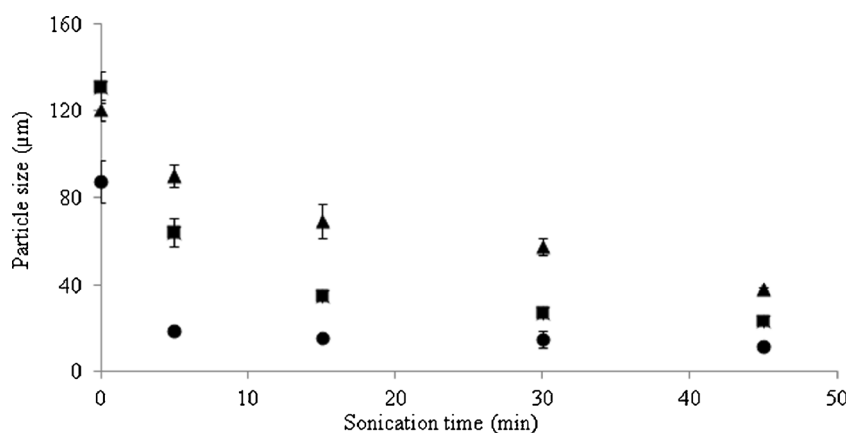


Fig. 4. Influence of sonication time on the particle size of PH102 dispersed in the different liquids; *black circle* water, *black square* ethyl alcohol, and *black up-pointing triangle* IPA. Error bars represent the standard deviations

proportion of alcohol (Fig. 3), following a decreasing trend opposite to that of the polarity of water–alcohol mixtures. Based on these observations, it is plausible that the influence of moistening liquid type on the extent of MCC particle de-aggregation is linked to the polarity of the moistening liquid. As de-aggregation of MCC involves breaking of hydrogen bonds, liquids or liquid mixtures with higher polarity are able to induce de-aggregation of MCC particles to a greater extent, yielding MCC dispersions with smaller particle sizes. Furthermore, a liquid with higher polarity may be more effective in interacting with the amorphous ends of MCC and in breaking the hydrogen bonds as indicated by the shorter sonication time required for the particle size of MCC to reach the plateau state (Fig. 4).

Extent of MCC Particle De-aggregation Based on Liquid Addition Order

The extent of MCC particle de-aggregation in IPA was much lower compared to that in water because of the lower polarity of IPA. Subsequent addition of water to dispersions of

MCC in IPA increased the polarity of the dispersion medium and caused further de-aggregation of the MCC particles (Fig. 5). The additional sonication treatment assisted in dispersing MCC sub-units resulting from the further de-aggregation of MCC.

In contrast, subsequent addition of IPA to dispersions of MCC in water decreased the polarity of the dispersion medium. However, as the polarity of the dispersion medium was at its highest when water alone was first used to disperse the MCC, MCC de-aggregated to a greater extent due to the higher polarity of water. The resultant MCC particle sizes in the final water–IPA mixtures upon addition of IPA were smaller than the individual or unit particle sizes of MCC dispersions prepared by directly dispersing MCC in corresponding water–IPA mixtures. Thus, the subsequent addition of different amounts of IPA to MCC dispersions in water did not have any significant influence on the resultant MCC particle size. These findings on the effect of liquid addition order demonstrated that the extent of MCC particle de-aggregation and the resultant MCC particle size are governed by the highest polarity achieved in the dispersion medium during the preparation of the MCC dispersions.

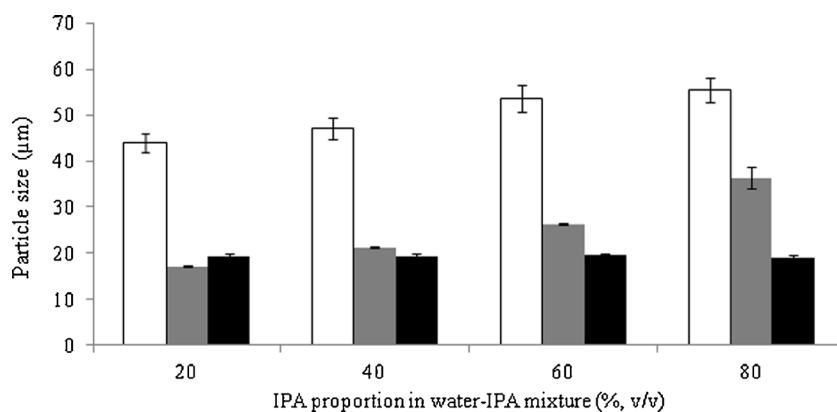


Fig. 5. Particle sizes of PH102 dispersed in water–IPA mixtures with different liquid addition orders; powder sample dispersed by 30 min sonication in (*white square*) IPA followed by addition of water to adjust IPA proportion, (*gray square*) IPA followed by addition of water to adjust IPA proportion and additional 5 min sonication, and (*black square*) water followed by addition of IPA to adjust IPA proportion. Error bars represent the standard deviations

Influence of Moistening Liquid Type and Extent of MCC Particle De-aggregation on Pellet Formation

During extrusion-spheronization, the wet mass obtained after the wet massing step is extruded as cylindrical extrudates

for spheronization. A wet mass with higher cohesive strength, indicated by higher torque, should produce extrudates with higher cohesive strength (12). The breaking of extrudates into smaller fragments during the start of the spheronization process is also governed by the strength of the extrudates. The weak

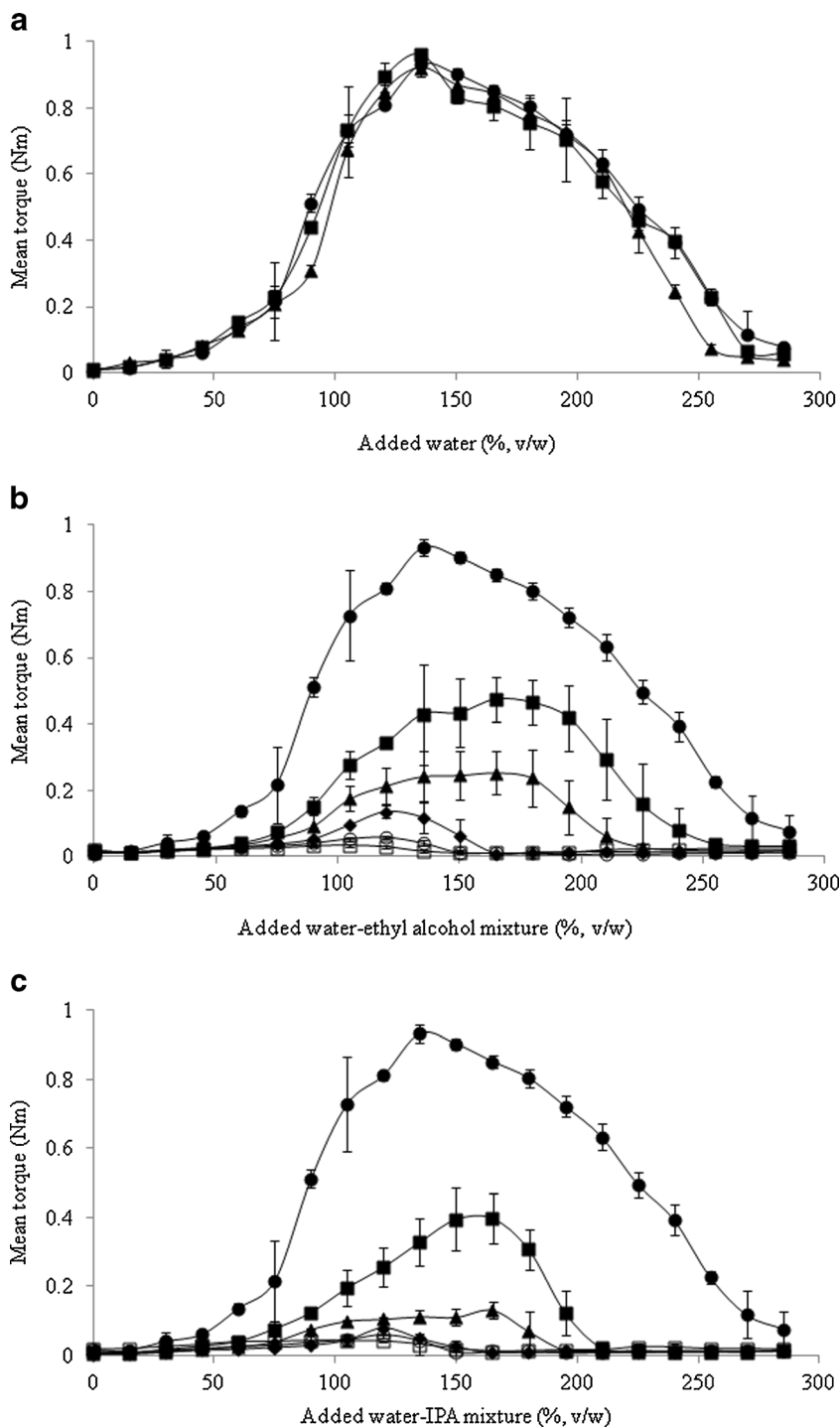


Fig. 6. Rheological profiles of **a** different MCC grades (black circle PH102, black square PH101, and black up-pointing triangle PH105) using water as moistening liquid; **b** PH102, using water-ethyl alcohol mixtures containing ethyl alcohol (black circle 0%, v/v; black square 20%, v/v; black up-pointing triangle 40%, v/v; black diamond suit 60%, v/v; white circle 80%, v/v; white square 100%, v/v); **c** PH102, using water-IPA mixtures containing IPA (black circle 0%, v/v; black square 20%, v/v; black up-pointing triangle 40%, v/v; black diamond suit 60%, v/v; white circle 80%, v/v; and white square 100%, v/v)

extrudates produced by low cohesive strength wet masses (prepared with moistening liquid containing higher proportions of alcohol) (Fig. 6b, c) tend to undergo a much higher degree of fragmentation, yielding fragments with wider size distribution. As the fragments tumble on the rotating frictional base plate, they experience collisions with other fragments and with the wall of the spheronizer. The tumbling rope-like motion facilitates the closer packing of component particles in the agglomerates, consolidating the agglomerates. Moistening liquid, squeezed out from the interior to the surface of the agglomerates, enhances the deformability of the agglomerates. It can also facilitate agglomerate growth by coalescence with other agglomerates.

As described by Ouchiyama and Tanaka (20–22), for two agglomerates to achieve successful coalescence upon collision, the forces of the bonds formed in the contact area should overcome the separating forces generated by the velocity of the agglomerates and the bending moment exerted by the moistened agglomerates during spheronization. Agglomerates grow by coalescence until a balance between bonding and separating forces is achieved in the area of contact. The maximum growth limit or the critical size of the agglomerate (D_c) was derived by Ouchiyama and Tanaka (21). Coalescence between agglomerates is not possible beyond the maximum growth limit.

$$D_c = \left(A Q^{3\zeta/2} K^{3/2} \sigma t \right)^{1/(4 - (\frac{3}{2})\eta)} \quad (5)$$

where A is a constant which relates agglomerate volume to impact compressive force (Q); ζ and η are constants dependent on the deformation mechanism within the contact area; K is agglomerate deformability, a function of available surface moisture and component particle size; and σt is the tensile strength of the bond in the contact area, dependent on the surface tension of moistening liquid and component particle size as described in Eq. (6) (23).

$$\sigma t = C S \frac{(1 - \varepsilon) \gamma}{\varepsilon d} \cos \theta \quad (6)$$

where C is a material constant, ε is the inter-particulate porosity in the contact area, d is the component particle

diameter, γ is the liquid surface tension, θ is the liquid–solid contact angle, and S is the liquid pore saturation.

Equation (6) indicates that the tensile strength of the bonds in the contact area between two particles could be increased by increasing the surface tension of the moistening liquid. In addition, higher tensile strength could be achieved using component particles with smaller size. Smaller particles can pack more closely together through decreased inter-particulate voids, i.e., the porosity in the contact area, and, in turn, increased the tensile strength. It was reported that the in-process particle sizes of MCC in different wet processed materials, wet mass, extrudates, or pellets were similar to the individual or unit particle size of MCC in the same moistening liquid (3). The smaller MCC particles (Table II; Fig. 3) in combination with higher surface tension (Table I) of the moistening liquid containing higher proportion of water could lead to increased σt of the bonds in the contact area between agglomerates.

Due to higher σt at the contact area, the D_c values for agglomerates should be higher for the formulations where the moistening liquid was water or a liquid mixture containing higher proportions of water. The probability for coalescence to occur between coarse and coarse, coarse and fine, and fine and fine agglomerates during the spheronization process was thus higher, assisting in the formation of larger size pellets with narrower size distribution. In addition, smaller MCC particles, generated from the de-aggregation of MCC in the presence of liquid mixtures containing higher proportions of water, should pack well due to better particle rearrangement. Therefore, liquid mixtures containing higher amounts of water yielded pellets with higher sphericity, larger median diameter, higher crushing strength, and narrow size distribution (Table III).

On the other hand, the D_c values for formulations with moistening liquids containing higher proportions of alcohol were expected to be smaller. Successful coalescence between two coarse agglomerates was thus less probable as the average size of the newly formed agglomerate may be beyond the critical size limit. Furthermore, the larger MCC particles from the de-aggregation of MCC in moistening liquids containing higher proportions of alcohol were not able to pack well due to difficulty in particle rearrangement with larger particles. As a result, the pellets produced from these formulations usually had lower sphericity,

Table III. Physical Properties of MCC PH102 Pellets Prepared by Extrusion–Spheronization Using the Different Liquids or Liquid Mixtures as Moistening Liquid

Ethyl alcohol (% v/v)	Water–ethyl alcohol				Water–IPA				
	D_{50} (μm)	SP_{pel}	Circularity	Crushing strength (N/mm^2)	IPA (% v/v)	D_{50} (μm)	SP_{pel}	Circularity	Crushing strength (N/mm^2)
0	988±11	0.52±0.02	0.903±0.028	17.6±1.9	0	988±11	0.52±0.02	0.903±0.028	17.6±1.9
20	720±14	0.60±0.02	0.881±0.030	13.3±1.8	20	615±21	0.66±0.01	0.875±0.046	11.6±2.0
40	628±18	0.66±0.02	0.867±0.051	9.8±1.2	40	523±39	0.74±0.01	0.859±0.060	8.2±1.3
60	450±28	0.75±0.03	0.854±0.058	6.6±1.7	60	440±21	0.85±0.02	0.845±0.062	4.2±1.8
80	230±28	0.99±0.15	0.833±0.079	–	80	–	–	–	–
100	–	–	–	–	100	–	–	–	–

D_{50} median diameter of pellets, SP_{pel} size distribution of pellets, IPA isopropyl alcohol, – pellets could not be produced

smaller median diameter, lower crushing strength, and wider size distribution (Table III).

CONCLUSION

This study showed that depending on its polarity, the type of moistening liquid employed could influence the extent to which MCC particles de-aggregate. Due to their lower polarity, liquid mixtures containing higher proportions of alcohol induced MCC particle de-aggregation to lower extent and yielded MCC dispersions with larger particle sizes. The larger particle size of MCC in combination with lower surface tension of the moistening liquid containing higher proportion of alcohol gave rise to moistened masses with lower cohesive strength. Growth of moist agglomerates by coalescence and closer packing of the component particles by rearrangement was thus limited. This resulted in the formation of weaker, less spherical pellets with smaller median diameter and wider size distribution.

ACKNOWLEDGMENTS

The authors wish to acknowledge research funding support from GEA-NUS Pharmaceutical Processing Research Laboratory fund (N-148-000-008-001) and A*STAR SERC grant number 102 161 0049 (R-148-000-157-305).

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