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The effect of the amount of binder liquid on the granulation mechanisms and structure of microcrystalline cellulose granules prepared by high shear granulation

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Abstract

The structure of granules changes during the high shear granulation process. The purpose of this research was to investigate the effect of the amount of binder liquid on the structure of the granules and the structural changes which occur during the granulation process, using microcrystalline cellulose (MCC) and water as the model system. The structure is the result of the granulation mechanism; therefore, conclusions can be drawn about the latter by studying the former. X-ray microtomography and scanning electron microscopy (SEM) were applied in order to visualise the densification process of granules, which were first freeze dried in order to preserve their structure. Variations in their porosity were quantified by applying image analysis to the tomography results. In order to link the granule mechanical properties to their structural differences, a micromanipulation technique was used to measure granule resistance to deformation. MCC granules granulated with 100% (w/w) water showed increased densification with time, as expected; detailed examination showed that densification is more pronounced in the core of the granule; whereas the outer part remained more porous. Increased densification reduces deformability, so that granules become more resistant to breakage. The lower deformability of the densified granules in the final stages of granulation might result in establishment of equilibrium between attrition and growth, without substantial gross breakage. On the other hand, when more water was used (125%, w/w), densification was hardly observed; the porosity of the granule core was still high even after prolonged granulation times. This may be explained by the fact that higher water content increases the ease of deformation of granules. This increased deformability led to significant granule breakage even during the final phases of the granulation process. Therefore, for these granules a final equilibrium between breakage and coalescence might be established. This also explains why more granules produced with 125% granulation liquid were composed of fragments of irregular shape.

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Our results establish the link between the granulation behaviour of MCC in the latter stages and the material structure of these granules, which is determined by their liquid content. The process conditions (amount of liquid) to be chosen depend largely on the final purpose for which the granular material is produced.

Keywords: X-ray tomography; Micromanipulation; MCC; High shear granulation; Porosity; Deformability; Attrition; Breakage

1. Introduction

Densification during the high shear granulation process has been commonly observed (Holm et al., 1984; Jægerskou et al., 1984; Lindberg, 1993), and it is also commonly accepted that granule plasticity is increased by addition of the liquid binder (Harrison et al., 1985; Kristensen et al., 1985a,b; Iveson et al., 2001). However, the effect of densification on the granule viscoelastic behaviour and resulting granule formation has not yet been investigated. The aim of this paper is to investigate how deformability, which depends on the amount of binder liquid and the granule porosity, affects the subsequent microcrystalline cellulose (MCC) granulation mechanisms and how this determines the final structure of granules produced in the high shear granulator. X-ray microtomography was applied in order to visualise and quantify the densification process of microcrystalline cellulose granules, comparing granules produced with different granulation times and with different amounts of liquid binder as well as comparing differences in the porosity at different sites in the granule. Scanning electron microscopy (SEM) pictures were made to show the external appearance of the granules. The deformability of the visualised granules was measured using micromanipulation.

The model compound MCC was chosen for its capability of absorbing large amounts of water. This enables granulation with different liquid amounts, probably leading to different internal structures (Abberger, 2001). Liquid contents from 75 to 125% relative to the powder mass were used.

2. Materials and methods

2.1. Materials

Granulation was performed with Microcrystalline Cellulose Pharmacel® 101, DMV-International, Veghel, The Netherlands. The binder liquid used was tap water.

2.2. Equipment

Granulation was performed in a vertical axis high shear mixer. Two different setups were used: a small-scale granulator MiPro 250 (ProCepT, Zelzate, Belgium) with a 250 ml bowl, and a home made large-scale granulator (University of Birmingham, UK) with a stainless steel 10 l bowl. The small-scale equipment was equipped with both an impeller and a chopper, whereas the large-scale granulator only had an impeller. The impellers of both granulators have bevelled blades, with an angle to the horizontal of approximately 40°.

2.3. Granulation

The small-scale equipment was operated with at an impeller speed of 1000 rpm (tip speed, 3.14 m/s) and chopper speed of 1500 rpm (tip speed, 1.6 m/s). Twenty-four grams of MCC (Pharmacel 101, lot 60841) was granulated with 24 or 30 ml water as binder liquid (100%, w/w, and 125%, w/w, respectively). Liquid was added at 48 ml/min. Total granulation time was 900 s. Samples of granular material were taken after 180 and 900 s.

The large-scale equipment was operated at an impeller speed of 400 rpm (tip speed, 6.28 m/s). A picture of the large-scale bowl is shown in Fig. 1. One thousand and four hundred grams of MCC (Pharmacel 101, lot 21153) was granulated with 1400 or 1750 ml water (again 100%, w/w, and 125%, w/w, respectively). Liquid was poured on the moving powder all at once, without spraying. Total granulation time was 900 s. Samples of granular material were taken after 180 and 900 s.

Two granulators were used, since we performed experiments at two different locations. At the same time, scale up could be tested. Scaling up is still performed empirical. Several methods were tested, which eventu-

Fig. 1. A picture of the inside of the bowl in the large-scale setup.

ally lead to using the settings described above. These settings resulted in granules similar in size and shape.

2.4. Micromanipulation

From every batch produced at large scale, 150 g of the wet granules were transferred from the granulator bowl into a plastic bag, which was sealed. These granules were used for micromanipulation measurements.

A micromanipulation rig was used to characterise the granules (Zhang et al., 1999; Stenekes et al., 2000). In this technique, a single wet granule was compressed between two parallel glass surfaces (one an extensive flat surface; the other a flat-ended probe of diameter 2.5 mm, which is significantly larger than the largest granule diameter) to a certain deformation and simultaneously the required force was measured. The probe had a sensitivity of 8.510 g/V (Model 407A, Aurora Scientific Inc., Ont., Canada). The force transducer was mounted on a three-dimensional (3D) fine micromanipulator (MicroInstruments Ltd., Oxon, UK) that was programmed to travel a given distance at a pre-set speed. The force being imposed on the compressed granule was measured simultaneously by sampling the voltage signal from the force transducer and transferred into a computer via a data acquisition board (Amplicon Liveline, Brighton, UK). The deformation processes were monitored with a side view COHU high performance CCD, which was connected to a screen and a video recorder. Deformation was expressed as the ratio of displacement of the probe in the granule to the original diameter of the granule.

Measurements were conducted within 45 s (±3 s) after the wet granules were taken out of their container, to prevent the occurrence of any effect caused by drying. The prevention of drying was crucial in these measurements since dried granules required much higher forces to produce a given deformation. The stress needed for deformation is called the 'pseudo' stress, since it is defined as the ratio of the applied force to the original cross-sectional area of the granules.

2.5. Freeze drying wet granules

Small-scale batches were freeze dried in the Christ Alpha 2–4 freeze dryer (Salm and Kipp, Breukelen, The Netherlands). The granules were instantly frozen in liquid nitrogen and then placed within the freeze dryer for 24 h with a shelf temperature of −35 °C and a pressure of 0.220 mbar. Subsequently, the temperature was increased in steps of 10–15 °C every 2–3 h (to room temperature). The pressure was lowered in steps to 0.050 mbar.

For large-scale batches, the freeze drying technique used was different. Granules were first instantly frozen in liquid nitrogen. A few grams of sieve fraction 1.00–1.18 mm were freeze dried in the Speedinvalve freeze dryer (Edwards, Tonawanda, NY, USA) for 21 h. The pressure was between 3.5 and 7 mbar. The refrigerator temperature was circa −55 °C.

During freeze drying the granules changed in size by less than 10%.

2.6. Scanning electron microscopy

Freeze dried granules were coated with approximately 10–20 nm of gold/palladium, using a sputter coater (Balzer AG, type 120B, Balzers, Liechtenstein). Scans were performed using a JEOL scanning electron microscope (JEOL, type JSM-6310F, Japan) and an acceleration voltage of 1.5 kV.

2.7. X-ray microtomography

The combination of the X-ray transmission technique with tomographical reconstruction provides three-dimensional information about the internal microstructure of materials. X-ray transmission depends on material density and atomic number; in this case, only the former is of interest. A SkyScan-1072 100 kV

(SkyScan, Aartselaar, Belgium) was used to obtain information about the 3D internal microstructure of individual wet MCC granules. The transmission geometry is a stationary fan beam in which the object, a single granule in this case, is rotated. Individual freeze dried granules were scanned in the 0–180° interval, using a 0.9° scan step. The cross-sectional pixel size was 2.73 μm. With Skyscan software programs 'Cone-Beam reconstruction' the X-ray images were reconstructed as two-dimensional (2D) slices (*y*- and *z*-axis) and 3D images. From these 3D images, digitised reconstructions were made using the '3D-Creator' software (SkyScan, Aartselaar, Belgium). Cross-sections of these reconstructions were made to in order to visualise the pores within the MCC granules.

2.8. Porosity measurement

The porosity of the 2D reconstructed pictures was measured using Matlab 6.1 (The MathWorks Inc., Gouda, The Netherlands). The pictures were transformed to binary images with the threshold at 50 on the scale of 256 grey colour tones. This means that every pixel with a colour value higher than 50 is regarded as solid, and every colour value lower than 50 is regarded as air. To be able to distinguish between the porosity of the core of the granule and the porosity of the outer layer, we defined the granule 'core' as the domain having the same geometry as the granule, with the diameter of the domain being half the diameter of the granule. The resulting core consists of 25% of the area of the granule. We assumed the very large longitudinal shapes visible on the pictures to be freeze cracks. These freeze cracks were left out of the measurements.

3. Results and discussion

Fig. 2 shows SEM pictures of the starting powder material and freeze dried granules obtained during different stages of the granulation process or from batches produced using different amounts of binder liquid. MCC powder (Fig. 2A) is a fibrous material, with an average length to width ratio of 4. The fibres can take up significant amounts of water (Zografi et al., 1984; Kleinebudde, 1997; Ek and Newton, 1998). Once enough water is present nuclei are formed. With the chosen settings, these nuclei grow so that granules were present after 180 s in both pieces of apparatus. A typical picture of such (early phase) granules is shown in

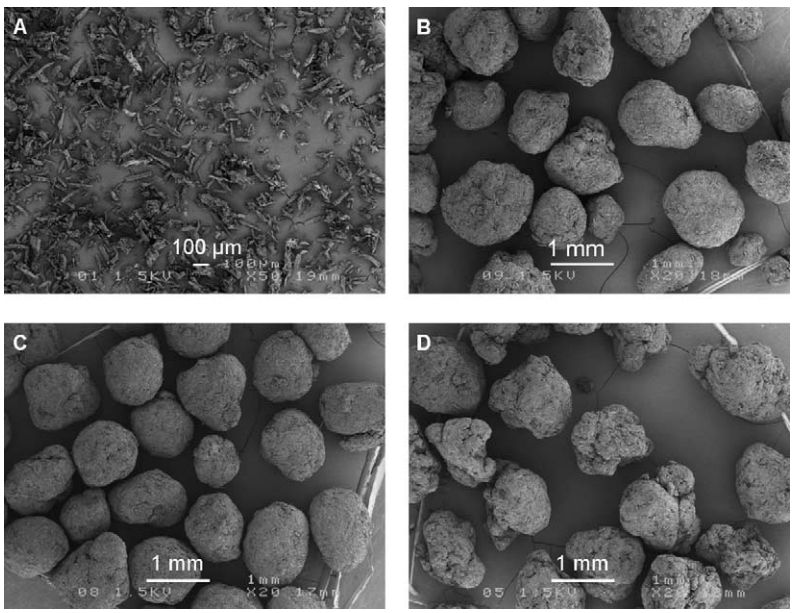

Fig. 2. SEM pictures of starting material (50× magnification) and freeze dried granules produced in the large-scale granulator (20× magnification). (A) MCC 101; (B) 100% granules, $t = 180$ s; (C) 100% granules, $t = 900$ s; (D) 125% granules, $t = 900$ s.

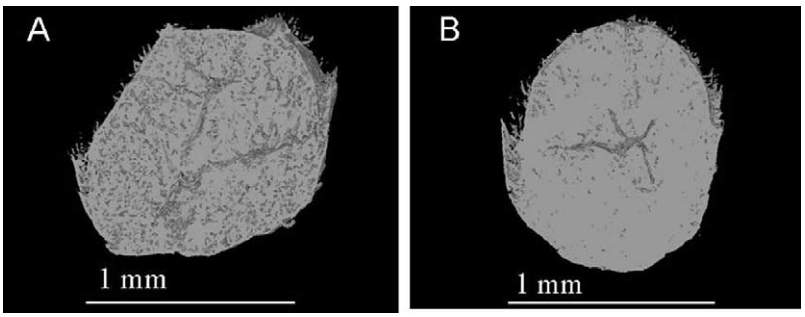

Fig. 3. Reconstructed X-ray microtomography pictures showing cross-sections through granules produced with 100% (w/w) liquid (large scale). A granule that was granulated for: (A) only 180 s and (B) 900 s.

Fig. 2B. Several sizes and various irregular shapes are visible. When granulation was continued after 180 s, consolidation and growth occurred, until the equilibrium between growth and breakage or attrition was reached. When the granulation process was stopped after 900 s the process had already entered the equilibrium phase, where granule size did not change. Fig. 2C shows that for the granules produced with a granulation time of 900 s, size and shape variation were strongly reduced compared to those produced after 180 s. Granules appeared to be strong because fragments were not seen, neither individually nor in partially coalesced form. This is in sharp contrast to the granules produced with 125% (w/w) water as a binding fluid (Fig. 2D). These granules are highly irregular and seem to consist of various (only partly) coalesced fragments. The structure of the granules looks more porous and less consolidated.

X-ray microtomography was applied to investigate the porosity of the different granules, as earlier described by Farber et al. (2003). Image analysis was used on the reconstructed cross-sections of the granules, on different locations within the granules and on different locations within the picture (kernel versus outer layer) to quantify porosity. One advantage of X-ray microtomography is that once the 3D reconstruction has been performed, any desired region can be investigated in detail.

In Fig. 3, reconstructed cross-sections of granules are presented that show the effect of process time. The left picture (Fig. 3A) shows the internal structure of a granule after 180 s, the right (Fig. 3B) after 900 s. It is clear that porosity decreased with time and that both large and small pores are closed up by the granulation process. Table 1 gives quantitative results from image analysis of the pictures. It can be seen that the corresponding porosity decreased from 26 to 9%. Although a decrease in average porosity with increasing process time has been demonstrated using porosity measurements like helium pycnometry (Kristensen et al., 1985a,b), X-ray microtomography enables clear visualisation of this densification. Moreover, X-ray microtomography together with image analysis enables differentiation between sites with higher and lower porosity in the granule. The advantage of such differentiation is that it can elucidate granulation mechanisms

Table 1
Porosities of the granules measured by image analysis of the 2D reconstructed X-ray microtomography images

Amount of water (%, w/w)	Granulator scale (l)	Granulation time (s)	Figure	Cross-section of the picture	Porosity kernel (%)	Porosity outer layer (%)	Total porosity (%)
100	10	900	Fig. 2A	Centre	8	10	9
100	10	180	Fig. 2B	Centre	19	28	26
100	0.25	900	Fig. 3A	Outside			7
100	0.25	900	Fig. 3B	Centre	3	7	5
125	10	900	Fig. 5	Centre	12	28	22

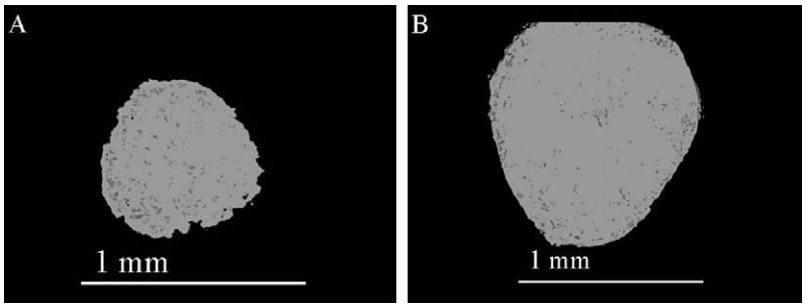

Fig. 4. Reconstructed X-ray microtomography pictures showing a cross-section through the outside of a small-scale granule (A) and through the centre (B) of the same granule produced with 100% (w/w) water after a granulation time of 900 s.

occurring during the different phases of the granulation process.

In Fig. 4, a slice of the outside of a consolidated granule is shown (Fig. 4A), together with a slice through the centre (Fig. 4B) of the same granule. This granule was made in the small-scale setup using 100% (w/w) granulation liquid. A porosity difference between the outer layer and the centre can be observed. This difference was quantified and the result is presented in Table 1. The outside (7%) was clearly more porous than the core (3%), which is because newly bonded material is less compacted.

Following the reasoning above, repeated impacts and the resulting densification might be expected to result in granules, which are stronger and less deformable. To establish this change in deformability during the granulation process the micromanipulation technique was applied on the wet granules. The results of this experiment are shown in Fig. 5. It can be seen that an increase in process time led to an increase in the pseudo stress for a given deformation; thus, an increase in process time led to formation of granules which are more resistant to deformation.

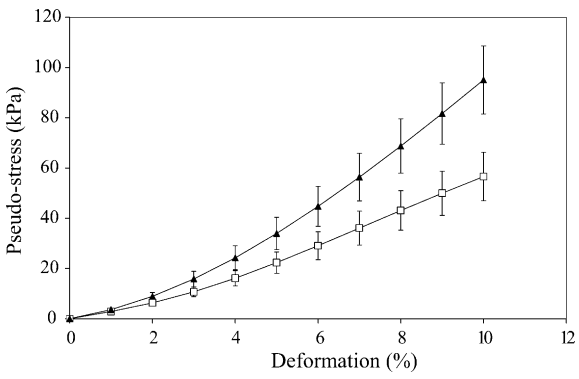

Fig. 5. The pseudo-stress against the deformation plots of granules (1.00–1.18 mm) produced with 100% (w/w) water: (□) after 180 s granulation time ($n = 23$, mean ± S.D.); (▲) after 900 s granulation time ($n = 24$, mean ± S.D.). Probe speed was 47.6 μm/s.

Resistance to deformation of MCC granules is related to strength, because if a certain limit of deformation is exceeded, gross breakage will result. Therefore, if a granule is more easily deformable it will also break more easily upon impaction with the impeller, wall, chopper or other particles. This is also shown by Iveson and Litster (1998) using the deformation number '*De*' as described below:

$$De = \frac{\rho_g U_c^2}{Y_g}$$

In this equation, the density of the granule (ρ_g), the velocity of the granule (U_c) and the dynamic yield stress (Y_g) are used. The addition of more binder fluid hardly influences the true density of the granule, and it does not influence granules velocity. However, the yield stress will be lowered, since the excess liquid facilitates deformation the granule. The resulting deformation number *De* will increase, which in the growth regime map leads to the crump regime.

In Fig. 6, the X-ray microtomography image of a granule produced with 125% (w/w) water after a granulation time of 900 s is shown. Clearly, the porosity of this granule was much higher than that of the granules produced with 100% (w/w) liquid (see also Table 1). Obviously, densification hardly occurred with the higher amount of water, even after 900 s of granulation. The absence of densification may be attributed

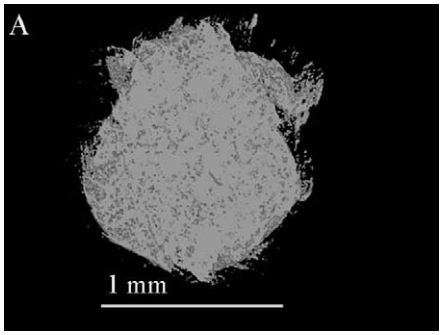

Fig. 6. Reconstructed X-ray microtomography picture showing the centre of a granule (large scale) produced with 125% (w/w) water after a granulation time of 900 s.

to the increased availability of water resulting in the increased deformability, which leads to breakage of these granules. In other words, impacts between these granules lead to breakage rather than densification. To justify this speculation, micromanipulation was also performed on the wet granules produced with 125% (w/w) water. The results are shown in Fig. 7. In order to investigate whether the granule deformation showed viscous character, the micromanipulation measurements were conducted at two different compression speeds. As can be seen there is no significant difference in the results obtained at the two speeds, which implies that the viscous behaviour was negligible at least for the compression speeds investigated. However, these speeds are not typical of the speeds used in the granulator. This leaves open the possibility that such granules behave in a viscous way in a granulation process. These granules do viscoelastic behaviour, as shown by Bouwman et al. (2004).

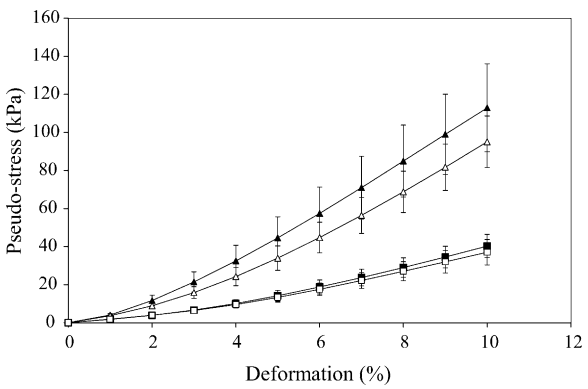

Fig. 7. The pseudo-stress against the deformation plots of granules (1.00–1.18 mm) produced with different amounts of water, sampled after 900 s granulation time: (□) 125% (w/w) water, probe speed 47.6 μm/s ($n = 22$); (■) 125% (w/w) water, probe speed 190.4 μm/s ($n = 25$); (△) 100% (w/w) water, probe speed 47.6 μm/s ($n = 24$); (▲) 100% (w/w) water, probe speed 190.4 μm/s ($n = 19$). Error bars represent standard error of the mean.

For comparison, the results of the granules produced with 100% water are also shown in the figure. Clearly, the granules produced at granulation with 125% (w/w) water required less pseudo stress to cause a give deformation than those with 100% (w/w) water. The micromanipulation results prove that the excess of water led to weaker granules. The granules produced with 125% (w/w) water after 900 s of granulation were even more easily deformed than the primary nuclei (100%, w/w, granules after 180 s). The liquid acted as a lubricant by reducing the particle interactions. This is in accordance with the measurements of Betz et al. (2003), who showed that with increased liquid content the tensile strength was reduced. These results lead to the hypothesis that the increased deformability of the granules resulted in a continuous breakage of the granules, which was balanced by coalescence (that also occurred easily since an excess of water was available) of the fragments during the final equilibrium phase of the process. The continuous breakage prevented the densification of the core of the granule. Consequently, the core remained highly porous, independently of the granulation time, and the granules remained as weak bodies consisting of coalesced fragments.

The type of granulation process to be preferred depends of course on the purpose for which the granules are produced. For example, if the granules are to be coated, strong and smooth granules are preferred and granulation should be performed (in this case) with 100% (w/w) of water. If, on the other hand, the granules are made to produce tablets with a very low drug content, the continuous breakage during the final phase of the granulation process, found when 125% (w/w) water was added, may prevent problems with inhomogeneous granular material, since this breakage would prevent the preferential binding/nucleation described by Dries van den and Vromans (2002). Moreover, the weaker granules will show more fragmentation when compressed to tablets thereby reducing lubricant sensitivity (Zuurman et al., 1999).

4. Conclusions

Our results show how the granulation behaviour of MCC depends on the liquid content. The liquid should not only be regarded as a binder but also its effects on deformability of the granules should be taken into account, since the deformability determines the granulation mechanism occurring during the latter phases (consolidation and growth, and breakage and attrition) of the granulation process. Liquid is necessary for binding the powder particles and making the wet mass more deformable. When a low amount of binder liquid is available, densification of the granule will occur and the final phase of the granulation process will result in equilibrium between attrition and growth. Since the granules are no longer broken during this phase, spheronisation of the material may occur. However, when an excess of binder liquid is used, the deformability of MCC granules increases, which will make them more easily subject to breakage upon continued granulation. Continued breakage will reduce the extent of densification of the granule core and the granules remain weak during the complete process. Even during the last (equilibrium) phase of the process, continuous breakage occurs. This breakage is now balanced by coalescence of the fragments with each other or with other granules. This results in weak, irregularly shaped granules.

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