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The effect of droplet size and powder particle size on the mechanisms of nucleation and growth in fluid bed melt agglomeration

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Abstract

This study was performed in order to evaluate the effects of binder droplet size and powder particle size on agglomerate formation and growth in fluid bed spray agglomeration using a meltable binder. Three different lactose grades, 100, 125 or 350 mesh, were agglomerated using polyethylene glycol (PEG) 3000 at two different concentrations, 11.5 or 22% (volume/mass), and three spray droplet sizes, 30, 60 or 90 μm were applied. The ratio of droplet size/particle size was found to determine whether the mechanism of nucleation was distribution or immersion. Distribution was promoted by a low ratio, whereas immersion was promoted by a high ratio. Distribution as nucleation mechanism led to a more open agglomerate structure and immersion to a denser structure. When the nucleation phase was terminated, coalescence between rewetted nuclei or agglomerates was the growth mechanism with both preceding mechanisms of nucleation. A larger particle size of the lactose led to larger agglomerates. The difference in the effect on growth between the 30 and 60 μm droplets was generally low. The 90 μm droplets at 22% binder concentration offered a potential for uncontrollable growth giving rise to markedly larger agglomerates and a lower reproducibility than 30 and 60 μm droplets.

Keywords: Binder droplet size; Fluid bed agglomeration; Growth mechanism; Melt agglomeration; Nucleation mechanism; Powder particle size

1. Introduction

Agglomeration is a unit operation, which is widely used in a range of industries. Traditionally, an aqueous binder liquid is applied. When the moisture causes problems, the use of organic solvents has been an alternative method. A recent trend in pharmaceutical and other industries is to replace the use of organic solvents due to an

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increase in safety, ecological and toxicological requirements. Therefore, solvent free agglomeration methods gain considerable attention. Melt agglomeration and roller compaction are such methods. Roller compaction is feasible only, when there is an appropriate compaction behaviour of the mixture.

Melt agglomeration has been shown to be a method of producing dosage forms with prolonged release properties (McTaggart et al., 1984; Flanders et al., 1987). The use of a wax-like prodrug with improved bioavailability as a binder in melt agglomeration was tested (Crowley et al., 2000). A combination of melt agglomeration and preparing solid dispersions by the fusion or melt method in order to make tablets with the desired release properties has been mentioned (Wells et al., 1975; Kinget and Kemel, 1985).

The two most important methods of agglomeration, which are actually applied in the pharmaceutical industry, are fluid bed agglomeration and agglomeration in high shear mixers with subsequent fluid bed drying (Wørts, 1998).

Agglomeration is a combination of three sets of rate processes: wetting and nucleation, consolidation and growth, and attrition and breakage (Iveson et al., 2001).

According to Schæfer and Mathiesen (1996), two different mechanisms of nucleation will be active in melt agglomeration in high shear mixers dependent on the relative size of the binder droplets to the powder particles. Distribution of the molten binder on the surface of the solid particles will occur when the molten binder droplets are not greater than the solid particles. The distribution leads to a formation of nuclei by collisions between wetted powder particles. This will produce nuclei which may have air entrapped. Immersion of the solid particles in the molten binder will occur when the molten binder droplets are larger than the solid particles. This produces nuclei with saturated voids.

Melt agglomeration is usually performed in high shear mixers. Fluid bed agglomeration is different from agglomeration in high shear mixers due to the lower shear forces and due to the fact that fluid bed agglomeration usually is performed as spray agglomeration with a continuous spraying of binder liquid, until the desired amount of liquid is added. In a high shear mixer, typically all the binder liquid is added at once or during a few minutes before starting the massing process.

It has been shown (Abberger and Henck, 2000; Abberger, 2001) that the two previously mentioned mechanisms of nucleation occurred in fluid bed melt agglomeration of lactose and polyethylene glycol (PEG) 4000. Distribution and subsequent coalescence occurred when molten binder was sprayed onto the powder bed. Immersion and subsequent layering occurred when PEG flakes greater than the lactose particles were added at once before starting the process and melted in the vessel by the heated inlet air during the process. Since the shearing forces in a fluid bed are smaller than in a high shear mixer, both mechanisms were not acting simultaneously.

It has been stated that the distribution mechanism will be the typical mechanism of agglomerate formation in a high shear mixer. In a conventional fluid bed, however, the agglomerate formation has been shown to be controlled by the droplet size of the binder liquid and consequently by the immersion mechanism when using an aqueous binder liquid (Schæfer, 2001).

The aim of the work carried out for this paper has been to investigate the effect of droplet size and powder particle size on the mechanisms of agglomerate formation and on the subsequent agglomerate growth in fluid bed melt agglomeration.

2. Materials and methods

2.1. Materials

Lactose (α-lactose monohydrate, Ph. Eur. grade) 100, 125 or 350 mesh (DMV, Veghel, The Netherlands) was used as starting material. PEG 3000 (Clariant, Burgkirchen, Germany) was used as meltable binder.

The size distribution by volume of the lactose was determined in triplicate by a Malvern Mastersizer S (Malvern Instruments, Malvern, UK). The span is the difference between the diameters at the 90 and 10% points relative to the median

diameter. The pycnometric density, the specific surface area, and the poured and tapped densities were determined in duplicate, and the methods have been described elsewhere (Seo and Schæfer, 2001). The results presented in Table 1 are the mean values of repeated estimations.

Table 2 shows the physical properties of the PEG 3000 applied in the experiments. The methods of their determination have been described previously (Seo and Schæfer, 2001).

2.2. Equipment

A fluid bed spray granulator Glatt GPCG-1 (Glatt, Dresden, Germany) with a control panel Coros OP35 (Siemens, München, Germany) and a pneumatic nozzle 0.8 mm Schlick Model 970 (Schlick Düsen, Untersiemau, Germany) was applied in the experiments. Heating systems for the atomising air (Isopad, Heidelberg, Germany) and for the tubes delivering the molten binder (Hillesheim, Waghäusel, Germany) were used. The position of the nozzle was approximately 15 cm above the bottom of the material container. The air cap of the nozzle was in position 2.

Pressured air was used for conveying the molten PEG using a heated (70 °C) pressured vessel (Alloy, Waukesha, USA) equipped with a manometer (Wika, Lawrenceville, USA). A flow meter type DK 800 N (Krohne, Duisburg, Germany) was used to control the volumetric air flow rate, and the pressure of the atomizing air was measured by a manometer (Wika). A PC was used for collecting fluidising air flow rate, filter resistance and temperature data.

2.3. Measurement of spray droplet size

The spray droplet size distributions by volume were measured using a Malvern 2601Lc laser diffraction particle sizer (Malvern Instruments). The focal lens length was 300 mm. The measurements were performed according to the procedure previously described (Juslin et al., 1995). PEG of 70 °C was sprayed at a rate of 15 g/min applying air flow rates corresponding to pressures of 0.5, 1.0 or 1.5 bar. The distance of the nozzle orifice opening to the laser beam was the same as the height of the nozzle in the fluid bed ($\approx$ 15 cm), and 28.5 cm lateral from the focal lens. At each air flow rate, three determinations were performed. By regression analysis the air flow rates were calculated, which produced spray droplet sizes $d_{50,3}$ of 30, 60 or 90 μm.

2.4. Agglomeration procedure

Five hundred gram of lactose were sieved using a 500 μm sieve and charged into the container. The PEG was melted and heated at 70 °C in an incubator (Termarks, Bergen, Norway) before it was transferred to the pressured vessel. The binder concentration expressed as a percentage volume/mass (v/m) of the total mass of lactose and PEG was calculated from the binder volume at 60 °C. The heating of the tube to the nozzle was set to 70 °C, and the nozzle was heated with air of 130 °C. The inlet air temperature of the fluid bed was set to 85 °C. The air flow rate in the heating phase was 60–70 m^3/h. When the product temperature reached 63 °C, the spraying was started. The air flow rate to the nozzle was set in order to obtain a spray droplet size of 30, 60 or 90 μm. The

Table 1
Physical properties of the lactose grades

Lactose grade (mesh)	Particle size		Specific surface area (m^2/g)	Pycnometric density (g/cm^3)	Poured density (g/ml)	Tapped density (g/ml)
	$d_{50,3}$ (μm)	Span				
100	164	1.24	0.14	1.543	0.75	0.83
125	66	1.44	0.35	1.545	0.64	0.79
350	32	2.36	0.47	1.549	0.56	0.69

Table 2
Physical properties of PEG 3000

Pycnometric density (g/cm^3)	Density (molten) (g/ml)			Melting characterization (°C)		Viscosity (mPas)	Moisture content (%)
	60 °C	65 °C	70 °C	Range	Peak	63 °C	
1.238	1.092	1.090	1.086	47–58	56	264	0.6

spray rate was set to 15 g/min. A deviation up to 2.5 g/min was accepted. The mean spray rate was 14.5 g/min (S.D. 0.7 g/min) for the 30 μm droplet size experiments, 15.0 (S.D. 1.0) for the 60 μm series, and 16.3 (S.D. 1.9) for the 90 μm series. When spraying started, the inlet air temperature was set to 80 °C, and in the course of spraying the inlet air flow rate had to be increased to obtain a proper fluidization. Air flow rates between 60 and 145 m^3/h were applied. After the ending of the spraying, the heater was turned off. During the cooling phase the inlet air flow rate was adjusted to obtain a proper fluidization. When the product temperature was decreased to 38 °C, the process was stopped, and the product was removed.

2.5. Agglomerate characterization

2.5.1. Size distribution

The final agglomerates were sieved on a 4 mm Jel-Fix 50 vibration sieve (Engelsmann, Ludwigshafen, Germany) for ~10 s, until the fraction smaller than 4 mm has passed. The agglomerate size distribution of the fraction <4 mm was determined by sieve analysis. The product was divided using a rotary cone sample divider Laborette 27 with a Laborette 24 vibratory feeder (Fritsch, Idar-Oberstein, Germany) in order to obtain representative samples of about 70 g. A series of 15 ASTM standard sieves in the range of 75–2800 μm was vibrated for 15 min at an amplitude of 7 using a Fritsch Analysette 3 vibrator (Fritsch, Idar-Oberstein). The geometric mean diameter, d_{gw}, and the geometric standard deviation, s_g, were calculated.

2.5.2. Scanning electron microscopy

Micrographs were taken with a DSM 940A (Zeiss, Oberkochen, Germany) after sputtering by a Polaron E5100. with gold/palladium.

2.5.3. Image analysis

From batches having a d_{gw} smaller than 1000 μm, at least 300 particles belonging to the size fractions, in which d_{gw} was included, and the following and the previous ones were investigated for the shape factor circularity, $\varnothing$, with a microscope Axioplan (Zeiss) and a video camera and a frame grabber using image analysis software package KS 400 (Kontron, Eching, Germany). The circularity was calculated according to Cox (cf. Hawkins, 1993) (Eq. (1)).

$$\varnothing = 4\pi \frac{\text{area of the particle outline}}{(\text{perimeter of the particle outline})^2} \quad (1)$$

An elongation factor, defined as the maximum Feret diameter divided by the minimum Feret diameter has been determined too.

2.6. Experimental design

A series of 18 repeated experiments, i.e. a total of 36 experiments in which the lactose particle size (100, 125 or 350 mesh), the spray droplet size (30, 60 or 90 μm), and the concentration of PEG 3000 (11.5 or 22% v/m) were varied, was carried out. The experiments were performed in a randomized order. The data presented in this paper are the mean values of the repeated experiments. The error bars in Figs. 1 and 5 represent half of the range of the variation between the results and the ± in Table 4 represent the range between the repeated experiments.

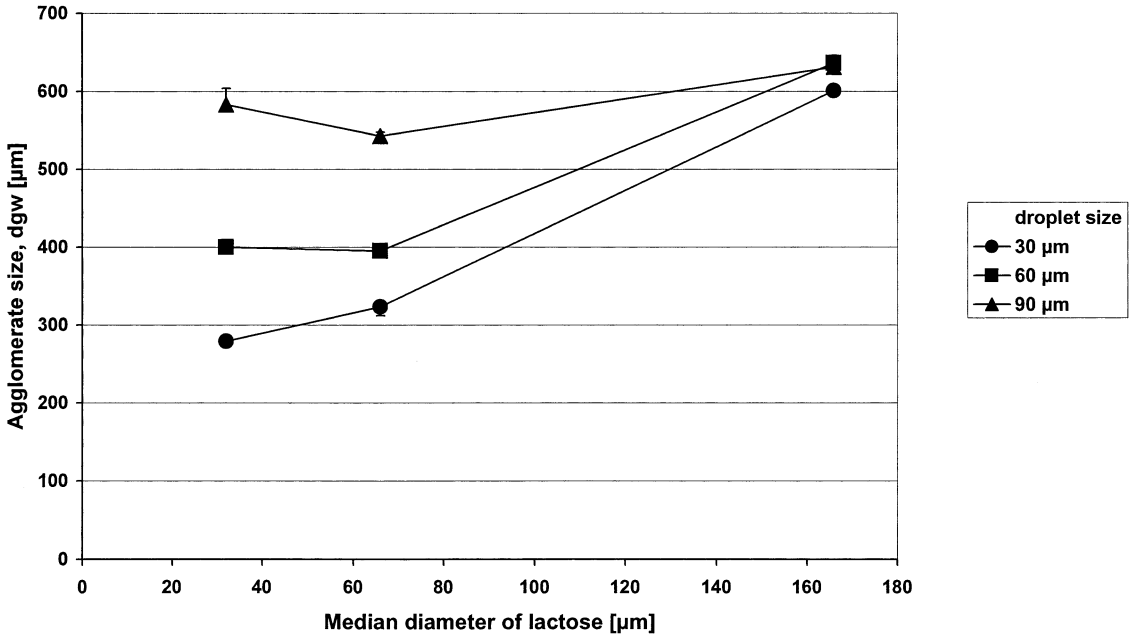

Fig. 1. Effects of lactose particle size and binder droplet size on the agglomerate size (d_{gw}) at a binder concentration of 11.5%.

3. Results and discussion

3.1. Effects on agglomerate size

In order to explain the interrelated effects of droplet size and particle size, a distinction between the nucleation phase and the growth phase is useful. A clear demarcation between these phases is difficult, however, since growth can start before nucleation of the primary particles is terminated.

3.1.1. Agglomerate formation

Table 3 predicts that distribution will be the dominant mechanism when the droplet size is smaller than the lactose particle size, whereas immersion will dominate when the droplet size is larger than the lactose particle size. When the droplet size is similar to the size of the lactose particles, distribution and immersion are expected to occur simultaneously.

Fig. 1 shows that the experiments are generally very reproducible at a binder concentration of 11.5%. With the 125 and 350 mesh lactose, the droplet size has a clear effect on the agglomerate size, whereas no clear effect is seen with the 100 mesh lactose. This is explained by differences in the agglomerate formation mechanisms (Table 3). For the 100 mesh lactose, the distribution mechanism dominates, and consequently no effect of droplet size is seen since the binder droplets spread over the surface of the particles/agglomerates. Although a larger droplet covers a greater surface fraction, this is compensated for by a greater number of smaller droplets. For the 125 and 350 mesh lactose, more immersion will occur with a larger droplet size. More immersion will result in a larger effect of droplet size during the nucleation phase since one nucleus is supposed to be created from one primary droplet or from one droplet created by coalescence between primary droplets.

The mechanisms indicated in Table 3 were generally confirmed by SEM micrographs of the agglomerates. Figs. 2 and 3 show the two extremes of distribution and immersion, respectively. When using the coarsest lactose grade and the smallest droplets (Fig. 2), the agglomerate structure is seen to be open since nuclei are formed by coalescence between wetted lactose particles. Using the finest lactose grade and the largest droplets, the agglomerates are seen to be denser (Fig. 3) since dense

Table 3
Agglomerate formation mechanisms expected from the ratios of droplet size to lactose particle size

Lactose particle size	Droplet size		
	30 μm	60 μm	90 μm
164 μm	Distribution	Distribution	Distribution
66 μm	Distribution	Distribution/immersion	Immersion
32 μm	Distribution/immersion	Immersion	Immersion

nuclei are formed by immersion. Subsequent growth occurs by layering of lactose particles in the surface of rewetted nuclei. When all fines are removed, the continued spraying promotes coalescence between rewetted nuclei or agglomerates. Consequently, the agglomerate size becomes larger than would be expected from immersion and subsequent layering only. Fig. 4 shows agglomerates being the result of distribution and immersion occurring simultaneously in the same batch. The agglomerates are formed by coalescence between wetted lactose particles as well as small nuclei formed by immersion. This results in an open agglomerate structure.

The 100 mesh lactose is seen to result in larger agglomerates than the 125 and the 350 mesh, especially with droplet sizes of 30 and 60 μm (Fig. 1). It is generally to be expected that a larger particle size will give rise to a higher liquid saturation and thus a larger agglomerate size if the binder concentration is kept constant. This is because the packing of the particles within the agglomerates is supposed to be denser (lower intragranular porosity) when the particle size becomes larger (Schæfer, 2001). This explanation is supported by the poured and the tapped densities of the three lactose grades (Table 1). However, the agglomerate growth is promoted by

Table 4
Effects of lactose particle size, binder concentration, and binder droplet size on the agglomerate size distribution described by the geometric standard deviation, s_g, and on the shape factors of the agglomerates

Lactose (mesh)	PEG% (v/m)	Droplet size (μm)	s_g	Circularity	Elongation
100	11.5	30	1.19 ± 0.01	0.66 ± 0.01	1.34 ± 0.01
100	11.5	60	1.18 ± 0.01	0.67 ± 0.01	1.34 ± 0.00
100	11.5	90	1.22 ± 0.01	0.68 ± 0.01	1.32 ± 0.01
100	22	30	1.49 ± 0.04	nd	nd
100	22	60	1.44 ± 0.03	nd	nd
100	22	90	1.60 ± 0.22	nd	nd
125	11.5	30	1.12 ± 0.01	0.71 ± 0.01	1.36 ± 0.00
125	11.5	60	1.17 ± 0.03	0.73 ± 0.00	1.32 ± 0.00
125	11.5	90	1.29 ± 0.01	0.77 ± 0.00	1.28 ± 0.01
125	22	30	1.31 ± 0.06	0.70 ± 0.02	1.34 ± 0.01
125	22	60	1.16 ± 0.01	0.71 ± 0.01	1.33 ± 0.01
125	22	90	1.31 ± 0.09	0.77[a]	1.30[a]
350	11.5	30	1.13 ± 0.01	0.78 ± 0.00	1.34 ± 0.01
350	11.5	60	1.23 ± 0.01	0.82 ± 0.01	1.31 ± 0.01
350	11.5	90	1.30 ± 0.02	0.88 ± 0.01	1.27 ± 0.00
350	22	30	1.20 ± 0.06	0.71 ± 0.00	1.33 ± 0.01
350	22	60	1.20 ± 0.01	0.76 ± 0.01	1.34 ± 0.01
350	22	90	1.37 ± 0.16	0.81[a]	1.30[a]

nd, not determined.
[a] one value only.

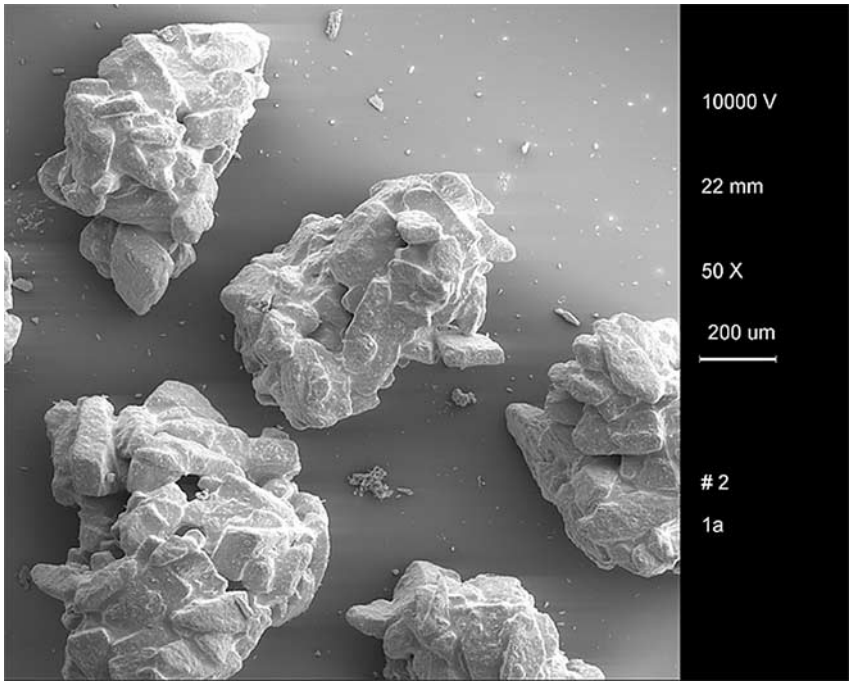

Fig. 2. SEM micrograph of agglomerates produced with lactose 100 mesh, 11.5% PEG and 30 μm droplet size.

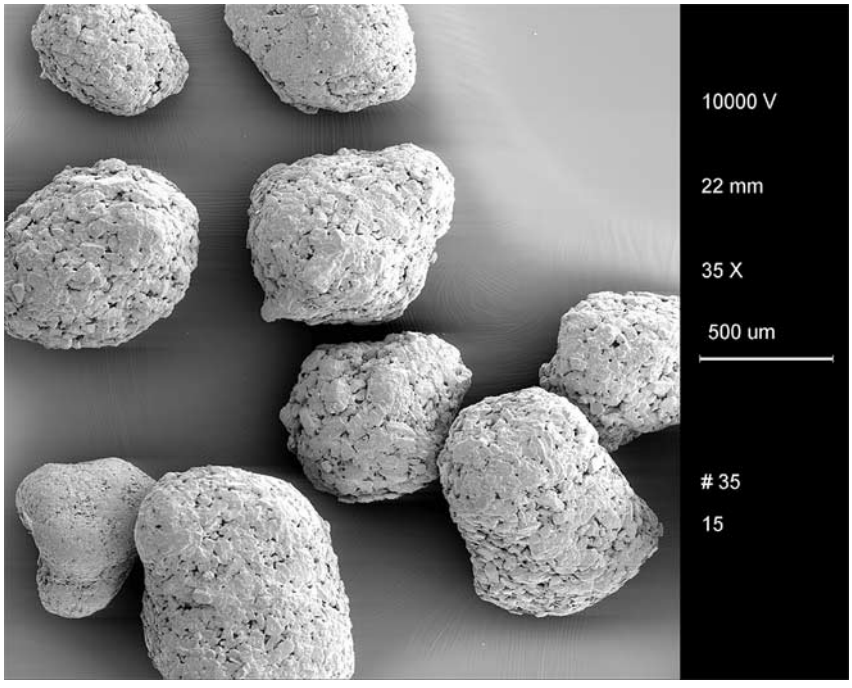

Fig. 3. SEM micrograph of agglomerates produced with lactose 350 mesh, 11.5% PEG and 90 μm droplet size.

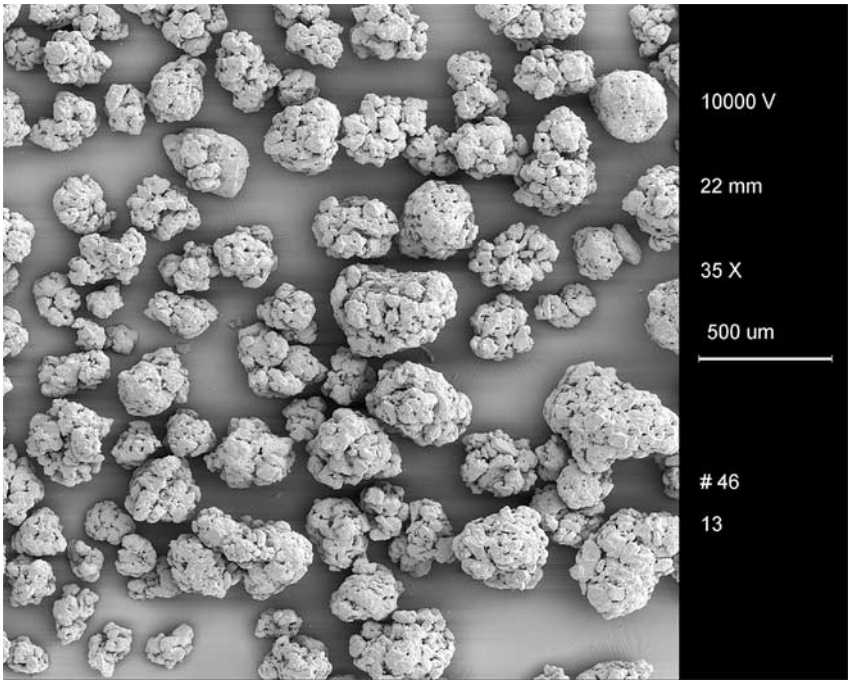

Fig. 4. SEM micrograph of agglomerates produced with lactose 350 mesh, 11.5% PEG and 30 μm droplet size.

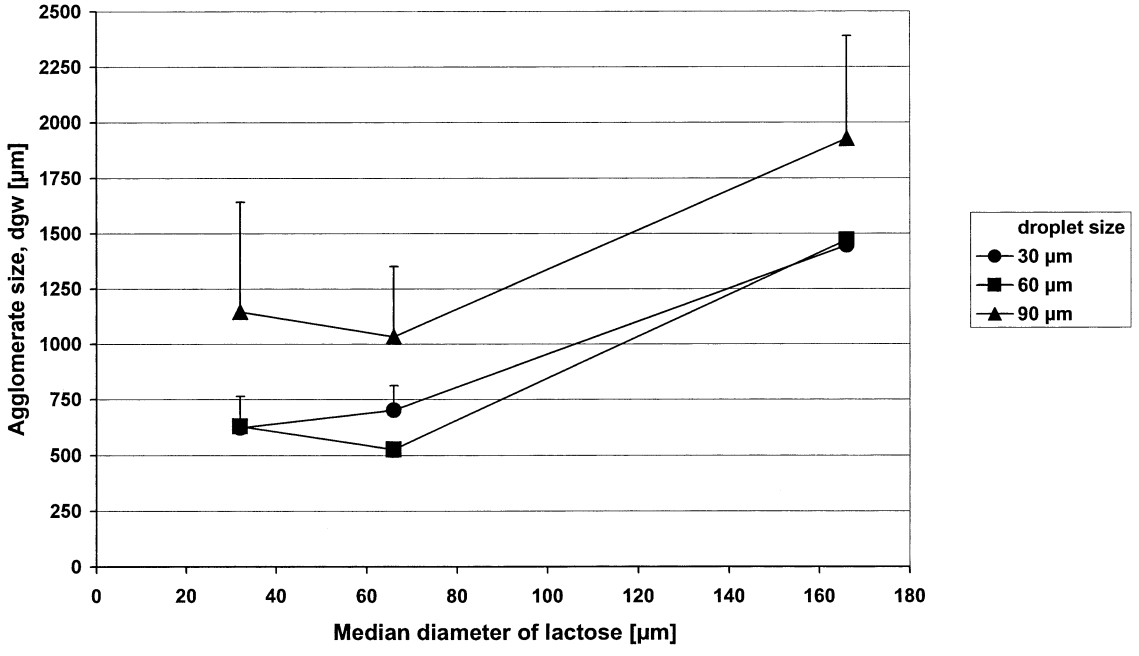

Fig. 5. Effects of lactose particle size and binder droplet size on the agglomerate size (d_{gw}) at a binder concentration of 22%.

a smaller particle size (Ennis et al., 1991). Therefore, the 350 mesh lactose results in a larger agglomerate size than to be expected from the poorer packing properties.

At a binder concentration of 11.5%, a larger droplet size is seen to result in a wider size distribution (Table 4), especially with the 125 and 350 mesh lactose where the agglomerate formation and growth are influenced by immersion.

3.1.2. Agglomerate growth

3.1.2.1. Effect of PEG concentration. A comparison of Fig. 1 with Fig. 5 shows that a higher PEG concentration gives rise to a larger agglomerate size. This is to be expected since a higher PEG concentration results in a higher liquid saturation. The SEM micrographs show clearly that the agglomerates become less porous at the high PEG concentration, and that more agglomerates are created by coalescence. Thus, Fig. 6 illustrates that the agglomerates in Fig. 4 have continued their growth by coalescence. Growth between 11.5 and 22% binder concentration occurs by coalescence between nuclei or agglomerates since all primary particles have disappeared. The sieve analysis data (not shown) reveal that practically no fines remain after addition of 11.5% of binder.

In most of the experiments, an increase in s_g is seen from 11.5 to 22% binder concentration (Table 4). This indicates that coalescence is the growth mechanism. Ouchiyama and Tanaka (1982) have shown by computer simulation of agglomerate growth that coalescence causes an increase in s_g.

3.1.2.2. Effect of droplet size. At a binder concentration of 22%, the reproducibility of the experiments is seen to be extremely poor with a droplet size of 90 μm, whereas the reproducibility is much better with droplet sizes of 30 and 60 μm (Fig. 5). Accordingly, the variations in s_g between repeated experiments are larger for the 90 μm droplets than for the 30 and 60 μm droplets (Table 4). The poor reproducibility with the 90 μm droplets indicates that the agglomerate growth is difficult to control,

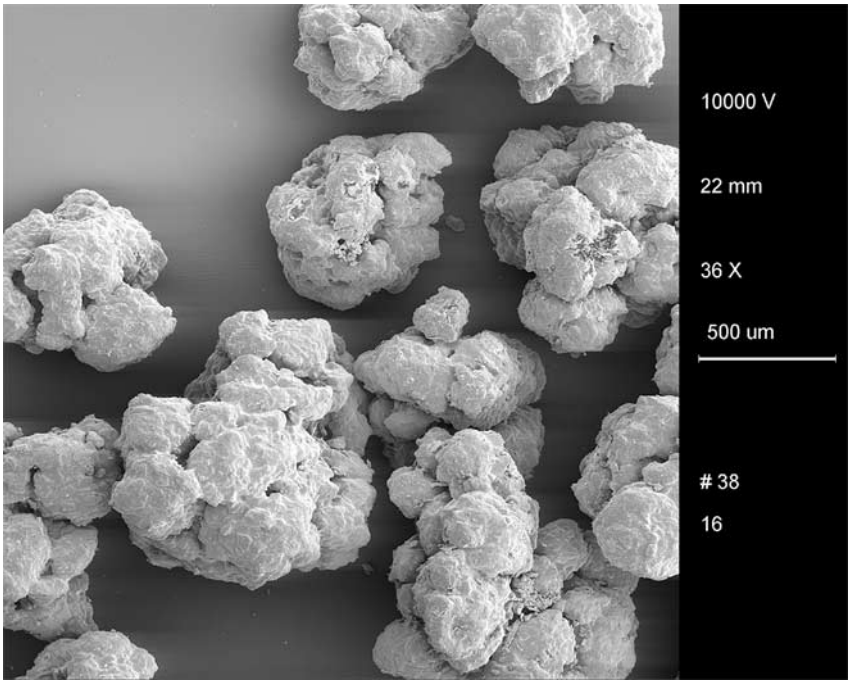

Fig. 6. SEM micrograph of agglomerates produced with lactose 350 mesh, 22% PEG and 30 μm droplet size.

and that random variations in process conditions, therefore, might give rise to an uncontrollable growth in some experiments. This is illustrated in Fig. 7 in which agglomerates from repeated experiments are compared. The figure shows an uncontrollable growth by coalescence between large agglomerates for the upper agglomerates, whereas no uncontrollable growth is seen for the lower agglomerates.

The SEM micrographs showed generally a denser surface structure of the agglomerates produced with the 90 μm droplets indicating a higher liquid saturation in the surface of the agglomerates. An example of this is shown in Figs. 8 and 9. Even at a binder concentration of 11.5%, the agglomerates made with the 90 μm droplets are denser (compare Figs. 3 and 4). The reason may be that 90 μm droplets offer a greater potential for nucleation by immersion than the smaller ones, and that immersion leads to denser nuclei than distribution as was discussed in Section 3.1.1. The denser structure obtained with the 90 μm droplets could not be quantitatively verified by the mercury immersion method that has been used for estimation of the intragranular porosity of agglomerates produced by melt agglomeration in high shear mixers (Schæfer et al., 1993). This was because no reliable estimates of the porosity could be obtained since the looser structure of the agglomerates produced by fluid bed melt agglomeration resulted in penetration of mercury into the largest pores.

A thicker surface liquid layer as well as smaller surface asperities will increase the probability of a successful coalescence between colliding agglomerates according to the theory of Ennis et al. (1991). Table 4 shows that the circularity, which is a measure of smoothness, is generally closest to 1, the value of a smooth sphere, for the 90 μm droplets. Consequently, the increased potential for agglomerate growth seen with the 90 μm droplets is most likely explained by more binder liquid at the agglomerate surface combined with less surface asperities. This means that the binder concentration has to be reduced in order to obtain a reproducible agglomerate growth with a droplet size of 90 μm.

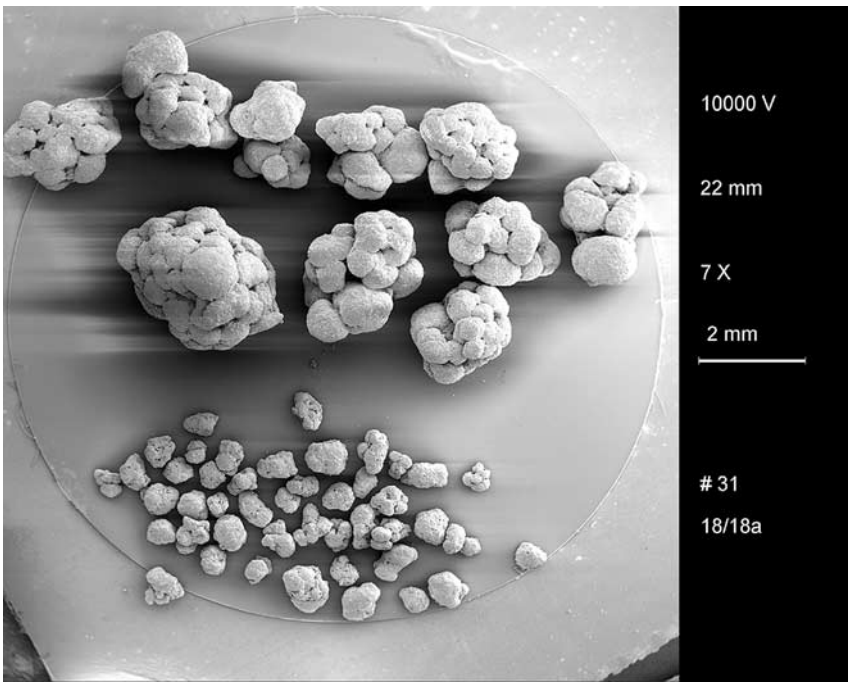

Fig. 7. SEM micrograph of agglomerates produced with lactose 350 mesh, 22% PEG and 90 μm droplet size. The upper and lower agglomerates are from different experiments.

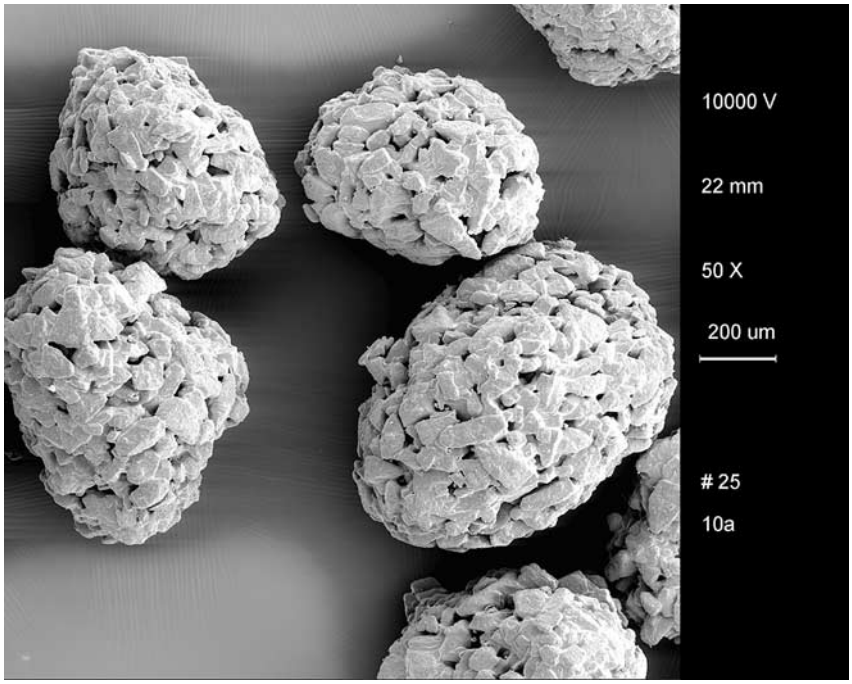

Fig. 8. SEM micrograph of agglomerates produced with lactose 125 mesh, 22% PEG and 30 μm droplet size.

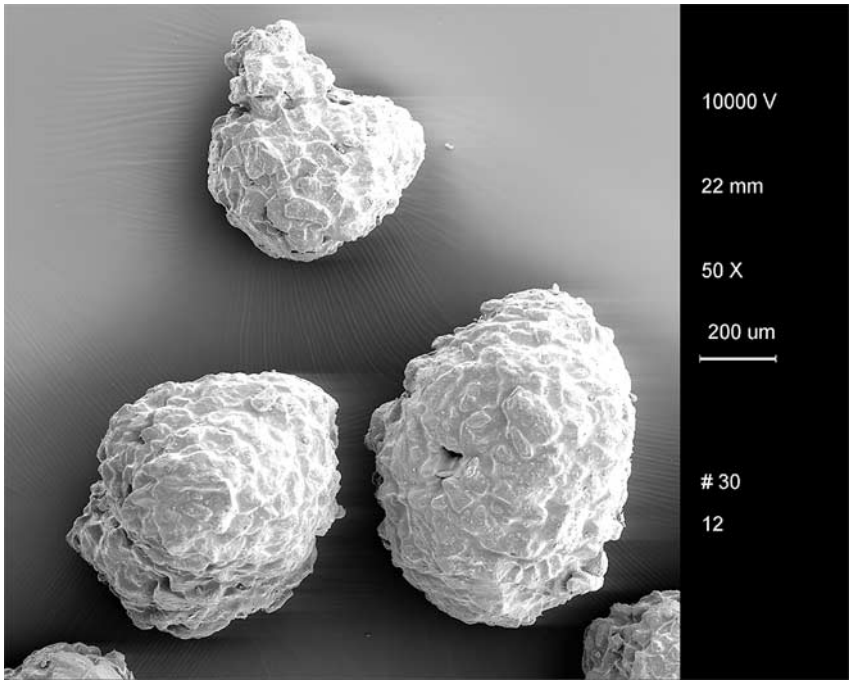

Fig. 9. SEM micrograph of agglomerates produced with lactose 125 mesh, 22% PEG and 90 μm droplet size.

For each of the lactose grades, droplet sizes of 30 and 60 μm are seen to result in approximately the same mean agglomerate size at a binder concentration of 22% (Fig. 5).

3.2. Effects on agglomerate shape

The interpretation is affected by the fact that it has not been possible to measure the shape of the largest agglomerates. It is seen that larger droplets give rise to more spherical and rounded agglomerates (Table 4). This is ascribed to the higher liquid saturation in the agglomerate surface making the surface more deformable. A smaller lactose particle size causes more spherical and rounded agglomerates. It is obvious that a smaller particle size will result in smoother agglomerates since smaller particles will cause smaller surface asperities.

4. Conclusions

The present study shows that the mechanism of agglomerate formation in fluid bed melt agglomeration is primarily dependent on the ratio of the size of the atomized binder droplets to the size of the solid particles. Distribution of the binder droplets on the surface of the solid particles followed by a sticking together between the wetted particles to form nuclei is the dominant nucleation mechanism when the solid particles are larger than the binder droplets. Immersion of the solid particles in the surface of the binder droplets is the dominant nucleation mechanism when the solid particles are smaller than the binder droplets. Distribution leads to a rather open agglomerate structure, whereas immersion results in a denser structure.

When the nucleation phase is terminated, and all fines are removed, further agglomerate growth occurs by coalescence between rewetted nuclei or agglomerates. A larger solid particle size was found to result in a larger agglomerate size when the amount of binder was kept constant, as expected. A large droplet size was found to promote the agglomerate growth by coalescence. This is ascribed to a higher liquid saturation in the agglomerate surface due to the denser agglomerate structure caused by the immersion in the nucleation phase being promoted by a larger droplet size. Consequently, a larger droplet size might give rise to an uncontrollable agglomerate growth.

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