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Effects of droplet size and type of binder on the agglomerate growth mechanisms by melt agglomeration in a fluidised bed

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Abstract

This study was performed in order to evaluate the effects of binder droplet size and type of binder on the agglomerate growth mechanisms by melt agglomeration in a fluidised bed granulator. Lactose monohydrate was agglomerated with melted polyethylene glycol (PEG) 3000 or Gelucire 50/13 (esters of polyethylene glycol and glycerol), which was atomised at different nozzle air flow rates giving rise to median droplet sizes of 40, 60, and 80 μm. Different product temperatures were investigated, below the melting range, in the middle of the melting range, and above the melting range for each binder. The agglomerates were found to be formed by initial nucleation of lactose particles immersed in the melted binder droplets. Agglomerate growth occurred by coalescence between nuclei followed by coalescence between agglomerates. Complex effects of binder droplet size and type of binder were seen at low product temperatures. Low product temperatures resulted in smaller agglomerate sizes, because the agglomerate growth was counteracted by very high binder viscosity or solidification of the binder. At higher product temperatures, neither the binder droplet size nor the type of binder had a clear effect on the final agglomerate size.

Keywords: Melt agglomeration; Fluidised bed; Binder viscosity; Droplet size; Polyethylene glycol; Agglomerate growth mechanisms

1. Introduction

Wet agglomeration performed in fluidised bed granulators is a commonly used method to produce agglomerates in the pharmaceutical industry. The agglomeration is carried out by spraying a binder liquid into a heated bed of fluidised particles. The most frequently used binder liquids are aqueous polymer solutions. Melt agglomeration is a wet agglomeration process in which a melted binder is applied. Melt agglomeration is usually performed in a high shear mixer. Recent studies have shown, however, that a meltable binder can be an alternative to a polymer solution in fluidised bed granulation (Abberger and Henck, 2000; Yanze et al., 2000; Abberger, 2001). The binder can be added either in a molten state or as solid particles, which melt during the process.

Previous studies with aqueous binder liquids in fluidised bed granulators have shown that larger binder droplet size (Schæfer and Wørts, 1978a; Watano et al., 1994; Lin and Peck, 1995; Juslin and Yliruusi, 1996; Schaafsma et al., 2000) as well as higher viscosity of the binder liquid (Schæfer and Wørts, 1978b; Wan and Lim, 1991; Kokubo et al., 1995) result in larger agglomerates.

In aqueous fluidised bed agglomeration, the agglomerate formation and growth can be described by initial formation of small agglomerates (nuclei) followed by growth by coalescence between the agglomerates (Schæfer and Wørts, 1978a; Andreev et al., 1980; Wan et al., 1992; Juslin and Yliruusi, 1996). The nuclei are formed by random collisions between the atomised liquid droplets and the powder particles. Due to evaporation of solvent during the process, the binder concentration in the surface of the nuclei will increase, and hence, the binder viscosity will increase causing the liquid bridges to become immobile. Thereby, the shape of the nucleus will be maintained during the agglomeration, and the size of the nuclei will depend on the droplet size. By continued liquid addition, the liquid saturation of the agglomerates will increase

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facilitating growth by coalescence between the agglomerates (Schæfer and Wørts, 1978a).

Abberger and Henck (2000) and Abberger (2001) studied the agglomerate formation mechanisms in fluidised bed melt agglomeration. They found that agglomeration occurred by distribution and coalescence when a melted binder was added through a nozzle. When the meltable binder was added as solid particles, coarse flakes resulted in agglomeration by immersion, whereas fine flakes resulted in agglomeration by distribution and coalescence. A meltable binder with higher viscosity gave rise to larger agglomerates (Abberger, 2001). It is difficult to decide whether this is an effect of viscosity on droplet size or on agglomerate growth, because the droplet size of the atomised binder liquid is affected by the viscosity (Schæfer and Wørts, 1978b; Juslin et al., 1995). Since the droplet size of the atomised binders was unknown in these studies, more studies are necessary to clarify the mechanisms of agglomerate formation and growth when the binder is added in a molten state through a nozzle.

By melt agglomeration in a high shear mixer, the binder is distributed on the surface of the powder particles due to the high shear forces, and nuclei are formed primarily by coalescence between the wetted particles unless the binder viscosity is extremely high (Schæfer and Mathiesen, 1996c).

The present work is based on the hypothesis that the mechanisms of agglomerate formation and growth in fluidised bed melt agglomeration are different from those seen by melt agglomeration in high shear mixers because of the lower shear forces in the fluidised bed, as well as different from those seen by aqueous fluidised bed agglomeration, because no evaporation of binder liquid occurs by melt agglomeration. The purpose of this study is to test this hypothesis by investigating the effects of droplet size and type of binder on the agglomerate formation and growth mechanisms by melt agglomeration in a fluidised bed.

2. Materials and methods

2.1. Materials

Lactose, 350 mesh (α-lactose monohydrate; DMV, The Netherlands) was used as starting material. Gelucire 50/13 (esters of polyethylene glycol and glycerol; Gattefossé, France) or polyethylene glycol (PEG) 3000 (Clariant, Germany) was used as meltable binder.

2.2. Methods

2.2.1. Primary characterisation of materials

The particle size distribution by volume of the lactose was determined in triplicate by a Malvern Mastersizer S laser diffraction particle sizer (Malvern Instruments, UK). The median particle diameter and the span were found to be 28 μm and 2.5, respectively. The span is the difference between the diameters at the 90 and the 10 percentage points relative to the median diameter.

The BET multipoint surface area of the lactose, determined in duplicate by a Gemini 2375 Surface Area Analyser (Micromeritics, USA) was 0.68 m^2/g.

The pycnometric densities of the lactose, the solid Gelucire, and the solid PEG were determined by an Accupyc 1330 gas displacement pycnometer (Micromeritics, USA) using helium purge. Analyses were performed in duplicate. Before the analysis, the Gelucire beads were milled in a coffee mill (Braun AG 4041, Spain) for 3 s followed by a 3-s pause to prevent melting of the Gelucire. This procedure was repeated until the beads were milled for 60 s in total. The pycnometric density of the lactose was 1.550 g/cm^3. The poured and tapped densities of the lactose were determined in duplicate according to the test for apparent volume (European Pharmacopoeia, 1999) and found to be 0.48 and 0.67 g/cm^3, respectively.

The melting range and the peak temperature of the Gelucire and the PEG were estimated in triplicate by a Perkin Elmer DSC 7 differential scanning calorimeter (Perkin Elmer, USA) as previously described (Seo and Schæfer, 2001).

The densities of the melted binders were estimated at 50, 55, and 60 °C for the Gelucire and at 60, 65, and 70 °C for the PEG as previously described (Eliasen et al., 1998). The analyses were performed in triplicate.

The viscosities of the melted binders were estimated in duplicate by a Rotovisco RV 20 (Haake, Germany) as previously described (Schæfer and Mathiesen, 1996b). The analyses were performed at 53 °C for the Gelucire and at 53 and 63 °C for the PEG.

The water contents on a wet-weight basis of the binders were estimated in triplicate by volumetric titration as previously described (Schæfer and Mathiesen, 1996a). A sample of ~1.5 g was used for the determinations. Before the titration, the Gelucire was milled according to the procedure described above.

All data on material properties presented here are the mean value of the repeated estimations.

2.2.2. Equipment

The agglomeration experiments were performed in a fluidised bed granulator, Glatt GPCG-1 (Glatt, Germany), modified in order to allow faster cooling of the product by passing air at ambient temperature into the plenum by means of a bypass valve. The nozzle (Schlick Model 970, Schlick Düsen, Germany) was pneumatic with an orifice diameter of 0.8 mm.

An electrically heated tube (Isopad, Germany) was used to heat the atomising air to a temperature of ~70 °C. A pressured vessel (Alloy, USA) heated to 70 °C and

equipped with a manometer (Wika, USA) was used to feed the melted binder to the nozzle. The tube delivering the melted binder from the pressured vessel to the nozzle was electrically heated to 70 °C with a heating device (Hillesheim, Germany). A manometer (Wika, USA) was used to measure the air pressure at the nozzle, and the volumetric air flow rate was regulated by a flowmeter DK 800N (Krohne, Germany).

The process data were logged to a PC recording the product temperature, the inlet and outlet air temperature, and the fluidising air flow rate. During the process, data were logged with intervals of 2.5 s.

2.2.3. Determination of spray droplet size

The droplet size distributions by volume of the atomised binders were measured by a Malvern 2601Lc laser diffraction particle sizer (Malvern Instruments, UK). The focal lens length was 300 mm. The measurements were performed according to the procedure previously described (Juslin et al., 1995). The nozzle orifice opening was positioned at a distance of 15 cm from the laser beam and at a position of 28.5 cm from the focal lens. The measurements were performed with a binder liquid flow rate of 30 g/min. The median droplet diameter was calculated as the mean value of three measurements.

2.2.4. Granulation procedure

A batch size of 500 g of lactose was used in all experiments. The lactose was sieved through a 1-mm sieve and charged into the product chamber. The fluidising air flow was initiated, and the flow rate was set to 60 m^3/h. The inlet air temperature was set to 50, 65 or 85 °C for the PEG and 45 or 65 °C for the Gelucire. This resulted in product temperatures of approximately 45, 53, and 63 °C for the PEG and 40 and 53 °C for the Gelucire. The inlet air temperature fluctuated approximately ±5 °C around the set value, whereas the fluctuation in product temperature was approximately ±1 °C. However, a minor increase in the product temperature was observed during the last part of the binder addition. The filter was shaken in alternate halves at 10-s intervals for 3 s without interrupting the fluidisation.

The air dome on the nozzle head was set in the number 2 position, and the nozzle was placed ~15 cm above the bottom of the chamber. The addition of the melted binder heated to 70 °C was started when the product temperature had reached the target value mentioned above, and the liquid flow rate was kept at 30±5 g/min.

Immediately after the end of the binder addition, the cooling of the product was started by opening the bypass valve and setting the inlet air temperature at 30 °C. The process was stopped when the product temperature had reached 32 °C for Gelucire and 40 °C for PEG in order to ensure a temperature below the melting range.

2.2.5. Agglomerate characterisation

2.2.5.1. Size distribution

The final agglomerates were sieved on a 2-mm Jel-Fix 50 vibration sieve (J. Engelsmann, Germany) for ~10 s, until the fraction smaller than 2 mm had passed.

The agglomerate size distribution of the agglomerates <2 mm produced with binder concentrations of 16.5 and 27.5% v/m was determined by sieve analysis of a sample of ~80 g prepared by a Laborette 27 automatic rotary sample divider (Fritsch, Germany). A series of 14 ASTM standard sieves in the range of 75–2000 μm was used for 5 min at low vibration level, and the fractions smaller than 250 μm were sieved for an additional 5 min at high vibration level by a Fritsch analysette 3 vibrator (Fritsch, Germany). The agglomerate size distributions were in good agreement with the log-normal distribution. Consequently, the mean agglomerate size was described by the geometric-weight mean diameter (d_{gw}) and the size distribution by the geometric standard deviation (s_g). The yield of the fraction 250–2000 μm was calculated as the percentage of the total amount of agglomerates smaller than 2 mm.

The agglomerate size distribution by volume of agglomerates produced with a binder concentration of 5.5% v/m was determined in triplicate by a Malvern Mastersizer S laser diffraction particle sizer.

2.2.5.2. Pycnometric density

Samples of ~4 g from the agglomerate size fraction 250–2000 μm were milled in a coffee mill as described above. The pycnometric densities of the milled agglomerates were determined by an AccuPyc 1330 gas displacement pycnometer using helium purge. The results are mean values of two determinations. The pycnometric densities of the agglomerate size fractions were used for indirect estimation of the binder content in the agglomerates as previously described (Schæfer and Mathiesen, 1996c).

2.2.5.3. SEM photographs

Photographs of selected agglomerates were taken by a scanning electron microscope (SEM) (Jeol JSM 5200, Japan). Prior to microscopy, the samples were coated with gold/palladium by sputtering for 150 s (Biorad, E5200 Auto Sputter Coater, UK).

2.2.6. Experimental design

Lactose was agglomerated with atomised Gelucire 50/13 or PEG 3000 at different nozzle air flow rates giving rise to median droplet sizes of 40, 60, and 80 μm. A binder concentration of 27.5% v/m of the amount of lactose based upon the binder volume at 60 °C was applied. The inlet air temperature was set to reach product temperatures corresponding to a temperature of 5 °C below the melting range of the binder, in the middle of the melting range, and 5 °C above the melting range. Experiments with Gelucire

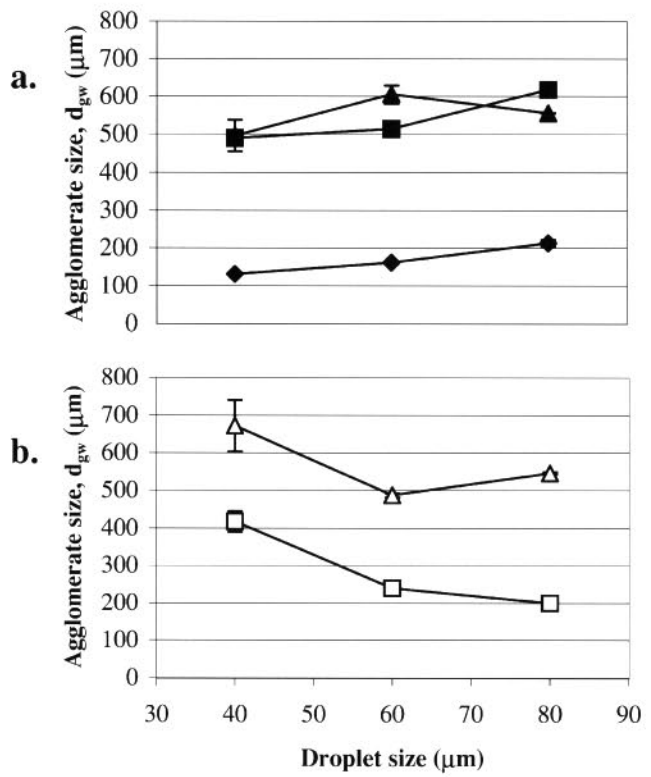

Fig. 1. Effects of droplet size and inlet air temperature on the agglomerate size. (a) PEG 3000. Inlet air temperature: 50 °C (♦); 65 °C (■); 85 °C (▲). (b) Gelucire 50/13. Inlet air temperature: 45 °C (□); 65 °C (△). Approximate product temperature: 5 °C below the melting range (♦); in the middle of the melting range (■), (□); 5 °C above the melting range (▲), (△).

at 5 °C below the melting range had to be excluded from the final series due to solidification of the Gelucire in the nozzle. The experiments were carried out in duplicate giving a total of 30 experiments.

Additional single experiments were performed with a binder concentration of 5.5 or 16.5% v/m with the droplet sizes 40 and 80 μm at two inlet air temperatures corresponding to product temperatures in the middle of and 5 °C above the melting range.

Experiments, in which the inlet air temperature was maintained for 5 min after the end of binder addition, were performed in duplicate with 27.5% v/m of binder and a droplet size of 60 μm at two inlet air temperatures corresponding to product temperatures in the middle of and 5 °C above the melting range.

The results of the repeated experiments shown in this paper are mean values. The range of the repeated experiments is indicated as '±' in Tables 2 and 3 and as error bars in Fig. 1.

3. Results and discussion

3.1. Binder properties

The binder properties are presented in Table 1. The temperatures for the determination of viscosity of the melted binder were chosen at the middle of the melting range and 5 °C above the melting range. Gelucire 50/13 has lower viscosity compared to PEG 3000 at the temperature corresponding to 5 °C above the melting range. The viscosity of the Gelucire 50/13 could not be measured at the temperature corresponding to the middle of the melting range due to extremely high viscosity caused by incomplete melting. It was found by DSC measurements that the two binders differed in melting behaviour. PEG 3000 had a narrow melting range, while Gelucire 50/13 had a wider two-peak melting range. Gelucire 50/13 consists of mixtures of glycerides and PEG esters of fatty acids, and segregation of the glycerides might cause the two-peak melting range (Sutananta et al., 1994).

The solubility of lactose in PEG 3000 as well as Gelucire 50/13 was found to be less than 0.1% m/m at 70 °C based on visual observation.

3.2. Agglomerate size and size distribution of final agglomerates

Generally, the variations between repeated experiments are seen to be small (Fig. 1), which indicate good reproducibility and controlled agglomeration. For both binders, the smallest agglomerates are obtained when the inlet air temperature corresponding to the lowest product temperature is used. In order to obtain agglomerate growth by coalescence between agglomerates, the surface deformability of the agglomerates has to be sufficiently high (Holm et al., 1985). In fluidised bed agglomeration, the surface deformability is supposed primarily to depend on the viscosity of the binder liquid layer on the agglomerate surface since the shear forces are low. Consequently, the agglomerate growth will be counteracted if the binder viscosity is high and cease if the binder solidifies. It was found in previous fluidised bed melt agglomeration experiments (Abberger, 2001) that higher binder viscosity resulted in larger agglomerates. No viscosity data were

Table 1
Physical properties of the binders

Type of binder	Pycnometric density (g/cm^3)	Density (melted) (g/cm^3)					Melting point (°C)		Viscosity (mPa·s)		Water content (%)
		50 °C	55 °C	60 °C	65 °C	70° C	Range	Peak temp.	53 °C	63 °C	
PEG 3000	1.238			1.092	1.090	1.086	47–58	56	369	264	0.6
Gelucire 50/13	1.129	1.008	1.004	1.000			32–48	42	101		0.5

presented in this paper but the different effect of viscosity might be explained by lower maximum viscosity in these experiments.

At the lowest product temperature, the PEG will solidify during fluidisation, because the temperature of the bed is below the melting range of the PEG. This is why only slight agglomerate growth is seen (Fig. 1a). Larger droplets are seen to result in larger agglomerates.

For the Gelucire, the lowest product temperature is in the middle of the melting range, and the Gelucire, therefore, will not solidify completely but the viscosity will be extremely high. Consequently, the experiments carried out at the lowest product temperatures are seen to result in more agglomerate growth for the Gelucire than for the PEG. For the Gelucire at the lowest product temperature, the droplet size has the opposite effect of that seen for the PEG since a smaller droplet size results in larger agglomerates (Fig. 1b).

At higher product temperatures, corresponding to temperatures in the middle of the melting range (PEG) or above the melting range (PEG, Gelucire), the binder viscosity will be markedly lower, and the agglomerate size will increase due to higher surface deformability of the agglomerates. The difference in viscosity (Table 1) has apparently not a major effect on the final agglomerate size (Fig. 1), as long as the surface of the agglomerates is sufficiently deformable for agglomerate growth by coalescence to occur. Accordingly, only a slight effect on agglomerate size of the viscosity changes caused by varying the inlet air temperature in the range of 70–90 °C was found in previous fluidised bed melt agglomeration experiments (Abberger, 2001).

At the higher temperatures (Fig. 1), there is no pronounced effect of the droplet size for either the PEG or the Gelucire. This disagrees with the previously mentioned results on the effect of the droplet size in aqueous fluidised bed agglomeration experiments showing clearly that a larger droplet size gives rise to a larger granule size. This different effect of droplet size is most likely explained by the evaporation of water that occurs from the binder liquid during the aqueous process. More evaporation is supposed to occur when the droplet size is smaller because of the larger surface area. Therefore, the smaller agglomerate size obtained with a smaller droplet size might simply be due to less growth by coalescence because of lower moisture content in the surface of the agglomerates. This explanation is supported by the fact that only a very slight effect of droplet size on agglomerate size was found in previous experiments (Watano et al., 1994) with water as the binder liquid where the moisture content of the product was kept constant by feed back control.

Table 2 shows that the agglomerate size distributions are generally narrow (s_g-values: 1.3–1.5) except for the experiments where the agglomerate growth is counteracted by a low product temperature. Low yields of the agglomerate size fraction 250–2000 μm are seen for each binder at the lowest product temperature due to insufficient agglomerate growth.

The highest binder concentrations in the size fraction 250–2000 μm are seen for agglomerates produced at the lowest product temperature. This indicates uneven distribution of the binder. Although the binder concentration is high, no overwetting occurs, because the deformability of the agglomerates is low due to solidification or high viscosity of the binder. At the lowest product temperature, a larger droplet size gives rise to a more even binder distribution for the PEG, whereas the opposite effect of droplet size is seen for the Gelucire. Further, the Gelucire results in more uniform binder distribution than the PEG. Thus, a more even binder distribution is obtained at the

Table 2
Effects of type of binder, droplet size, and inlet air temperature on the size distribution (s_g), the yield of the agglomerate size fraction 250–2000 μm, and the estimated binder concentration (% m/m of the amount of lactose) of the agglomerate size fraction 250–2000 μm

Binder/droplet size /temperature	s_g	Yield of the fraction 250–2000 μm (%)	Binder concentration in the fraction 250–2000 μm (%)
PEG 3000/40 μm/50 °C	1.9 (±0.0)	14.3 (±0.6)	62.7 (±2.7)
PEG 3000/40 μm/65 °C	1.4 (±0.0)	96.7 (±0.7)	32.3 (±0.9)
PEG 3000/40 μm/85 °C	1.4 (±0.0)	96.4 (±0.4)	32.5 (±1.8)
PEG 3000/60 μm/50 °C	2.0 (±0.0)	28.3 (±0.2)	60.5 (±0.2)
PEG 3000/60 μm/65 °C	1.5 (±0.0)	96.8 (±0.5)	33.9 (±0.5)
PEG 3000/60 μm/85 °C	1.3 (±0.0)	99.7 (±0.2)	33.0 (±1.0)
PEG 3000/80 μm/50 °C	2.2 (±0.0)	48.4 (±2.3)	49.6 (±3.0)
PEG 3000/80 μm/65 °C	1.5 (±0.1)	98.7 (±0.5)	35.0 (±1.2)
PEG 3000/80 μm/85 °C	1.4 (±0.0)	98.7 (±0.1)	34.9 (±0.2)
Gelucire 50/13/40 μm/45 °C	1.6 (±0.0)	86.3 (±1.8)	27.7 (±0.7)
Gelucire 50/13/40 μm/65 °C	1.4 (±0.0)	99.0 (±0.2)	26.8 (±0.9)
Gelucire 50/13/60 μm/45 °C	1.7 (±0.1)	50.7 (±4.9)	34.9 (±0.4)
Gelucire 50/13/60 μm/65 °C	1.5 (±0.0)	96.4 (±0.1)	26.7 (±0.1)
Gelucire 50/13/80 μm/45 °C	2.1 (±0.0)	42.7 (±3.1)	44.4 (±1.6)
Gelucire 50/13/80 μm/65 °C	1.5 (±0.1)	96.9 (±1.3)	27.0 (±0.8)

Theoretical binder concentration: PEG 3000: 30%; Gelucire: 27.5% (m/m of the amount of lactose).

lowest product temperature when the agglomerate size becomes larger (Fig. 1).

At higher product temperatures, the binder concentrations are seen to be close to the theoretical value.

3.3. Intragranular porosity

The agglomerates in Fig. 2 have a looser structure than that obtained by melt agglomeration of lactose 350 mesh and PEG 3000 in a high shear mixer (Schæfer et al., 1992). The difference in structure might be caused by the lower shear forces in fluidised bed granulators compared with high shear mixers (Schaafsma et al., 2000). The final porosities of agglomerates produced by melt agglomeration with PEG 3000 in a high shear mixer have been estimated typically to be 4–5% (Schæfer et al., 1993). No reliable estimates of the intragranular porosity could be obtained in the present experiments, because the loose structure of the agglomerates resulted in penetration of mercury into the largest pores. The loose structure, however, indicates markedly higher porosity of the fluidised bed agglomerates.

In previous melt agglomeration experiments with lactose 350 mesh and PEG 3000 in a high shear mixer (Schæfer et al., 1992), a maximum of 22% m/m PEG could be incorporated compared with 30% m/m in the present experiments. This is probably because of the much lower densification occurring in a fluidised bed granulator due to the lack of shear forces.

3.4. Mechanisms of agglomerate formation and growth

Fig. 3 illustrates that the binder concentration has to be between 5.5 and 16.5% v/m before significant agglomerate growth occurs. Preliminary experiments at a product temperature above the melting range of the binder showed that a binder concentration slightly higher than 27.5% v/m resulted in overwetting and defluidization. At a product temperature in the middle of the melting range, the agglomerate growth rate is affected by both the type of binder and the droplet size (Fig. 3a). The agglomerate growth rate is seen to be higher with the PEG than with the Gelucire due to the higher viscosity of the Gelucire. Larger PEG droplets result in larger agglomerates. For Gelucire, the opposite effect of the droplet size is seen.

The effects of type of binder and droplet size are less clear when the product temperature is kept above the

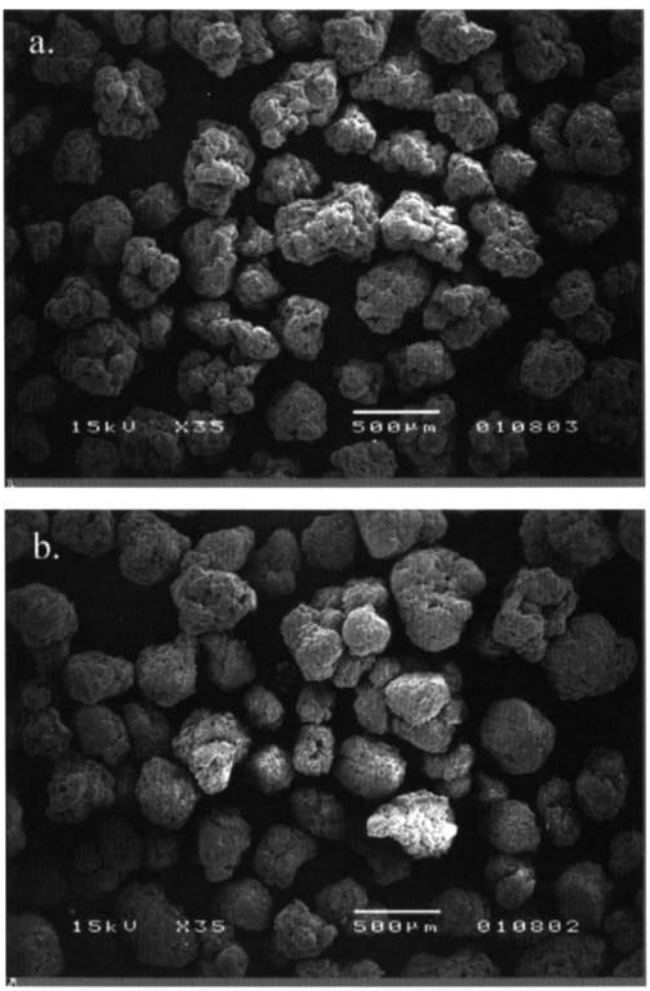

Fig. 2. SEM photographs of agglomerates produced with PEG 3000. Inlet air temperature: 85 °C. Binder concentration: 27.5% v/m. Droplet size: (a) 40 µm; (b) 80 µm.

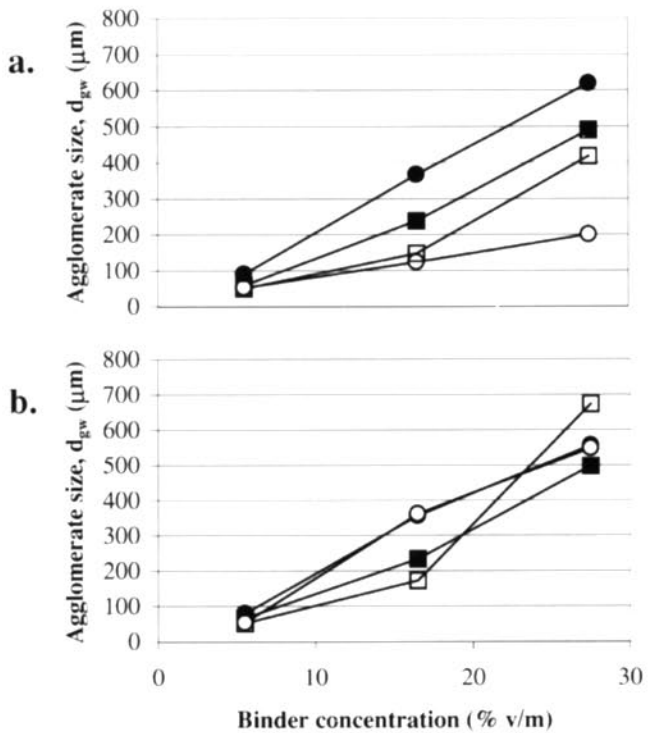

Fig. 3. Effects of binder concentration, type of binder, and droplet size on the agglomerate size. PEG 3000, 40 µm (■), PEG 3000, 80 µm (●), Gelucire 50/13, 40 µm (□), and Gelucire 50/13, 80 µm (○). Product temperature: (a) middle of the melting range, (b) 5 °C above the melting range.

melting range (Fig. 3b). After addition of up to 16.5% v/m of binder, it is obvious that larger droplets result in larger agglomerates. Increasing the binder concentration from 16.5 to 27.5% results in the highest agglomerate growth rate for agglomerates produced with the smallest droplet size. At 27.5% of binder, there is no clear effect of the droplet size.

The changes in the agglomerate size distribution caused by an increasing amount of binder are similar for the Gelucire and the PEG at a product temperature 5 °C above the melting range. Fig. 4a shows that after addition of 5.5% of Gelucire, there is a high content of particles <75 μm, which is supposed primarily to be unagglomerated lactose particles but also small nuclei might be included. At that time, only a very few agglomerates >250 μm have been formed indicating that nucleation is the dominant mechanism. After addition of 16.5% of Gelucire (Fig. 4b), practically all the particles <75 μm have disappeared, because they have been immersed in binder droplets, and larger agglomerates have been formed by coalescence. The largest agglomerates are formed with the largest droplet size. Further addition of binder (Fig. 4c), however, gives rise to agglomerate size distributions that are similar for both droplet sizes.

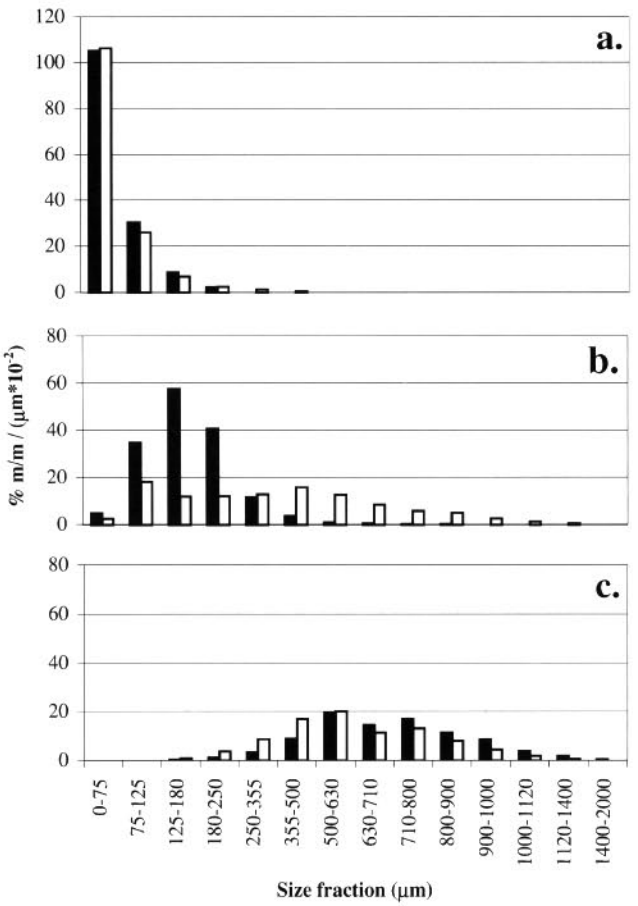

Fig. 4. Effects of droplet size on the size distribution of agglomerates produced with Gelucire 50/13. Product temperature: 5 °C above the melting range. Binder concentration: (a) 5.5% v/m; (b) 16.5% v/m; (c) 27.5% v/m. Droplet size: 40 μm (■); 80 μm (□).

In order to explain the complex effect of droplet size, it is necessary to distinguish between the nucleation phase and the coalescence phase of the process. As long as nucleation is the dominant mechanism, larger droplet size will result in larger agglomerate size since a nucleus is formed from one primary droplet or from a larger droplet that has been formed by coalescence between two or more primary droplets (Schaafsma et al., 2000). This is most clearly seen in Fig. 1a for the PEG at a product temperature below the melting range since the solidification of the PEG prevents coalescence between agglomerates. This is further seen at binder concentrations between 5.5 and 16.5% in Fig. 3b and in Fig. 4b. In Fig. 3a, the same effect of droplet size is seen for the PEG but not for the Gelucire. This might be because the distribution of the highly viscous Gelucire is affected by the droplet size as will be discussed below.

When coalescence between agglomerates becomes the dominant growth mechanism, the role of the binder droplets is to wet the surface of the agglomerates making it possible for liquid bridges to form between agglomerates. In this phase, the agglomerate growth rate, dD/dt, where D is the mean diameter of the agglomerates and t is the time after the end of nucleation, is supposed to be proportional to the number of droplets and consequently to $1/d^3$, where d is the mean droplet size. Further, the agglomerate growth rate is supposed to be proportional to the area, A, being wetted by a single droplet. This leads to a simplified description of the effect of droplet size on the agglomerate growth rate in the phase of random coalescence based upon the assumption that other factors affecting the growth rate are kept constant:

$$dD/dt = k_1 A/d^3 \quad (1)$$

where k_1 is a constant.

If the binder has low viscosity, the droplet will be able to spread over the agglomerate surface, and A will be proportional to d^3. This means that the droplet size will have no effect on the growth rate according to Eq. (1). If a highly viscous binder is applied, the droplet will not spread significantly over the agglomerate surface, and the wetted area will be approximately proportional to the projected area of the droplet and consequently to d^2. Then Eq. (1) becomes:

$$dD/dt = k_2/d \quad (2)$$

where k_2 is a different constant.

This means that the agglomerate growth rate is supposed to be inversely proportional to the droplet size. Accordingly, the smallest droplet size results in the highest growth rate for the highly viscous Gelucire (Fig. 3a). This is further illustrated in Fig. 5 where clear agglomerate growth by coalescence is seen with the smallest droplet size (Fig.

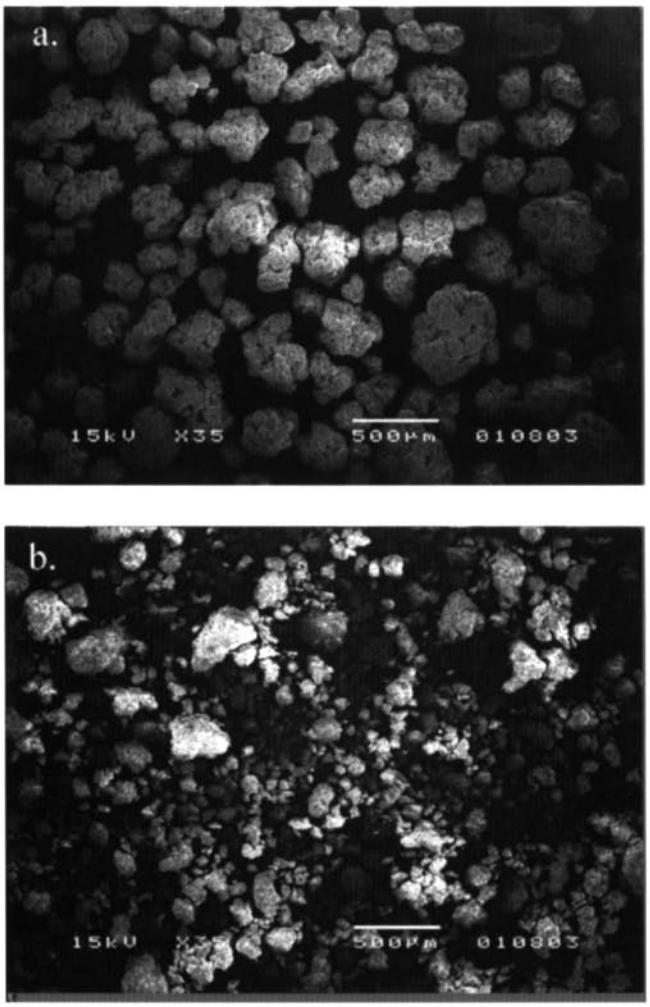

Fig. 5. SEM photographs of agglomerates produced with Gelucire 50/13. Inlet air temperature: 45 °C. Binder concentration: 27.5% v/m. Droplet size: (a) 40 µm; (b) 80 µm.

5a), whereas only limited agglomerate growth by coalescence is seen with the largest droplet size (Fig. 5b).

In Fig. 3b, the agglomerate growth rate between 16.5 and 27.5% of binder is also inversely proportional to the droplet size. This seems to be inconsistent with Eq. (1) according to which the growth rate should be independent of the droplet size at low binder viscosity. However, the agglomerate growth rate will also be dependent on the agglomerate size. Collision between two wetted agglomerates will result in either rebound or coalescence. The probability of successful coalescence is higher for smaller agglomerates, and the coalescence between agglomerates will cease when they have reached a critical size (Tardos et al., 1997). This explains the lowering of the growth rate seen between 16.5 and 27.5% of binder for a droplet size of 80 µm (Fig. 3b). It is most likely that the final agglomerate size becomes approximately the same, because the mean agglomerate size approaches the critical size. Fig. 2 illustrates that although different droplet sizes give rise to final agglomerates of approximately the same size, the agglomerates are formed by coalescence between a larger number of smaller nuclei/agglomerates when the binder droplet size is small (Fig. 2a).

Maintaining the inlet air temperature for 5 min after the end of liquid addition did not result in a clear effect on the agglomerate size (Table 3). This indicates that no binder liquid is squeezed to the agglomerate surface due to densification during prolonged fluidisation. By wet agglomeration in high shear mixers, massing after the end of liquid addition is often seen to increase the agglomerate size, because densification of the agglomerates gives rise to higher liquid saturation. A similar investigation of the effect of the massing time after the end of liquid addition is impossible in aqueous fluidised bed agglomeration since evaporation of binder liquid from the agglomerate surface will impede further agglomerate growth. When the moisture content in a fluidised bed granulator was kept constant by feed back control, no further increase in agglomerate size was seen (Watano et al., 1991). Therefore, an increase in the amount of binder liquid seems to be a general prerequisite of further agglomerate growth in a fluidised bed granulator.

The above-mentioned results indicate the agglomerate formation and growth mechanisms that are shown schematically in Figs. 6 and 7. Fig. 6 illustrates the agglomerate formation and growth in the experiments where the binder viscosity was very high, i.e. the PEG at 5 °C below the melting range and the Gelucire in the middle of the melting range. The mean size of the

Table 3
Effect of maintaining the inlet air temperature for 5 min after the end of liquid addition on d_{gw} and s_g

Binder	Inlet air temp. (°C)	Direct cooling after liquid addition		Maintaining inlet air temp. for 5 min after liquid addition	
		d_{gw} (µm)	s_g	d_{gw} (µm)	s_g
PEG 3000	65	515 (±2)	1.5 (±0.0)	568 (±39)	1.4 (±0.0)
PEG 3000	85	606 (±25)	1.3 (±0.0)	693 (±154)	1.4 (±0.1)
Gelucire 50/13	45	240 (±15)	1.8 (±0.1)	284 (±42)	1.7 (±0.0)
Gelucire 50/13	65	487 (±6)	1.5 (±0.0)	484 (±11)	1.5 (±0.0)

Droplet size: 60 µm.

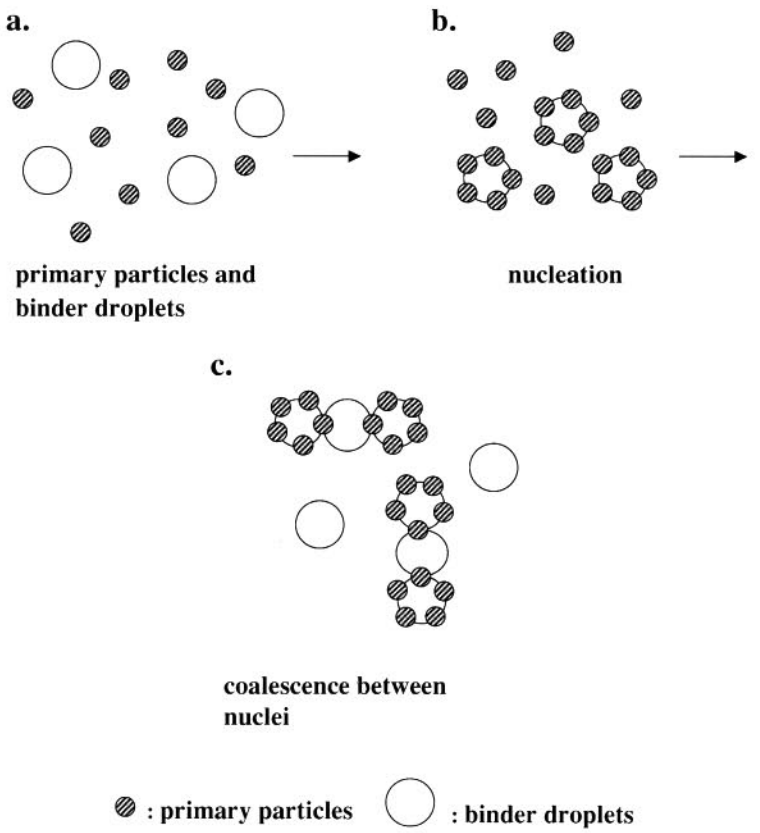

Fig. 6. Agglomerate formation and growth mechanisms in fluidised bed melt agglomeration at high binder viscosity.

atomised droplets (40, 60 or 80 μm) is larger than that of the lactose particles (28 μm) (Fig. 6a). No comminution of the droplets is supposed to occur during the process because of the lack of shear forces. Initially, nuclei are formed by immersion of lactose particles into the binder droplets (Fig. 6b). Smaller droplet size will result in smaller nuclei. Due to the high binder viscosity, no binder liquid becomes drained to the surface. Only a surface layer of lactose particles, therefore, can be immersed. This might lead to nearly complete surface coverage of all the binder droplets by a layer of lactose, which will prevent or limit further growth by coalescence. The result will be a mixture of unagglomerated lactose particles and nuclei with high binder content causing uneven binder distribution in the final agglomerates (Table 2). By further binder addition, more lactose particles will be captured either by immersion into atomised droplets or to re-wetted nuclei. Coalescence between wetted nuclei might occur (Fig. 6c) but this will be difficult or even hindered, because the droplets are highly viscous or solidify. If the droplets solidify, a coating of the nuclei with the binder might occur instead.

Fig. 7 illustrates the agglomerate formation and growth in the experiments where the binder viscosity was low, i.e. the PEG in the middle of the melting range as well as the PEG and the Gelucire at 5 °C above the melting range. The initial nucleation (Fig. 7a and b) is similar to that seen in Fig. 6. When the viscosity is low, however, binder liquid will be drained from the inside of the agglomerate to the surface due to a capillary pressure difference (Schaafsma et al., 1998). This makes it possible for more lactose particles to become immersed in the surface (Fig. 7c). In previous melt agglomeration experiments in a fluidised bed (Abberger, 2001), initial distribution of the binder on the surface of the solid particles was found instead of immersion when the melted binder was sprayed onto the powder bed. This is probably due to the larger particle size of the solid particles applied in these experiments. Pronounced coalescence between nuclei will not occur until the major part of the lactose particles is agglomerated since the potential for agglomerate growth is inversely proportional to the size of the particles/agglomerates (Ennis et al., 1991; Tardos et al., 1997). A presupposition for agglomerate growth by coalescence between nuclei is that the surface of a nucleus becomes wetted by a droplet making it possible to form a liquid bridge between nuclei (Fig. 7d). Continued addition of binder will result in coalescence between agglomerates (Fig. 7e) until overwetting occurs.

When no further binder liquid is added, the surface wetness will be insufficient for further agglomerate growth by coalescence, and the mean agglomerate size will be approximately constant during further processing (Table 3).

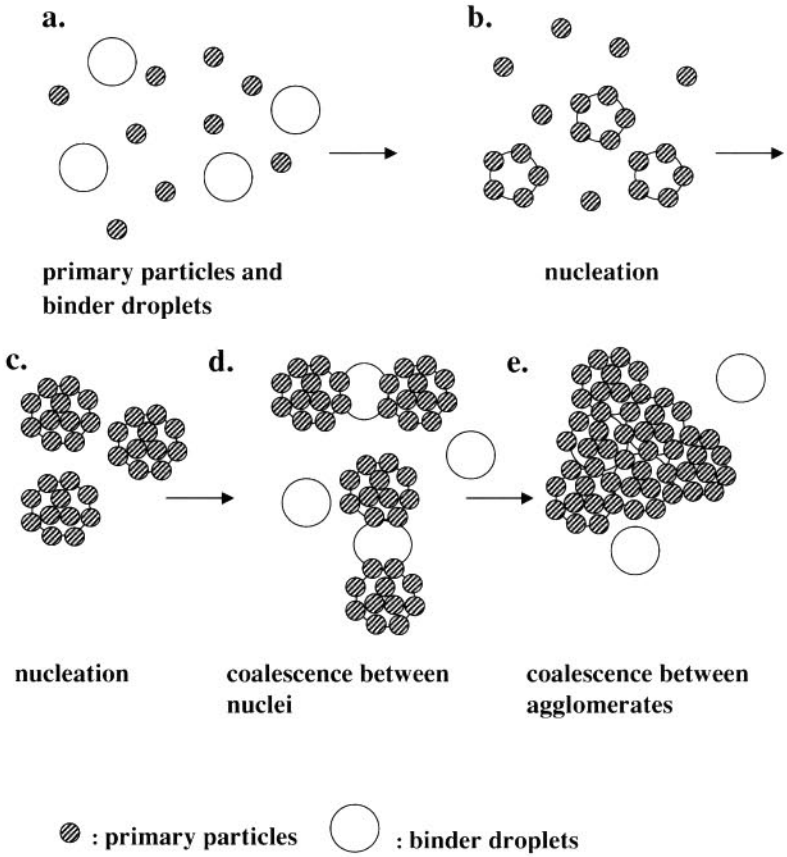

Fig. 7. Agglomerate formation and growth mechanisms in fluidised bed melt agglomeration at low binder viscosity.

4. Conclusions

The present study shows that melt agglomeration by atomization of a melted binder in a fluidised bed occurs by initial nucleation followed by coalescence between nuclei. The nuclei are formed by immersion of the solid particles in the binder droplets provided that the droplet size is larger than the size of the solid particles. Larger droplets will form larger nuclei.

Agglomerate growth by coalescence between nuclei will occur if the surface of the nuclei becomes wetted by continued addition of binder droplets. This coalescence will be counteracted or even hindered if the droplets are highly viscous or solidify due to low inlet air temperature. The agglomerate growth rate is supposed to be practically independent of the droplet size if the binder viscosity is so low that the droplets are able to spread over the agglomerate surface. If the droplets are unable to spread because of high viscosity, the growth rate is supposed to be inversely proportional to the droplet size. These effects of droplet size are different from those seen in fluidised bed agglomeration with aqueous binder liquids, probably because the aqueous process is affected by evaporation of binder liquid.

In contrast to melt agglomeration in a high shear mixer, the agglomerate growth in a melt agglomeration process in a fluidised bed is unaffected by further processing after the end of binder addition since no densification occurs due to the lower shearing forces in the fluidised bed. Because of the low densification in a fluidised bed, a higher content of binder can be incorporated.

References

Abberger, T., 2001. Influence of binder properties, method of addition, powder type and operating conditions on fluid-bed melt granulation and resulting tablet properties. Pharmazie 56, 949–952.

Abberger, T., Henck, J.O., 2000. Kornbildungsmechanismen bei der Schmelzgranulierung in der Wirbelschicht und ihre Auswirkungen auf die Tablettierung. Pharmazie 55, 521–526.

Andreev, B.V., Gorodnichev, V.I., Minina, S.A., El-Banna, H.M., 1980. Granule growth of pharmaceutical powders in a fluidized bed. Pharm. Ind. 42, 1304–1306.

Eliasen, H., Schæfer, T., Kristensen, H.G., 1998. Effects of binder rheology on melt agglomeration in a high shear mixer. Int. J. Pharm. 176, 73–83.

Ennis, B.J., Tardos, G., Pfeffer, R., 1991. A microlevel-based characterization of granulation phenomena. Powder Technol. 65, 257–272.

European Pharmacopoeia, 3rd Edition. Council of Europe, Strasbourg, pp. 141–142.

Holm, P., Schæfer, T., Kristensen, H.G., 1985. Granulation in high-speed mixers. Part V. Power consumption and temperature changes during granulation. Powder Technol. 43, 213–223.

Juslin, L., Yliruusi, J., 1996. Granule growth kinetics and attrition of

granules made of different materials in a fluidized bed granulator. Stp Pharma Sci. 6, 321–327.

Juslin, L., Antikainen, O., Merkku, P., Yliruusi, J., 1995. Droplet size measurement: I. Effect of three independent variables on droplet size distribution and spray angle from a pneumatic nozzle. Int. J. Pharm. 123, 247–256.

Kokubo, H., Nakamura, S., Sunada, H., 1995. Effect of several cellulosic binders on particle size distribution in fluidized bed granulation. Chem. Pharm. Bull. 43, 1402–1406.

Lin, K., Peck, G.E., 1995. Development of agglomerated talc. I. Evaluation of fluidized bed granulation parameters on the physical properties of agglomerated talc. Drug Dev. Ind. Pharm. 21, 447–460.

Schaafsma, S.H., Vonk, P., Segers, P., Kossen, N.W.F., 1998. Description of agglomerate growth. Powder Technol. 97, 183–190.

Schaafsma, S.H., Vonk, P., Kossen, N.W.F., 2000. Fluid bed agglomeration with a narrow droplet size distribution. Int. J. Pharm. 193, 175–187.

Schæfer, T., Mathiesen, C., 1996a. Melt pelletization in a high shear mixer. VII. Effects of product temperature. Int. J. Pharm. 134, 105–117.

Schæfer, T., Mathiesen, C., 1996b. Melt pelletization in a high shear mixer. VIII. Effects of binder viscosity. Int. J. Pharm. 139, 125–138.

Schæfer, T., Mathiesen, C., 1996c. Melt pelletization in a high shear mixer. IX. Effects of binder particle size. Int. J. Pharm. 139, 139–148.

Schæfer, T., Wørts, O., 1978a. Control of fluidized bed granulation. V. Factors affecting granule growth. Arch. Pharm. Chem., Sci. Ed. 6, 69–82.

Schæfer, T., Wørts, O., 1978b. Control of fluidized bed granulation. IV. Effects of binder solution and atomization on granule size and size distribution. Arch. Pharm. Chem., Sci. Ed. 6, 14–25.

Schæfer, T., Holm, P., Kristensen, H.G., 1992. Melt pelletization in a high shear mixer. III. Effects of lactose quality. Acta Pharm. Nord. 4, 245–252.

Schæfer, T., Taagegaard, B., Thomsen, L.J., Kristensen, H.G., 1993. Melt pelletization in a high shear mixer. V. Effects of apparatus variables. Eur. J. Pharm. Sci. 1, 133–141.

Seo, A., Schæfer, T., 2001. Melt agglomeration with polyethylene glycol beads at a low impeller speed in a high shear mixer. Eur. J. Pharm. Biopharm. 52, 315–325.

Sutananta, W., Craig, D.Q.M., Newton, J.M., 1994. The effects of ageing on the thermal behaviour and mechanical properties of pharmaceutical glycerides. Int. J. Pharm. 111, 51–62.

Tardos, G.I., Khan, M.I., Mort, P.R., 1997. Critical parameters and limiting conditions in binder granulation of fine powders. Powder Technol. 94, 245–258.

Wan, L.S.C., Lim, K.S., 1991. Action of binders in the fluidized bed granulation of lactose. Stp Pharma Sci. 1, 248–255.

Wan, L.S.C., Heng, P.W.S., Muhuri, G., 1992. Analysis of growth of granules in a fluidized bed granulator. Stp Pharma Sci. 2, 381–386.

Watano, S., Terashita, K., Miyanami, K., 1991. Determination of endpoint with a complex granulation applying infrared moisture sensor. Chem. Pharm. Bull. 39, 1013–1017.

Watano, S., Yamamoto, A., Miyanami, K., 1994. Effects of operational variables on the properties of granules prepared by moisture control method in tumbling fluidized bed granulation. Chem. Pharm. Bull. 42, 133–137.

Yanze, F.M., Duru, C., Jacob, M., 2000. A process to produce effervescent tablets: fluidized bed dryer melt granulation. Drug Dev. Ind. Pharm. 26, 1167–1176.