Effects of binder rheology on melt agglomeration in a high shear mixer

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Abstract

Lactose monohydrate was melt agglomerated in an 8-l high shear mixer using Gelucire 50/13, Stearate 6000 WL 1644, or polyethylene glycol (PEG) 3000 as meltable binder. The impeller speed was varied at two levels, and massing time was varied at six levels. In order to obtain a similar agglomerate growth, a larger binder volume had to be used with Gelucire 50/13 than with Stearate 6000 WL 1644 and PEG 3000. The lower viscosity of Gelucire 50/13 gave rise to agglomerates of a wider size distribution and a higher porosity as well as more adhesion of mass to the bowl. A lower binder viscosity resulted in more spherical agglomerates at the low impeller speed. © 1998 Published by Elsevier Science B.V. All rights reserved.

Keywords: Binder viscosity; Melt agglomeration; High shear mixer; Adhesion; Porosity; Water of crystallization

1. Introduction

In a wet agglomeration process, the agglomerate growth is affected by the viscosity of the binder liquid. Initially, the agglomerate formation and growth depend on the distribution of the binder, which is facilitated by a low viscosity. The subsequent agglomerate growth by coalescence is promoted by a higher binder viscosity (Ennis et al., 1991; Schæfer and Mathiesen, 1996b). Keningley et al. (1997) found that the minimum binder viscosity required to form granules increased with the particle size of the solid material.

A prerequisite of a formation of agglomerates in a mixer granulator is that the agglomerates are able to resist the impact with the rotating impeller. The strength of the dynamic liquid bridges within an agglomerate is dominated by viscous forces (Mazzone et al., 1987). A lower binder viscosity and a larger particle size will decrease the agglomerate strength (Schæfer and Mathiesen, 1996b; Keningley et al., 1997). When the agglomerate strength is so low that fracture occurs, no agglomerates will be formed, and an adhesion of

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moist mass to the wall of the mixer bowl will be seen instead (Keningley et al., 1997). This means that a lower binder viscosity might augment the adhesion of mass to the wall. It has also been found, however, that the adhesion becomes increased at a very high binder viscosity (Schæfer and Mathiesen, 1996b).

The densification of the agglomerates during mixing is promoted by a lower binder viscosity (Ennis et al., 1991; Schæfer and Mathiesen, 1996b; Iveson, 1997). With low viscosity binders, the densification is primarily affected by frictional forces between the particles within the agglomerate, whereas viscous forces dominate when the viscosity is above 1000 mPa·s (Keningley et al., 1997). The densification increases the liquid saturation of the agglomerates, and more binder liquid is squeezed to the surface at collisions between agglomerates. A lower binder viscosity will cause a higher surface plasticity, which will promote the rounding of the agglomerates (Schæfer and Mathiesen, 1996b).

In previous melt agglomeration experiments, no effect of binder viscosity on the agglomeration properties of eight hydrophobic binders all having viscosities below 50 mPa·s was found (Thomsen et al., 1994), whereas marked effects of binder viscosity were found in experiments with the more hydrophilic polyethylene glycols having viscosities in the range 100–26500 mPa·s (Schæfer and Mathiesen, 1996b). The hydrophilicity of the meltable binder is assumed to affect the wetting of the material and the adhesion of mass to the mixing bowl (Schæfer et al., 1990; Thomsen et al., 1994; Peerboom and Delattre, 1995). It is difficult to distinguish clearly between the effects of viscosity and hydrophilicity on the basis of the previous melt agglomeration experiments since the low viscosity binders examined were hydrophobic, and the high viscosity binders examined were hydrophilic.

The purpose of the present work was to elucidate the effects of viscosity of three hydrophilic meltable binders covering the viscosity range from approximately 30 to 400 mPa·s.

2. Materials and methods

2.1. Materials

Lactose 450 mesh (α-lactose monohydrate, DMV, The Netherlands) was used as starting material.

Polyethylene glycol (PEG) 3000 (Hoechst, Germany), Gelucire 50/13 (esters of polyethylene glycol and glycerol) (Gattefossé, France), and Stearate 6000 WL 1644 (esters of polyethylene glycol) (Gattefossé, France) were used as meltable binders. Gelucire 50/13 has a HLB value of 13, and Stearate 6000 WL 1644 has a HLB value of 18 (Product information, Gattefossé, France). PEG 3000 is indicated to have a HLB value of 20 (Attwood and Florence, 1983). PEG 3000 was used as flakes whilst Gelucire 50/13 and Stearate 6000 WL 1644 were provided as blocks, which were rasped prior to use.

The size distribution by volume of the lactose was determined by a Malvern 2601Lc laser diffraction particle sizer (Malvern Instruments, UK). The median particle diameter and the span were found to be 23 μm and 2.2. 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 by a Gemini 2375 surface area analyzer (Micromeritics, USA), was 0.94 m^2/g.

The true densities of the materials were determined by an AccuPyc 1330 gas displacement pycnometer (Micromeritics) using helium purge. The density of the lactose was 1.545 g/cm^3. The densities of the molten binders were estimated at 70, 80, and 90°C by weighing a known volume of the binder in a volumetric flask with a nominal volume of 50 ml. The exact volume of the volumetric flask at each of the temperatures was determined on the basis of the weight of thermally equilibrated water and the density of the water.

The water contents on a wet weight basis were estimated by volumetric titration as previously described (Schæfer and Mathiesen, 1996a). The water content was found to be 5.0% for the lactose.

The melting ranges of the meltable binders were estimated by a Perkin Elmer DSC 7 differential scanning calorimeter as previously described (Schæfer and Mathiesen, 1996a).

The viscosities of the molten binders were estimated at 70, 80, and 90°C by a rotation viscosimeter, Rotovisco RV 12 (Haake, Germany), with a MV sensor system and MV II K rotor. The viscosity values used are the results obtained at the highest rpm that gave rise to a deflection within the scale. The results did not indicate that the viscosity values were dependent on the rotation speed of the rotor.

The loss modulus and the storage modulus of the molten binders were estimated with a controlled stress rheometer, Carri-Med Rheometer CSL^{2}100 (TA Instruments, Leatherhead, UK). The measurements were performed at 70°C at a frequency of 1 Hz in oscillatory mode using a cone and plate measuring system. The cone was a 6-cm 1° stainless steel cone. A sinusoidal oscillatory shear stress was applied and the strain response was monitored. The data were collected by a computer, and the loss modulus and the storage modulus were calculated by computer software (TA Instruments Rheology Solutions Software CSL V1.1.6) from data within the linear viscoelastic region.

2.2. Equipment

The 8-l laboratory scale high shear mixer (Pellmix PL 1/8, Niro A/S, Denmark), described in a previous paper (Schæfer et al., 1993a), was employed in the experiments. The temperature of the heating jacket was set to 35°C in all the experiments.

2.3. Mixing procedure

The load of the mixer was 1 kg of lactose. The concentration of the meltable binders was kept constant at 23% m/m of the amount of lactose.

In all the experiments, the starting material and the meltable binder were dry mixed at an impeller speed of 1300 rpm. The impeller speed was either lowered to 1000 rpm or raised to 1500 rpm after 3 min of mixing for Gelucire 50/13, after 8 min of mixing for Stearate 6000 WL 1644, and after 10 min of mixing for PEG 3000. These different mixing times correspond to a change in impeller speed when the product temperature was about 1°C below the melting point of the binder. The melting point was observed as an inflection point on the recorded product temperature curve. This inflection point was defined as the start of massing time.

The procedures for cooling of the agglomerates and for estimation of the adhesion to the bowl were the same as described in a previous paper (Schæfer, 1996).

2.4. Granule characterization

2.4.1. Size distribution

The amount of lumps larger than 4 mm was determined as previously described (Schæfer, 1996).

The granule size distribution was estimated by a sieve analysis of a sample of about 100 g drawn by scooping from the cooled fraction finer than 4 mm, and the geometric mean diameter (d_{gw}) and the geometric standard deviation (s_g) were calculated. A series of 12 ASTM standard sieves was vibrated for 10 min by a Fritsch analysette 3 vibrator (Fritsch, Germany). Sieves in the range of 180–2000 μm were used for all the experiments.

Size fractions including the three sieve fractions closest to the mean diameter were prepared by vibrating for 5 min, and these size fractions were applied for the measurements in Sections 2.4.2, 2.4.3 and 2.4.4.

2.4.2. Porosity and liquid saturation

The intragranular porosity, ϵ, was calculated from the equation:

$$\epsilon = \frac{v_g - v_t}{v_g} = 1 - \frac{\rho_g}{\rho_t} \tag{1}$$

where v_g is the volume and ρ_g the density of the granule sample including all intragranular pores and voids, and v_t is the true volume, i.e. the volume exclusive of intragranular pores and voids, and ρ_t the true density of the granule sample. v_g is estimated by a mercury immersion

method (Schæfer et al., 1992a), and ρ_g is calculated from $\rho_g = M/v_g$, where M is the mass of the granule sample. ρ_t is either determined by a gas displacement pycnometer on a ground granule sample or calculated from the mixing ratio and the true densities of the constituents.

In order to estimate the porosity in the agglomeration phase of the process in which the molten binder acts like a liquid, the porosity values are corrected for the volume of solidified binder within the intragranular pores and voids. The corrected intragranular porosity, ϵ_{corr}, is given by:

$$\epsilon_{corr} = \epsilon + \frac{v_{bs}}{v_g} \tag{2}$$

where

$$v_{bs} = \frac{Mw_b}{(1 + w_b)\,\rho_{bs}} \tag{3}$$

and

$$v_g = \frac{v_t}{1 - \epsilon} = \frac{v_s + v_{bs}}{1 - \epsilon} \tag{4}$$

where

$$v_s = \frac{M}{(1 + w_b)\,\rho_s} \tag{5}$$

v_{bs} is the true volume of binder in the solidified granule sample, w_b is the ratio of the mass of binder to the mass of solid particles, ρ_{bs} is the true density of the solid binder, v_s is the true volume of the solid particles, and ρ_s is the true density of the solid particles.

By inserting Eqs. (3) and (5) into Eq. (4) and then Eqs. (3) and (4) into Eq. (2), the latter becomes:

$$\epsilon_{corr} = \epsilon + \frac{1 - \epsilon}{1 + \dfrac{\rho_{bs}}{\rho_s w_b}} \tag{6}$$

The calculation of the corrected porosity is based on the assumption that the total volume of binder is deposited within intragranular pores and voids.

The liquid saturation of the agglomerates is given by:

$$S = \frac{v_{bm}}{\epsilon_{corr} v_g} \tag{7}$$

where

$$v_{bm} = \frac{Mw_b}{(1 + w_b)\rho_{bm}} \tag{8}$$

and

$$v_g = \frac{v_s}{1 - \epsilon_{corr}} \tag{9}$$

and where v_{bm} is the volume of molten binder in the sample and ρ_{bm} the density of the molten binder at the actual product temperature.

By inserting Eq. (5) into Eq. (9) and then Eqs. (8) and (9) into Eq. (7), the latter becomes:

$$S = \frac{(1 - \epsilon_{corr})\,w_b\rho_s}{\epsilon_{corr}\rho_{bm}} \tag{10}$$

The calculation of the liquid saturation is based on the assumption that the packing of the solid particles within the agglomerates is unaffected by the solidification of the molten binder during cooling.

2.4.3. Water content

The water content on a wet weight basis, i.e. the water content corresponding to the loss on drying, was estimated by volumetric titration as previously described (Schæfer and Mathiesen, 1996a).

2.4.4. Image analysis

The agglomerates were placed on an illuminated desk, and measurements were carried out using a video camera (MTI CCD72EX, DAGE-MTI, USA) connected to a 55-mm lens (Micro-Nikkor, Nikon, Japan), video digitiser software (Media Pro + /HiRes v2.01 + , Rombo Productions, Scotland, UK), and image analysis software (Global Lab, Image Version 3.1, Data Translation Inc., USA); 200 agglomerates were used for one analysis.

2.4.5. Scanning electron microscopy

Photographs were taken by a scanning electron microscope (SEM) (Jeol JSM 5200, Japan).

Table 1
Physical properties of the meltable binders

Binder	True density (g/cm^3)	Density of molten binder (g/cm^3)			Water content (%)	Melting range (°C)	Peak temperature (°C)
		70°C	80°C	90°C			
Gelucire 50/13	1.120	0.99	0.98	0.98	0.2	35–44	42
Stearate 6000 WL 1644	1.191	1.06	1.05	1.04	0.2	46–58	55
PEG 3000	1.225	1.08	1.07	1.07	0.2	49–57	55

2.5. Experimental design

A series of 66 factorially designed experiments was carried out using either Gelucire 50/13, Stearate 6000 WL 1644 or PEG 3000 as the meltable binder. For each binder, the massing times were varied at 1, 3, 5, 10, 15, and 20 min at an impeller speed of 1000 rpm and 1, 3, 5, 10, and 15 min at an impeller speed of 1500 rpm. All experiments were carried out in duplicate.

The results shown in this paper are mean values of two experiments unless otherwise stated. The data were analysed by analysis of variance.

3. Results and discussion

3.1. Binder properties

The binder properties are presented in Tables 1 and 2. It appears from Table 2 that Gelucire 50/13 has the lowest viscosity, Stearate WL 1644 the highest viscosity, and PEG 3000 an intermediate viscosity. The loss modulus indicates the dynamic viscous behavior connected with the ability to dissipate the energy associated with irreversible deformation, whereas the storage modulus indicates the amount of energy stored elastically upon deformation (Radebaugh et al., 1989). It is seen from Table 2 that Stearate 6000 WL 1644 has distinct viscoelastic properties since the value of the storage modulus is high and larger than the value of the loss modulus. Gelucire 50/13 and PEG 3000 show no elastic deformation at all. Although Gelucire 50/13 is less hydrophilic than Stearate 6000 WL 1644 and PEG 3000, all three binders are primarily hydrophilic. The comparison of the effects of their rheological properties on agglomeration is assumed, therefore, not to be markedly affected by differences in hydrophilicity.

3.2. Mean granule size and granule size distribution

The appropriate binder concentration was found by trial and error in preliminary experiments. A binder concentration of 23% m/m was chosen independently of the type of binder since this gave rise to a similar agglomerate growth. This indicates that different binder volumes have to be used for different binders in accordance with previous findings (Thomsen et al., 1994) since the corresponding binder concentrations expressed as % v/m are 23.5 for Gelucire 50/13, 21.9 for Stearate 6000 WL 1644, and 21.5 for PEG 3000 at 80°C.

The effects of type of binder and impeller speed on the mean granule size and the granule size distribution are presented in Fig. 1. From 5 min of massing, there is a significant effect ($p < 0.001$) of the impeller speed on mean granule size (Fig. 1a) but no significant effect of the type of binder in accordance with the fact that different binder volumes were chosen in order to obtain a similar agglomerate growth. A higher impeller speed increases the mean granule size because of a higher deformability of the agglomerates at collisions (Adetayo et al., 1993; Schæfer and Mathiesen, 1996a). Further, the deformability is augmented due to a lower viscosity at a higher impeller speed, because a higher impeller speed increases the product temperature (Fig. 2a).

Table 2
Rheological properties of meltable binders

	Gelucire 50/13	Stearate 6000 WL 1644	PEG 3000
Viscosity (mPa·s)			
70°C	49	414	217
80°C	39	316	158
90°C	29	217	118
Loss modulus (Pa)	0.33	46	1.3
Storage modulus (Pa)	0	166	0

The initial agglomerate growth, however, is affected by the type of binder. With Stearate 6000 WL 1644 and PEG 3000, a higher impeller speed results in a larger mean granule size at 1 min of massing, whereas no effect of impeller speed is seen with Gelucire 50/13. This is reflected in a significant interaction ($p < 0.05$). Early in an ag-glomeration process, the risk of comminution of agglomerates will be higher, because agglomerates of a rather loose structure are formed. A comminution is promoted by a higher impeller speed and a lower agglomerate strength. The loose structure combined with the lower binder viscosity of Gelucire 50/13 gives rise to weaker agglomerates. The higher growth rate to be expected at the higher impeller speed is counteracted, therefore, by an increased comminution. Consequently, no effect of impeller speed is seen initially with Gelucire 50/13.

Later in the process, and especially at the high impeller speed, the agglomerate growth becomes more difficult to control. This is reflected in a poor reproducibility of the mean granule size. From 5 to 15 min of massing, the standard deviation estimated by the analysis of variance was found to be 102 μm at the low impeller speed and 210 μm at the high impeller speed. This explains why the differences in agglomerate growth between binders seen in Fig. 1a were not found to be significant. With the PEG 3000, one of the replicates at 20 min of massing at the low impeller speed had to be interrupted owing to formation of large balls caused by an uncontrollable agglomerate growth. This illustrates the poor reproducibility of the process. Consequently, all the results with PEG 3000 at 20 min and 1000 rpm are results of single experiments.

In accordance with previous findings (Schæfer and Mathiesen, 1996b), the initial amount of lumps was found to be relatively high (10–30%), but a marked comminution of lumps occurred by further massing. The effect of the impeller speed on the initial amount of lumps was similar to the
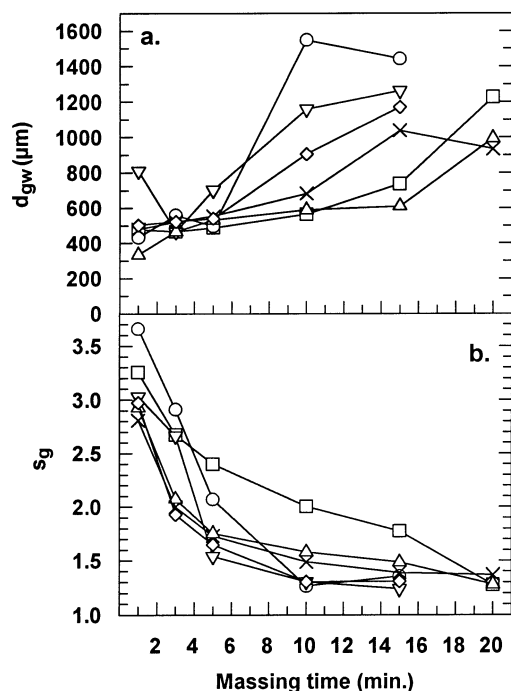

Fig. 1. Effects of type of binder and impeller speed on the mean granule size (a) and the geometric standard deviation (b) during massing. (□) Gelucire 50/13, 1000 rpm; (○) Gelucire 50/13, 1500 rpm; (×) Stearate 6000 WL 1644, 1000 rpm; (▽) Stearate 6000 WL 1644, 1500 rpm; (△) PEG 3000, 1000 rpm; (◇) PEG 3000, 1500 rpm.

effect on the mean granule size since no effect was seen with Gelucire 50/13, whereas a higher impeller speed resulted in more lumps with Stearate WL 1644 and PEG 3000.

As can be seen from Fig. 1b, the granule size distribution becomes significantly narrower ($p < 0.001$) at prolonged massing, because loose lumps are broken down. Gelucire 50/13 gives rise to a significantly wider size distribution ($p < 0.001$) than do the other binders. The lower agglomerate strength makes the agglomerates produced with Gelucire 50/13 more susceptible to comminution. This causes breakdown to occur simultaneously to the formation of agglomerates resulting in a larger variation of the size of the agglomerates. At prolonged massing, the agglomerates gain strength by densification. Consequently, they will be more able to resist the comminution. Therefore, no difference in size distribution between binders is seen from 5 min of massing at the high impeller speed and from 15 min of massing at the low impeller speed. This indicates that the densification occurs more rapidly at a higher impeller speed.

3.3. Porosity and liquid saturation

The product temperature increases during massing because of heat of friction (Fig. 2a), a higher impeller speed giving rise to a significantly higher ($p < 0.001$) product temperature. Previous experiments (Schæfer and Mathiesen, 1996a) have shown that an escape of water of crystallization commences at a product temperature between 80 and 90°C, and that this will delay the agglomerate growth because of a formation of small pores in the surface of the lactose particles. Accordingly, a clear fall in the water content of the agglomerates is seen between 3 and 5 min of massing at the high impeller speed and between 10 and 15 min of massing at the low impeller speed (Fig. 2b). From 10 min of massing, the water content is significantly lower ($p < 0.001$) at the high speed. The evaporation of water of crystallization is seen to be unaffected by the type of binder.

Fig. 3a shows the effects of the type of binder and impeller speed on the corrected intragranular porosity. Normally, a fall in the intragranular porosity will be seen at prolonged massing, because
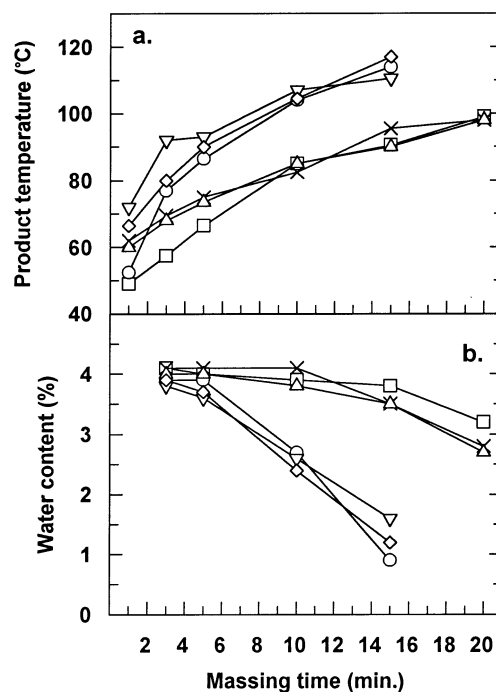

Fig. 2. Effects of type of binder and impeller speed on the product temperature (a) and the water content (b) during massing. (□) Gelucire 50/13, 1000 rpm; (○) Gelucire 50/13, 1500 rpm; (×) Stearate 6000 WL 1644, 1000 rpm; (▽) Stearate 6000 WL 1644, 1500 rpm; (△) PEG 3000, 1000 rpm; (◇) PEG 3000, 1500 rpm.

the agglomerates become densified. This might, however, be counteracted by the pore formation caused by the evaporation of water of crystallization, resulting in an increase in the porosity (Schæfer and Mathiesen, 1996a). In the present experiments, a significant increase ($p < 0.001$) in the porosity is seen at prolonged massing, except for Gelucire 50/13 at the low impeller speed (Fig. 3a). Gelucire 50/13 results in a significantly higher ($p < 0.001$) porosity than do Stearate 6000 WL 1644 and PEG 3000, which have similar porosities. Since a higher binder concentration promotes a densification of agglomerates due to a larger lubrication effect (Schæfer et al., 1990), the higher porosity obtained with Gelucire 50/13 cannot be explained by the larger binder volume used for this binder. Generally, a significantly higher porosity ($p < 0.001$) is obtained at the high impeller speed.
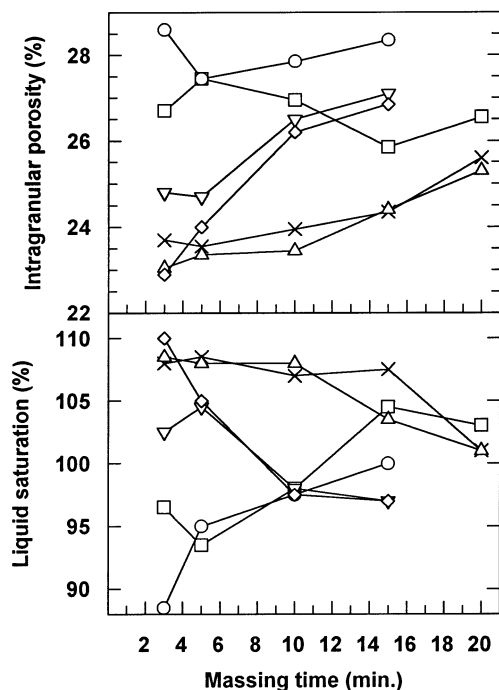
Fig. 3. Effects of type of binder and impeller speed on the corrected intragranular porosity (a) and the liquid saturation (b) during massing. (□) Gelucire 50/13, 1000 rpm; (○) Gelucire 50/13, 1500 rpm; (×) Stearate 6000 WL 1644, 1000 rpm; (▽) Stearate 6000 WL 1644, 1500 rpm; (△) PEG 3000, 1000 rpm; (◇) PEG 3000, 1500 rpm.

Initially, the formation of agglomerates of a loose structure is promoted by a high impeller speed, because it is more likely for comminution to occur simultaneously with the formation of agglomerates at high shear forces. Subsequently, the agglomerates become densified, and a higher impeller speed causes a higher porosity, because more water of crystallization evaporates (Fig. 2b). The pores formed by evaporation of water of crystallization are not assumed to affect the agglomerate strength since the intragranular packing of the particles is unaffected by these small pores in the particle surface. This means that the agglomerates in the present experiments become stronger due to a denser particle packing, although an increasing porosity is observed.

As mentioned above, the agglomerates prepared with Gelucire 50/13 have a lower strength due to the lower viscosity of that binder. The lower strength promotes comminution. A simultaneous comminution and formation of agglomerates delay the densification. Therefore, Gelucire 50/13 gives rise to a higher porosity than the more viscous binders.

Previous melt agglomeration experiments in high shear mixers (Schæfer et al., 1992b, 1993b; Knight, 1993) have shown that the liquid saturation of the agglomerates has to be about 100% in order to obtain a marked agglomerate growth by coalescence. As can be seen in Fig. 3b, the differences in the intragranular porosity are reflected in the liquid saturation, a higher porosity giving rise to a lower liquid saturation. At the high impeller speed, a higher porosity was obtained. Consequently, a higher impeller speed gives rise to a lower liquid saturation. The fall in the liquid saturation that has to be expected at an increasing porosity is partly counteracted by a thermal expansion of the binder liquid caused by the increasing product temperature.

Fig. 4 illustrates that the surface of the agglomerates becomes smoother at the high impeller speed. At 1000 rpm, lactose particles can be identified. This indicates that more binder liquid is squeezed to the surface at the high impeller speed in spite of the lower value of the liquid saturation. This documents that the higher porosity and the lower liquid saturation found at the high speed are not due to less densification, but are caused by the above-mentioned formation of small pores in the surface.

The higher porosity caused by Gelucire 50/13 gives rise to a lower liquid saturation initially in the process only. This is because different % v/m of the binders are used. Since the liquid saturation has to be similar in order to obtain a similar agglomerate growth with different binders, the higher porosity caused by Gelucire 50/13 had to be compensated for by using a larger volume of binder.

3.4. Adhesion

It appears from Fig. 5 that Gelucire 50/13 gives rise to a significantly larger ($p < 0.001$) adhesion of mass to the bowl than do Stearate 6000 WL 1644 and PEG 3000. The lower viscosity of Gelu-

cire 50/13 makes the agglomerates more deformable when hitting the wall. This will cause an increased contact area between agglomerate and wall resulting in more adhesion. The agglomerates are deformed to a larger extent at a higher impeller speed, and a higher speed, therefore, gives rise to a larger adhesion in the case of Gelucire 50/13. The higher viscosity of Stearate 6000 WL 1644 and PEG 3000 makes the agglomerates less deformable. Consequently, these binders give rise to an adhesion that is rather low and independent of the impeller speed.
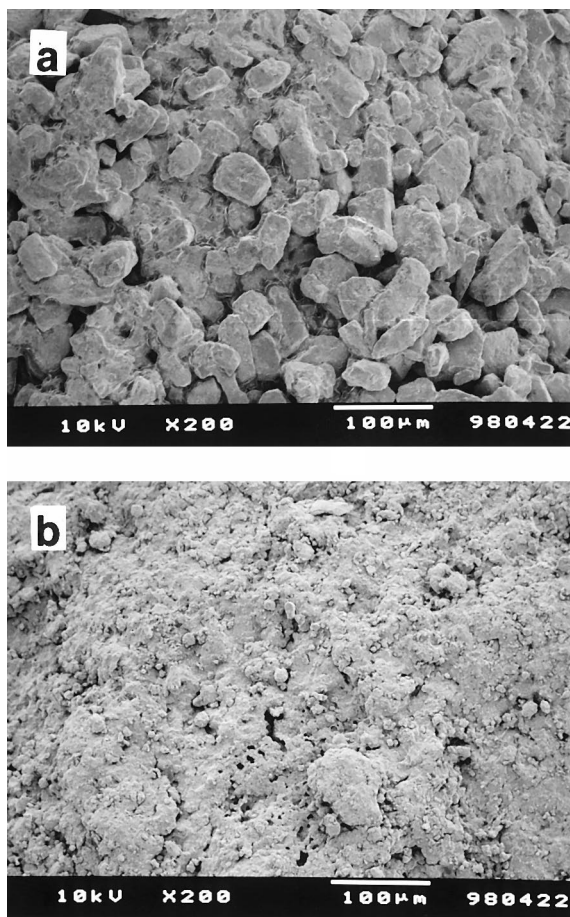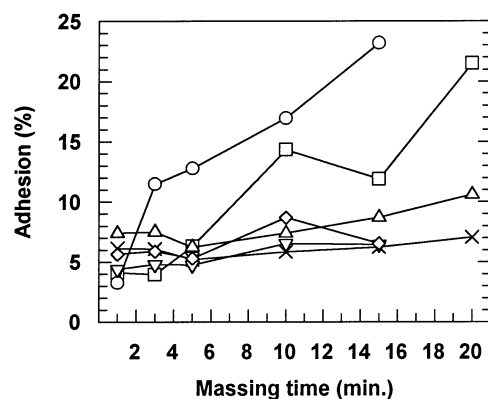

Fig. 5. Effects of type of binder and impeller speed on the amount of adhesion to the bowl during massing. (□) Gelucire 50/13, 1000 rpm; (○) Gelucire 50/13, 1500 rpm; (×) Stearate 6000 WL 1644, 1000 rpm; (▽) Stearate 6000 WL 1644, 1500 rpm; (△) PEG 3000, 1000 rpm; (◇) PEG 3000, 1500 rpm.

3.5. Agglomerate shape

The shape of the agglomerates is expressed as the aspect ratio, which is the ratio of length to width (Fig. 6). The type of binder, the impeller speed, and the massing time were found to have significant effect ($p < 0.001$) on the aspect ratio. A longer massing time and a higher impeller speed result in more spherical agglomerates. A significant interaction ($p < 0.001$) between the type of binder and the impeller speed was found, because

Fig. 4. SEM photographs of agglomerates produced with Gelucire 50/13 at 1000 rpm (a) and 1500 rpm (b). Massing time: 15 min.
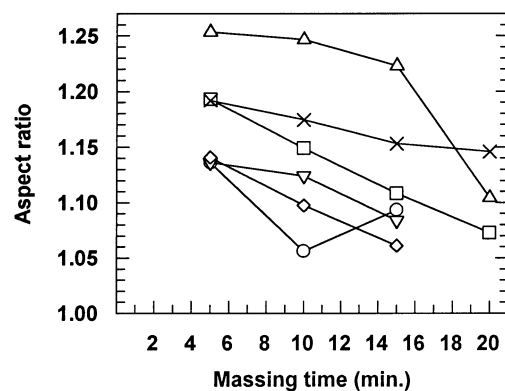

Fig. 6. Effects of type of binder and impeller speed on the aspect ratio. (□) Gelucire 50/13, 1000 rpm; (○) Gelucire 50/13, 1500 rpm; (×) Stearate 6000 WL 1644, 1000 rpm; (▽) Stearate 6000 WL 1644, 1500 rpm; (△) PEG 3000, 1000 rpm; (◇) PEG 3000, 1500 rpm.

the effect of the type of binder is significant only at the low impeller speed. At low speed, the most spherical agglomerates are formed with Gelucire 50/13. This is because a lower binder viscosity causes a higher surface plasticity of the agglomerates making the rounding of the agglomerates easier, even at liquid saturations being lower than those of the other binders. Since a higher impeller speed promotes the rounding, the effect of the binder viscosity on the rounding disappears at the high level of impeller speed.

The effect of binder viscosity on the surface plasticity cannot explain why Stearate 6000 WL 1644 at the low impeller speed gives rise to more spherical agglomerates than does PEG 3000, although Stearate 6000 WL 1644 has the highest viscosity. The viscoelastic properties of the Stearate 6000 WL 1644 might explain these findings. A formation of spherical agglomerates is likely to be a result of shear forces generated because of the sliding of the agglomerates across each other. This rounding of the agglomerates will be counteracted by a flattening of the agglomerates caused by direct impacts between the agglomerates, between the agglomerates and the rotating impeller, and between the agglomerates and the wall of the bowl. Agglomerates prepared with Stearate 6000 WL 1644 might become less flattened at direct impacts, because the binder liquid is able to deform elastically, and because the higher binder viscosity makes the agglomerates less deformable. Thus, agglomerates prepared with Stearate 6000 WL 1644 might become more spherical, because they are more able to withstand the flattening at direct impacts.

The formation of spherical agglomerates is assumed to be a result of complex interactions between flattening and rounding. This might explain why PEG 3000 gives rise to more spherical agglomerates than Stearate 6000 WL 1644 at 20 min of massing, where the effect of surface plasticity on the rounding might be more important, because the agglomerates have become more densified.

4. Conclusions

In a high shear mixer, agglomeration is a result of the balance between coalescence of agglomerates and breakdown of agglomerates. A lower binder viscosity will decrease the agglomerate strength and thus promote a comminution of the agglomerates. The present experiments indicate that the agglomerate growth becomes clearly influenced by comminution at a binder viscosity being below approximately 50 mPa·s, but this viscosity limit will depend on other variables such as the impeller speed and the particle size of the solid.

The agglomerate properties might be affected by a low binder viscosity, because a formation of agglomerates simultaneous to a breakdown of agglomerates will result in porous agglomerates of a rather wide size distribution. The higher intragranular porosity caused by a low binder viscosity might increase the required amount of binder liquid in order to obtain a liquid saturation that is sufficiently high for agglomerate growth by coalescence. The densification of the agglomerates will become delayed if a marked comminution occurs, but a densification will gradually increase the agglomerate strength and might finally make the agglomerates able to resist the comminution.

A low binder viscosity seems to cause an increased adhesion of mass to the bowl due to a higher deformability of the mass. More studies of factors influencing the adhesion might be useful, however, since the adhesion is also supposed to be influenced by electrostatic charging and by the affinity of the binder to the bowl.

A lower binder viscosity gives rise to a higher surface plasticity of the agglomerates and consequently to more spherical agglomerates. The present results indicate that a binder having viscoelastic properties might improve the rounding of the agglomerates, but there is a need for further investigations in order to clarify if viscoelasticity plays an important role in agglomerate growth.

References

Adetayo, A.A., Litster, J.D., Desai, M., 1993. The effect of process parameters on drum granulation of fertilizers with broad size distributions. Chem. Eng. Sci. 48, 3951–3961.

Attwood, D., Florence, A.T., 1983. Surfactant Systems. Their Chemistry, Pharmacy and Biology, Chapman and Hall, London, p. 472.

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

Iveson, S.M., 1997. Fundamentals of granule consolidation and deformation. PhD thesis, University of Queensland, Australia.

Keningley, S.T., Knight, P.C., Marson, A.D., 1997. An investigation into the effects of binder viscosity on the agglomeration behaviour. Powder Technol. 91, 95–103.

Knight, P.C., 1993. An investigation of the kinetics of granulation using a high shear mixer. Powder Technol. 77, 159–169.

Mazzone, D.N., Tardos, G.I., Pfeffer, R., 1987. The behavior of liquid bridges between two relatively moving particles. Powder Technol. 51, 71–83.

Peerboom, C., Delattre, L., 1995. Influence of the nature of the excipients on the feasibility and the release characteristics of granules made by a thermoplastic pelletization method. Proc. 1st World Meet. Pharm. Biopharm. Pharm. Technol., Budapest, pp. 361–362.

Radebaugh, G.W., Babu, S.R., Bondi, J.N., 1989. Characterization of the viscoelastic properties of compacted pharmaceutical powders by a novel nondestructive technique. Int. J. Pharm. 57, 95–105.

Schæfer, T., 1996. Melt pelletization in a high shear mixer. VI. Agglomeration of a cohesive powder. Int. J. Pharm. 132, 221–230.

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., Holm, P., Kristensen, H.G., 1990. Melt granulation in a laboratory scale high shear mixer. Drug Dev. Ind. Pharm. 16, 1249–1277.

Schæfer, T., Holm, P., Kristensen, H.G., 1992a. Melt pelletization in a high shear mixer. I. Effects of process variables and binder. Acta Pharm. Nord. 4, 133–140.

Schæfer, T., Holm, P., Kristensen, H.G., 1992b. Melt pelletization in a high shear mixer. II. Power consumption and granule growth. Acta Pharm. Nord. 4, 141–148.

Schæfer, T., Taagegaard, B., Thomsen, L.J., Kristensen, H.G., 1993a. Melt pelletization in a high shear mixer. IV. Effects of process variables in a laboratory scale mixer. Eur. J. Pharm. Sci. 1, 125–131.

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

Thomsen, L.J., Schaefer, T., Kristensen, H.G., 1994. Prolonged release matrix pellets prepared by melt pelletization. II. Hydrophobic substances as meltable binders. Drug Dev. Ind. Pharm. 20, 1179–1197.