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Research paper

Melt agglomeration with polyethylene glycol beads at a low impeller speed in a high shear mixer

Anette Seo, Torben Schæfer*

Department of Pharmaceutics, The Royal Danish School of Pharmacy, Copenhagen, Denmark

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Abstract

This study was performed in order to evaluate the possibility of obtaining spherical agglomerates with a high content of meltable binder by a melt agglomeration process in a high shear mixer. Lactose monohydrate was melt agglomerated with polyethylene glycol (PEG) 1500 or 6000 in a 10-l high shear mixer at an impeller speed of 400 rpm. The PEG 1500 was used as a size fraction of beads, and the PEG 6000 as a fine powder, a powder, unfractionated beads, and size fractions of beads. It was found to be possible to incorporate a high amount of PEG (28% m/m of the amount of lactose), because the rather low impeller speed applied in the present experiments caused less densification of the agglomerates. The fine powder of the PEG 6000 caused a complete adhesion of the mass to the bowl shortly after melting. A rapid agglomerate growth by coalescence was found to be the dominant growth mechanism when agglomeration was performed with the PEG 6000 powder. The PEG beads resulted in a slow and more controllable agglomerate growth, because the growth occurred primarily by an immersion of the lactose particles in the surface of the molten binder droplets. The initial shape of the agglomerates produced with the PEG beads was similar to the spherical shape of the beads. This shape could not be maintained during the process due to a breakage of the agglomerates caused by a hollow structure of the PEG beads. © 2001 Elsevier Science B.V. All rights reserved.

Keywords: Melt agglomeration; High shear mixer; Binder particle size; Polyethylene glycols; Agglomerate growth mechanisms

1. Introduction

Melt agglomeration is a one-step procedure whereby agglomeration is achieved by using a meltable binder. The binder that is solid at room temperature can be added in a solid or molten state. The final product will either be granules, which are irregular agglomerates of a wide size distribution, or pellets, which are spherical agglomerates of a narrow size distribution. Pellets might be favourable in the production of multiple unit dosage forms.

Melt agglomeration can be applied for a production of agglomerates containing a solid dispersion [1–3] or for a production of sustained release products [4–6]. In both applications, a high binder content might be favourable. In the case of solid dispersions, a high binder content might be necessary to ensure incorporation of an adequate drug content. In sustained release products, a high binder content makes it easier to obtain a complete embedding of the drug substance in a matrix of a hydrophobic meltable binder [5].

Previous melt agglomeration studies in high shear mixers have shown that the liquid saturation of the agglomerates should be approximately 100% to get a significant agglomerate growth which is a prerequisite for obtaining pellets [7,8]. A higher liquid saturation is obtained with a higher binder content as well as a lower intragranular porosity. This means that in order to incorporate a high binder content without getting overwetted agglomerates, the porosity should be kept as high as possible. In a high shear mixer, a lower impeller speed has been found to make the addition of a higher content of meltable binder possible [9,10], probably because a lower impeller speed caused a higher porosity [11,12]. However, the formation of pellets at a low impeller speed will be difficult since spheronization [11,13] and a narrowing of the agglomerate size distribution [2,11] are promoted by a high impeller speed.

An alternative method for increasing the binder content is to initiate the agglomeration by the immersion mechanism, which means that agglomerates are formed by an immersion of solid particles in the surface of the molten droplets. Normally, agglomeration in a high shear mixer occurs by the distribution mechanism, i.e., a distribution of the binder liquid on the surface of the solid particles and a subsequent coalescence between the wetted particles. The immersion

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* Corresponding author. The Royal Danish School of Pharmacy, Department of Pharmaceutics, 2 Universitetsparken, Copenhagen, DK-2100 Denmark. Tel.: +45-35-30-60-00; fax: +45-35-30-60-31.

E-mail address: ts@dfh.dk (T. Schæfer).

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mechanism will be favoured by applying binder particles that are large compared to the solid particles combined with a low impeller speed and/or a high binder viscosity [14]. By maintaining the product temperature within or slightly below the melting range of the binder, the binder will become softened, but no complete melting will occur. This results in a very high binder viscosity, and consequently the agglomerate formation will be controlled by the immersion mechanism. By this method, it has been possible to incorporate a binder content between 18.75 and 50% in a melt agglomeration process in a high shear mixer [15].

A high binder viscosity, however, will make a spheronization of the agglomerates more difficult since their surface plasticity becomes decreased [16]. The agglomerate shape will depend on the shape of the solid binder particles when the agglomerates are formed by immersion [14]. This indicates that it should be possible to obtain spherical agglomerates provided that the binder particles are spherical, and the agglomeration takes place primarily by immersion.

The polyethylene glycols (PEGs) are suitable in order to achieve melt agglomeration by the immersion mechanism because of their high viscosity compared to other meltable binders [4]. Some of the PEGs are available as solid beads, but the use of PEG beads for melt agglomeration in high shear mixers has so far not been investigated. Previous melt agglomeration studies concerning the immersion and distribution mechanisms have been performed at a high impeller speed causing a high product temperature [14]. There is a need, therefore, for investigations to elucidate the agglomeration mechanisms, e.g., the balance between the distribution and the immersion mechanism, at a low impeller speed and a product temperature close to the melting range of the binder.

The present work is based on the hypothesis that spherical agglomerates with a high content of meltable binder are obtainable in a high shear mixer by combining an addition of spherical binder particles with the application of a low impeller speed. The purpose of this study is to test this hypothesis by carrying out melt agglomeration experiments with PEG beads of different sizes, and to investigate the mechanisms of agglomerate formation and growth at these process conditions.

2. Materials and methods

2.1. Materials

Lactose, 450 mesh (α-lactose monohydrate, DMV, Veghel, The Netherlands) was used as starting material. Polyethylene glycol (PEG) 1500 or 6000 was used as meltable binder. PEG 1500 (BASF, Ludwigshafen, Germany) was used as beads, and PEG 6000 was used as a fine powder (Clariant, Burgkirchen, Germany),or as a powder (Clariant) or as beads (BASF).

The size distributions by volume of the lactose, the PEG 6000 powder and fine powder were determined by a Malvern Mastersizer S laser diffraction particle sizer (Malvern Instruments, Worcs, UK). The results presented here are mean values of three estimations. The median particle diameter and the span for the lactose were found to be 19 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 particle size distributions of the PEG beads were determined by sieve analysis with a series of 14 ASTM standard sieves (Retsch, Haan, Germany) in the range 75–2000 μm.

A sample of about 100 g, obtained by an automatic rotary cone sample divider (Laborette 27 with a Laborette 24 vibratory feeder, Fritsch, Idar-Oberstein, Germany), was sieved 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, Idar-Oberstein, Germany). The values of the median diameter and the span are mean values of two estimations.

The BET multipoint surface area of the lactose, determined by a Gemini 2375 Surface Area Analyzer (Micromeritics, Norcross, USA), was 0.88 m^2/g estimated as the mean value of two determinations.

The true densities of the lactose and the solid PEGs were determined by an AccuPyc 1330 gas displacement pycnometer (Micromeritics, Norcross, USA) using helium purge. The density values are the mean values of two determinations. Before the measurement, the PEG beads were milled in a coffee mill (Braun AG 4041, Braun, Barcelona, Spain) in 3 s followed by 3 s pause. The procedure was repeated until the beads were milled for 60 s in total. The density of the lactose was 1.558 g/cm^3.

The poured and the tapped densities of the lactose were determined as mean values of two determinations according to the test for apparent volume [17] and found to be 0.46 and 0.62 g/ml, respectively.

The densities of the molten PEGs were estimated at 44 and 54°C for the PEG 1500 and at 58 and 68°C for the PEG 6000 as previously described [18]. The density values presented here are mean values of three estimations.

The water contents on a wet-weight basis of the PEGs were estimated as the mean values of three determinations by volumetric titration as previously described [19]. A sample of about 1.5 g was used for the measurements. Before the titration, the sample was milled as described above.

The melting range and the peak temperature of the PEGs were estimated by a Perkin Elmer DSC 7 differential scanning calorimeter (Perkin Elmer, Norwalk, USA). A sample of about 4 mg was sealed in a 40-μl aluminium pan and scanned between 20 and 80°C (PEG 1500) or between 40 and 80°C (PEG 6000) at a heating rate of 2°C per min. The results are mean values of three determinations.

The viscosities of the molten PEGs were estimated as the mean values of two estimations at 44 and 54°C for PEG

1500 and at 58 and 68°C for PEG 6000 by a rotation viscosimeter, Rotovisco RV 12 (Haake, Karlsruhe, Germany), as previously described [16].

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

2.2. Equipment

A water-jacketed 10-l high shear mixer (PMA1 Pellet Processor, Aeromatic-Fielder, Hampshire, UK) equipped with a two-bladed impeller was used in the experiments. The tips of the impeller blades were curved. The bowl was lined with polytetrafluoroethylene (PTFE) in order to reduce the adhesion of material to the bowl. A refrigerated circulator (DC50-K41, Haake, Karlsruhe, Germany) was used for heating and cooling of the mixing bowl. During the process, the power consumption of the impeller motor, the impeller speed, the product temperature, and the circulator temperature were recorded.

2.3. Granulation procedure

The jacket of the bowl was preheated to 70°C not less than 30 min before an experiment was performed. The load of the mixer was 1250 g of lactose in all the experiments. The PEG concentration was kept constant at 28% m/m of the amount of lactose, i.e. a liquid to solid mass ratio of 0.28. An impeller speed of 400 rpm was used in all experiments. The lactose and the PEG were dry mixed and heated until the melting of the PEG was observed as an inflection point in the power consumption of the impeller motor. This inflection point was defined as the start of massing time. At that time, the temperature of the circulator was decreased to 50°C. After predetermined massing times, the process was stopped and a sample of approximately 60 g was withdrawn with a beaker. The process was started again immediately after the sample was taken. After either 10 or 20 min of massing, the process was finally stopped.

The samples as well as the final agglomerates were spread out in thin layers on trays allowing them to cool at ambient temperature. The adhesion of mass to the bowl was estimated as the difference between the amount of materials added to the bowl and the amount freely emptied.

2.4. Agglomerate characterization

2.4.1. Size distribution

The amount of agglomerates larger than 4 mm in the final product was determined as the retained fraction after sieving the agglomerates through a 4-mm ASTM standard sieve.

The agglomerate size distribution was determined by sieve analysis. The samples taken during the process were sieved without pre-treatment. The final product was divided with the rotary cone sample divider in order to obtain representative samples of approximately 70 g. A series of 12 ASTM standard sieves in the range 180–2000 μm was vibrated for 10 min at low vibration level.

Size fractions to be used for the measurements in Sections 2.4.2, 2.4.3, 2.4.5, and 2.4.6 were prepared by vibration at low vibration level for 5 min. The size fraction 500–4000 μm was collected when the mass median diameter was ≥1000 μm, whereas the size fraction 250–2000 μm was collected for a mass median diameter <1000 μm.

2.4.2. Density

The agglomerates were milled in a coffee mill as described above. The true densities of the milled agglomerates were determined by an AccuPyc 1330 gas displacement pycnometer using helium purge.

2.4.3. Intragranular porosity

The intragranular porosity was estimated by a mercury immersion method similar to that described by Strickland et al. [20]. A sample of 2–3 g was placed in a glass pycnometer with an approximate volume of 30 ml having a calibrated scale. By applying vacuum, the pycnometer was filled with mercury. The apparent volume of the sample was estimated by displacement of mercury after increasing the intrusion pressure to 98.7 kPa (740 mm Hg). At this intrusion pressure, mercury will penetrate into pores greater than approximately 20 μm in diameter. The corrected porosity and the liquid saturation were calculated as previously described [18]. The porosity results presented here are mean values of two estimations.

The true densities of the agglomerate size fractions used in the calculations of the porosity were calculated from the nominal PEG concentration for the samples drawn after 10, 15, and 20 min (PEG beads) or 5, 7, and 10 min (PEG powder). For the samples drawn earlier in the process (cf. Section 2.5), the true densities estimated as described in Section 2.4.2 were used instead. This was done, because the size fractions used for the porosity measurements of the samples drawn early in the process were found to contain a PEG concentration that was higher than the nominal one. The reason for this was that a large amount of fines having a rather low PEG concentration were removed when preparing the size fractions.

2.4.4. Binder distribution in size fractions

The content of PEG in different size fractions was estimated indirectly on the basis of the true density of the ground size fractions as previously described [14].

2.4.5. Water content

In the size fraction of the final product, the water content on a wet-weight basis was estimated as the mean value of two estimations by a volumetric titration as previously described [19]. A sample of about 0.5 g was used for the measurements.

2.4.6. Scanning electron microscopy

Photographs were taken by the scanning electron microscope (SEM) mentioned above.

Table 1
Physical data of the PEGs

Type of PEG	Water content	True density (solid)	Density (molten)				Melting point		Viscosity				Median diameter	Span
	%	g/cm^3	44°C g/ml	54°C g/ml	58°C g/ml	68°C g/ml	Range °C	Peak temp. °C	44°C mPa·s	54°C mPa·s	58°C mPa·s	68°C mPa·s	µm	
1500 beads	1.0	1.215	1.106	1.098			26–45	44	171	118			276	1.1
6000 beads	0.4	1.209			1.092	1.085	51–60	58			1299	975	475	1.4
6000 powder	0.4	1.233			1.093	1.086	48–60	58			1298	954	244	2.1
6000 fine powder	0.4	1.243			1.093	1.086	47–61	58			1247	908	55	2.5

2.5. Experimental design

A series of five repeated experiments, i.e. a total of 10 experiments, was carried out in which the particle size and the type of PEG were varied. PEG 6000 was used as powder, unfractionated beads, and size fractions (500–630 μm and 710–800 μm) of beads. PEG 1500 was used as a size fraction of beads (500–630 μm). In the experiments with PEG beads, samples were taken out after 1, 5, 10, and 15 min of massing, and the process was finally stopped after 20 min. In the experiments with PEG powder, samples were taken after 1, 3, 5, and 7 min of massing, and the process was finally stopped after 10 min. The results shown in this paper are mean values of the repeated experiments. The error bars in the figures represent the range, i.e. the difference between the results.

3. Results and discussion

3.1. PEG properties

The physical properties of the PEGs are presented in Table 1 and Figs. 1 and 2. The temperatures for the determination of viscosity and density of the molten binder were chosen at the melting peak and 10°C above the melting peak. The beads are seen to be smooth and spherical although some of the beads look like being formed by coalescence between beads (Figs. 1 and 2a). Fig. 2b shows that the PEG 6000 beads have a hollow structure. The same observation was made for the PEG 1500 beads. SEM photographs of the PEG 6000 powder particles showed irregular particles with a markedly wider size distribution compared with the beads. The wider size distribution of the powder is confirmed by a larger span value (Table 1). The largest particles of the powder were seen to be of a size similar to that of the PEG 1500 beads.

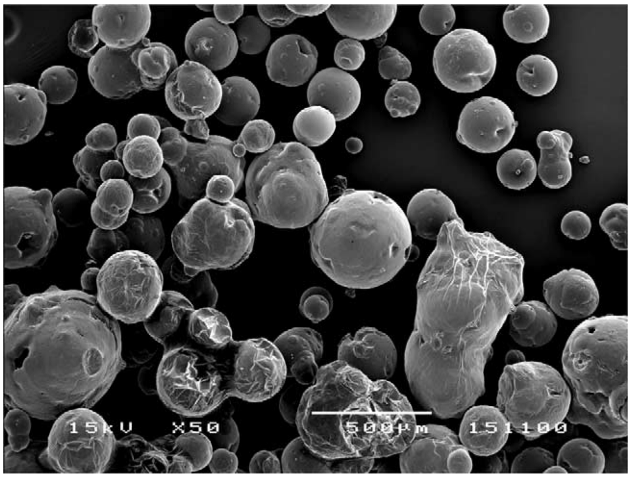

Fig. 1. SEM photograph of unfractionated PEG 1500 beads.

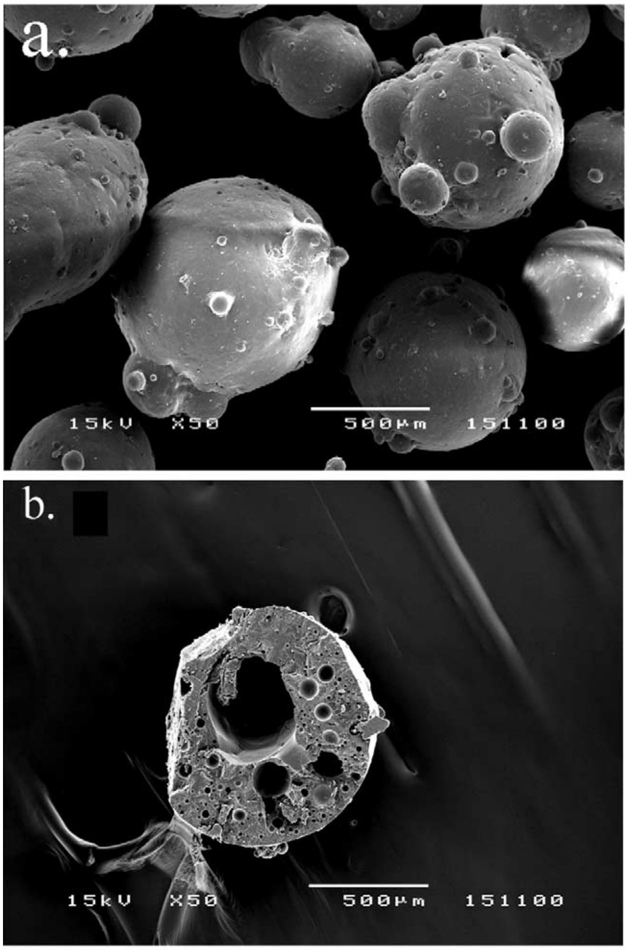

Fig. 2. SEM photographs of PEG 6000 beads, unfractionated (a) and cross section (b).

3.2. Preliminary experiments

The impeller speed could be varied continuously within the range of 300–1500 rpm. The intention was to use the lowest possible impeller speed in order to minimize the energy input during the process. An impeller speed of 300 rpm, however, did not ensure an appropriate movement of the mass. Therefore, 400 rpm were chosen for the present study.

Preliminary experiments confirmed that the agglomerate growth was not significantly influenced by the sampling during the process.

The PEG concentration was chosen as the highest possible. A concentration of 28% was chosen since 29% resulted in overwetting.

The PEG fine powder had to be excluded from the final series of experiments since it resulted in a total adhesion of the mass to the wall of the bowl shortly after melting of the PEG. In previous melt agglomeration experiments, a PEG fine powder has been applied without adhesion problems [14,21], probably because of a combination of a higher impeller speed and a lower PEG concentration.

3.3. Agglomerate size

Fig. 3 shows that the PEG powder gives rise to a markedly higher agglomerate growth rate than the PEG beads indicating different agglomerate growth mechanisms, as will be discussed in Section 3.5. The process had to be stopped after 10 min of massing with the PEG powder, because further massing caused an overwetting. This disagrees with results on the effects of the binder particle size reported from previous melt agglomeration experiments in which the size of the PEG particles had only a slight effect on the agglomerate size [14]. This disagreement can be explained by the markedly higher impeller speed (1500 rpm) that was used in the previous experiments. In other experiments at an impeller speed of 1150 rpm, a fine powder of PEG 6000 caused a markedly larger agglomerate size than a coarse powder and flakes, especially at a high binder content [21]. In melt agglomeration experiments at an impeller speed of 300 rpm, comparing flakes, a powder, and a fine powder of PEG 6000, a larger binder particle size resulted in a larger agglomerate size [10], i.e. an effect of binder particle size that is different from that seen in Fig. 3.

Further, the unfractionated beads are seen to result in a larger agglomerate size than the fractionated beads. The fractionated PEG 1500 beads give rise to larger agglomerates than the PEG 6000 beads of the same size fraction. The larger size fraction of the PEG 6000 beads causes only a slightly larger agglomerate size than the smaller one, and the final agglomerate size is smaller than the size of the initial beads. The smallest variation in agglomerate size between repeated experiments is obtained with the fractionated beads.

Table 2 shows that the PEG 6000 powder causes a larger adhesion than the beads. The reason for the total adhesion of the mass with the PEG fine powder might be that the particle size is closer to the particle size of the lactose. This will promote the distribution of molten PEG on the surface of lactose particles, and the wetted particles will adhere to the bowl. With a larger binder particle size, the surface wetness becomes reduced, because lactose particles are immersed in the surface of the molten binder particles, as will be further discussed in Section 3.5. This explains why the lowest adhesion is seen with the beads.

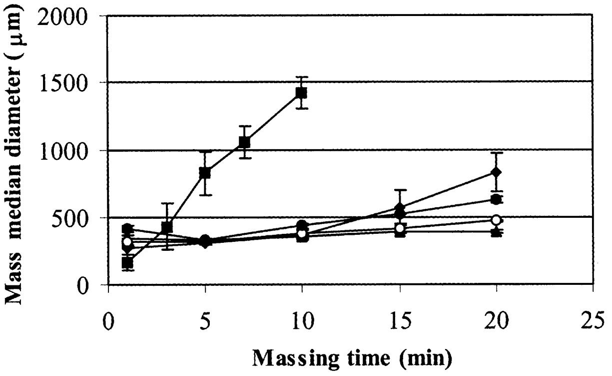

Fig. 3. Effects of type and particle size of the PEG on the agglomerate size. (●) PEG 1500 beads, 500–630 μm; (◆) PEG 6000 beads, unfractionated; (▲) PEG 6000 beads, 500–630 μm; (○) PEG 6000 beads, 710–800 μm; (■) PEG 6000 powder.

Table 2

Effects of type and particle size of the PEG on the amount of adhesion to the bowl and the content of agglomerates >4 mm at the end of the process[a]

PEG	Adhesion (%)	Agglomerates >4 mm (%)
1500 beads, 500–630 μm	6.0 (±0.0)	3.4 (±0.3)
6000 beads, unfractionated	7.5 (±0.5)	2.7 (±1.1)
6000 beads, 500–630 μm	8.5 (±1.5)	0.4 (±0.0)
6000 beads, 710–800 μm	6.5 (±1.5)	0.5 (±0.2)
6000 powder	18.0 (±0.0)	8.4 (±4.5)

[a] The range of two repeated experiments is given in parentheses.

The content of agglomerates > 4 mm (Table 2) is seen to be related to the agglomerate growth rate, the highest content being obtained with the PEG 6000 powder and the lowest content with the fractionated PEG 6000 beads.

The mean maximum product temperature during the process of all the experiments was found to be 63.6°C with a standard deviation of 2.6°C. There was no systematic effect of type and particle size of the PEG on the temperature. The intention was to keep the product temperature within the melting range of the PEG 6000 by using a jacket temperature of 50°C. This was not possible since the PTFE-lining of the bowl has a poor thermal conductivity making the cooling less effective. The fact that the maximum product temperature was practically independent of the type of PEG means that the temperature rise above the melting point (Table 1) was larger for the PEG 1500. This is ascribed to the lower viscosity of the PEG 1500 making the agglomerates more deformable thus increasing the heat generated by friction.

Previous melt agglomeration experiments have shown that an evaporation of water of crystallization from lactose monohydrate affects the agglomerate growth [19]. In the present experiments, the water content in the final product varied between 3.7 and 4.0%. The theoretical value, i.e. the value calculated from the moisture content of the raw materials and the mixing ratio, was 4.0%. This indicates that no significant evaporation of water of crystallization occurred during the process.

3.4. Intragranular porosity and liquid saturation

The highest densification rate was observed for the agglomerates produced with the PEG powder (Fig. 4a). The high initial porosity of these agglomerates is explained by an initial agglomerate structure being rather loose. The high initial porosity obtained with the PEG beads is ascribed to their hollow structure.

Fig. 4b shows the corrected porosity, which is an estimate of the packing of the solid particles within the agglomerate when the binder is in the molten state, i.e. the corrected

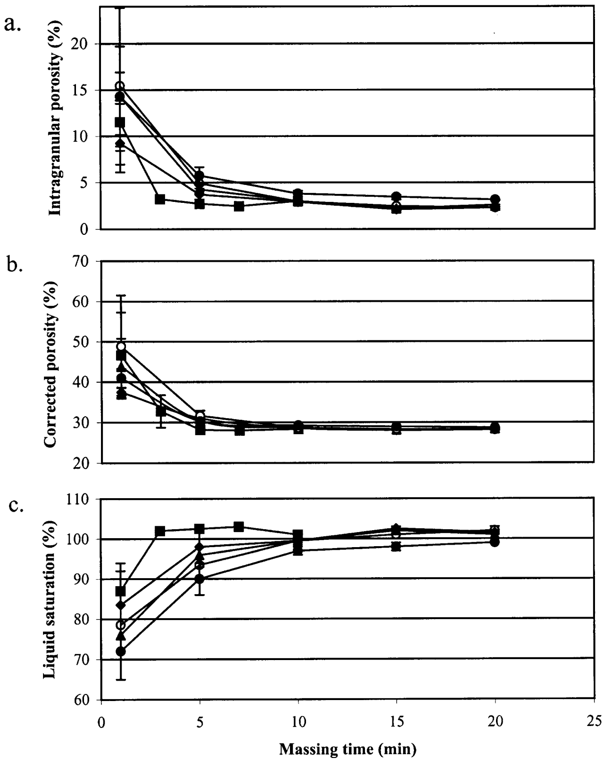

Fig. 4. Effects of type and particle size of the PEG on the intragranular porosity (a), the corrected porosity (b), and the liquid saturation (c). (●) PEG 1500 beads, 500–630 μm; (◆) PEG 6000 beads, unfractionated; (▲) PEG 6000 beads, 500–630 μm; (○) PEG 6000 beads, 710–800 μm; (■) PEG 6000 powder.

porosity corresponds to the pore volume of the agglomerates with the binder removed. Previous studies with a 450 mesh lactose and PEG 3000 at an impeller speed of 800 rpm [22] resulted in a corrected porosity of 24–25%. This indicates that the lower impeller speed applied in the present experiments results in less densification.

A higher liquid saturation is observed initially for the PEG powder compared with the PEG beads (Fig. 4c) because of the lower porosity obtained with the PEG powder. The rapid rise in liquid saturation explains the higher agglomerate growth rate obtained with the PEG powder (Fig. 3). The liquid saturation approximates to 100% in the experiments with the PEG beads. In previous melt agglomeration experiments with a 450 mesh lactose and PEG at a markedly higher impeller speed in a similar high shear mixer, a liquid saturation of approximately 100% was obtained with a PEG concentration of 23% [8,16], i.e. a concentration that is significantly lower than the 28% applied in the present experiments. This shows that the lower impeller speed applied in the present experiments makes it possible to incorporate a higher amount of PEG, because the lower impeller speed causes less densification. It might have been possible to incorporate the same amount of PEG using a higher impeller speed but a shorter processing time. However, such a procedure is supposed to make the agglomerate growth less controllable, because a higher impeller speed will increase the agglomerate growth rate. Preliminary experiments at an impeller speed of 1200 rpm in the present high shear mixer have shown that a 450 mesh lactose became overwetted at a PEG concentration of 24% using the same processing time as in the present study.

3.5. Mechanisms of agglomerate formation and growth

Since the agglomerate size distributions are considerably different, the mass median diameter alone is insufficient to explain the differences in agglomerate growth. The discussion of the agglomerate growth mechanisms, therefore, is based upon the agglomerate size distributions and SEM photographs.

SEM photographs and size distributions of agglomerates produced with the PEG powder are presented in Figs. 5 and 6. Already after 1 min of massing, rather large agglomerates are obtained (Fig. 5a). The agglomerate structure is rather loose, and the lactose particles can be clearly identified. The agglomerates have been formed primarily by the distribution mechanism, because the high content of fine particles in the PEG powder will promote a distribution of the molten PEG on the surface of the lactose particles and a subsequent agglomerate growth by coalescence between wetted particles. Some agglomerates are supposed to be formed, however, by an immersion of lactose particles in the surface of droplets of molten PEG since the PEG powder contains a few particles of a large size. The 1 min sample has a high content (40% m/m) of the fraction <180 μm (Fig. 6a), and SEM photographs of this fraction showed the presence of a large number of unagglomerated lactose particles.

After 3 min of massing (Fig. 5b), the agglomerate shape has become more irregular because of a coalescence between agglomerates and a layering of lactose particles on the surface of agglomerates. The layering mechanism will dominate as long as lactose particles are present, because small particles will be preferentially captured by larger ones [23]. Consequently, a marked decrease in the content of the fraction <180 μm is seen (Fig. 6b).

The agglomerate growth by coalescence and layering results in a higher content of agglomerates in the larger size fractions.

After 5 min of massing, the surface structure of the agglomerates was seen to be more dense, because molten PEG had become squeezed out to the surface due to a densification of the agglomerates. At the same time, the liquid saturation had exceeded 100% (Fig. 4c). The increased surface wetness made it possible for larger agglomerates to coalesce. Consequently, the size distribution (Fig. 6c) shows a decrease in the content of smaller agglomerates and an increase in the content of larger agglomerates.

This tendency continues by a further massing (Fig. 6d). The final product consists of clusters formed by a coalescence between large agglomerates (Fig. 5c). These clusters are able to survive, because the shearing forces are low due to the low impeller speed. Agglomerates like those shown in

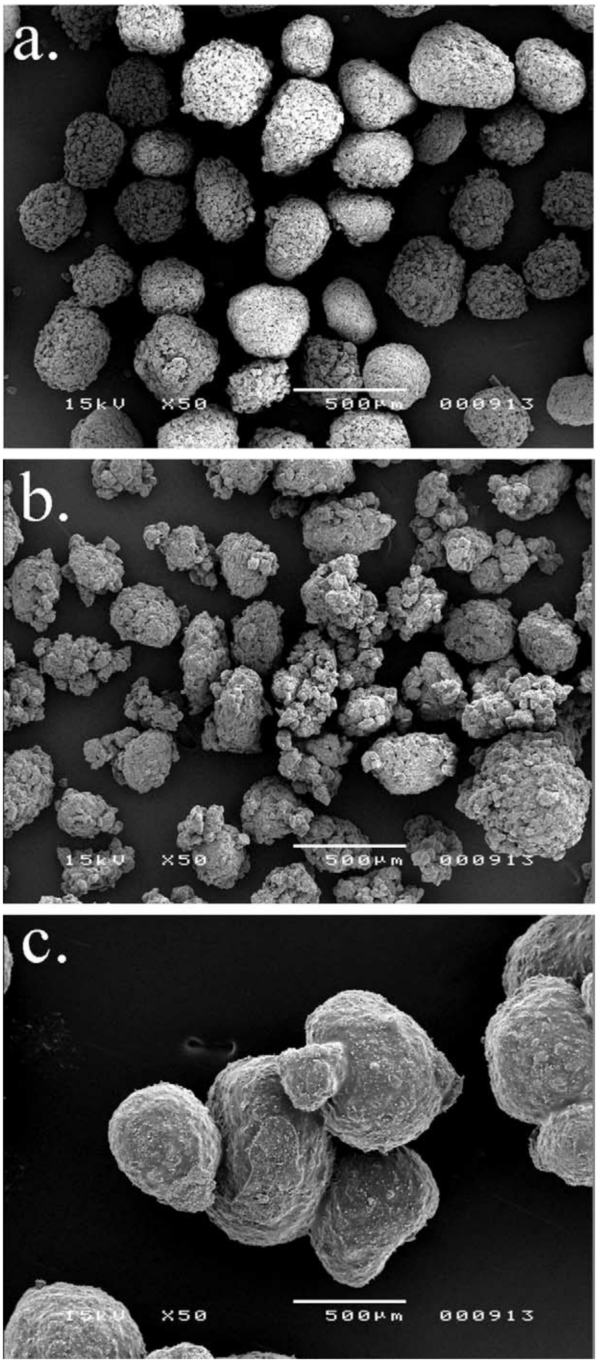

Fig. 5. SEM photographs of agglomerates produced with PEG 6000 powder. Massing time: (a) 1 min (agglomerate size fraction 250–2000 µm); (b) 3 min (agglomerate size fraction 250–2000 µm); (c) 10 min (agglomerate size fraction 500–4000 µm).

Fig. 5c will not be seen at a high impeller speed, which will counteract a coalescence between agglomerates of that size and will cause a spheronization of the agglomerates.

Figs. 7 and 8 show SEM photographs and size distributions of agglomerates produced with PEG 6000 beads. After 1 min of massing, lactose particles can be identified on the surface of the agglomerates (Fig. 7a). The size and shape of the agglomerates are similar to the original size and shape of the PEG beads (Fig 2a). This indicates that the agglomerates are formed by immersion. Accordingly, the agglomerate size distributions obtained with the size fractions of the PEG 6000 beads (Fig. 8a) show a maximum at 710–800 µm for the 500–630 µm bead fraction and at 800–900 µm for the 710–800 µm bead fraction. This confirms that the original beads have grown in size by an immersion of lactose particles in the surface of the molten beads. No such maximum in agglomerate size distribution is seen for the unfractionated beads, due to the wider size distribution of these beads. A high content of the size fraction <180 µm indicates that an immersion of the lactose particles has not been completed yet. Generally, SEM photographs of cross sections of agglomerates showed that the large agglomerates were hollow after 1 min of massing. This confirms the previous assumption that the high initial porosity (Fig. 4a) is due to the presence of internal cavities.

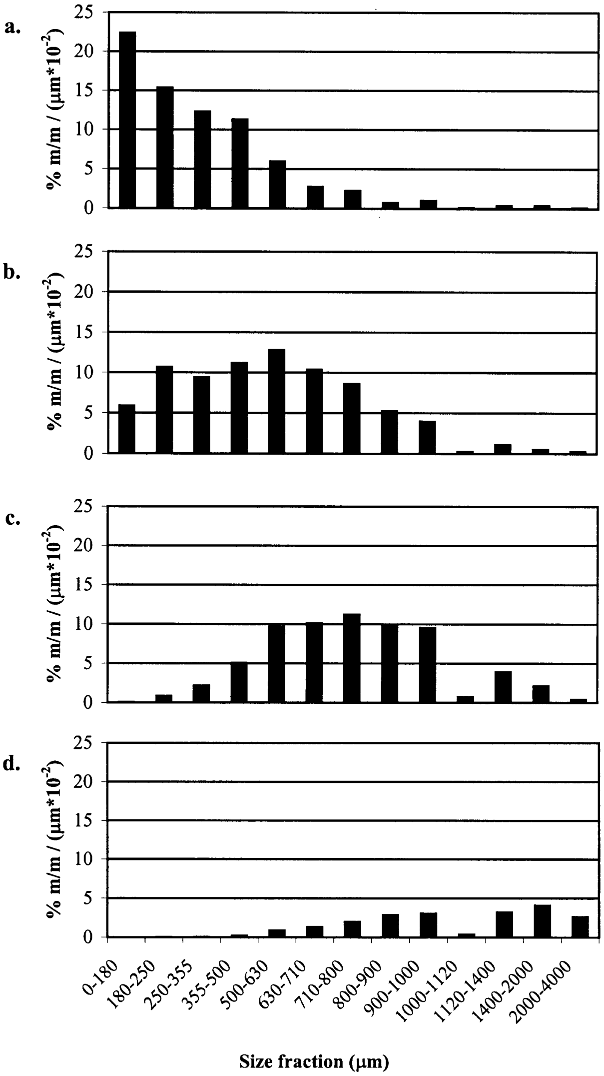

Fig. 6. Effect of massing time on the size distribution of agglomerates produced with PEG 6000 powder. Massing time: (a) 1 min; (b) 3 min; (c) 5 min; (d) 10 min.

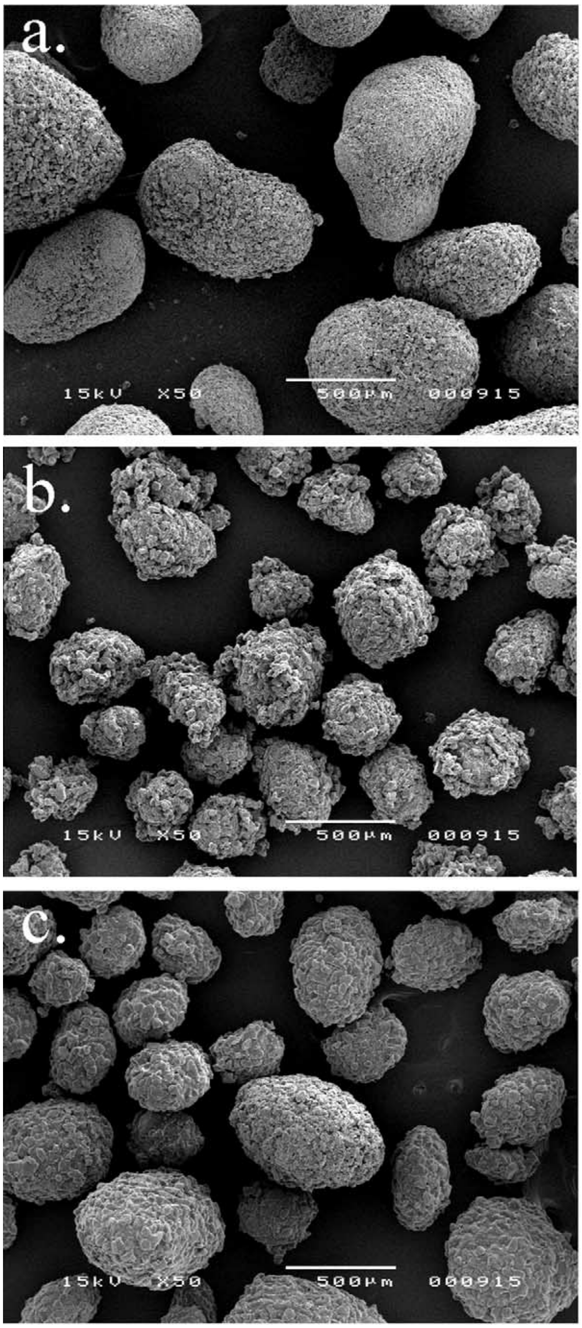

Fig. 7. SEM photographs of agglomerates (agglomerate size fraction 250–2000 µm) produced with PEG 6000 beads, 500–630 µm. Massing time: (a) 1 min; (b) 5 min; (c) 20 min.

Figs. 7b and 8b show that the agglomerate size has become reduced after 5 min of massing. The explanation for this can be the hollow structure of the agglomerates that will make them weaker and more deformable and thus promote a breakage of the agglomerates by a continued massing. Further, the cavities become smaller by the marked densification occurring between 1 and 5 min of massing, and this reduces the volume of the agglomerates. The diminution of the cavities by a prolonged massing was confirmed by SEM photographs of cross sections of agglomerates. More of the lactose particles become immersed in the surface of the agglomerates (Fig. 7b), and consequently the content of the fraction <180 µm becomes lower (Fig. 8b). At a longer massing time, the agglomerate size increases slightly, primarily by capturing unagglomerated lactose particles (Fig. 7c). Accordingly, the agglomerate size distributions are similar after 10 and 20 min of massing for agglomerates produced with the size fractions of the PEG 6000 beads (500–630 µm and 710–800 µm). This indicates that the agglomerate growth continues to proceed primarily by immersion. Contrary to the agglomerates produced with the PEG 6000 powder (Fig. 5c), the agglomerate surface was still seen to be covered with lactose particles after 10 min of massing, and this will prevent an agglomerate growth by coalescence. More molten PEG will slowly become squeezed to the agglomerate surface and penetrate the lactose particles. The surface structure,

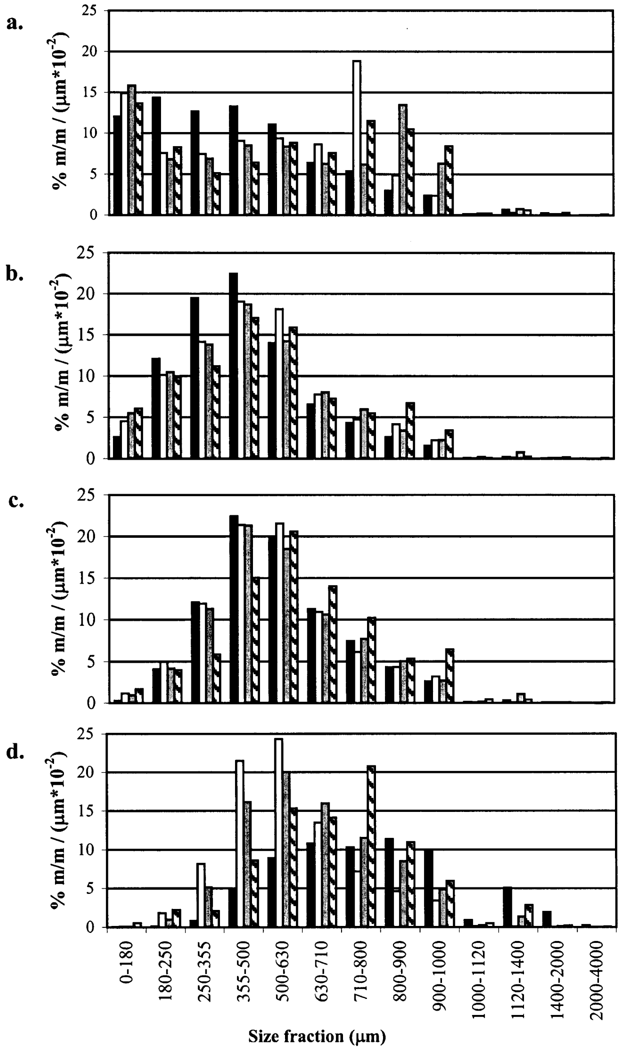

Fig. 8. Effect of massing time on the size distribution of agglomerates produced with PEG 6000 beads, unfractionated (■), PEG 6000 beads, 500–630 µm (◆), PEG 6000 beads, 710–800 µm (▤), and PEG 1500 beads 500–630 µm (▧). Massing time: (a) 1 min; (b) 5 min; (c) 10 min; (d) 20 min.

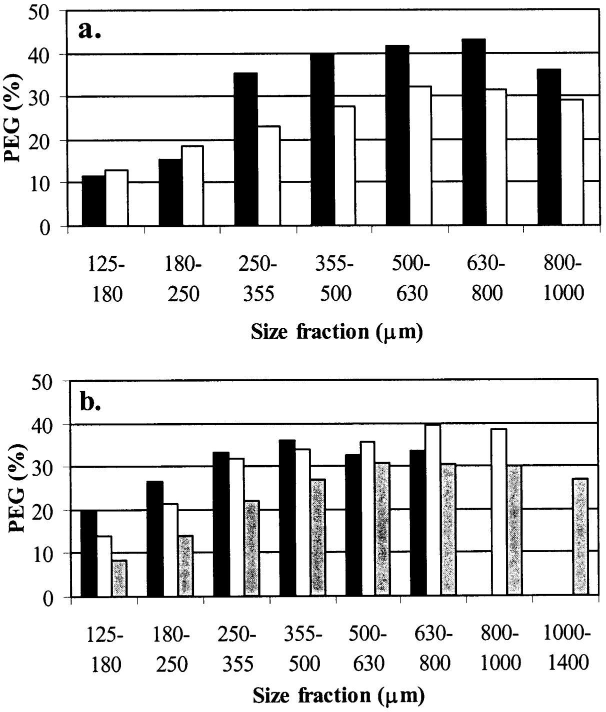

Fig. 9. Content of PEG in selected agglomerate size fractions produced with: (a) PEG 6000 beads, unfractionated. Massing time: 1 min (■); 5 min (◆). (b) (■) PEG 6000 powder; (◇) PEG 6000 beads, 500–630 μm; (▤) PEG 6000 beads, 710–800 μm. Massing time: 1 min. Theoretical PEG content: 28%.

therefore, is seen to be slightly denser after 20 min of massing (Fig. 7c), but still the surface wetness is insufficient for an appreciable coalescence between agglomerates.

In previous melt agglomeration experiments, at a high impeller speed [14], immersion was described as an initial mechanism of agglomerate formation followed by an agglomerate growth by coalescence at the time when binder liquid was squeezed to the surface of the agglomerates owing to densification. In the present experiments, immersion is the agglomerate growth mechanism since the densification is lower because of the lower impeller speed. Generally, immersion will yield a lower growth rate than coalescence [23].

The unfractionated and the fractionated PEG 6000 beads show a similar behaviour until the end of the process where a higher content of larger agglomerates is seen with the unfractionated PEG 6000 beads (Fig. 8d). Although the immersion mechanism will also dominate with the unfractionated PEG beads, the wider size distribution of the beads will result in some distribution of the smallest beads on the surface of the lactose particles. Consequently, the initial content of fines, i.e. the size fraction <180 μm, is slightly lower with the unfractionated beads (Fig. 8a,b). Since the distribution mechanism contributes more to the agglomerate formation with the unfractionated beads, some agglomerate growth by coalescence will be possible at the end of the process.

The effect of viscosity on the agglomerate growth was evaluated by using the same fraction of PEG 1500 and PEG 6000 beads (Fig. 8). As can be seen, the PEG 1500 results in a higher content of large agglomerates, especially at prolonged massing. This is supposed to be due to the lower viscosity of the PEG 1500, which makes the agglomerates more deformable promoting an agglomerate growth by coalescence between agglomerates. In spite of the rather low viscosity of the PEG 1500, the agglomerate formation and growth occur primarily by immersion. Although the PEG 1500 beads results in larger agglomerates, all the PEG beads generate appreciably smaller agglomerates than the PEG powder (Fig. 3). This indicates that the binder particle size has a larger effect on the mechanisms of agglomerate formation and growth than the viscosity when using a low impeller speed.

The shape of the final agglomerates produced with all the PEG beads was similar to that seen in Fig. 7c. Although the agglomerates are seen to be rounded, no spherical shape was obtained. Further, the surface structure of the agglomerates is rough and not smooth. This means that the final agglomerates cannot be characterized as pellets. The reason why pellets were not obtained is that the initial shape of the agglomerates was not remained during the process, because the hollow structure of the PEG beads caused a breakage of the agglomerates. Further, the impeller speed applied in the present experiments was too low to produce round and smooth agglomerates.

3.6. Binder distribution

Fig. 9 shows examples of the distribution of the PEG in selected agglomerate size fractions. With the unfractionated PEG 6000 beads, the distribution is very inhomogeneous after 1 min of massing (Fig. 9a). The binder content is seen to be low in the size fractions smaller than the initial particle size of the beads. This confirms that the agglomeration proceeds primarily by immersion. After 5 min of massing, more lactose particles have been incorporated in the surface of the molten binder particle, and the distribution of the PEG becomes more uniform.

The binder distribution becomes more uniform with the PEG powder compared to the fractionated PEG beads (Fig. 9b). This is because the distribution mechanism is dominant in the case of the powder. Although the agglomerate growth proceeds by distribution and coalescence, there is still a higher binder content in the larger size fractions in accordance with previous melt agglomeration experiments performed in a high shear mixer [24]. For fractionated PEG 6000, the binder distribution is similar to that seen in Fig. 9a confirming that the immersion mechanism is dominant.

4. Conclusions

The present study shows that it will be difficult to produce pellets with a high content of a meltable binder in a high shear mixer. It has been shown that it is possible to incorporate a higher content of binder by applying a lower impeller speed, but a low impeller speed counteracts a spheronization of the agglomerates and a narrowing of the agglomerate size distribution. Agglomerate growth by the immersion mechanism is possible provided that the impeller speed is low, and the meltable binder is added as solid beads; it is advantageous in that it enables a slow and controllable growth with a high binder content to be obtained. The hollow structure of the binder beads might cause a breakage of the initial agglomerates, and this makes it difficult to maintain the spherical shape of the beads in the shape of the final agglomerates. In order to become more successful in producing pellets with a high content of a meltable binder, it will be essential to be able to avoid a breakage of the initial binder beads. This might be done by applying beads without a hollow structure, by keeping the product temperature slightly below the melting point of the binder, and/or by using beads of a highly viscous binder.

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References

[1] J.L. Ford, M.H. Rubinstein, Formulation and ageing of tablets prepared from indomethacin-polyethylene glycol 6000 solid dispersions, Pharm. Acta Helv. 55 (1980) 1–7.

[2] R. Kinget, R. Kemel, Preparation and properties of granulates containing solid dispersions, Acta Pharm. Technol. 31 (1985) 57–62.

[3] R. Kinget, R. Kemel, The compression of granulates containing solid dispersions, Pharmazie 40 (1985) 475–477.

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

[5] F. Zhou, C. Vervaet, J.P. Remon, Matrix pellets based on the combination of waxes, starches and maltodextrins, Int. J. Pharm. 133 (1996) 155–160.

[6] D. Voinovich, M. Moneghini, B. Perissutti, J. Filipovic-Grcic, I. Grabnar, Preparation in high-shear mixer of sustained-release pellets by melt pelletisation, Int. J. Pharm. 203 (2000) 235–244.

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

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

[9] R. Thies, P. Kleinebudde, Melt pelletisation of a hygroscopic drug in a high shear mixer Part 1. Influence of process variables, Int. J. Pharm. 188 (1999) 131–143.

[10] K. Ukita, T. Murakami, Preparation of essential oils loaded granule by melt granulation, Drug Dev. Ind. Pharm. 20 (1994) 981–992.

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

[12] F. Zhou, C. Vervaet, J.P. Remon, Influence of processing on the characteristics of matrix pellets based on microcrystalline waxes and starch derivatives, Int. J. Pharm. 147 (1997) 23–30.

[13] P.W.S. Heng, T.W. Wong, L.W. Chan, Influence of production variables on the sphericity of melt pellets, Chem. Pharm. Bull. 48 (2000) 420–424.

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

[15] C.M. McTaggart, J.A. Ganley, A. Sickmueller, S.E. Walker, The evaluation of formulation and processing conditions of a melt granulation process, Int. J. Pharm. 19 (1984) 139–148.

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

[17] European Pharmacopoeia 3rd ed., Council of Europe, Strasbourg, France, 1997, pp. 141–142.

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

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

[20] W.A. Strickland, L.W. Busse, T. Higuchi, The physics of tablet compression XI. Determination of porosity of tablet granulations, J. Am. Pharm. Assoc. Sci. 45 (1956) 482–486.

[21] T.W. Wong, L.S.C. Wan, P.W.S. Heng, Effects of physical properties of PEG 6000 on pellets produced by melt pelletization, Pharm. Dev. Technol. 4 (1999) 449–456.

[22] T. Schæfer, Melt pelletization in a high shear mixer X. Agglomeration of binary mixtures, Int. J. Pharm. 139 (1996) 149–159.

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

[24] P.C. Knight, T. Instone, J.M.K. Pearson, M.J. Hounslow, An investigation into the kinetics of liquid distribution and growth in high shear mixer agglomeration, Powder Technol. 97 (1998) 246–257.