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Agglomerate formation and growth mechanisms during melt agglomeration in a rotary processor

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Abstract

The purpose of this study was to investigate the effect of the binder particle size and the binder addition method on the mechanisms of agglomerate formation and growth during melt agglomeration in a laboratory scale rotary processor. Lactose monohydrate was agglomerated with molten polyethylene glycol (PEG) 3000 by adding the PEG either as solid particles from the size fraction 0–250, 250–500, or 500–750 μm or as droplets with a median size of 25, 48, or 69 μm. It was found that the PEG particle size, the PEG droplet size, and the massing time significantly influenced the agglomerate size and size distribution. Agglomerate formation and growth were found to occur primarily by distribution and coalescence for the PEG size fraction 0–250 μm and mainly by the immersion mechanism for the PEG size fractions 250–500 and 500–750 μm. When the PEG was sprayed upon the lactose, the mechanism of agglomerate formation was supposed to be a mixture of immersion and distribution, and the agglomerate growth was found to occur by coalescence regardless of the PEG mean droplet size. Compared to high shear mixers and conventional fluid bed granulators, the mechanisms of agglomerate formation and growth in the rotary processor resembled mostly those seen in the fluid bed granulator.

Keywords: Rotary processor; Melt agglomeration; Agglomerate growth mechanisms; Binder addition procedure; Binder particle size

1. Introduction

Agglomeration is a size enlargement technique where a powder is processed into agglomerates of a certain size and shape. In a wet agglomeration process, agglomeration is obtained by adding a binder liquid to a powder, which enables the powder particles to stick together and grow in size. The state of the liquid in the agglomerates has been distinguished as pendular, funicular, or capillary depending on the liquid saturation of the agglomerates (Newitt and Conway-Jones, 1958). The pendular state is at a liquid saturation below approximately 25%, the funicular state is at a liquid saturation between approximately 25 and 80%, and in

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the capillary state where the entire pore spaces in the agglomerates are nearly or completely filled with liquid, the liquid saturation is above approximately 80% (Kristensen and Schæfer, 1987).

The agglomeration process can be divided into formation (nucleation) and growth by coalescence, by layering, and/or by ball growth (Sherrington and Oliver, 1981). The growth is a balance between size enlargement and size reduction (Kristensen, 1996; Tardos et al., 1997). Melt agglomeration experiments have shown that the liquid saturation has to be around 100% for agglomerate growth to occur by coalescence (Knight, 1993).

The agglomerate formation and growth mechanisms for a melt agglomeration process have been studied in high shear mixers and conventional fluid bed granulators. The formation mechanism has been described as a distribution or an immersion mechanism (Schæfer and Mathiesen, 1996; Abberger et al., 2002; Schæfer et al., 2004). By the distribution mechanism, small agglomerates (nuclei) are formed by initial solid particles being wetted by distribution of molten binder on their surface enabling agglomerate formation by coalescence between the wetted solid particles. Further agglomerate growth occurs by coalescence between the nuclei provided that the liquid saturation is sufficiently high (Knight, 1993; Schæfer and Mathiesen, 1996). By the immersion mechanism, initial solid particles become immersed in the surface of a molten binder particle, and further immersion of initial particles gives rise to agglomerate growth. Agglomerate growth by coalescence between agglomerates will primarily occur when no more initial particles are available (Knight, 1993). This is because the tendency for coalescence between initial particles or between initial particles and agglomerates is larger than the tendency for coalescence between two agglomerates since the tendency is inversely proportional to the size (Ennis et al., 1991; Tardos et al., 1997). Agglomerate growth by coalescence will only occur until a critical agglomerate size is reached. This size depends on a balance between coalescence and breakage and can be increased by e.g. using smaller powder particles, by increasing the binder viscosity, and by reducing the energy input (Ennis et al., 1991; Tardos et al., 1997).

For melt agglomeration in high shear mixers and fluid bed granulators, it has been found that a binder particle size being smaller than that of the solid particles promotes the distribution mechanism (Schæfer and Mathiesen, 1996; Abberger and Henck, 2000; Abberger, 2001; Abberger et al., 2002). On the other hand, a binder particle size being larger than that of the solid particles promotes the immersion mechanism. Furthermore, it has been found for high shear mixers that a low viscosity of the binder and/or high shearing forces will promote the distribution mechanism whereas a high viscosity of the binder and/or low shearing forces will promote the immersion mechanism (Schæfer and Mathiesen, 1996). Consequently, the immersion mechanism can be promoted by keeping the process temperature within or slightly below the melting range of the meltable binder (McTaggart et al., 1984) since this will increase the viscosity of the binder markedly.

In a melt agglomeration process, both mechanisms might be active simultaneously, although one of the mechanisms will normally be dominant (Schæfer and Mathiesen, 1996; Abberger et al., 2002). In high shear mixers, the dominant mechanism will usually be the distribution mechanism because of the high shearing forces. In fluid bed granulators, the agglomerate formation occurs to a larger extent by the immersion mechanism due to the lower shearing forces (Schæfer, 2001).

A rotary processor, which is a fluid bed granulator equipped with a rotating friction plate, has been shown to be suitable for a melt agglomeration process (Reo and Roche, 1996; Vilhelmsen et al., 2004). For optimum use of a melt agglomeration process in the rotary processor, it is necessary to be able to control the agglomerate size. This requires an understanding of the influence of process conditions on agglomerate properties and of the fundamental mechanisms of agglomerate formation and growth. Vilhelmsen et al. (2004) reported that process conditions such as binder concentration, massing time, friction plate rotation speed, and surface of the friction plate significantly influenced the agglomerate size. However, no fundamental studies of the mechanisms of agglomerate formation and growth in a melt agglomeration process in a rotary processor have been carried out.

The present work was based on the hypothesis that the mechanisms of agglomerate formation and growth in a melt agglomeration process in a rotary processor differ from those seen in high shear mixers as well as conventional fluid bed granulators because of

differences in shearing forces. The aim of this study was to test this hypothesis by investigating the effects of binder particle size and binder addition method on the mechanisms of agglomerate formation and growth in a rotary processor.

2. Materials and methods

2.1. Materials

Lactose 350 mesh (α-lactose monohydrate, DMV, The Netherlands) was used as filler and polyethylene glycol (PEG) 3000P powder (Clariant, Germany) was used as binder. The PEG size fractions 0–250, 250–500, and 500–750 μm prepared by sieving were used for the melt-in procedure while unfractionated PEG was used for the spray-on procedure.

2.2. Methods

2.2.1. Primary characterization of materials

The particle size distributions by volume of the lactose and the PEG size fractions were determined in triplicate by a Malvern Mastersizer S laser diffraction particle sizer (Malvern Instruments, UK) fitted with a dry powder feeder operating at 3 bar. The span was calculated as the difference between the volume diameters at the 90 and 10 percentage points relative to the volume median diameter.

The BET multipoint surface areas were determined in duplicate for the lactose by a Gemini 2375 Surface Area Analyzer (Micromeritics, USA).

The pycnometric densities of the lactose and the PEG were determined in duplicate by an AccuPyc 1330 gas displacement pycnometer (Micromeritics, USA) using helium purge.

The melting range and the melting peak temperature of the PEG were estimated in triplicate by a Perkin-Elmer DSC 7 differential scanning calorimeter (Perkin-Elmer, USA). Samples of about 4 mg were sealed in 40-μl aluminum pans with holes and scanned from 45 to 70 °C at a heating rate of 2 °C/min.

The density of the molten PEG was determined in triplicate at 60 and 70 °C as previously described (Eliasen et al., 1998).

The viscosity of the molten PEG was determined in duplicate by a RV20 Rotovisco (Haake, Germany) with a NV sensor system and a measuring system M. The viscosity was determined at 60 and 70 °C as the slope of the linear part of the obtained flow curve.

The droplet size distributions by volume of the molten PEG were determined in duplicate by a Malvern 2600 C laser diffraction particle sizer (Malvern Instruments, UK).

2.2.2. Agglomeration equipment

The melt agglomeration experiments were performed in a rotary processor (Glatt GPCG-1, Glatt, Germany) fitted with a friction plate of 28 cm in diameter and a surface consisting of elevated cubes in a cross-hatched pattern. An additional temperature sensor was inserted and used to monitor the product temperature as previously described (Vilhelmsen et al., 2004). The rotary processor was connected to a computer, which monitored and recorded the process data. To add the molten PEG, a pneumatic nozzle was used with an orifice of 1.2 mm and an air dome setting of 2. The spray was placed tangentially to the moving powder. The atomizing air was heated to 160 °C by an electrically heated tube (Isopad, Germany), and a pressure vessel (Alloy, USA) heated to 75 °C delivered the molten PEG to the nozzle through a tube (Hillesheim, Germany) electrically heated to 80 °C.

2.2.3. Agglomeration procedure

Before each experiment, the rotary processor was preheated to a temperature of 50 °C. The rotary processor was operated at a fluidizing airflow of 70 m^3/h, an inlet fluidizing air temperature of 70 °C, a fluidizing air gap pressure drop of 2000 Pa, and a friction plate rotation speed of 1000 rpm. The amount of lactose was 700 g, and the concentration of PEG was 24% (m/m) of that amount. Two different procedures, melt-in or spray-on, were used for adding the binder.

When the melt-in procedure was applied, the lactose and the fractionated PEG were manually mixed for 20 s before they were placed at the center of the friction plate. After the fluidizing airflow was started, the fluidizing air gap pressure drop was adjusted, and finally the rotation of the friction plate was started. When the product temperature reached 60 °C, the timing of the massing time was started.

When the spray-on procedure was applied, the PEG was melted in an oven at 80 °C and added to the pressure vessel. Then the lactose was weighed and placed at the

center of the friction plate, and the process was started as described above. When the temperature of the lactose reached 60 °C, the molten PEG was sprayed into the lactose by adjusting the atomization air pressure to 1, 2, or 3 bar depending on the PEG mean droplet size needed and by adjusting the pressure in the pressure vessel to 2 bar. The time was around 55 s for spraying the molten PEG into the lactose. The massing time was started when the entire amount of molten PEG was sprayed into the product container. After spraying of the molten PEG, the atomization air pressure was kept at a cleaning pressure of 1 bar.

The product temperature profiles did not differ for the melt-in and spray-on procedures, and after 8 min of massing the product temperature was around 65 °C.

For both procedures, a valve conducting unheated air of room temperature into the container was opened at the end of massing time, and the cooling was started. During the cooling, the fluidizing airflow was set to approximately 100 m^3/h, the friction plate rotation speed to 500 rpm, and the atomizing air pressure was turned off. After 3 min of cooling, the product temperature was around 50 °C, and the rotary processor was stopped. The product was removed immediately from the rotary processor, weighed, and spread out on a tray at ambient conditions.

2.2.4. Agglomerate characterization

2.2.4.1. Yield. The yield was calculated as the total amount of end product expressed as a percentage of the amount of starting materials.

2.2.4.2. Size distribution. The amount of agglomerates >4 mm was determined as the retained fraction after vibration sieving of the end product for approximately 10 s by a Jel-Fix 50 (J. Engelsmann, Germany). The result was expressed as a percentage of the total amount of end product.

Sieve analyses were performed on samples of approximately 45 g of the agglomerates <4 mm. The samples were prepared by a Laborette 27 automatic rotary sample divider (Fritsch, Germany) and added to a series of 15 standard ASTM sieves ranging from 75 to 2800 μm. As can be seen from Figs. 2 and 5, the class intervals do only partly follow a square root two-progression since further sieves were added in order to obtain a higher resolution within the size range of 500–1400 μm. Due to this difference in the width of the class intervals, the data do not permit a direct comparison between sieve fractions on the basis of percentage. The sieves were vibrated without interruptions for 10 min with a vertical amplitude of 6 mm. The agglomerate median diameter and the span were calculated from the sieve analysis data.

2.2.4.3. PEG content. The PEG content in agglomerates from the size fraction containing the largest amount of agglomerates together with the agglomerates from the size fractions just below and above was determined. If an agglomerate size distribution was multimodal, the PEG content of the agglomerates from the other modes was additionally determined by selecting the agglomerates as described above. However, if the other mode was within the agglomerate size fraction 0–250 μm, then the PEG content of the agglomerates from the agglomerate size fraction 0–250 μm was determined. The PEG content was determined indirectly as the difference between the weighed amount of agglomerates and the amount of lactose determined colorimetrically as previously described (Thomas, 1984). The content was determined in duplicate, and approximately 1.5 g of sample were used for each determination. The content of PEG was expressed as a percentage of the amount of lactose.

2.2.4.4. Scanning electron microscopy. SEM images of the agglomerates from selected size fractions were taken by a scanning electron microscope (SEM) (JSM 5200, JEOL, Japan). The size fractions were selected as described in Section 2.2.4.3. The agglomerates were fixed with carbon double adhesive tape and sputtered with gold (E5200 Auto Sputter Coater, BioRad, UK) for 120 s before microscopy.

2.2.5. Experimental design

The two binder addition procedures, melt-in and spray-on, were performed with three different binder particle sizes and droplet sizes, respectively, and the experiments were stopped at four different massing times (Table 1). Since the experiments were performed in duplicate, a total of 48 experiments were performed. The experiments were performed in a random order with six experiments each day. The results from the experiments were analyzed by analysis of variance (ANOVA) using the agglomerate median size, span, yield, and agglomerates >4 mm as response variables.

Table 1
The values of the variables in the experimental design

Variable	Values			
Binder addition procedure	Melt-in	Spray-on		
Binder particle size fraction (melt-in) (μm)	0–250	250–500	500–750	
Binder droplet size $d_{v,0.5}$ (spray-on) (μm)	25	48	69	
Massing time (min)	0	1	4	8

3. Results and discussion

3.1. Material properties

It is seen from Table 2 that the size distributions of the fractionated PEG particles become narrower when going from the size fraction 0–250 to 500–750 μm. The size distributions of the droplets become wider when the mean droplet size decreases. This is because it was difficult to sufficiently reduce the amount of large droplets when increasing the atomization air pressure to reduce the mean droplet size. The PEG mean droplet sizes are smaller than the particle sizes of the solid PEG's, because it was impossible to produce droplets of the same size with the actual spray system.

From the densities in Table 2, it can be calculated that the PEG concentration of 24% (m/m) of the lactose corresponds to a concentration of 22.0% (v/m) of the lactose or 33.9% (v/v) of the lactose at 60 °C.

3.2. Agglomerate size and yield

As shown in Fig. 1a by the error bars, the variation between the duplicate experiments is seen to be small indicating a repeatable process except for the spray-on experiments at 8 min of massing. Uncontrollable agglomerate growth occurs between 4 and 8 min of massing for the spray-on procedure. Therefore, the values from the spray-on procedure at 8 min of massing were omitted from the statistical testing. The yield of the process was between 88 and 95% for all the experiments and was significantly increased when the PEG particle size or droplet size was decreased (Table 3).

By the statistical analysis, it was found that the agglomerate size was significantly influenced by the PEG particle size fraction, by the PEG mean droplet size, and by the massing time for the melt-in procedure as well as the spray-on procedure. Furthermore,

Table 2
The physical properties of the materials

Material	Particle sizes		Droplet sizes		Specific surface area (m^2/g)	Pycnometric density (g/ml)	Density molten (g/ml)		Melting (°C)		Viscosity (mPa/s)	
	$D_{(v0.5)}$ (μm)	Span	$D_{(v,0.5)}$ (μm)	Span			60 °C	70 °C	Range	Peak	60 °C	70 °C
Lactose	30	2.47	–	–	0.78	1.54	–	–	–	–	–	–
PEG 3000	94[a]	2.33[a]	25	4.6	–	1.23	1.09	1.09	57–61	59	267	194
	339[b]	1.06[b]	48	2.9								
	541[c]	0.85[c]	69	2.1								

[a] Size fraction: 0–250 μm.
[b] Size fraction: 250–500 μm.
[c] Size fraction: 500–750 μm.

Table 3
The results of the statistical analysis of the yield, agglomerate median size, span of the agglomerate size distribution, and amount of agglomerates >4 mm

Factors and interactions	Yield (p)	Median size (p)	Span (p)	Agglomerates >4 mm (p)
(1) PEG particle size	0.0000	0.0000	0.0000	0.0001
(2) Massing time for melt-in	0.0724	0.0001	0.0020	0.4485
(1) × (2)	0.2122	0.0001	0.1177	0.5214
(3) PEG mean droplet size	0.0068	0.0021	0.0000	0.0000
(4) Massing time for spray-on	0.1813	0.0013	0.1799	0.4160
(3) × (4)	0.4228	0.0003	0.0053	0.1152

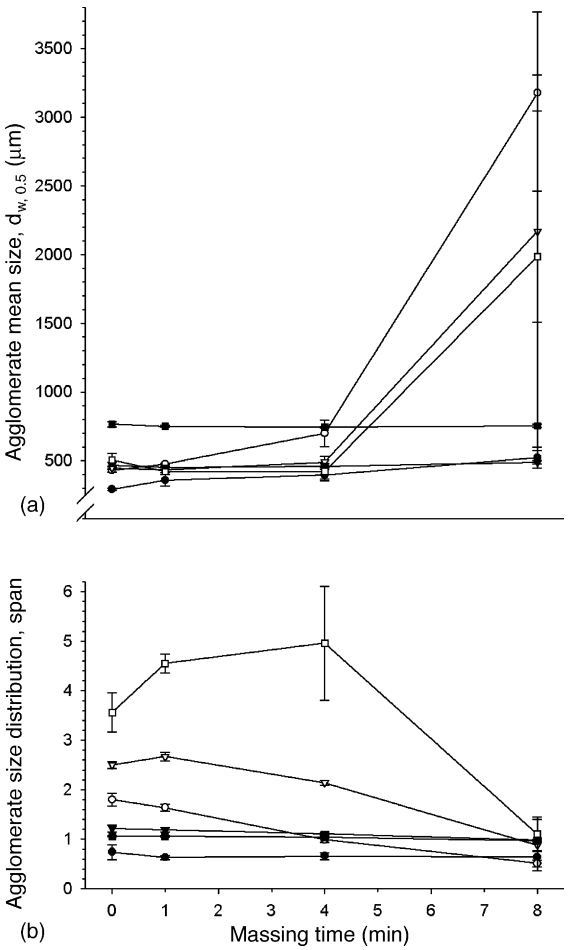

Fig. 1. Effect of binder addition procedure, PEG particle size, PEG droplet size, and massing time on (a) the agglomerate size and (b) the agglomerate size distribution. Binder addition procedure: (●, ▼, ■) melt-in and (◯, ▽, □) spray-on. PEG particle size fraction: (●) 0–250 μm, (▼) 250–500 μm, and (■) 500–750 μm. PEG droplet size: (◯) 25 μm, (▽) 48 μm, and (□) 69 μm. The bars represent the range between the repeated experiments.

the agglomerate size was influenced by the interaction between the massing time and the PEG particle size fraction or the PEG mean droplet size. The agglomerate size distribution was significantly influenced by the PEG particle size fraction and the PEG mean droplet size as well as by the massing time for the melt-in procedure and by the interaction between the massing time and PEG mean droplet size for the spray-on procedure.

For the melt-in experiments (Fig. 1a), the size fraction 0–250 μm results in a small increase of the agglomerate size during massing time, whereas no change in the agglomerate size is seen during massing for the agglomerates produced with the PEG size fractions 250–500 or 500–750 μm. Further, it can be seen that a larger PEG particle size results in a larger agglomerate size at 0, 1, and 4 min of massing.

For the spray-on experiments, the agglomerate size is seen to increase markedly during the last 4 min of massing regardless of the PEG droplet size (Fig. 1a) due to an uncontrollable agglomerate growth. Only agglomerates produced with the PEG droplet size of 25 μm are seen to increase in size during the first 4 min of massing, whereas the agglomerates produced by the PEG droplet sizes of 48 or 69 μm are seen to decrease slightly in size at first and then start to increase.

The agglomerate size distributions become narrower during 8 min of massing regardless of the binder addition procedure. The agglomerate size distributions produced by the PEG droplets of 48 and 69 μm, however, are seen to widen before narrowing (Fig. 1b). The narrowest agglomerate size distributions at 0 and 1 min of massing are produced by the melt-in procedure. Decreasing the PEG mean droplet size narrows the agglomerate size distribution, although droplets of a smaller mean size have a wider size distribution (Table 2).

The amount of agglomerates >4 mm was found to significantly decrease when increasing the PEG particle size fraction and to increase when increasing the PEG mean droplet size (Table 3). The amount of agglomerates >4 mm was generally between 0 and 2% except for the spray-on experiments after 8 min of massing where the PEG mean droplet sizes of 25, 48, and 69 μm resulted in 37, 24, and 15% of agglomerates >4 mm, respectively.

The different agglomerate growth rates and changes in size distribution observed in Fig. 1 indicate that the mechanisms of agglomerate formation and growth change when the PEG particle/droplet size and addition procedure change.

3.3. Mechanisms of agglomerate formation and growth by the melt-in procedure

In Fig. 2, it can be seen that agglomerates are already formed at 0 min of massing. This is because softening and melting of the PEG particles occur before the product temperature reaches 60 °C since the melting range of the PEG 3000 is 57–61 °C (Table 2). This makes it difficult to determine the exact mechanism of agglomerate formation. However, for the agglomerates produced with the PEG size fraction 0–250 μm, it can be seen that agglomerate growth is occurring during massing time (Figs. 1a and 2a), and that no fines (0–75 μm) are left at 0 min of massing (Fig. 2a). This indicates that the PEG is readily available at the surface of the agglomerates, and that the PEG is uniformly distributed and accessible from the beginning of the agglomerate formation. The agglomerate formation mechanism for agglomerates produced with the PEG size fraction 0–250 μm is therefore most likely dominated by distribution causing a nucleation. However, the largest PEG particles in the size fraction might form nuclei by immersion. Further agglomerate growth is occurring by coalescence between nuclei and/or larger agglomerates.

SEM images support that the mechanisms of agglomerate formation and growth for agglomerates produced with the PEG size fraction 0–250 μm are primarily distribution followed by coalescence. It can be seen (Fig. 3a) that the agglomerates at 0 min of massing are formed from multiple smaller agglomerates. The PEG appears to be uniformly distributed all over the lactose particles making it difficult to distinguish single

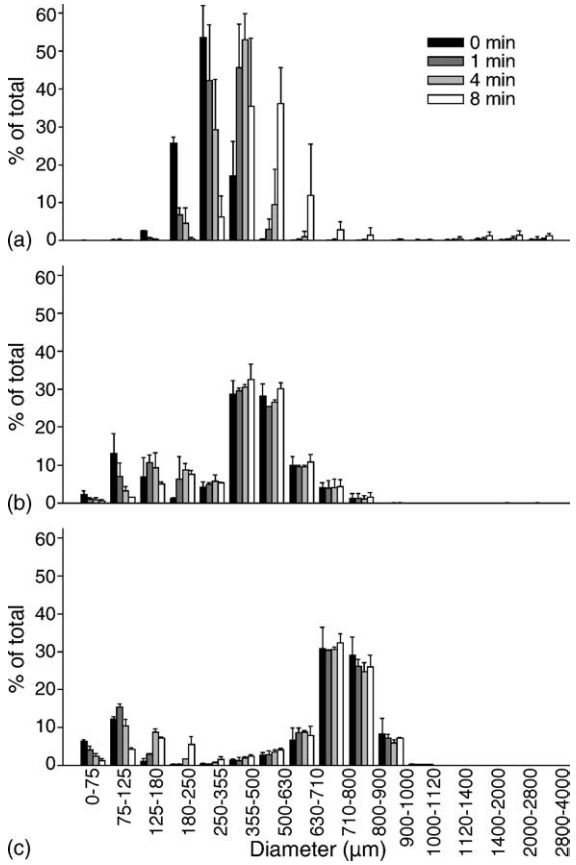

Fig. 2. Effect of PEG particle size fraction and massing time on size distributions of agglomerates produced by the melt-in procedure. PEG particle size fraction: (a) 0–250 μm, (b) 250–500 μm, and (c) 500–750 μm. The bars represent the range between the repeated experiments.

lactose particles. Further agglomerate growth occurs by coalescence between agglomerates since multiple agglomerates of the size shown in Fig. 3a form the agglomerates in Fig. 3b.

A theoretical calculation of the agglomerate size that can be formed from a single PEG particle from the size fraction 0–250 μm by immersion was carried out based on the mean PEG particle size of 94 μm (Table 2) with the assumption that the particle is spherical (Schæfer et al., 2004). The theoretical PEG content in the agglomerates is 23.1% (v/v) of the total volume at room temperature. If an intragranular porosity of 0% is assumed, the calculation results in a theoretical agglomerate size of 159 μm that can be formed by immersion. In practice, the intragranular porosity will be higher than zero.

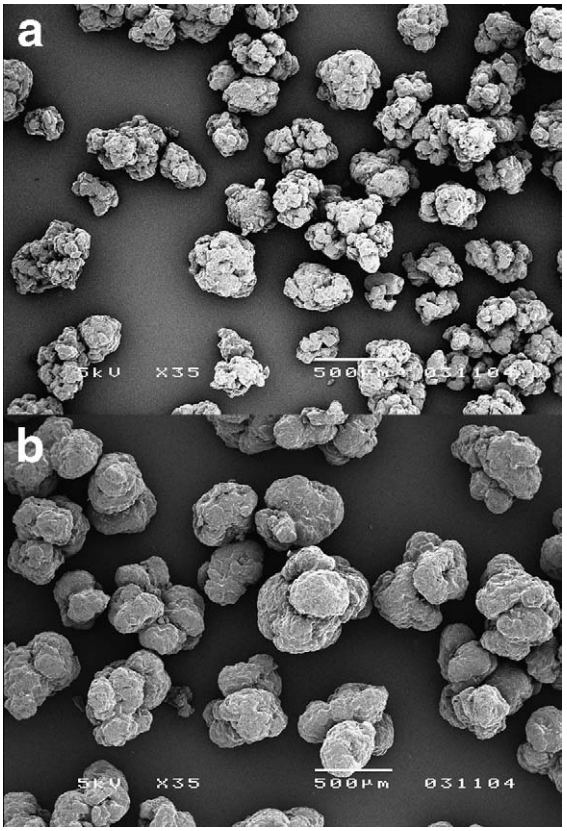

Fig. 3. SEM images of agglomerates produced by the melt-in procedure with PEG particle size fraction 0–250 μm. Agglomerate sieve fraction (a) 180–500 μm at 0 min and (b) 355–710 μm at 8 min of massing.

The intragranular porosities of the actual agglomerates were not estimated. However, based upon a visual evaluation of SEM images of the agglomerates, the intragranular porosity is supposed typically to be less than 10%. If the intragranular porosity is assumed to be 10% instead of zero, the theoretical agglomerate size will be 165 μm, i.e. the porosity value will only have a slight influence on the result of the calculation within the expected range of porosities. Therefore, the calculations mentioned below are all based upon an intragranular porosity of 0%. The agglomerates at 0 min of massing in Fig. 2a are larger than 159 μm indicating that they have been formed from multiple PEG particles.

Table 4 also indicates that the mechanisms of agglomerate formation and growth for agglomerates

Table 4
Effect of PEG particle size and massing time on the PEG content in selected agglomerate size fractions produced by the melt-in procedure

PEG particle size (μm)	Massing time (min)	Agglomerate size fraction (μm)	PEG content (% m/m of lactose)
0–250	0	180–500[a]	30
0–250	8	355–710[a]	28
250–500	0	250–630[a]	42
250–500	8	250–630[a]	34
250–500	0	0–250	12
250–500	8	0–250	16
500–750	0	630–900[a]	41
500–750	8	630–900[a]	32
500–750	0	0–250	10
500–750	8	0–250	10

[a] Main agglomerate size fraction.

produced with PEG from the size fraction 0–250 μm are mainly distribution and coalescence since the PEG content in the main agglomerate size fractions does not change markedly with the massing time. This is because the PEG is evenly distributed on the lactose particles from the start of the agglomeration.

For agglomerates produced with PEG from the size fractions 250–500 and 500–750 μm, it can be seen (Fig. 2b and c) that the size of the main agglomerate size fraction is slightly larger than the size of the respective PEG particles. This indicates that the agglomerate size is dependent on the PEG particle size, which is the case when the agglomerate formation and growth occur by immersion of lactose particles in the surface of the molten PEG particle (Schæfer and Mathiesen, 1996). Calculations of the agglomerate size that can be formed from a single PEG particle of mean size from the size fractions 250–500 and 500–750 μm by immersion resulted in agglomerate sizes of 575 and 918 μm, respectively. This supports that the agglomerates in the main agglomerate size fractions are formed from a single PEG particle by the immersion mechanism. The absence of significant agglomerate growth during massing time (Figs. 1a, 2b and c) also supports that the mechanism of agglomerate formation and growth is primarily immersion (Seo and Schæfer, 2001). An immersion of lactose in the surface of an agglomerate will decrease the liquid saturation of the surface layer and thus counteract agglomerate growth by coalescence.

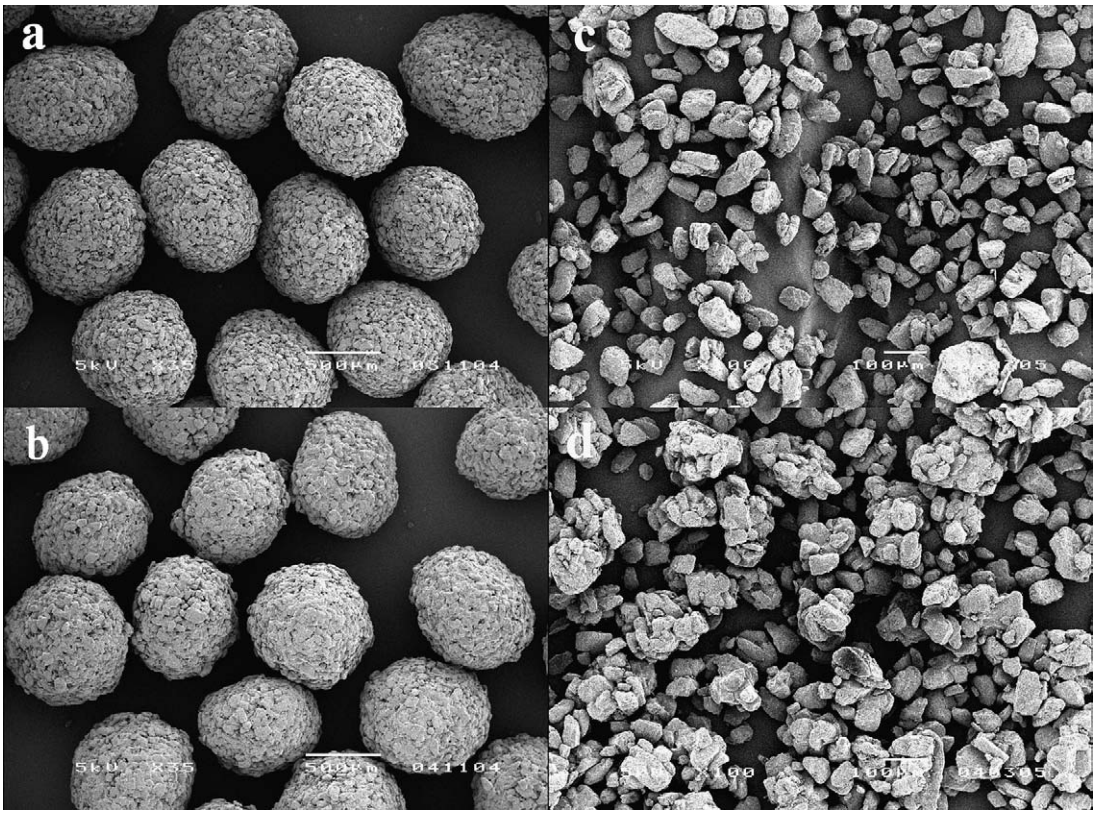

Fig. 4. SEM images of agglomerates produced by the melt-in procedure with PEG particle size fraction 500–750 μm. Agglomerate sieve fraction (a) 630–900 μm at 0 min, (b) 630–900 μm at 8 min, (c) 0–250 μm at 0 min, and (d) 0–250 μm at 8 min of massing.

The immersion mechanism is further supported by the presence of fines in the agglomerates made with the PEG size fractions 250–500 and 500–750 μm (Fig. 2b and c). By immersion, fines will be present at the beginning of agglomeration, because the lactose particles, which initially are captured by a molten PEG particle, have to penetrate into the PEG particle, before the PEG particle will be able to capture more lactose particles. Furthermore, the amount of fines present is seen to increase with increasing PEG particle size since the immersion rate of lactose particles will become slower due to the decreasing surface area of the larger PEG particles.

Fig. 4 indicates that the mechanism of agglomerate formation and growth is mainly immersion for agglomerates produced with PEG from the size fraction 500–750 μm. Similar SEM images were obtained with the PEG size fraction 250–500 μm. It appears (Fig. 4a) that the agglomerates at 0 min of massing are most likely formed from a single PEG particle, and that the lactose particles seem to be immersed in the surface of the agglomerates. After 8 min of massing (Fig. 4b), the PEG is beginning to cover the surface of the agglomerates indicating that the PEG moves slowly to the surface of the agglomerates due to a densification.

In Fig. 4c, it can be seen that the agglomerate size fraction 0–250 μm mainly consists of unagglomerated lactose particles, especially lactose particles being considerably larger than the mean particle size (30 μm) of the lactose. This is probably because it is more difficult to immerse a large particle in a PEG droplet than a smaller one (Schæfer et al., 2004). After 8 min of massing (Fig. 4d), the agglomerate size fraction 0–250 μm contains fewer unagglomerated lactose particles. The agglomerates seen in this size fraction appear to have been formed by distribution and coalescence. Collisions between the largest lactose particles and large agglomerates having a high concentration of PEG on

the surface (Fig. 4b) will typically result in a rebound because of insufficient binding forces. By such collisions, however, some PEG might be transferred to the lactose particles making it possible for them to form small agglomerates by distribution and coalescence (Fig. 4d). No indications of breakage could be seen in the SEM images.

Table 4 indicates that the mechanism of agglomerate formation and growth for agglomerates produced with PEG from the size fractions 250–500 and 500–750 μm is immersion since the PEG content in the larger agglomerate size fractions is high at 0 min of massing and considerably decreased after 8 min of massing. The PEG content becomes decreased, because more lactose particles become immersed in the agglomerates during massing. The PEG content in the larger agglomerate size fraction is further decreased, and the PEG content in the smaller agglomerate size fractions is seen to become increased during massing for the PEG size fraction 250–500 μm due to a transfer of PEG from the agglomerates to lactose particles by collisions as described above.

Melt agglomeration experiments with PEG 3000 in a high shear mixer (Schæfer and Mathiesen, 1996) showed that the agglomerate formation and growth occurred by distribution and coalescence regardless of the size of the PEG particles. This was because the high shearing forces from the impeller rapidly distributed the molten binder. In a fluid bed granulator, the mechanisms of agglomerate formation and growth with PEG 4000 have been shown to be distribution and coalescence when the PEG particle size was 108 μm and immersion when the PEG particle size was 390 or 549 μm (Abberger, 2001).

3.4. Mechanisms of agglomerate formation and growth by the spray-on procedure

Fig. 5 shows that agglomerates are already formed at 0 min of massing. This is because of the 55 s of continuous spraying of PEG upon the lactose before the massing time was started. This makes it difficult to determine the exact mechanism of agglomerate formation. Furthermore, the continuous spraying of molten PEG might cause a surface wetting of agglomerates formed by immersion giving rise to growth by coalescence. Therefore, nuclei are supposed to be formed by the distribution as well as the immersion mechanism,

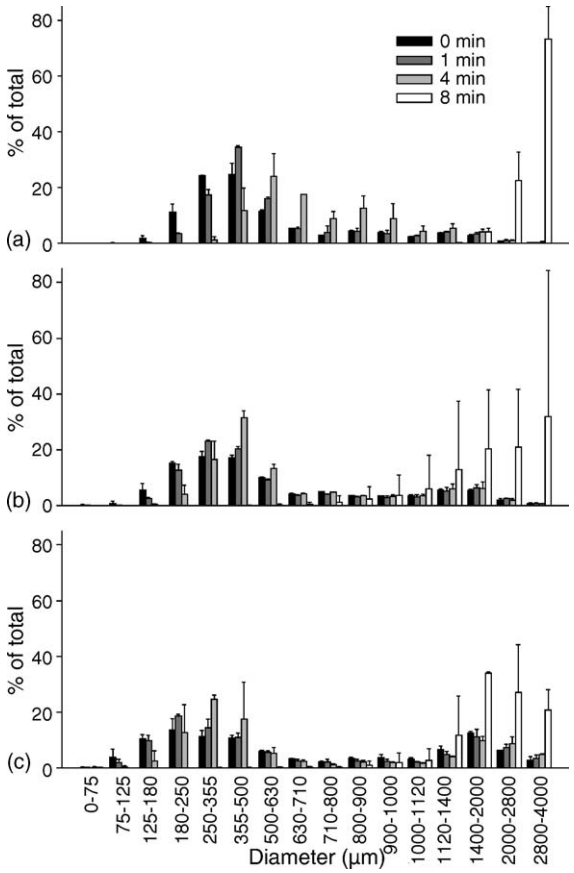

Fig. 5. Effect of PEG mean droplet size and massing time on size distributions of agglomerates produced by the spray-on procedure. PEG mean droplet size of (a) 25 μm, (b) 48 μm, and (c) 69 μm. The bars represent the range between the repeated experiments.

the smaller droplets of the spray causing distribution and the larger droplets causing immersion.

Figs. 1a and 5 indicate that the agglomerate growth primarily occurs by coalescence between nuclei since most of the agglomerates are markedly larger than those that can be formed by immersion. Theoretical calculations of the agglomerate size that can be formed from a single PEG droplet by immersion based on the PEG mean droplet sizes of 25, 48, and 69 μm result in agglomerate sizes of 41, 78, and 112 μm, respectively.

Agglomerate formation by immersion will be more pronounced at a larger droplet size (Abberger et al., 2002). An immersion will delay an agglomerate growth by coalescence as discussed in relation to Fig. 2b and

c. A larger droplet size, therefore, is seen (Fig. 5) to give rise to a lower agglomerate growth rate. In addition, the agglomerate size distribution at 0 min of massing becomes more bimodal when the PEG mean droplet size is increased. This is because a larger droplet sprayed upon an agglomerate will result in a larger local overwetting enabling coalescence between the larger agglomerates.

SEM images show (Fig. 6a) that agglomerates at 0 min of massing appear to be irregular in shape indicating that they are formed from multiple smaller agglomerates by coalescence. Furthermore, single lactose particles are indistinguishable supporting that PEG covers the surface of the initial agglomerates due to the continuous spraying of PEG. After 4 min of massing (Fig. 6b), the agglomerates have become densified resulting in more PEG at the agglomerate surface. This gives rise to more agglomerate growth by coalescence between agglomerates. Further densification gives rise to an uncontrollable agglomerate growth resulting in the agglomerates shown in Fig. 6c. Similar SEM images were obtained with the larger droplet sizes.

Contrary to the melt-in procedure, the spray-on procedure results in an uncontrollable agglomerate growth between 4 and 8 min of massing (Fig. 1a). This is explained by a higher surface wetness of the agglomerates produced by the spray-on procedure because of the continuous spraying of PEG upon the initial agglomerates. Further, the atomized droplets are smaller than the solid PEG particles (Table 2), and this will promote a distribution of PEG on the surface of the initial lactose particles.

Table 5 shows that the variation in the PEG content between agglomerate size fractions is smaller than that seen in Table 4 for the PEG size fractions 250–500 and 500–750 μm, which primarily gave rise to agglomerate growth by immersion. This supports that the spray-on procedure results in agglomerate growth by coalescence. During the last 4 min of massing, a slight increase in PEG content in the agglomerates in the main agglomerate size fractions can be seen because of a higher probability of coalescence between agglomerates with a higher binder content (Knight et al., 1998; Johansen and Schæfer, 2001). Furthermore, it can be seen that the PEG content is high in large agglomerates (1120–2800 μm) produced with a PEG mean droplet size of 69 μm at 0 and 4 min of massing in accordance

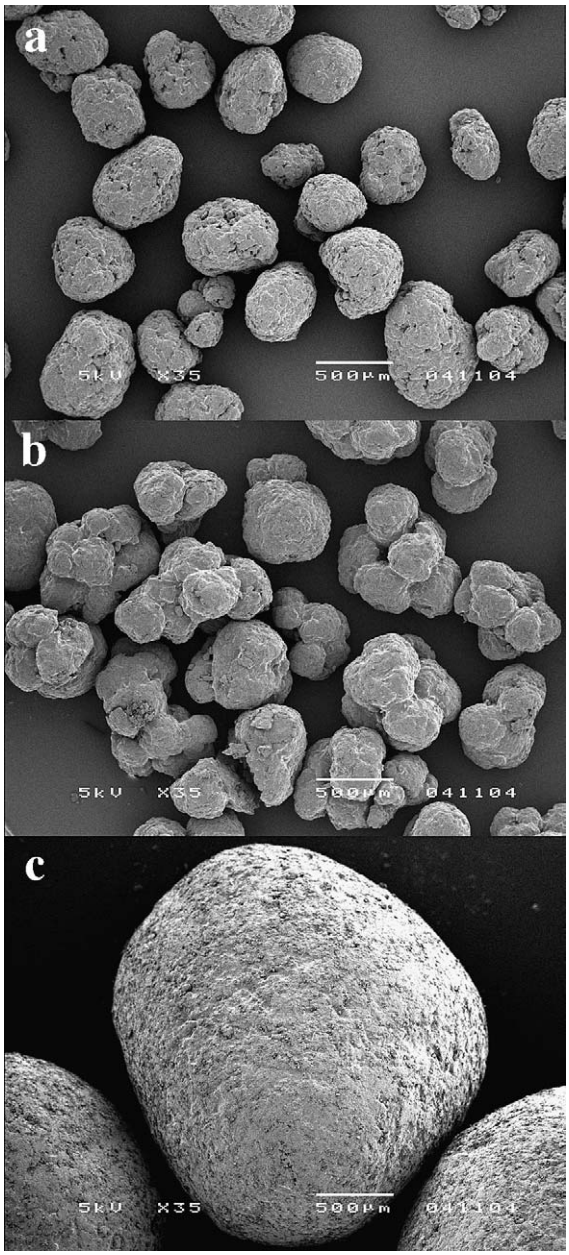

Fig. 6. SEM images of agglomerates produced by the spray-on procedure with a PEG mean droplet size of 25 μm. Agglomerate sieve fraction (a) 250–630 μm at 0 min, (b) 355–710 μm at 4 min, and (c) 2000–4000 μm at 8 min of massing.

Table 5
Effect of PEG droplet size and massing time on the PEG content in selected agglomerate size fractions produced by the spray-on procedure

PEG droplet size (μm)	Massing time (min)	Agglomerate size fraction (μm)	PEG content (% m/m of lactose)
25	0	250–630[a]	24
25	4	355–710[a]	23
25	8	2000–4000[a]	28
48	0	180–500[a]	26
48	4	250–630[a]	27
48	8	2000–4000[a]	28
69	0	125–355[a]	23
69	4	180–500[a]	26
69	8	1120–2800[a]	28
69	0	1120–2800	33
69	4	1120–2800	36

[a] Main agglomerate size fraction.

with the assumption that a larger droplet size results in a less uniform distribution of the PEG.

Melt agglomeration experiments with PEG 3000 in a fluid bed granulator (Abberger et al., 2002; Seo et al., 2002) have shown that the agglomerate formation occurred by distribution when the PEG droplet size was smaller than the particle size of the lactose and by immersion when the PEG droplet size was larger than the lactose particle size. Furthermore, it was found that continued spraying of molten PEG enabled agglomerate growth by coalescence between nuclei due to wetting of the surface of the nuclei. However, in contrast to the findings in the rotary processor, it was found that the agglomerate growth in the fluid bed granulator was unaffected by further processing after the end of binder addition due to the low shearing forces (Seo et al., 2002).

4. Conclusions

The binder addition procedure and the binder particle/droplet size influence the mechanisms of agglomerate formation and growth during melt agglomeration in a rotary processor. If the size of the binder particles or droplets is markedly larger than the size of the solid particles, agglomerate formation and growth are expected primarily to occur by the immersion mechanism. If the size of the binder particles or droplets is smaller than or at the most only slightly larger than the size of the solid particles, the formation of nuclei is expected primarily to occur by distribution and coalescence. Further agglomerate growth will occur by coalescence between nuclei and/or agglomerates.

The melt agglomeration process seems to be more controllable when the binder is added as solid particles instead of a continuous spraying of molten binder, and if the binder particle/droplet size is so large that it gives rise to immersion as the main agglomerate formation and growth mechanism. A continuous spraying of molten binder will wet the surface of the initially formed nuclei and agglomerates thereby promoting rapid agglomerate growth by coalescence.

Compared to high shear mixers, the effect of the binder particle or droplet size is more pronounced in a rotary processor due to the lower shearing forces. A rotary processor resembles conventional fluid bed granulators in the mechanisms of agglomerate formation and growth. However, a rotary processor differs from fluid bed granulators since agglomerate growth by coalescence can occur at prolonged massing. This is due to the higher shearing forces in a rotary processor compared to fluid bed granulators, which give rise to a densification of the agglomerates during massing time.

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