Melt pelletization in a high shear mixer
VI. Agglomeration of a cohesive powder

Torben Schæfer

Royal Danish School of Pharmacy, Department of Pharmaceutics, 2 Universitetsparken, DK-2100 Copenhagen, Denmark

Abstract

A cohesive grade of anhydrous lactose was melt pelletized in an 8-l high shear mixer using polyethylene glycol (PEG) 3000 or 6000 as meltable binder in varying concentrations. The agglomerate growth was dependent on the liquid saturation of the agglomerates. The process was difficult to control, because the liquid saturation had to exceed 100% in order to produce agglomerates of pellet size. PEG 6000 gave rise to agglomerates that were more sticky than those produced with PEG 3000. The pelletization properties were not improved by the addition of 10% or 20% of a coarser anhydrous lactose.

Keywords: Particle size; Polyethylene glycols; Pellet; Melt pelletization; Melt granulation; High shear mixer

1. Introduction

Agglomeration processes are strongly affected by the particle size and size distribution of the starting materials. It is a general experience that a decrease in mean particle size demands an increase in the amount of binder liquid in order to keep the mean size of the agglomerates constant. This correlation was also found to be valid in melt agglomeration experiments (Kinget and Kemel, 1985; Schæfer et al., 1990; Schæfer et al., 1992c).

Schæfer et al. (1992c) have previously claimed that the optimal mean particle size for melt pelletization in a high shear mixer is 20–25 μm. A mean particle size smaller than about 10 μm was assumed to give rise to a process that is difficult to control, but no experiments were carried out with such a strongly cohesive material. Melt granulation of a drug with a mean particle size of 5 μm was, however, found to be possible in a high shear mixer (McTaggart et al., 1984), probably because of a lower risk of overwetting due to a smaller size of the final agglomerates. Holm et al. (1993) were able to wet pelletize a material with a mean particle size of 8.5 μm in a high shear mixer by controlled evaporation of the free moisture, which was forced to the agglomerate surface due to densification.

The purpose of the present work was to investigate how a melt pelletization process is affected by a strongly cohesive material.

2. Materials and methods

2.1. Materials

Anhydrous lactose (Pharmatose DCL 21, DMV, The Netherlands) of two different particle sizes was used as starting material. Polyethylene glycol (PEG) 3000 and 6000 (Hoechst, Germany) were used as meltable binders. PEG 3000 was used as flakes and PEG 6000 as a fine powder.

The size distribution by volume of the fine grade of the anhydrous lactose was determined by a Malvern 2601Lc laser diffraction particle sizer (Malvern Instruments, UK). The size distribution by weight of the coarse grade material was determined by sieve analysis. The geometric mean particle diameter and the geometric standard deviation were calculated to be 6.8 μm and 2.0 for the fine grade and 127 μm and 2.2 for the coarse grade.

The BET multipoint surface area of the anhydrous lactose, determined by a Gemini 2375 Surface Area Analyzer (Micromeritics Instrument Corporation, USA), was 1.49 m^2/g for the fine grade and 0.24 m^2/g for the coarse grade. The densities of the fine and the coarse grades were 1.61 g/cm^3 and 1.58 g/cm^3, respectively, determined by an AccuPyc 1330 gas displacement pycnometer (Micromeritics, USA) using helium purge.

The melting range of the PEGs was estimated by a Perkin Elmer DSC 7 differential scanning calorimeter (Perkin Elmer, USA). A sample of about 4 mg was sealed in a 40-μl aluminium pan and scanned between 40°C and 80°C at a heating rate of 2°C per min. The melting range of PEG 3000 was found to be 46–59°C with a peak temperature of 57°C. PEG 6000 had a melting range of 54–63°C with a peak temperature of 61°C.

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., 1993), was employed in the experiments. The temperature of the heating jacket was set to 50°C in all the experiments.

2.3. Mixing procedure

The load of the mixer was 1 kg of anhydrous lactose in all the experiments, and varying amounts of PEG were added in a solid state. The PEG concentration is expressed as the percentage (% m/m) of the amount of lactose.

Lactose and PEG were dry mixed at an impeller speed of 1300 rev./min. The impeller speed was changed to either 900 rev./min or 1450 rev./min 2 min after the melting point of the PEG was observed as an inflection point on the product temperature curve from the recorder. This inflection point was defined as the start of massing time.

At the end of the process, the amount of agglomerate which flowed from the bowl when tilted was weighed, sieved as discussed in Section 2.4.1 and then spread out in thin layers on trays in order to cool at ambient temperature. The adhesion to the bowl was estimated as the difference between the amount of material left in the bowl and the amount freely emptied.

2.4. Granule characterization

2.4.1. Size distribution

Immediately after emptying the bowl, the amount of lumps larger than 4 mm was determined as the retained fraction after vibrating the agglomerates on a Jel-Fix 50 vibration sieve (J. Engelsmann AG, Germany) for about 10 s.

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 in the range of 75–4000 μm was vibrated as previously described (Schæfer et al., 1992a).

2.4.2. Intragranular porosity

The intragranular porosity was estimated by a mercury immersion method, and the liquid saturation was calculated as previously described (Schæfer et al., 1992a). In the calculation of the liquid saturations a correction was made for changes in the volume of binder liquid owing to

changes in product temperature during the process. A size fraction including the three sieve fractions closest to the mean diameter was used for the measurements. All results are mean values of two estimations.

2.4.3. Scanning electron microscopy

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

2.5. Experimental design

All experiments were carried out in duplicate. The results were subjected to analysis of variance when possible. The results shown in this paper are mean values of two experiments unless otherwise stated.

3. Results and discussion

3.1. Experiments with the fine grade of the anhydrous lactose

In all the experiments in the present paper frictional heat owing to the impeller gave rise to product temperatures, which were markedly above the melting points of the PEGs (Schæfer et al., 1993). The product temperatures at 17 min of massing in the experiments in Fig. 1 were between 79°C and 109°C.

The effects of impeller speed and type of PEG on mean granule size, granule size distribution and amount of lumps at varying massing times are shown in Fig. 1. Preliminary experiments showed the process to be more sensitive to variations in binder concentration than previously seen (Schæfer et al., 1990; Schæfer et al., 1992a; Knight, 1993). An increase in binder concentration to 0.5–1% above the concentrations used in Fig. 1 gave rise to overwetting, and a similar decrease resulted in a final product that was a powder or very small granules.

In previous experiments with lactose monohydrates with mean particle sizes of 22 μm and 68 μm (Schæfer et al., 1990; Schæfer et al., 1992a), it was possible to compare PEG 3000 with PEG 6000 at the same binder concentration. In the

experiments at 900 rev./min (Fig. 1) however, it was necessary to use a slightly higher concentration of PEG 6000 in order to obtain agglomeration. This is ascribed to the higher viscosity of the molten PEG 6000 (Schæfer et al., 1990). The combination of a cohesive powder and a highly viscous binder liquid will give rise to agglomerates that are difficult to densify and deform. An increased binder concentration will promote densifi-
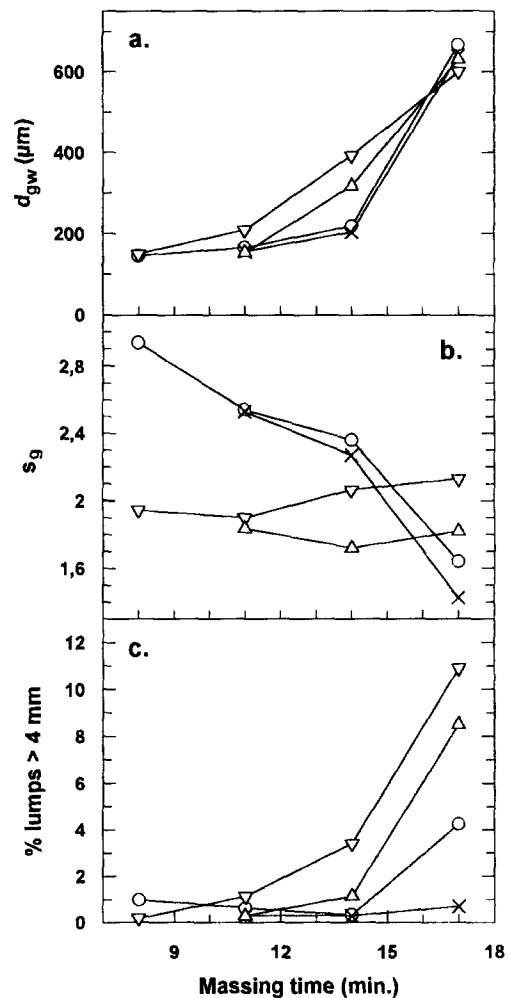

Fig. 1. Effects of impeller speed (rev./min) and type and concentration of PEG on the mean granule size (a), the geometric standard deviation (b) and the amount of lumps (c) during massing. (○) PEG 3000, 29%, 900 rev./min; (▽) PEG 6000, 30.5%, 900 rev./min; (×) PEG 3000, 26%, 1450 rev./min; (△) PEG 6000, 26%, 1450 rev./min.
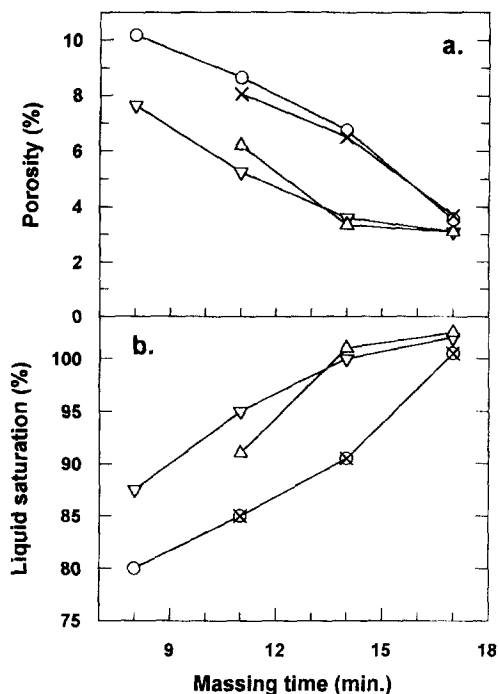
Fig. 2. Effects of impeller speed (rev./min) and type and concentration (%) of PEG on the intragranular porosity (a) and the liquid saturation (b) during massing. (○) PEG 3000, 29%, 900 rev./min; (▽) PEG 6000, 30.5%, 900 rev./min; (×) PEG 3000, 26%, 1450 rev./min; (△) PEG 6000, 26%, 1450 rev./min.

cation and deformability and thus promote agglomerate growth by coalescence.

A higher impeller speed will overcome the strong cohesion forces within the agglomerates and thus increase the densification rate. Consequently, the liquid saturation being sufficient for agglomerate growth is obtained at a lower binder concentration (Fig. 2). This is why the binder concentration had to be reduced from 29% or 30.5% to 26% when the impeller speed was increased from 900 to 1450 rev./min. At 1450 rev./min, PEG 3000 and PEG 6000 could be used in the same concentration. This indicates that the effect of viscosity on densification disappears when the impeller speed becomes sufficiently high. The effect of impeller speed was less pronounced in previous experiments with less cohesive materials (Kinget and Kemel, 1985; Schæfer et al., 1992a), because an increase in particle size pro-

motes the densification.

Fig. 1a shows that when PEG 3000 is used as the binder, the agglomerate growth curves are nearly coincident in spite of marked differences in binder concentration and impeller speed. This is explained by the fact that the liquid saturations are coincident (Fig. 2b). Slight differences in the growth curves are seen in the experiments with PEG 6000. However, the final mean granule size is at the same level independent of impeller speed and type of PEG. This is in agreement with Fig. 2b showing that the final liquid saturations become similar.

Fig. 1b shows that the type of PEG has a significant effect on the granule size distribution. With PEG 3000, a marked decrease in s_g is seen by prolonged massing, whereas the s_g-value is nearly unaffected by the massing time when PEG 6000 is used. In accordance with previous results (Kinget and Kemel, 1985; Schæfer et al., 1990; Schæfer et al., 1992a; Schæfer et al., 1993), a higher impeller speed results in a narrower size distribution. The effect of type of PEG on the size distribution was unexpected, since a similar effect was not seen in previous experiments with lactose of a coarser particle size (Schæfer et al., 1990; Schæfer et al., 1992a). It was expected that the higher viscosity of the PEG 6000 might have caused a wider size distribution due to a more difficult distribution of the binder in the powder mass (Kinget and Kemel, 1985).

Fig. 3 gives a more detailed description of the changes in size distribution during the experiments at 1450 rev./min. The agreement with the log-normal distribution is reasonably good. However, there is an over-representation of larger granules, especially in the experiments with PEG 6000. Fig. 3 indicates that the agglomerate growth mechanisms are dependent on the type of PEG. With PEG 3000 (Fig. 1b and Fig. 3a), the size distribution becomes markedly narrowed by prolonged massing in contrast to the size distributions obtained with PEG 6000 (Fig. 1b and Fig. 3b). Similar changes were seen during the experiments at 900 rev./min.

Previous melt granulation (Knight, 1993) and wet granulation (Schæfer et al., 1987) experiments have shown size distribution curves similar to

those in Fig. 3b in experiments with no chopper action, whereas the distributions obtained in experiments with an active chopper changed similar to those in Fig. 3a. This narrowing was ascribed to a comminution of larger agglomerates by the chopper. Fig. 3 indicates that agglomerate growth is affected by comminution in the experiments with PEG 3000, whereas comminution is insignificant with PEG 6000. The latter assumption is supported by the over-representation of larger granules seen with PEG 6000. The lower intragranular porosity obtained with PEG 6000 (Fig. 2a) will increase the strength of the agglomerates (Kristensen et al., 1985a), and this explains why

agglomerates produced with PEG 6000 are more resistant to comminution than those produced with PEG 3000.

The distribution of the binder is assumed to be especially critical when granulating fine powders (Ennis et al., 1991). It is assumed that the cohesiveness of the anhydrous lactose makes it difficult to obtain a uniform distribution of molten flakes, whereas finely powdered PEG gives rise to a more homogeneous distribution of the binder liquid after melting. Agglomeration with PEG 6000 causes denser granules and a higher liquid saturation early in the process.

The higher strength of the agglomerates containing PEG 6000 is reflected in the amount of lumps in the product as presented in Fig. 1c. PEG 6000 gives rise to a higher amount of lumps than does PEG 3000. A higher impeller speed reduces the amount of lumps. This confirms the assumption that the amount of lumps is related to the strength of the agglomerate.

Since the results in Fig. 1 are mean values of the results of two experiments, the figure gives no indication of the reproducibility of the experiments. On the basis of the experiments at massing times of 8, 11 and 14 min, the standard deviations of the mean granule size, the geometric standard deviation and the amount of lumps were estimated by the analysis of variance. Reproducibility was found to be similar to results from previous experiments with the same load in the same mixer (Schæfer et al., 1993), i.e. the standard deviation of the mean granule size was about 20 μm. At a massing time of 17 min, however, the process was less reproducible. The two experiments with PEG 3000 at 900 rev./min resulted in mean granule sizes of 441 μm and 894 μm and amount of lumps of 0.4% and 8.1%. Although the variations between the other repeated experiments at 17 min were found to be much lower, it seems to be difficult to control the pelletization of a cohesive material.

The loss of material due to adhesion to the bowl and the impeller was about 5% in all the experiments independent of process conditions. This is slightly higher than the adhesion found with a less cohesive material in the same mixer (Schæfer et al., 1993).
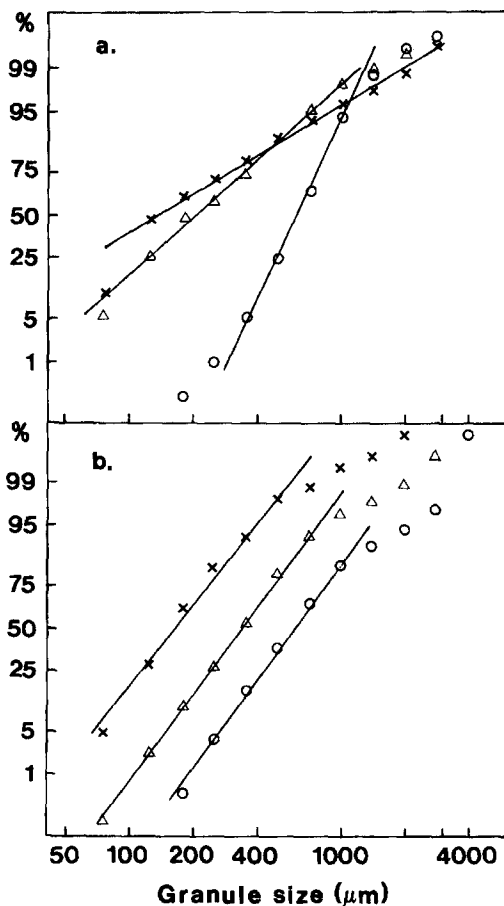

Fig. 3. Log-probability plot of cumulative weight distributions during massing with PEG 3000 (a) and PEG 6000 (b). Binder concentration: 26%; impeller speed: 1450 rev./min; massing time: (×) 11 min, (△) 14 min, (○) 17 min.
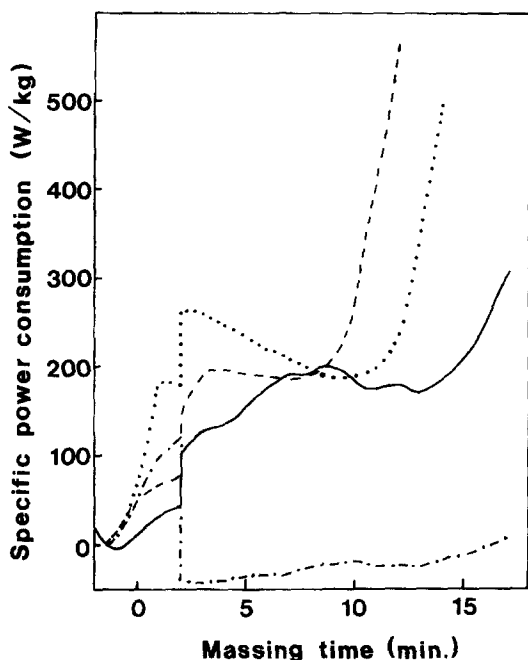
Fig. 4. Effects of binder concentration (%) and impeller speed (rev./min) on the specific power consumption during massing. Binder: PEG 6000. (———) 26%, 1450 rev./min; (⋯) 27%, 1450 rev./min; (- - -) 28%, 1450 rev./min; (- · - · - ·) 30.5%, 900 rev./min.

It was previously shown that the agglomerate growth during melt pelletization was reflected in the power consumption of the impeller motor (Schæfer et al., 1992b). Fig. 4 shows the changes in power consumption during four single experiments with PEG 6000 in varying concentrations. The marked changes in power consumption after 2 min of massing are due to the change in impeller speed at that time. As expected, the power consumption is seen to be markedly lower at 900 rev./min than at 1450 rev./min. The experiments with 27% and 28% of binder had to be stopped after 14 min and 12 min of massing respectively, because agglomerate growth was becoming uncontrollable. In the remaining experiments, which were stopped after 17 min, the product was close to being overwetted. It is seen that the start of uncontrollable growth is reflected in an increase in power consumption. This increase is steepest at a high impeller speed due to a higher densification

rate. A steeper increase in power consumption is further caused by a higher binder concentration. In all the experiments shown in Fig. 4, the final liquid saturations were found to be 102–103%. This indicates that the occurrence of uncontrolled growth is closely related to the liquid saturation.

It was found in melt granulation experiments (Knight, 1993) that granules had to be saturated, or near saturated, in order to obtain agglomerate growth by coalescence. In previous melt pelletization experiments, the liquid saturations, which gave rise to formation of pellets, were 90–100% (Schæfer et al., 1992b; Schæfer et al., 1993) or 80–90% (Schæfer et al., 1990). In the present experiments, the liquid saturations after 17 min of massing were 100–101% with PEG 3000 and 102–103% with PEG 6000. Since the agglomerate strength is increased due to the small particle size of the anhydrous lactose, the liquid saturation must slightly exceed 100% in order to obtain a deformability that is sufficient for agglomerate growth by coalescence (Kristensen et al., 1985b). A higher viscosity makes the agglomerates less deformable. In order to compensate this, the liquid saturation has to be slightly higher with PEG 6000 than with PEG 3000.

When the liquid saturation exceeds 100%, binder liquid will be present on the surface of the agglomerates, and this will increase the risk of uncontrolled agglomerate growth. Fig. 5 shows that the high liquid saturation causes coalescence between relatively large agglomerates. With PEG 3000 (Fig. 5a), this typically gave rise to pellets with an irregular shape. With PEG 6000, the volume of binder liquid on the surface will be slightly larger. Small pellets, therefore, formed clusters (Fig. 5b), which could not be separated into the initial agglomerates by sieving, either before or after the congealing of the binder. This means that such clusters were estimated as large agglomerates by the sieve analysis.

3.2. Experiments with mixtures of the fine and the coarse grades of the anhydrous lactose

In order to investigate whether the admixture of a small amount of a free-flowing material might improve the pelletization properties of a
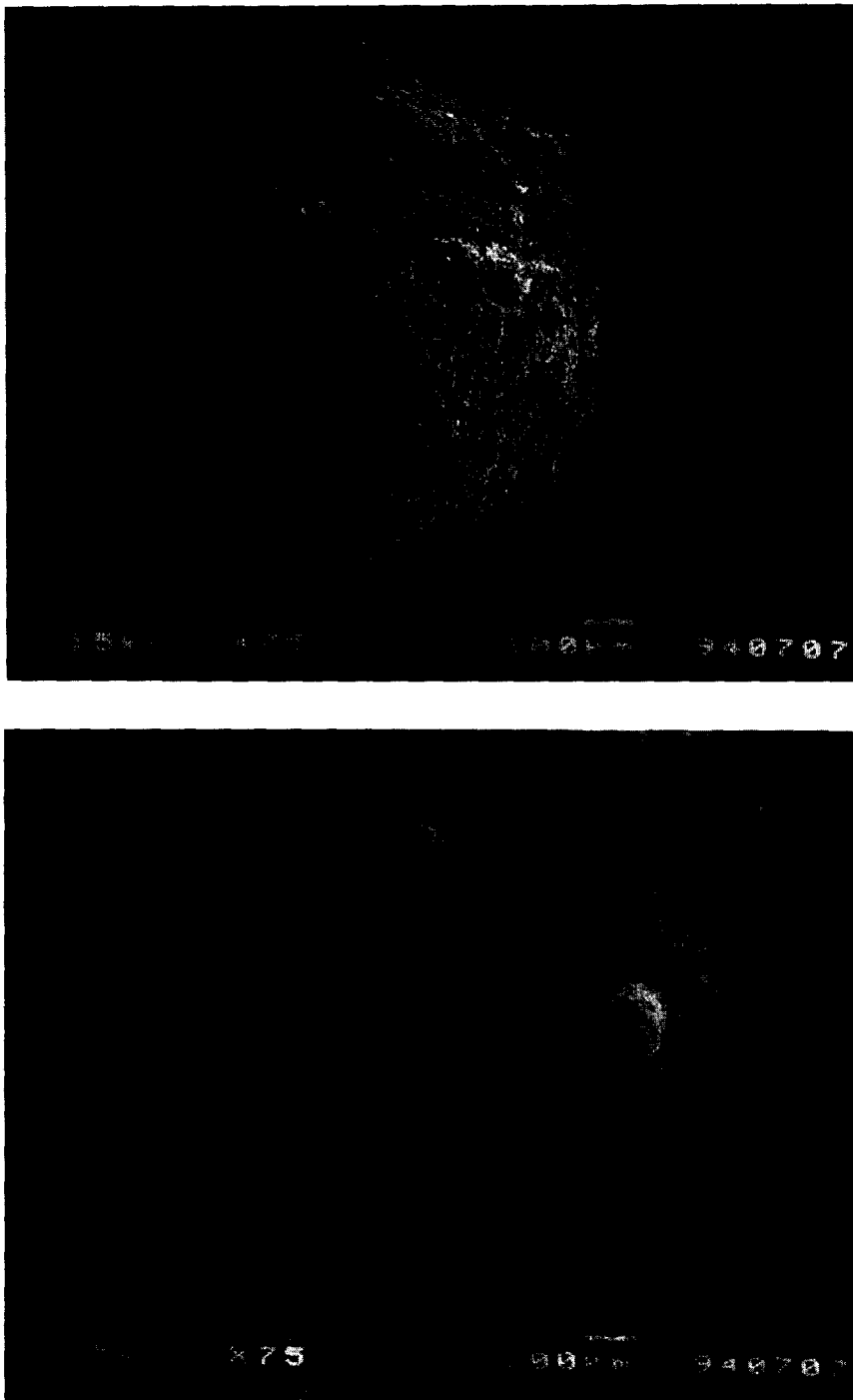
Fig. 5. SEM photographs of pellets produced with 29% PEG 3000 (a) and 30.5% PEG 6000 (b). Impeller speed: 900 rev./min; massing time: 17 min.

cohesive material, further experiments were carried out. In these experiments, 10% or 20% of the coarse grade of the anhydrous lactose was added to the fine grade. PEG 3000 was used as binder. In the figures, the results are compared with some of the above-mentioned results of experiments with the fine lactose.

Fig. 6 shows the effects of mixing ratio on intragranular porosity and liquid saturation. The binder concentrations used in the experiments were chosen on the basis of preliminary experiments. The formulations were still found to be sensitive to variations of 0.5–1% in the binder concentration. The binder concentration had to be decreased when the percentage of coarse lactose was increased. The amount of PEG per surface area (BET) was calculated to be 0.195 g/m^2 in the case of no addition of coarse lactose and 0.190 g/m^2 in the experiments with 10% as well as

Fig. 7. Effects of addition of coarse lactose on the mean granule size (a), the geometric standard deviation (b) and the amount of lumps (c) during massing. Binder: PEG 3000; impeller speed: 900 rev./min. Percentage of coarse lactose: (○) 0%; (△) 10%; (×) 20%. Binder concentration: (○) 29%; (△) 26%; (×) 23.5%.
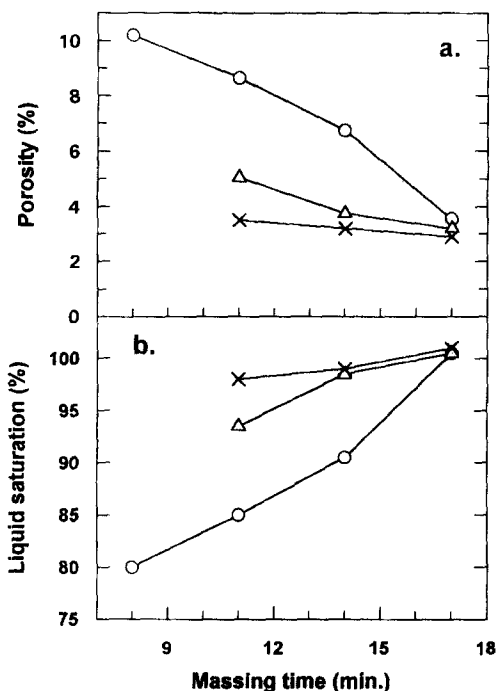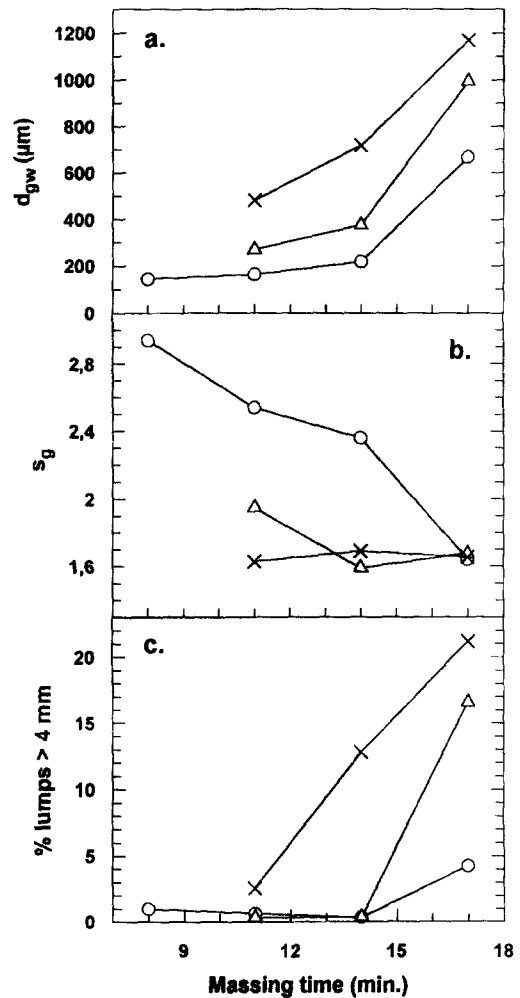
Fig. 6. Effects of addition of coarse lactose on the intragranular porosity (a) and the liquid saturation (b) during massing. Binder: PEG 3000; impeller speed: 900 rev./min. Percentage of coarse lactose: (○) 0%; (△) 10%; (×) 20%. Binder concentration: (○) 29%; (△) 26%; (×) 23.5%.

20% of coarse lactose. Thus, the optimal amount of PEG seems to be approximately proportional to the surface area of the powder mass.

As can be seen in Fig. 6a, the addition of coarse lactose makes the mixture less cohesive, and this increases the densification rate. The final porosity becomes slightly lower at an increasing percentage of coarse lactose. The final liquid saturations are all 100–101% (Fig. 6b). This indicates that the

risk of uncontrolled agglomerate growth is not reduced by the addition of coarse particles.

The differences in liquid saturation during the process are reflected in the agglomerate growth (Fig. 7a). It is seen that the addition of coarse lactose results in a higher agglomerate growth rate early in the process in accordance with the higher liquid saturation. The tendency for the above-mentioned formation of clusters of pellets after 17 min of massing was larger by increasing the content of coarse lactose, although the liquid saturations were similar. The differences in mean granule size after 17 min, therefore, are partly due to differences in cluster formation.

After 17 min of massing, the addition of coarse particles has no effect on the geometric standard deviation (Fig. 7b). Earlier in the process, the size distribution becomes narrower by the addition of coarse lactose.

Fig. 7c shows that the addition of coarse lactose results in a marked increase in the content of lumps in the final product. Some of the lumps, however, were flat lumps, which were a result of a detachment of mass, which had been adhering to the bowl. This type of lump was particularly seen in the experiments with 20% of coarse lactose.

4. Conclusions

The melt pelletization of a cohesive material was found to be controlled by the liquid saturation of the agglomerates. The small size of the initial particles gives rise to agglomerates of a high strength and a low deformability. Consequently, the liquid saturation had to be increased to a value slightly above 100% in order to obtain a deformability which was sufficiently high for a marked agglomerate growth by coalescence. At such liquid saturations, there will be free binder liquid on the surface of the agglomerates. This results in a high risk of uncontrollable agglomerate growth and a risk of formation of clusters due to a sticking together of agglomerates.

It was found to be possible to produce rounded agglomerates with reproducible physical properties within the agglomerate size range of 200–400

μm. Larger agglomerates could be produced, but the reproducibility was found to be rather poor, and the agglomerates were sticky. PEG 3000 caused less sticky agglomerates than did PEG 6000, probably owing to a lower viscosity and a slightly lower liquid saturation. Admixture of 10% or 20% of a coarser material did not improve the pelletization properties of the cohesive powder.

The experiments indicate that the granule size distribution and the agglomerate growth mechanisms are affected by the viscosity as well as by the initial particle size of the binder. Therefore, there is a need for further investigations into the effects of type and particle size of the PEG.

References

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

Holm, P., Schæfer, T. and Kristensen, H.G., Pelletization by controlled wet granulation in a high-shear mixer. *Stp Pharma Sci.*, 3 (1993) 286–293.

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

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

Kristensen, H.G., Holm, P. and Schæfer, T., Mechanical properties of moist agglomerates in relation to granulation mechanisms. Part I. Deformability of moist, densified agglomerates. *Powder Technol.*, 44 (1985a) 227–237.

Kristensen, H.G., Holm, P. and Schæfer, T., Mechanical properties of moist agglomerates in relation to granulation mechanisms. Part II. Effects of particle size distribution. *Powder Technol.*, 44 (1985b) 239–247.

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

Schæfer, T., Bak, H.H., Jægerskou, A., Kristensen, A., Svensson, J.R., Holm, P. and Kristensen, H.G., Granulation in different types of high speed mixers. Part 2: Comparisons between mixers. *Pharm. Ind.*, 49 (1987) 297–304.

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

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

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

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

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