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Melt pelletization in a high shear mixer. X. Agglomeration of binary mixtures

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Abstract

Mannitol of three different particle sizes and lactose were melt pelletized in an 8 l high shear mixer, separately and in binary mixtures containing 25, 50 or 75% of lactose. Polyethylene glycol 3000 was used as meltable binder. Mannitol was found to be unsuitable for melt pelletization without an admixture of lactose, because the plate-like shape of the particles gave rise to agglomerates of an irregular shape. An increasing content of lactose in the binary mixture resulted in smoother and more spherical agglomerates. The mannitol grade with a median particle size of 36 μm was found to be the most suitable for pelletization.

Keywords: Mannitol; Binary mixture; Particle shape; Particle size; Melt pelletization; High shear mixer

1. Introduction

Most pharmaceutical formulations for agglomeration contain two or more components, the agglomeration properties of which might interact. Detailed studies on wet granulation of binary (Opakunle and Spring, 1976a,b,c) and ternary (Jaiyeoba and Spring, 1979, 1980a,b, 1981) mixtures have shown that the agglomerate properties are markedly dependent on the physical properties of the individual components and on the mixing ratio between the components. Similar conclusions were drawn from experiments on wet pelletization by extrusion/spheronization (Wan et al., 1993; Nymo et al., 1995) and from wet pelletization experiments in a high shear mixer (Kleinebudde and Nymo, 1995).

Usteri and Leuenberger (1989) employed the percolation theory to describe wet agglomeration of binary mixtures in a high shear mixer. They concluded that the agglomerate growth properties are additive, if the components exhibit similar growth properties. If components of different growth properties are used, the mixing ratio will decide whether one of the components will predominate the growth properties of the mixture or

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Table 1
Physical properties of the materials

Materials	M.D. (μm)	Span	Tr.D. (g/cm^3)	S.A. (m^2/g)	Wa.C. (%)
Mannitol 25	17	2.7	1.493	0.65	0.0
Mannitol 35	36	2.7	1.488	0.42	0.0
Mannitol 60	66	2.9	1.486	0.30	0.0
Lactose	20	2.1	1.547	0.81	5.1

M.D.: median particle diameter; Span, difference between the diameters at the 90 and 10% points relative to the median diameter; Tr.D., true density; S.A., BET surface area; Wa.C., water content on wet-weight basis.

intermediate growth properties will occur.

The interpretation of the results of most of the above-mentioned experiments is complicated by the fact that one or more of the components became partly dissolved in the aqueous binder liquid during the process. Provided that the components are insoluble in the molten binder, the melt agglomeration process is favourable for fundamental agglomeration studies, because no evaporation of binder liquid occurs.

Melt pelletization in a high shear mixer is a process that is rather sensitive to the physical properties of the materials to be pelletized (Schæfer et al., 1992b; Schæfer and Mathiesen, 1996a). It was found to be possible, however, to melt pelletize theophylline of mean particle sizes ranging from 8 to 100 μm in a binary mixture containing a filler of good pelletization properties and up to 50% of theophylline (Thomsen, 1994). This indicates that it might be possible to melt pelletize a drug substance of poor pelletization properties in a mixture with a proper filler.

Thus, further knowledge of melt pelletization of binary mixtures might form the basis for a wider applicability of the process.

Lactose has previously been found to be a material that is easy to melt pelletize (Schæfer and Mathiesen, 1996a). The purpose of the present work was to investigate the ability of lactose to improve the pelletization properties of a model substance of poor pelletization properties. Mannitol of three different particle sizes was chosen as the model substance.

2. Materials and methods

2.1. Materials

Lactose 450 mesh (α-lactose monohydrate, DMV, The Netherlands) and three particle size grades (referred to as 25, 35, 60) of mannitol (Roquette, France) were used as starting materials. The physical properties of the materials, determined as previously described by Schæfer and Mathiesen (1996a) are presented in Table 1. SEM photographs showed that the shape of the mannitol particles is platelike and needlelike, whereas the lactose particles are more rounded.

The poured and the tapped densities of the starting materials and of the binary mixtures used in the pelletization experiments were determined according to the test for apparent volume (Ph. Eur.). The interparticular porosities were calculated on the basis of the true and the tapped densities.

Polyethylene glycol (PEG) 3000 (Hoechst, Germany) in flakes was used as the meltable binder. The melting range estimated by a differential scanning calorimeter, as previously described by Schæfer and Mathiesen (1996a), was found to be 48–58°C with a peak temperature of 57°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 either lactose, mannitol or a binary mixture of lactose and mannitol. The PEG concentration is expressed as the percentage (% m/m) of the 1 kg of starting material.

In all the experiments, the starting material and the PEG were dry mixed at an impeller speed of 1300 rpm. The impeller speed was decreased to 800 rpm 2 min after the melting point of the PEG was observed as an inflection point on the recorded product temperature curve. This inflection point was defined as the start of massing time. The power consumption of the impeller motor was measured by a power consumption meter and recorded during the process.

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

2.4. Granule characterization

2.4.1. Size distribution

The amount of lumps larger than 4 mm was determined as previously described (Schæfer, 1996). The granule size distribution was estimated by sieve analysis (as previously described by Schæfer and Mathiesen (1996b)) using sieves in the range of 180–2000 μm, and the geometric mean diameter (d_{gw}) and the geometric standard deviation (s_g) were calculated.

Size fractions including the three sieve fractions being closest to the mean diameter were applied for the measurements in Section 2.4.2, Section 2.4.3, Section 2.4.4.

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; Schæfer and Mathiesen, 1996a). Further, porosity values, corrected for the volume of PEG deposited within the pores, were calculated according to the method described by Schæfer et al. (1990).

2.4.3. Water content

The water content on a wet-weight basis, i.e. the water content corresponding to the loss on drying, was estimated by volumetric titration as previously described (Schæfer and Mathiesen, 1996a) using a sample of about 1 g.

2.4.4. Image analysis

The procedure was as previously described (Schæfer and Mathiesen, 1996b). The shape of the agglomerates was characterized by the aspect ratio (length/width), by the roundness ($4\pi \cdot$area/perimeter^2), and by the two-dimensional shape factor, e_R, devised by Podczeck and Newton (1994).

2.4.5. Scanning electron microscopy

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

2.5. Experimental design

A series of 48 experiments with each of the three grades of mannitol and a complementary series of 12 experiments with the lactose were carried out. The mixing ratios mannitol/lactose (% m/m) were varied at 100/0, 75/25, 50/50, 25/75, and 0/100. With each of these mixtures, the concentration of PEG was varied at three levels at a massing time of 17 min. At the highest PEG concentration, further experiments were carried out using massing times of 8, 11 and 14 min. All experiments were carried out in duplicate. The results shown in this paper are mean values of two experiments unless otherwise stated.

The results were subjected to analysis of variance. Certain reservations have to be made, however, by the interpretation of the effects of the mixing ratios, because the PEG concentrations could not be kept constant as will be discussed below.

3. Results and discussion

The impeller speed and the levels of PEG concentration were chosen on the basis of preliminary experiments. An impeller speed of 800 rpm was preferred for the final experiments. A larger amount of lumps in the product resulted when a speed of 1000 rpm was used, and a generation of heat of friction caused a product temperature exceeding 120°C in the experiments without an addition of lactose. Speeds of 400 rpm and 600 rpm resulted in a smaller mean granule size and a wider size distribution.

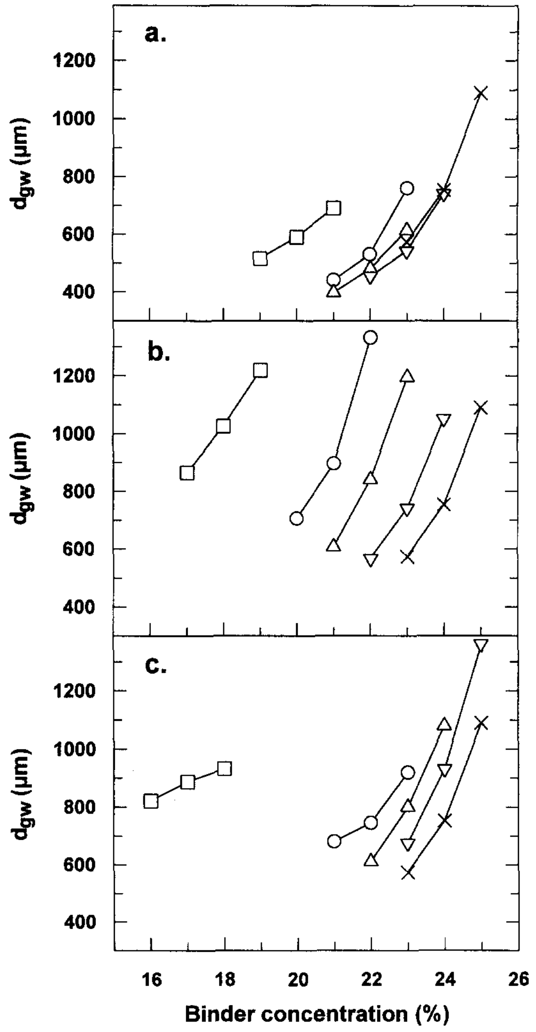

Fig. 1. Effects of binder concentration and content of lactose in the binary mixture on the mean granule size. (a) Mannitol 25/lactose; (b) mannitol 35/lactose; (c) mannitol 60/lactose. Massing time: 17 min. Content of lactose: (□) 0%; (○) 25%; (△) 50%; (▽) 75%; (×) 100%.

Fig. 1 shows the correlation between the PEG concentration and the mean granule size for all the mixtures used in the present experiments. Regression analysis indicated an exponential increase in mean granule size with increasing amount of binder in accordance with previous wet granulation (Usteri and Leuenberger, 1989) and melt granulation (Kinget and Kemel, 1985) experiments. The highest concentration was generally chosen in such a way that a further increase in concentration of 1% caused an uncontrollable agglomerate growth. An uncontrollable growth occurred at a smaller mean granule size in the case of mannitol 25, because the smaller particle size increased the cohesiveness (Schæfer, 1996). The lowest agglomerate growth rate is generally observed with 100% of mannitol.

It appears from Fig. 1 that the PEG concentration had to be increased with an increasing content of lactose in the mixture in order to keep the mean granule size at the same level. This is partly explained by the fact that a smaller particle size of the starting material demands a larger amount of meltable binder (Kinget and Kemel, 1985; Schæfer et al., 1992b; Peerboom and Delattre, 1995). However, the effect of the lactose content seen in Fig. 1a cannot be explained by a smaller particle size of the lactose, because the particle size of the mannitol 25 is smaller than that of the lactose (Table 1).

For practical formulation purposes, it would be useful if it was possible to predict the optimum amount of binder on the basis of some physical properties of the starting materials. Some authors (Pendharkar et al., 1990; Carius, 1992; Schæfer, 1996) suggest a correlation between the surface area of the materials and the amount of binder. It is seen from Table 2 that the amount of PEG per surface area of the powder mass has to be increased at a larger particle size. This means that the lower agglomerate strength caused by a larger particle size has to be compensated for by a larger amount of binder per surface area. In the case of mixtures of mannitol 25 and lactose, the amount of PEG per surface area is approximately constant. This indicates that a correlation between surface area and amount of binder exists only for powder masses of a similar particle size.

Table 2
The amount of PEG per surface area of the powder (g/m^2) in the experiments with mixtures of mannitol and lactose at the high level of PEG concentration

	% Lactose in the mixture				
	0	25	50	75	100
Mannitol 25	0.323	0.333	0.315	0.312	0.309
Mannitol 35	0.452	0.425	0.374	0.337	0.309
Mannitol 60	0.600	0.538	0.432	0.366	0.309

The agglomerate growth is primarily controlled by the liquid saturation of the agglomerates (Schæfer et al., 1990), i.e. the degree of filling of the intragranular pores with the binder liquid. The amount of binder liquid, therefore, might be related to the packing of the powder. Fig. 2 compares the interparticular porosities of the powder mixtures with the corrected porosities of the agglomerates. The corrected porosities reflect approximately the packing of the particles within the agglomerates. The packing is seen to be much closer in the agglomerates than in the powder mass since the binder liquid acts as a lubricant, and since the shearing and compaction forces are much higher in the mixer than in the tapping apparatus (Jaiyeoba and Spring, 1981; Kristensen et al., 1985). This is why the effects of particle size and mixing ratio are more pronounced in Fig. 2a than in Fig. 2b. It is clearly seen, however, that the lowest intragranular porosities are obtained from the powder mixtures with the lowest interparticular porosities. The better packing properties of the pure mannitol explain why mannitol demands a markedly lower amount of binder than do the binary mixtures (Fig. 1). This indicates that the optimum amount of binder is related to the packing properties of the powder, although the intragranular porosity cannot be directly predicted from the tapped density of the powder.

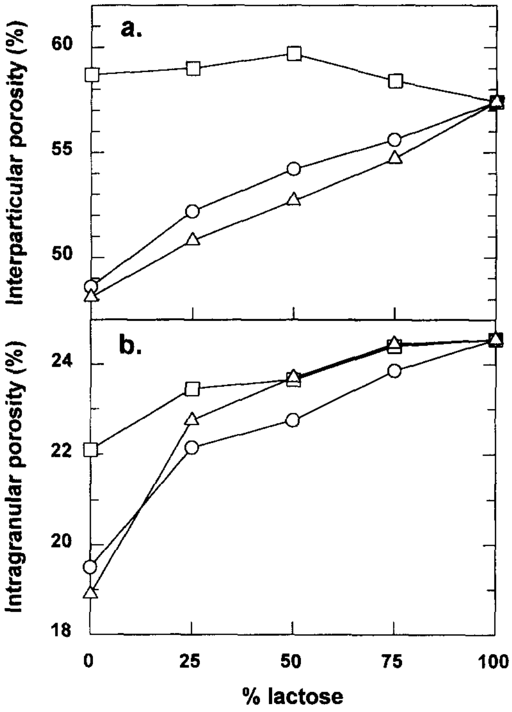

Fig. 2. Effects of type of mannitol and content of lactose in the binary mixture on the interparticular tapped porosity of the powder mixture (a) and the corrected intragranular porosity at 8 min of massing (b). Binder concentration in (b) the highest level (Fig. 1). (□) Mannitol 25/lactose; (○) mannitol 35/lactose; (△) mannitol 60/lactose.

Fig. 3 shows that the mean granule size is gradually increased by prolonged massing. In the case of mannitol 60 (Fig. 3c), the agglomerate growth rate is very low with no addition of lactose, but the growth rate obtained with the binary mixture becomes higher, the higher the content of lactose. With mannitol 25 and 35, no clear effect of mixing ratio on growth rate is seen. In accordance with previous results (Schæfer et al., 1993), the power consumption of the impeller motor was found to be unsuitable for controlling the agglomerate growth, because the changes in power consumption during the process were too slight owing to the rather low impeller speed.

Agglomerates larger than 4 mm are referred to as lumps. It appears from Fig. 4 that the amount of lumps in the product becomes higher ($P < 0.001$) by agglomeration of the pure mannitol. Further, the amount of lumps becomes higher, the larger the particle size of the mannitol. An addition of 25% of lactose only, causes a marked reduction in the amount of lumps. With the pure mannitol, irregular lumps of a loose structure are formed early in the process, and a slight comminution of these lumps is seen by further mass-

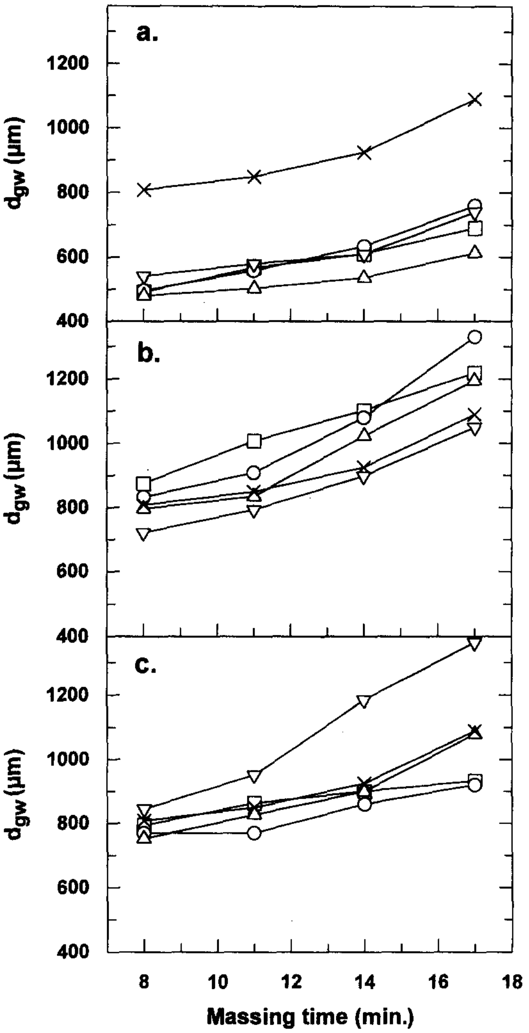

Fig. 3. Effects of massing time and content of lactose in the binary mixture on the mean granule size. (a) Mannitol 25/lactose; (b) mannitol 35/lactose; (c) mannitol 60/lactose. Binder concentration: the highest level (Fig. 1). Content of lactose: (□) 0%; (○) 25%; (△) 50%; (▽) 75%; (×) 100%.

ing. With the binary mixtures and the lactose, an increase in the amount of lumps occurs between 14 and 17 min of massing owing to agglomerate growth. These lumps are primarily dense and ball-like.

An evaluation of the granule size distributions showed a reasonable agreement with the log-normal distribution. It appears from Table 3 that the pure mannitol gives rise to a significantly ($P < 0.001$) wider size distribution than the binary mixtures and the lactose. With the pure mannitol, the size distribution becomes wider, the larger the particle size of the mannitol.

Adhesion of mass to the bowl of the mixer reduces the yield of the process. Table 4 shows that the adhesion becomes larger when the particle size of the mannitol becomes smaller. This is ascribed to the increased cohesiveness of the

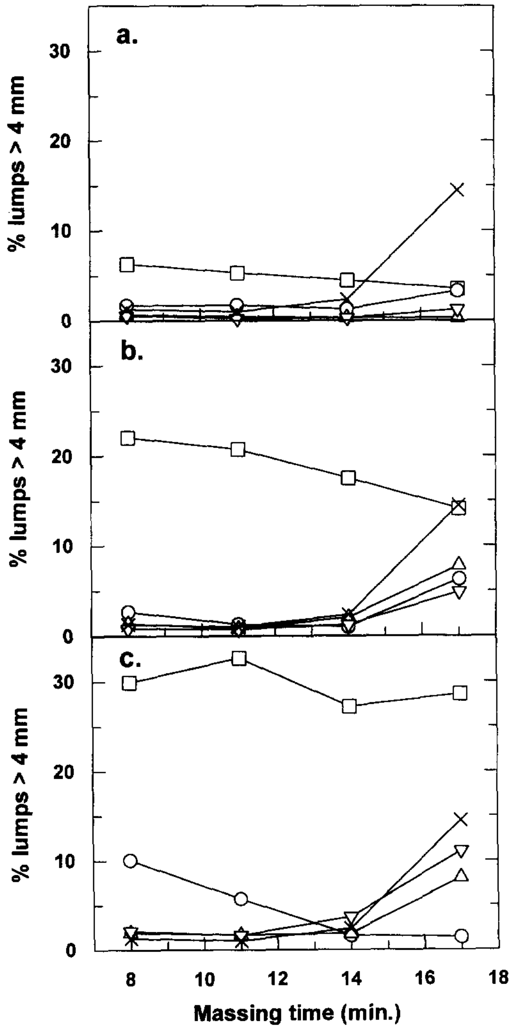

Fig. 4. Effects of massing time and content of lactose in the binary mixture on the amount of lumps. (a) Mannitol 25/lactose; (b) mannitol 35/lactose; (c) mannitol 60/lactose. Binder concentration: the highest level (Fig. 1). Content of lactose: (□) 0%; (○) 25%; (△) 50%; (▽) 75%; (×) 100%.

Table 3
The granule size distribution expressed as the geometric standard deviation in repeated experiments with mixtures of mannitol and lactose at the high level of PEG concentration

	% Lactose in the mixture				
	0	25	50	75	100
Mannitol 25	1.61	1.44	1.46	1.45	1.44
	1.57	1.47	1.44	1.44	1.45
Mannitol 35	1.71	1.41	1.42	1.43	1.44
	1.72	1.43	1.42	1.45	1.45
Mannitol 60	2.14	1.34	1.46	1.40	1.44
	2.10	1.36	1.44	1.42	1.45

Massing time: 17 min.

smaller particles. The lactose gives rise to an intermediate adhesion, and this is why the adhesion is reduced by an admixture of lactose in the case of the mannitol 25 and increased in the case of the mannitol 60.

The effects of mixing ratio and mannitol particle size on the intragranular porosity and the liquid saturation at 8 min and 17 min of massing are shown in Fig. 5 and Fig. 6. The intragranular porosities are generally found to be low compared with the porosities obtained by melt pelletization of other materials (Schæfer and Mathiesen, 1996a). This is ascribed to a low cohesiveness of the mannitols and the lactose. With the mannitol 35 and 60, the porosity at 8 min of massing is low and independent of the mixing ratio. The corresponding liquid saturations (Fig. 6a) exceed 100%, because the pores are almost filled up by the varying amounts of PEG. These values might be slightly overestimated since the calculation of the liquid saturation is based on the assumption that the packing of the particles within the agglomerates in the molten state is the same as in the solidified state. The mannitol 25 causes the highest porosities.

Table 4
The adhesion of material (%) to the bowl of the mixer at the end of the process in repeated experiments with mixtures of mannitol and lactose at the high level of PEG concentration

	% Lactose in the mixture				
	0	25	50	75	100
Mannitol 25	6.4	6.9	5.1	5.4	3.8
	7.3	6.1	6.6	5.0	4.4
Mannitol 35	4.8	4.5	4.8	4.8	3.8
	4.5	4.1	4.7	4.7	4.4
Mannitol 60	1.8	2.7	4.0	5.5	3.8
	1.6	2.1	4.3	4.6	4.4

Massing time: 17 min.

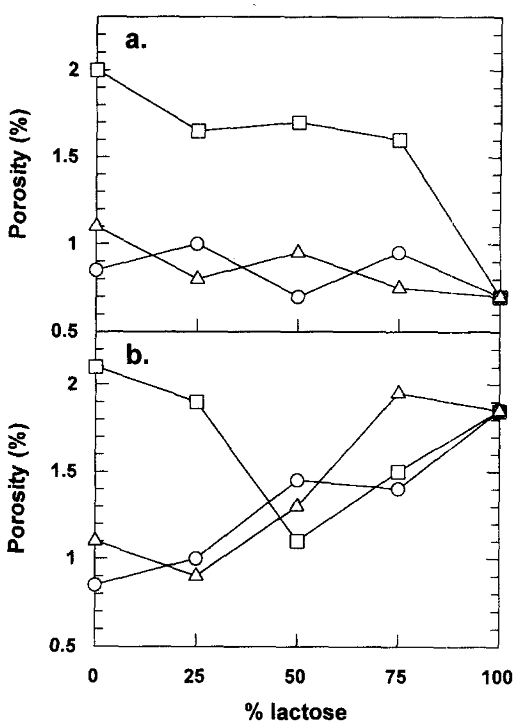

Fig. 5. Effects of type of mannitol and content of lactose in the binary mixture on the intragranular porosity. Massing time: (a) 8 min; (b) 17 min. Binder concentration: the highest level (Fig. 1). (□) Mannitol 25/lactose; (○) mannitol 35/lactose; (△) mannitol 60/lactose.

At 17 min of massing, the temperature of the products containing lactose had been increased to between 85 and 94°C owing to heat of friction. This was found to cause an evaporation of approximately 10% of the water of crystallization of the lactose. As previously shown (Schæfer and Mathiesen, 1996a), evaporation of water of crystallization will give rise to an increase in the intragranular porosity. This explains why the porosity becomes slightly higher on prolonged massing (Fig. 5b) when the mixture contains 50% or more of the lactose. A simultaneous fall in the liquid saturation is seen (Fig. 6b). The results demonstrate that the mixtures are so easily densified that the minimum porosities and the maximum liquid saturations are obtained at 8 min of massing. This means that the agglomerate growth seen in Fig. 3 is caused by coalescence between fully saturated agglomerates.

It appears from Fig. 7a that the shape and the surface structure of the agglomerates produced with pure mannitol 60 are very irregular. The plate-like mannitol particles are clearly seen in the surface. The agglomerates produced with pure lactose (Fig. 7c) are more rounded and of a rather uniform surface structure. The addition of 50% of lactose to the mannitol 60 results in agglomerates (Fig. 7b) that are most similar to the lactose agglomerates. A smaller particle size of the mannitol gives rise to smoother agglomerates, but it is still possible to identify the primary particles in the surface when no lactose is added (Fig. 8).

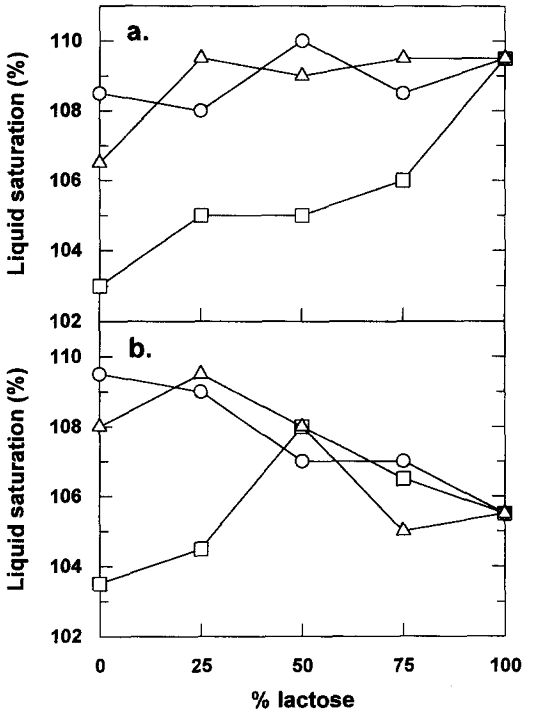

Fig. 6. Effects of type of mannitol and content of lactose in the binary mixture on the liquid saturation. Massing time: (a) 8 min; (b) 17 min. Binder concentration: the highest level (Fig. 1). (□) Mannitol 25/lactose; (○) mannitol 35/lactose; (△) mannitol 60/lactose.

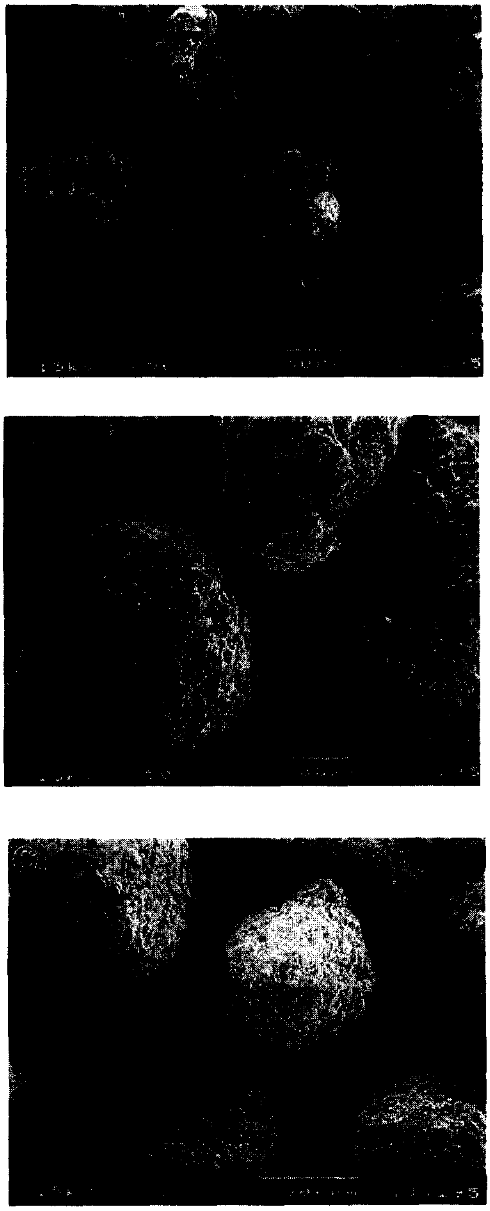

Fig. 7. SEM photographs of pellets produced from: (a) mannitol 60; (b) mannitol 60/lactose (50/50%); (c) lactose. Massing time: 17 min. Binder concentration: the highest level (Fig. 1).

The loose surface structure seen in Fig. 7a is not in accordance with the extremely low values of intragranular porosity (Fig. 5). By the intrusion pressure applied for the measurements of the porosity, mercury will penetrate into pores greater than approximately 20 μm in diameter (Jægerskou et al., 1984). This means that the presence of such pores in the surface will lead to an underestimation of the porosity and an overestimation of the liquid saturation. Consequently, the values of porosity and liquid saturation obtained with a high content of mannitol (Fig. 2b, Fig. 5, and 6) will be slightly biased, the more, the larger the particle size of the mannitol.

The loose surface structure of the agglomerates produced with pure mannitol explains why these agglomerates are less sensitive to variations in binder concentration (Fig. 1). An increased binder concentration will result in a filling up of the large pores. Consequently, the surface plasticity of the agglomerates will only be slightly increased, and the effect of a higher binder concentration on the agglomerate growth rate will be low, as long as unfilled pores are present. Accordingly, the increase in binder concentration in Fig. 1 was found to result in a slightly higher ($P < 0.01$) liquid saturation with the pure mannitol 25, whereas no effect on the liquid saturation was found with the mannitol 35 and 60. A lower surface plasticity, because of unfilled pores, can further explain the low agglomerate growth rate seen with the pure mannitol 60 in Fig. 3c.

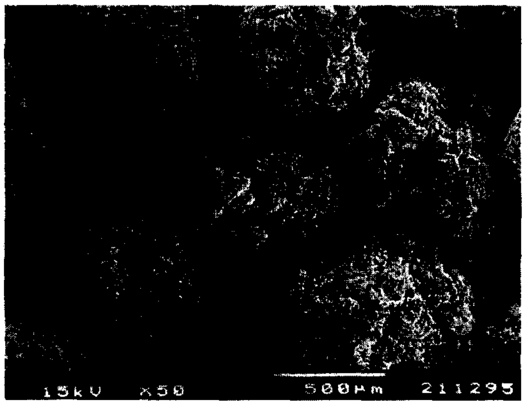

Fig. 8. SEM photograph of pellets produced from mannitol 25. Massing time: 17 min. Binder concentration: 21%.

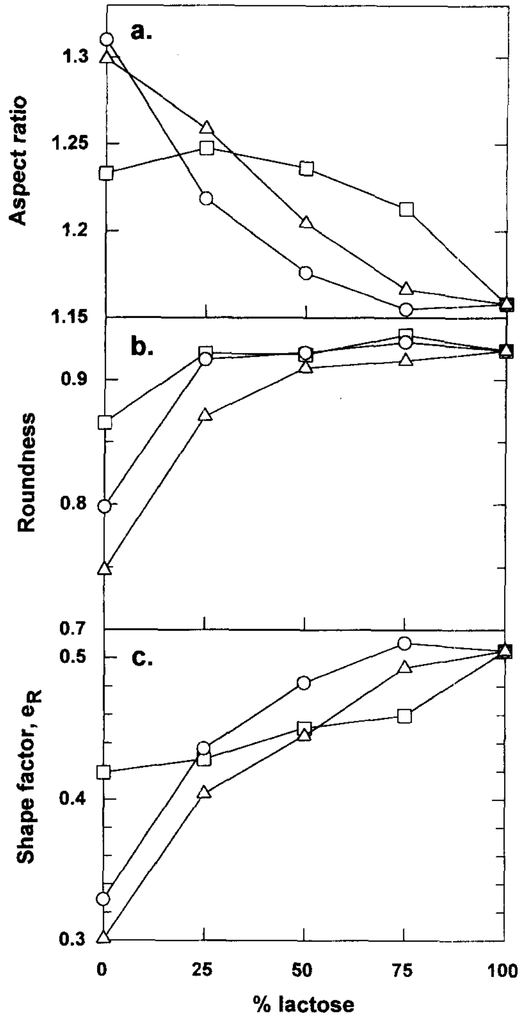

Fig. 9. Effects of type of mannitol and content of lactose in the binary mixture on the aspect ratio (a), the roundness (b), and the shape factor e_R (c). Massing time: 17 min. Binder concentration: the highest level (Fig. 1). (□) Mannitol 25/lactose; (○) mannitol 35/lactose; (△) mannitol 60/lactose.

The aspect ratio of a particle (Fig. 9a) describes the deviation of shape from a circle towards an elipse, the roundness (Fig. 9b) is primarily a measure of the surface irregularities, and the shape factor (Fig. 9c), e_R, considers both ellipticity and surface roughness (Podczeck and Newton, 1994). A circle will theoretically give rise to a value of 1 of the aspect ratio, the roundness as well as the shape factor.

The values of aspect ratio (Fig. 9a) show that the agglomerates become more spherical, the higher the content of lactose. Without addition of lactose, the agglomerates of the mannitol 25 are the most spherical. The smaller particle size of the mannitol 25 will cause a higher agglomerate strength and consequently a lower deformability. This explains why the sphericity of the agglomerates of mannitol 25 becomes only slightly improved by an addition of lactose. Because of the lower impeller speed, the present agglomerates are less spherical than those previously produced with the same lactose quality (Schæfer and Mathiesen, 1996b).

Fig. 9b shows that a larger particle size of the mannitol makes the surface structure less regular ($P < 0.001$) (Fig. 7a and Fig. 8). By a lactose content of $\geq 25\%$ (mannitol 25 and 35) or $\geq 50\%$ (mannitol 60), the smoothness of the agglomerates is similar to that obtained with pure lactose (Fig. 7b and c).

It appears from Fig. 9c that the optimum pellets considering sphericity as well as smoothness are obtained with binary mixtures of mannitol 35 and lactose. A higher lactose content improves the pellet quality ($P < 0.001$). The e_R-values obtained are assumed to be acceptable since two sets of apparently spherical pellets produced by extrusion/spheronization gave e_R-values of 0.568 and 0.416 (Podczeck and Newton, 1994).

4. Conclusions

The present experiments indicate that it might be a prerequisite of melt pelletization that the shape of the particles to be pelletized is rounded. The plate-like and needle-like shape of the mannitol particles resulted in irregular agglomerates, a wide granule size distribution, and a formation of a large amount of loose lumps in the product. A smaller particle size of the mannitol improved the pelletization properties, but did not result in acceptable pellets, although the mean particle size of two of the mannitol qualities examined was within the range of 10–50 μm, which was assumed to be suitable for formation of pellets (Schæfer et al., 1992b).

An admixture of 25–50% of lactose to the mannitol caused a marked improvement of the pelletization properties. In accordance with percolation theory (Usteri and Leuenberger, 1989), an addition of 50–75% of lactose resulted in pellets with properties similar to those obtained with the pure lactose, because the excellent pelletization properties of the lactose were dominating. This indicates that generally it will be possible to pelletize a material with poor pelletization properties by an addition of a proper filler.

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References

Carius, V.W., Prozess-Monitoring bei konventioneller Granulierung. *Pharm. Ind.*, 54 (1992) 543–546.

Jaiyeoba, K.T. and Spring, M.S., The granulation of ternary mixtures containing lactose and boric acid with different starches. *J. Pharm. Pharmacol.*, 31 (1979) 197–200.

Jaiyeoba, K.T. and Spring, M.S., The granulation of ternary mixtures: the effect of the solubility of the excipients. *J. Pharm. Pharmacol.*, 32 (1980a) 1–5.

Jaiyeoba, K.T. and Spring, M.S., The granulation of ternary mixtures: the effect of the wettability of the powders. *J. Pharm. Pharmacol.*, 32 (1980b) 386–388.

Jaiyeoba, K.T. and Spring, M.S., Analysis of factors affecting the mean sizes of granules produced from ternary mixtures of powders. *J. Pharm. Pharmacol.*, 33 (1981) 5–8.

Jægerskou, A., Holm, P., Schæfer, T. and Kristensen, H.G., Granulation in high speed mixers. Part 3: Effects of process variables on the intragranular porosity. *Pharm. Ind.*, 46 (1984) 310–314.

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

Kleinebudde, P. and Nymo, L., Homogeneous pellets of binary mixtures, comparison between extruder/spheronizer and high-shear mixer. *Proc. 1st World Meeting Pharm. Biopharm. Pharmaceutical Technol.*, Budapest (1995) 343–344.

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 (1985) 227–237.

Nymo, L., Schröder, M., Schultz, P., Müller, B.W., Waaler, T. and Kleinebudde, P., Properties of extruded pellets made from binary mixtures. *Proc. 1st World Meeting Pharm. Biopharm. Pharmaceutical Technol.*, Budapest (1995) 367–368.

Opakunle, W.O. and Spring, M.S., The granulation of binary mixtures. *J. Pharm. Pharmacol.*, 28 (1976a) 508–511.

Opakunle, W.O. and Spring, M.S., The granulation of binary mixtures: the effects of the composition of the granulating solution and the initial particle size of one component on granule properties. *J. Pharm. Pharmacol.*, 28 (1976b) 806–809.

Opakunle, W.O. and Spring, M.S., The granulation of binary mixtures: the effects of the properties of the component powders on granules. *J. Pharm. Pharmacol.*, 28 (1976c) 915–918.

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

Pendharkar, C.M., Jhawar, R.J., Rutledge, J.M., Hause, W., Grim, W.M. and Harwood, R.J., Influence of the specific surface area of selected raw materials on the granulation process using an instrumented mixer. *Pharm. Technol.*, 14 (1990) (4) 44–53.

Podczeck, F. and Newton, J.M., A shape factor to characterize the quality of spheroids. *J. Pharm. Pharmacol.*, 46 (1994) 82–85.

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

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

Schæfer, T. and Mathiesen, C., Melt pelletization in a high shear mixer. VIII. Effects of binder viscosity. *Int. J. Pharm.*, 139 (1996b) 123–136.

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. III. Effects of lactose quality. *Acta Pharm. Nord.*, 4 (1992b) 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.

Thomsen, L.J., Prolonged release matrix pellets prepared by melt pelletization. Part IV: Drug content, drug particle size, and binder composition. *Pharm. Technol. Eur.*, 6 (1994) (9) 19–24.

Usteri, M. and Leuenberger, H., Agglomeration of binary mixtures in a high-speed mixer. *Int. J. Pharm.*, 55 (1989) 135–141.

Wan, L.S.C., Heng, P.W.S. and Liew, C.V., Spheronization conditions on spheroid shape and size. *Int. J. Pharm.*, 96 (1993) 59–65.