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MELT GRANULATION IN A LABORATORY SCALE HIGH SHEAR MIXER

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ABSTRACT

The applicability of a 10 litre high shear mixer for melt granulation of dicalcium phosphate and lactose is examined. Polyethylene glycol (PEG) 3000 and 6000 were used as melting binders in concentrations of 15-20% w/w. The effects of binder concentration, massing time, impeller speed, and particle size of the PEG 6000 on granule size, granule size distribution and intragranular porosity are investigated.

It is shown that pellets of a narrow size distribution can be produced by the use of a high impeller speed. Granule size and size distribution are markedly influenced by binder concentration and massing time. The particle size of the PEG has only a minor effect on the granule growth. Granule growth mechanisms by melt granulation are discussed on the basis of the liquid saturations and the amounts of binder liquid and are compared with previous results on wet granulation.

INTRODUCTION

Melt granulation (thermoplastic granulation) is a process in which granulation is obtained through the addition of a binder which melts or softens at a relatively low temperature. After melting, the binder acts like a binding liquid. The binders normally used for melt granulation are polyethylene glycols (1-4), different waxes (5,6) or stearic acid (7).

Melt granulation is advantageous compared with an ordinary wet granulation process, since the liquid addition phase as well as the drying phase of the process is eliminated. Consequently, melt granulation requires less heat energy (3). Melt granulation is an alternative to the use of solvents when granulating water-sensitive materials. By selecting a melting binder which is insoluble in water, melt granulation might be a way of producing sustained release granulations (5,6). Solid dispersions can be prepared by dissolving a drug in the molten binder (2,4).

By melt granulation in a high shear mixer the binder is added either in powder form to the starting materials at ambient temperature (5,6) followed by heating to above the melting point of the binder or in molten form to the heated materials (4,5). The temperature of the mixture is increased by a heating jacket (4) or by heat of friction solely (5,6).

Heating by a heating jacket is possible in a laboratory scale mixer but might be inconvenient in a production scale mixer. It is advantageous, therefore, to use a high shear mixer with a power input sufficiently high to generate the heat of friction required to melt the binder within a reasonably short time. In the Baker Perkins® high shear mixers the maximum impeller

speed is very high. Flanders et al. (6) examined a 10 litre, a 60 litre and a 600 litre Baker Perkins mixer and found that melt granulation by heat of friction was possible in all of them. In the 60 litre mixer the temperature increased to about 100°C during 15 minutes. They mentioned that Fielder® and Diosna® high shear mixers are unsuitable for melt granulation because of a long granulation time. The shorter granulation time in the Baker Perkins mixer is due to a larger relative swept volume of the impeller in that mixer (8).

Kinget and Kemel (4) carried out factorially designed experiments in a 10 litre Gral® mixer equipped with a heating jacket adding the binder in molten form. They found that the main factors influencing the granule properties were the amount and viscosity of the molten binder, the particle size of the starting material, the speed of the impeller and the addition of a sieving procedure prior to cooling of the granules.

A previous paper (8) deals with the applicability of a 10 litre Baker Perkins high shear mixer for wet granulation. The high power input in that mixer indicates that it might be especially suitable for melt granulation. Flanders et al. (6) examined only melt granulation of potassium chloride in the Baker Perkins mixers. The purpose of the present investigation is to examine melt granulation of other materials in the Baker Perkins laboratory scale mixer in order to elucidate the granule growth mechanisms involved in the melt granulation process.

MATERIALS

Dicalcium phosphate (calcium hydrogen phosphate, Albright and Wilson Ltd.) and lactose (200 mesh, DMV

Veghel) - both of Ph.Eur. grade - were used as starting materials. The mean particle size of the dicalcium phosphate was 23 µm, and that of the lactose was 68 µm estimated by counting the particles microscopically. The particle size distributions were shown in a previous paper (8).

Polyethylene glycols (PEG) 3000 and 6000 (Ph.Nord. 63) were used as melting binders. PEG 6000 was used in three grades: a fine powder, a coarse powder and flakes. PEG 3000 was used as flakes. The melting point of the PEG 3000 was 62-63°C and of all the PEG 6000 grades 65-66°C estimated by the capillary method. Freezing points were found to be 50-53°C and 56-60°C, respectively. Approximate values of the viscosities of the molten binders were determined by a Brookfield Viscosimeter, Type LVT at 65°C. The viscosity of the PEG 3000 was about 280 mPa·s and of the PEG 6000s about 1100 mPa·s.

METHODS

A 10 litre Baker Perkins vertical laboratory scale high shear mixer was used for the experiments. The impeller speed as well as the chopper speed was continuously adjustable over the ranges of 0-1500 rpm and 0-3000 rpm respectively. The chopper speed was kept constant at 3000 rpm. The load of the mixer was 2 kg of either dicalcium phosphate or lactose in all the experiments. Additional varying amounts of PEG were added in powder form or as flakes.

In order to standardize the heating procedure the starting material and the binder were dry mixed at an impeller speed of 1400 rpm until the temperature of the mixture had reached 25°C due to heat of friction. The bowl was not equipped with a thermoresistance probe

allowing the temperature of the mass to be recorded continuously. Therefore the bowl had to be opened when measuring the temperature.

The moment when the temperature reached 25°C was defined as the starting point of the massing time, i.e. massing time was 0 minutes at 25°C. From that time mixing proceeded, normally at an impeller speed of 1400 rpm giving rise to an increasing temperature. Samples of about 100 g were drawn at predetermined intervals. The process was stopped during sampling. The first sample was drawn a few minutes after the temperature had reached the melting point of the binder. In a few of these experiments the impeller speed was lowered after the first sample was drawn. The samples were spread out in thin layers on trays in order to cool at ambient temperature.

The temperature of the mass was measured by a thermoresistance probe each time the bowl was opened for sampling. Opening of the bowl during sampling gives rise to cooling of the mass and thus to slight fluctuations in the temperature. Previous results (4) show, however, that it is likely to assume that granule properties are not significantly affected by slight temperature fluctuations provided that the temperature exceeds the melting point of the binder.

Granule size and size distribution and amount of lumps larger than 2 mm were estimated by sieve analysis of the cooled samples as described in a previous paper (9). There was no indication of further agglomeration during cooling on the trays.

The intragranular porosity was estimated by the pycnometric method described before (10). In order to estimate the porosities in the agglomeration phase of

the process in which the molten binder acts like a liquid, the porosity values have been corrected for the volume of binder deposited in the granules during cooling. As mentioned by Ritala et al. (11) this corrected porosity value reflects the true porosity of the wet granules provided that all the binder is deposited within the pores after cooling. The liquid saturation of the granules was calculated as the ratio between the volume of the molten binder and the intragranular voids, determined on the basis of the corrected porosity. The volume of the molten binder was calculated on the basis of the density at 70°C.

RESULTS AND DISCUSSION

Granulation of dicalcium phosphate

Figure 1 shows the effect of the amount of binder (finely powdered PEG 6000) on the granule growth. Granule growth is delayed at the lowest amounts of binder, and therefore samples were drawn at different massing times.

By aqueous wet granulation of dicalcium phosphate in the same mixer adhesion of moist mass to the bowl was found to be a serious problem (8). In the present experiments practically no adhesion was observed.

As can be seen the amount of PEG 6000 has a marked effect on granule growth. The larger the amount of binder, the higher the growth rate. With 400 g of PEG 6000 growth rate is very high, but there was no tendency of ball growth caused by overwetting. The effect of the binder concentration is similar to the results of previous experiments on wet granulation of dicalcium phosphate, which showed that granule growth was very dependent on the moisture content (9).

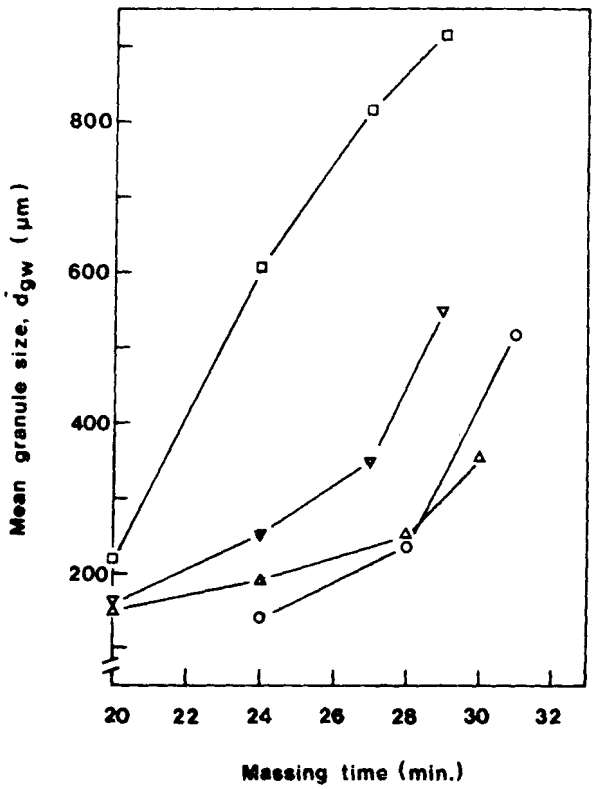

FIGURE 1
Effect of massing time at varying amounts of finely powdered PEG 6000 on the mean granule size. Starting material: Dicalcium phosphate. Impeller speed: 1400 rpm. Amount of PEG: o : 340 g; Δ : 360 g; ∇ : 380 g; □ : 400 g.

The granule size distributions were in good agreement with the log-normal distribution. Consequently, the size distribution is described by the geometric standard deviation (Figure 2). The size distribution becomes narrower at prolonged massing time until a certain point. The narrowest size distribution is obtained at a high amount of binder.

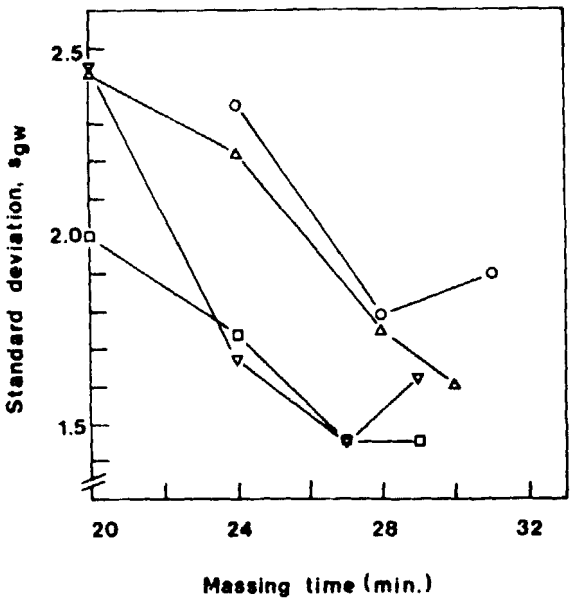

FIGURE 2
Effect of massing time at varying amounts of finely powdered PEG 6000 on the granule size distribution expressed by the geometric standard deviation. Starting material: Dicalcium phosphate. Impeller speed: 1400 rpm. Amount of PEG: o : 340 g; Δ : 360 g; ∇ : 380 g; □ : 400 g.

The granule size distributions are narrower than those of dicalcium phosphate granules prepared by conventional wet granulation with an aqueous binder solution. In the previous wet granulation experiments in the same mixer (8) the standard deviations were found to be between 2.2 and 3.8, most of them being about 2.5. The lowest standard deviation obtained by Holm in a Fielder PMA 25 high shear mixer was about 2.0 (12).

Holm concluded that a high energy input is associated with the formation of narrow granule size distributions.

The energy input in the Baker Perkins mixer is extremely high due to the very high impeller speed and that would explain the extremely narrow granule size distribution which is obtained by melt granulation in that mixer. The reason why a similar granule size distribution cannot be obtained by wet granulation in the same mixer is that wet granulation contrary to melt granulation gives rise to a marked adhesion to the bowl. This adhesion results in heterogeneous granules.

In the experiments in Figure 2 all the fines smaller than 75 μm had disappeared at the end of massing independent of the amount of PEG. The amount of lumps larger than 2 mm was below 4% except for the experiment with 340 g of PEG in which the amount of lumps increased to about 10% during the last 3 minutes of massing. This confirms the assumption that a narrow size distribution is favoured by a relatively large amount of binder. In the experiment with 400 g of PEG, 85-86% of the granules were within the size range of 500 to 1400 μm after 27 and 29 minutes of massing. Thus, melt granulation seems to be a way of producing pellets of dicalcium phosphate.

The changes in the intragranular porosity are shown in Figure 3. A slight decrease is seen during massing. The uncorrected values reflect the porosities of the final granules, whereas the corrected values are assumed to reflect the porosities during the process where the binder is molten. The porosities of the final granules are low, because the pores are nearly filled up with the binder which hardens during cooling. A larger amount of binder results in more filling of the pores and consequently in a lower porosity. The uncorrected porosities obtained by conventional wet granulation are

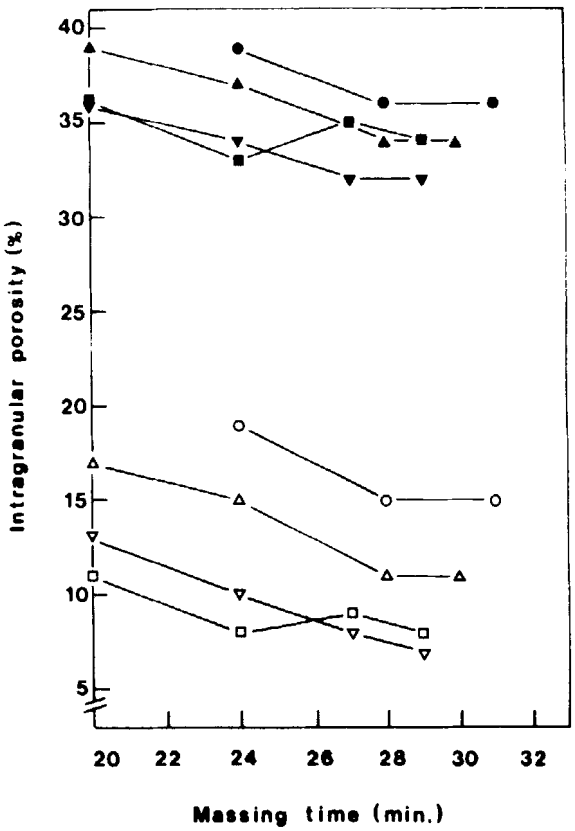

FIGURE 3
Effect of massing time at varying amounts of finely powdered PEG 6000 on the intragranular porosity. Starting material: Dicalcium phosphate. Impeller speed: 1400 rpm. ○ , △ , ▽ , □ : Porosities of the final granules. ● , ▲ , ▼, ■ : Porosity values corrected for the volume of binder deposited in the pores of the granules. Amount of PEG: ○ , ● : 340 g; △ , ▲ : 360 g; ▽ , ▼ : 380 g; □ , ■ : 400 g.

higher, since the amount of binder is smaller by wet granulation.

The corrected porosities, however, are higher by melt granulation than by wet granulation. The lowest uncorrected porosities obtained by wet granulation of

the same batch of dicalcium phosphate in the same mixer (8) were about 20% corresponding to corrected porosities of about 25%. By melt granulation some of the binder is assumed to be deposited on the surface of the granules. The true corrected porosities, therefore, will be lower than the values shown in Figure 3. The differences in corrected porosities between melt granulation and wet granulation, however, are larger than what can be explained by deposition of PEG on the surface of the granules.

Although the corrected porosity values are corrected for the volume of binder, the values seem to be affected by the amount of binder, a lower amount giving rise to a higher porosity. That might be due to a lubricating effect of the molten binder on densification, the lubricating effect being more pronounced at increased binder concentration.

The effect of the impeller speed on granule growth was examined in two additional experiments. In order to raise the temperature the impeller speed was kept at 1400 rpm during the first 20 minutes of massing, after which it was lowered to 800 rpm or 500 rpm, respectively. In Figure 4 the granule size distributions obtained at the end of massing are compared with the distribution found at 1400 rpm. As can be seen a decrease in impeller speed results in a smaller granule size and a wider granule size distribution.

These findings agree with the assumption that the granule size distribution becomes narrower at a higher energy input. At massing times between 20 and 24 minutes the geometric standard deviation decreases, i.e. the size distribution becomes narrower, independent of the

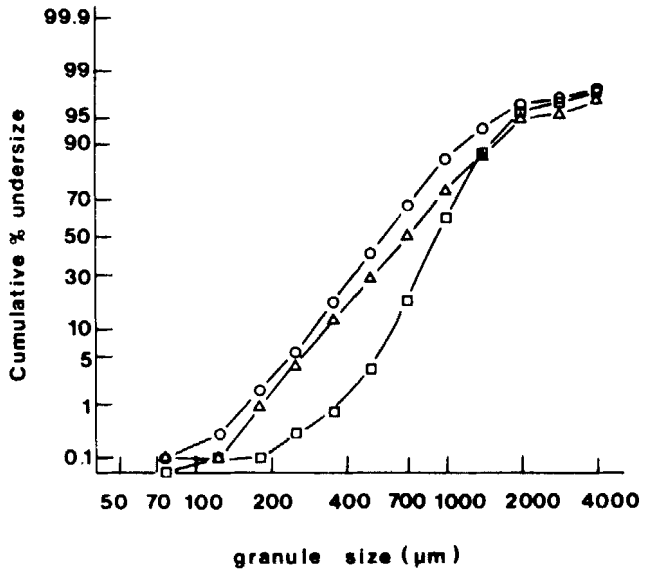

FIGURE 4
Effect of the impeller speed on the granule size distribution. Starting material: Dicalcium phosphate. Amount of finely powdered PEG 6000: 400 g. Massing time: 29 min. Impeller speed during the first 20 min. of massing: 1400 rpm. Impeller speed after 20 min. of massing: o : 500 rpm; Δ : 800 rpm; □ : 1400 rpm.

impeller speed. Between 24 and 27 minutes a further decrease in standard deviation is found at 1400 rpm, whereas an increase is seen at 500 rpm and 800 rpm. After 27 minutes of massing no further change in standard deviation was observed.

Within the range of massing times examined the correlation between massing time and granule size was almost linear, the highest granule growth rate being found at 1400 rpm. No significant effect of impeller speed on the intragranular porosity was found. The effect on granule growth therefore can not be explained by differences in liquid saturation.

The different impeller speeds result in different temperatures of the mass. At 1400 rpm the temperature increases to 74°C during massing. At 500 rpm and 800 rpm a constant decrease in temperature is observed after lowering of the impeller speed, the final temperatures being 61°C and 63°C, respectively. The fall in temperature will increase the viscosity of the molten PEG. Since Kinget and Kemel (4) found no effect of the temperature of PEG in the range of 60°C to 70°C, it is not likely that temperature differences are the main reason for the effect of the impeller speed on granule size. It is more likely that the effect might be due to increased deformation of granules by collisions at higher impeller speed, which will increase the granule growth by coalescence.

Granule growth by wet granulation of dicalcium phosphate can be described by the effect of the liquid saturation of the intragranular pores (13). The liquid saturation increases during massing due to densification of the granules. The correlation between liquid saturation and granule size in the six melt granulation experiments with dicalcium phosphate is shown in Figure 5. The results indicate that the granule growth by melt granulation, too, is primarily controlled by the liquid saturation, although deviations are seen, especially at the lowest amount of binder. Granule growth occurs at liquid saturations which are slightly lower than those of the granules in the similar wet granulation experiments (8).

At liquid saturations between 80 and 90% granule growth rate becomes very high. It is most likely that the surface of the granules is saturated with liquid. It is assumed that liquid is pressed out to the surface

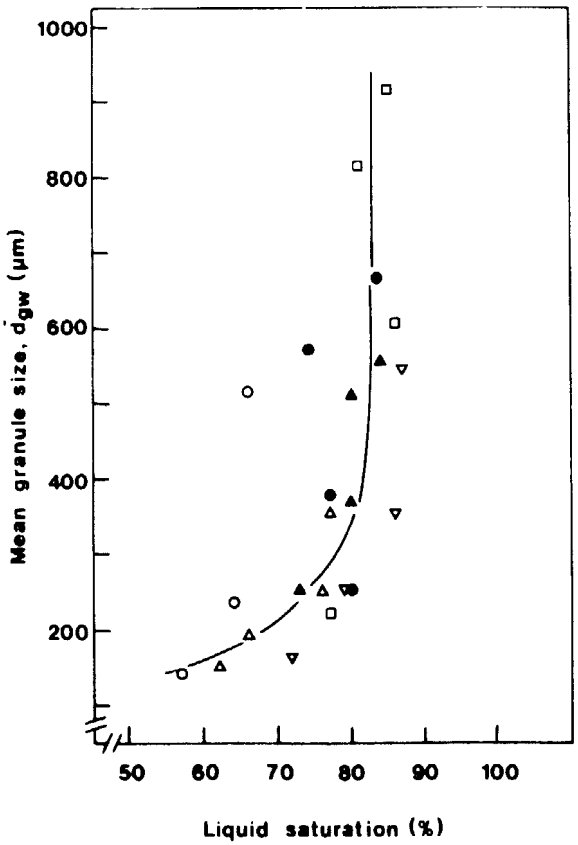

FIGURE 5
Effect of liquid saturation on the growth of dicalcium phosphate granules. Binder: Finely powdered PEG 6000. Amount of PEG: ○ : 340 g; △ : 360 g; ▽ : 380 g; □ , ● , ▲ : 400 g. Impeller speed during the first 20 min. of massing: 1400 rpm. Impeller speed after 20 min. of massing: ▲ : 500 rpm; ● : 800 rpm; ○ , △ , ▽, □ : 1400 rpm.

by densification of the granules. Accordingly, a concentration gradient of the PEG could be observed by division of granules. Since the liquid saturation of the surface is about 100%, the surface plasticity of the granules becomes high. The high surface plasticity combined with the very high impeller speed will give

rise to a marked granule growth by coalescence. The high power input prevents the formation of large lumps, and therefore an uncontrollable granule growth is avoided, although the growth rate is very high.

Granulation of lactose

A factorially designed experiment was carried out using lactose as starting material in order to elucidate the effect of the amount, the type and the particle size of the melting binder. Four grades of PEG were included in the experiments, PEG 3000 in flakes and PEG 6000 as a fine powder, a coarse powder and in flakes. All the grades of PEG were used in amounts of 320 g, 340 g and 360 g. In the case of the finely powdered PEG 6000 an additional experiment was carried out with 300 g of binder. The impeller speed was varied at 500, 800 and 1400 rpm with 360 g of the finely powdered PEG 6000 as binder.

Aqueous wet granulation of the same quality of lactose caused a marked adhesion of mass to the bowl in the same mixer (8). With the two exceptions mentioned below melt granulation of lactose gave rise to negligible adhesion only. In a few preliminary melt granulation experiments with glycerol monostearate, cetyl alcohol, stearyl alcohol or stearic acid as melting binders adhesion of moist mass to the bowl was a problem. This adhesion resulted in a poor reproducibility and a wider size distribution. Thus polyethylene glycols seem to be particularly suitable for melt granulation. The reason why adhesion is a problem when using an aqueous binder solution and some other melting binders, but not PEGs is unknown. A probable explanation is that the PEGs have some physical properties that give rise to a lubricant effect of the molten binder.

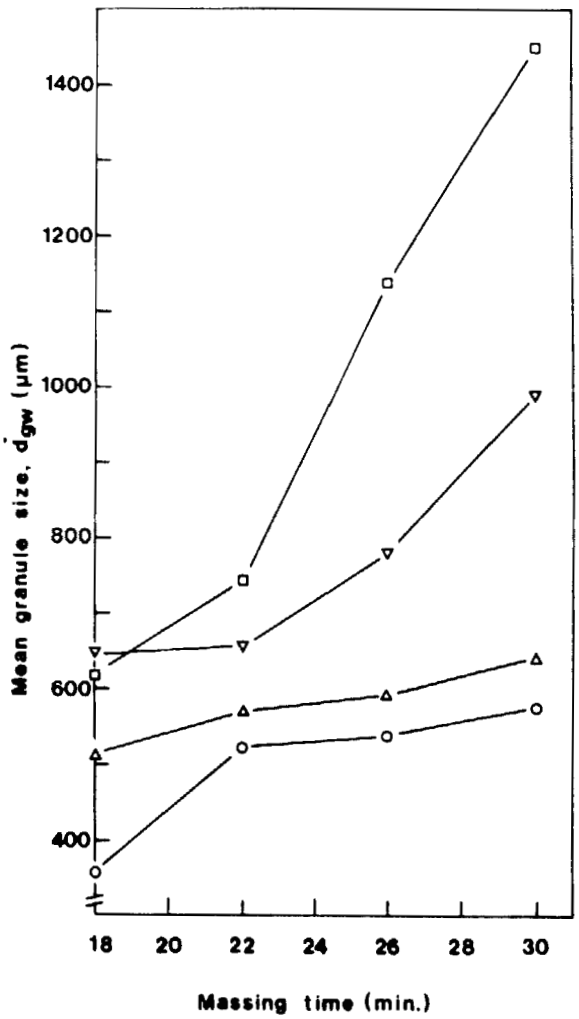

FIGURE 6
Effect of massing time at varying amounts of finely powdered PEG 6000 on the mean granule size. Starting material: Lactose. Impeller speed: 1400 rpm. Amount of PEG: ○ : 300 g; △ : 320 g; ▽ : 340 g; □ : 360 g.

Figure 6 shows the effect of varying amounts of PEG on granule size with the finely powdered PEG 6000 as an example. As can be seen granule growth rate is low at the smallest amounts of binder. Granule growth rate is markedly increased with larger amounts of binder. The amounts of binder used in the experiments in Figure 6 correspond to binder concentrations between 13.0 and 15.3% w/w of the final granules. Kinget and Kemel (4) used concentrations of PEG 6000 between 10 and 16% w/w for granulation of lactose. The granule sizes obtained by Kinget and Kemel at the same binder concentrations were smaller than the granule sizes found in the present experiments, probably because of a smaller particle size of the lactose.

Contrary to dicalcium phosphate, lactose is easily densified (10). The lactose granules, therefore, quickly reach their final porosities. With 300 g and 320 g of PEG 6000 a slight decrease in intragranular porosity was seen between 18 and 22 minutes of wet massing. With 340 g and 360 g, only random variations in porosity were observed independent of the grade of PEG. That indicates that densification had been finished after 18 minutes of massing, because densification is promoted by a larger amount of binding liquid.

The porosities of the final granules were about 5% and the corresponding corrected porosity values were about 21%. The corrected porosities obtained by melt granulation were slightly higher than the uncorrected porosities obtained by aqueous wet granulation of the same lactose quality (8). The corrected porosities were not calculated in the wet granulation experiments, since the values will be biased because of dissolution of some of the lactose in the binder solution.

Due to the almost constant porosity found by melt granulation, only random variations were observed in the degree of liquid saturation, too. Consequently, the granule growth cannot be explained by an increase in liquid saturation during massing but might be caused by coalescence due to deformation at collisions of granules at very high speed as discussed above. Granule growth of lactose by melt granulation occured at liquid saturations between 80 and 90%, i.e. within the same range as dicalcium phosphate (Figure 5). These findings are unexpected since wet granulation of 200 mesh lactose occurs at markedly lower liquid saturations than dicalcium phosphate, normally in the range between 40 and 60% (8,13).

Similar differences between melt granulation and wet granulation are seen when the amounts of binder liquid are compared. The amount of binder liquid was 46.6% v/v of the dry starting material by wet granulation (8) and is between 36.5 and 42.9% v/v by melt granulation of the same batch of dicalcium phosphate in the same mixer. By wet granulation, however, the actual amount of binder liquid will be lower due to evaporation of water during massing. If this evaporation is incorporated, it can be concluded that the amount of binder liquid has to be at the same level by melt granulation as well as wet granulation of dicalcium phosphate. By granulation of the same batch of lactose, however, the amount of binder liquid necessary for wet granulation (14.4% v/v) was only slightly more than half of the amount to be used for melt granulation (21.2-25.4% v/v).

It is likely that the difference in the ranges of liquid saturations and amounts of binder liquid necess-

ary to cause granule growth of lactose by melt granulation and wet granulation, respectively, is due to dissolution of lactose by wet granulation. Dissolution of lactose on the surface of the particles in an aqueous system will reduce particle interactions and hence improve the deformability of the moist agglomerates. Therefore, the ability of the granules to grow by coalescence at lower liquid saturations is increased.

Since lactose as well as dicalcium phosphate are insoluble in molten PEG, the different amounts of binder liquid to be used by melt granulation of these materials are due to differences in size, size distribution and shape of the particles. The dicalcium phosphate particles are smaller than those of the lactose, and consequently the %v/v of molten binder has to be larger.

The lowest amount of PEG (300 g) was omitted in the experiments with the other PEG grades due to the low granule growth rate at that binder concentration. An effect of the amount of binder similar to the effect seen in Figure 6 was found in the experiments with the other PEG grades.

Figure 7 shows the amount of lumps in the experiments in Figure 6. During the massing time between 18 and 22 minutes a decrease in the amount of lumps is seen independent of the amount of binder, because the very high impeller speed gives rise to comminution of large agglomerates. At the end of massing the amount of lumps increases with 320 g, 340 g and 360 g of binder. With 360 g of PEG a sudden increase in the amount of lumps is seen after 26 minutes. An examination of the granule size distribution showed that this increase is not caused by an uncontrollable granule growth. The amount

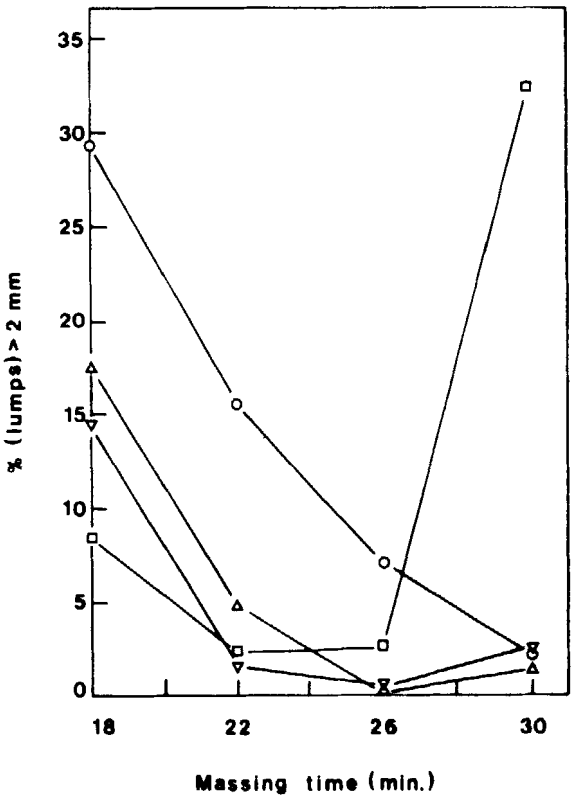

FIGURE 7
Effect of massing time at varying amounts of finely powdered PEG 6000 on the amount of lumps larger than 2 mm. Starting material: Lactose. Impeller speed: 1400 rpm. Amount of PEG: o : 300 g; Δ : 320 g; ∇ : 340 g; □ : 360 g.

of lumps larger than 4 mm is about 9% only. The large amount of lumps larger than 2 mm is seen because the mean granule size is increased to 1450 µm. Consequently, a controlled granule growth will result in a considerable part of the granules being larger than 2 mm. The experiments with the other PEG grades showed similar variations in the amount of lumps.

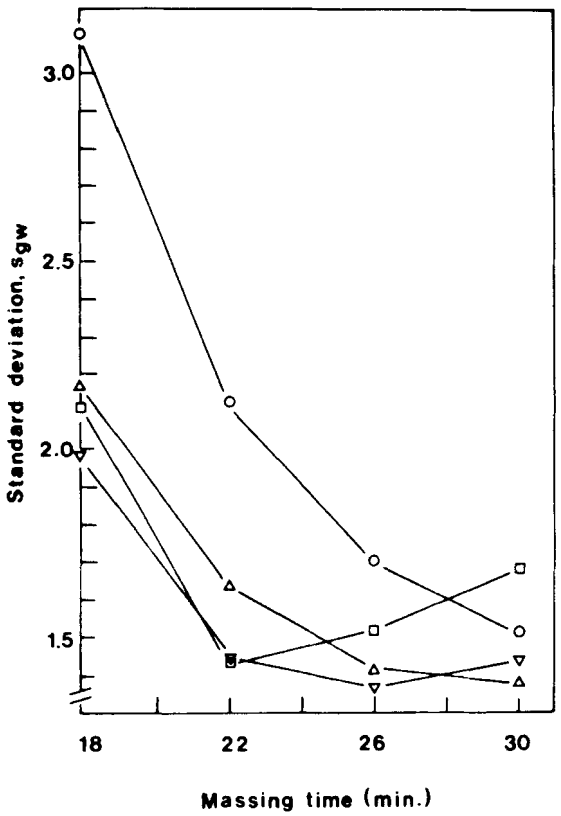

FIGURE 8
Effect of massing time at varying amounts of finely powdered PEG 6000 on the granule size distribution expressed by the geometric standard deviation. Starting material: Lactose. Impeller speed: 1400 rpm. Amount of PEG: o : 300 g; Δ : 320 g; ▽ : 340 g; □ : 360 g.

The geometric standard deviations obtained from the same experiments are shown in Figure 8. The variations in s_{gw} are similar to the variations in the amount of lumps (Figure 7). However, a slight increase in s_{gw} is seen instead of the sudden increase in the amount of lumps at the end of massing with 360 g of PEG. This further indicates that the lumps are caused by a con-

trolled granule growth. The lowest value of s_{gw} found by other authors (4) by granulation of lactose with PEG 6000 was about 1.8. It is likely that the narrower granule size distribution obtained in the present mixer is due to a higher impeller speed in that mixer.

The lowest s_{gw} values of the lactose granules are slightly lower than the lowest values of the dicalcium phosphate granules (Figure 2). After 26 minutes of massing with 340 g of PEG, 93% of the granules were within the size range of 500 to 1400 μm, 80% being between 500 and 1000 μm. A narrow size distribution with a smaller or a larger mean granule size can be obtained by reducing or increasing the amount of PEG, respectively. With a lower amount of PEG the massing time has to be longer in order to obtain a narrow size distribution. The effect of the amount of binder on s_{gw} was similar in the experiments with the other PEG grades. The results demonstrate that it is possible to produce pellets of lactose by melt granulation.

The effect of impeller speed was more pronounced when granulating lactose instead of dicalcium phosphate. In an experiment with 360 g of finely powdered PEG 6000 where impeller speed was lowered to 500 rpm granule growth became uncontrollable and large balls occured after 22 minutes of massing. That means that the power input at this rotation speed is insufficient to comminute the largest agglomerates. At 800 rpm granule growth was controllable, but the growth rate was lower than at 1400 rpm similar to what was seen by melt granulation of dicalcium phosphate. These findings are partly in accordance with the results of other authors (4), who found that an increased impeller speed resulted

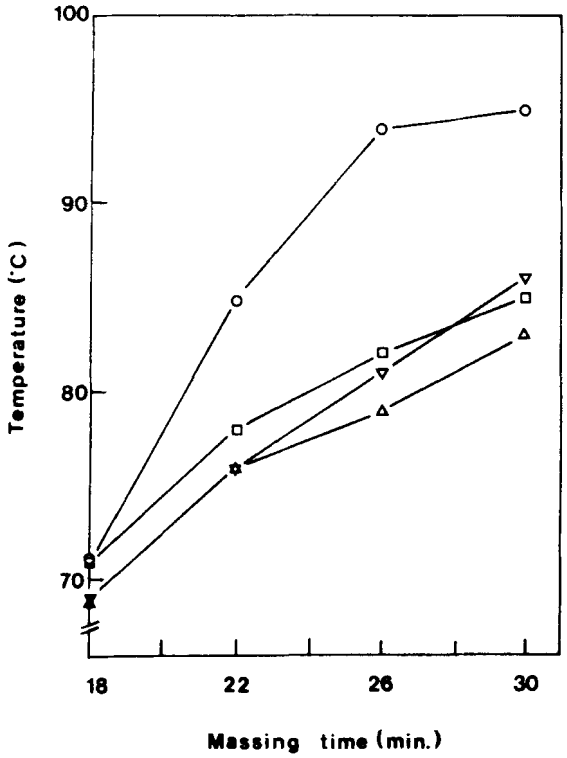

FIGURE 9
Effect of varying grades of PEG on the temperature during massing. Starting material: Lactose. Impeller speed: 1400 rpm. Amount of PEG: 340 g. Binder: ○ : PEG 3000, flakes; △ : PEG 6000, fine powder; ▽ : PEG 6000, coarse powder; □ : PEG 6000, flakes.

in a coarser but more homogeneous size distribution by melt granulation of lactose.

Adhesion of a cake of moist mass to the bottom of the bowl was found to be a problem at 500 rpm as well as 800 rpm. Most adhesion was seen at 500 rpm, however. The reason for the caking might be that the formation of large agglomerates is not sufficiently prevented when the impeller speed is lowered.

Figure 9 shows the temperature rise during massing with 340 g of different grades of PEG. Although the values of temperature might be biased to a different extent due to cooling during sampling, there is a clear tendency for a higher temperature when using PEG 3000 instead of PEG 6000. Since the same tendency was seen with 320 g and 360 g of binder, it is not ascribed to random variations. The three qualities of PEG 6000 do not differ significantly with respect to temperature rise. The reason for the higher temperature seen with PEG 3000 might be the lower viscosity of that binder. A lower viscosity of the molten binder might increase the deformability of the agglomerates and might thus give rise to more friction between the particles which generates more heat of friction.

There was, however, no clear indication of the physical properties of the granules being affected by the lower viscosity of the PEG 3000. Figure 10 shows the granule growth during massing with 340 g of the different grades of PEG, and Figure 11 shows the geometric standard deviations obtained in the same experiments.

Kinget and Kemel (4) compared PEG 4000 with PEG 6000 and found that PEG 6000 resulted in larger granules of wider size distributions. This effect of the type of PEG was explained by a more difficult distribution of PEG 6000 in the powder mass due to a higher viscosity. No such effect was observed in the present experiments. The reason might be that the higher impeller speed results in a uniform distribution of PEG 3000 as well as PEG 6000.

In Figure 10 a fall in granule growth rate is seen after 26 minutes of massing with PEG 3000. A similar fall was observed in the experiment with 360 g of PEG

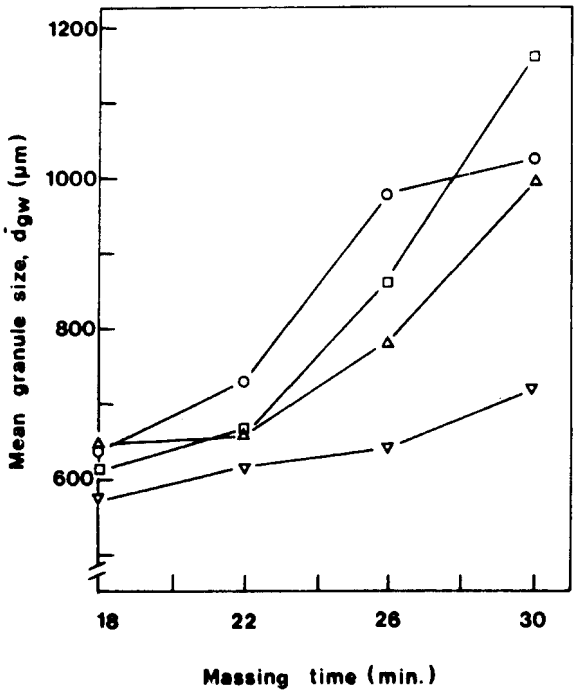

FIGURE 10
Effect of massing time at varying grades of PEG on the mean granule size. Starting material: Lactose. Impeller speed: 1400 rpm. Amount of PEG: 340 g. Binder: o : PEG 3000, flakes; Δ : PEG 6000, fine powder; ▽ : PEG 6000, coarse powder; □ : PEG 6000, flakes.

3000. A possible explanation might be that the large granules are more easily comminuted when PEG 3000 is used as a binder. PEG 6000 might give rise to stronger granules which are more able to resist comminution.

In Figure 10 and in the corresponding experiments with 320 g and 360 g of binder there is a slight tendency for a larger granule size when PEG is used as flakes. This might be due to a heterogeneous distribution of the PEG due to the large size of the flakes.

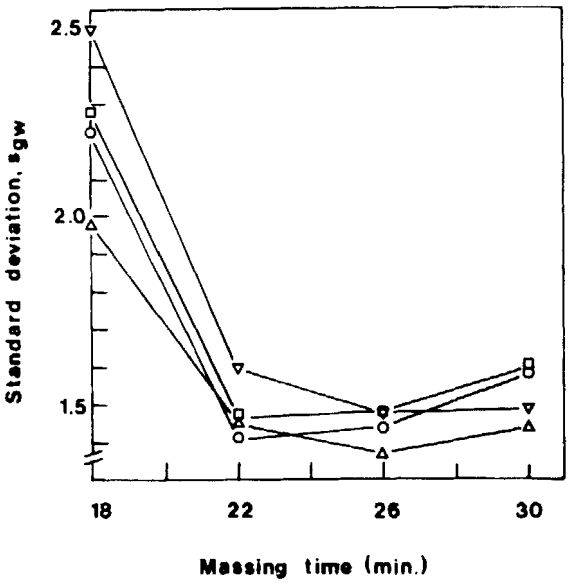

FIGURE 11
Effect of massing time at varying grades of PEG on the granule size distribution expressed by the geometric standard deviation. Starting material: Lactose. Impeller speed: 1400 rpm. Amount of PEG: 340 g. Binder: ○ : PEG 3000, flakes; △ : PEG 6000, fine powder; ▽ : PEG 6000, coarse powder; □ : PEG 6000, flakes.

If that was the case, however, the granule size distribution should be wider, when the binder is used as flakes. The variations in s_{gw} were assumed to be random between binders in Figure 11 and in the corresponding experiments with 320 g and 360 g of PEG. There is no clear indication, therefore, of a heterogeneous binder distribution if the binder is added as flakes. It is likely that the power input at a high impeller speed is adequate to distribute the flakes uniformly in the powder mass during melting.

In Figure 10 the coarse powder of PEG 6000 results in a smaller granule size than the fine powder and the flakes. The same tendency, although less clear, was found in the experiments with 320 g and 360 g of binder. No difference in melting point or viscosity was found between the three grades of PEG 6000. Therefore, no obvious explanation can be given for the apparent effect of the particle size of PEG 6000 on granule size. The granule size distribution is not significantly affected by the grade of PEG 6000.

CONCLUSIONS

The small laboratory scale high shear mixer is very suitable for melt granulation, because the maximum impeller speed is so high that the binder can be heated to its melting point by heat of friction within 15-20 minutes. Contrary to aqueous wet granulation practically no adhesion to the bowl of the mixer is seen by melt granulation with PEG.

Melt granulation of materials of different particle size is possible with PEG 3000 and 6000 in concentrations within the range of 15 to 20% w/w of the materials to be granulated. The high binder concentration results in granules which are denser than the granules obtained by wet granulation. The optimum concentration of the melting binder depends on the particle size of the starting materials. By variation of binder concentration and massing time it is possible to produce granulations of wide size distributions as well as pellets of size distributions, which are much narrower than the size distributions obtained by wet granulation in high shear mixers.

The reason for the narrow size distributions obtained by melt granulation in the present mixer is the very high impeller speed combined with no adhesion of mass to the bowl. A decrease in impeller speed results in a wider size distribution and might give rise to adhesion. The high impeller speed results in a uniform distribution of the binder during melting, and the physical properties of the final granules, therefore, are only slightly dependent on the primary particle size of the PEG and the viscosity of the molten PEG.

By granulation of dicalcium phosphate the granule growth mechanisms are similar by melt granulation and wet granulation, which is reflected by the fact that the liquid saturation and the amount of binder liquid is nearly the same by both granulation methods. Lactose, however, acts differently by melt granulation and wet granulation, because lactose is soluble in an aqueous binder solution. The liquid saturation and the amount of binder liquid, therefore, have to be markedly lower by wet granulation.

Preliminary experiments with some other melting binders indicate that the PEGs are especially suitable for melt granulation, since the other binders gave rise to adhesion and wider size distributions. There is a need, therefore, for further research on melt granulation in order to clarify the influence of the physical properties of different melting binders on the melt granulation process.

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