ELSEVIER International Journal of Pharmaceutics 183 (1999) 155–164

international journal of pharmaceutics

Evaluation of melt agglomeration properties of polyethylene glycols using a mixer torque rheometer

Anita Johansen, Torben Schæfer *, H. Gjelstrup Kristensen

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

Received 25 September 1998; received in revised form 24 February 1999; accepted 28 February 1999

Abstract

Lactose was melt agglomerated in a mixer torque rheometer with polyethylene glycol (PEG) 2000, 3000, 6000, 8000, 10 000, or 20 000 as meltable binder. A longer massing time caused an increase in mean torque until a maximum value after which the torque decreased. A smaller particle size of the PEG gave rise to a faster initial rise in mean torque. The higher viscosity of the PEG 20 000 resulted in a higher mean torque, whereas no clear difference in mean torque was obtained with the other PEGs. The binder concentration could be varied within a rather wide range without causing overwetting, the range being wider with PEG 3000 than with PEG 20 000. The mean torque values obtained were found to be related to the liquid saturation of the agglomerates. The reproducibility of the experiments was found to be very dependent on the experimental conditions, the highest binder viscosities and binder concentrations giving rise to a poor reproducibility. The results were compared with a few melt agglomeration experiments with PEG 3000 in a high shear mixer. The mixer torque rheometer was found not to be suitable for predicting melt agglomeration properties in the high shear mixer because of a marked difference in the shear forces in the two mixers.

Keywords: Binder particle size; Binder viscosity; High shear mixer; Melt agglomeration; Mixer torque rheometry; Polyethylene glycols

---

1. Introduction

The rheology of a wet powder mass has an important effect on agglomerate growth in wet granulation processes, as an adequate consistency is necessary for a controllable growth of smaller agglomerates into larger agglomerates by coalescence. The rheological properties of wet powder masses can be monitored using mixer torque rheometry. The use of mixer torque rheometry has been reviewed by Rowe and Parker (1994) and Rowe (1996).

---

* Corresponding author. Tel.: +45-35-37-08-50; fax: +45-35-37-12-77.

PII: S0378-5173(99)00093-9

In the mixer torque rheometer, two different parameters can be measured. These are the mean torque increase from the baseline (mean torque) and the difference in amplitude of the oscillations (torque range). The mean torque describes the mean resistance of the mass to mixing, while the torque range reflects the rheological heterogeneity of the mass (York and Rowe, 1994).

The equilibrium torque profiles obtained from a mixer torque rheometer have been related to the different states of liquid saturation of the mass (Rowe and Sadeghnejad, 1987; Hancock, 1991). As the moisture content increases, the torque will increase as the liquid saturation goes through the pendular and the funicular state. A maximum in mean torque will be reached at complete saturation in the capillary state. A further increase in the amount of liquid results in the formation of a slurry causing a fall in torque. The maximum torque range usually occurs at a slightly lower liquid saturation than the corresponding maximum in mean torque (Hancock et al., 1994).

The mixer torque rheometer has been shown to be useful for predicting agglomeration properties of wet masses in other mixer granulators. The amount of water added at the maximum torque was found to be comparable with that found for the optimum production of pellets by spheronization (Rowe and Sadeghnejad, 1987; Souto et al., 1998), whereas typical pharmaceutical granules were indicated to be formed at liquid saturations immediately prior to the torque maximum (Hancock et al., 1991). Further, the mixer torque rheometer can be used to examine the effect of mixing time on the rheology of wet masses (Parker et al., 1990a). The rheological properties of wet samples drawn from mixer granulators have been measured in a mixer torque rheometer in order to monitor batch variations in a pharmaceutical production (Janin et al., 1990) or to obtain a viscosity value for a scale-up of a granulation process by applying dimensionless numbers (Landin et al., 1996a,b).

Up to now, the binder liquids used for mixer torque rheometry have been water or aqueous solutions. Melt agglomeration experiments have been performed in a high shear mixer with polyethylene glycols covering a wide range of viscosities (Schæfer and Mathiesen, 1996a,b). The purpose of the present work was to examine the applicability of the mixer torque rheometer for a characterization of the melt agglomeration properties of the same polyethylene glycols, and for a prediction of their agglomeration properties in a high shear mixer.

2. Materials and methods

2.1. Materials

Lactose 450 mesh (α-lactose monohydrate, DMV, The Netherlands) was used as starting material. Polyethylene glycol (PEG) 2000, 3000, 6000, 8000, 10 000, or 20 000 (Hoechst, Germany) was used as meltable binder. All the PEGs were used as flakes. In addition, PEG 3000 was used as powder and fine powder, and PEG 20 000 as powder. All the PEGs were of the same batches as previously employed (Schæfer and Mathiesen, 1996a,b), except for the experiments in the high shear mixer.

The size distribution by volume of the lactose was determined by a Malvern 2601Lc laser diffraction particle sizer (Malvern Instruments, UK). The median particle diameter of the lactose was found to be 21 μm, and the span was 2.5. The span is calculated as the difference between the diameters at 90 and 10 percentage points relative to the median diameter.

The BET multipoint surface area of the lactose, determined by a Gemini 2375 Surface Area Analyzer (Micromeritics, USA) was 0.83 m^2/g.

The true density of the lactose was found to be 1.546 g/cm^3, determined by an Accupyc 1330 gas displacement pycnometer (Micromeritics, USA) using helium purge. The poured and tapped density of the lactose was determined according to the test for apparent volume (European Pharmacopoeia, 1997) and found to be 0.46 and 0.67 g/ml, respectively.

The true densities of the solid PEGs were determined in an earlier work (Schæfer and Mathiesen, 1996a,b), and found to vary between 1.221 and 1.227 g/cm^3. The densities of molten PEGs at 75°C were estimated to be 1.082 g/cm^3 (Hoechst, 1992).

The melting ranges of the PEGs and the viscosities of the molten PEGs are shown in Table 1, which is based on previously published data (Schæfer and Mathiesen, 1996a). The viscosities at 75°C are calculated from the regression lines as previously described (Schæfer and Mathiesen, 1996a). The viscosities of the molten fine powders and powders were found to be identical or close to the value of the flakes (Schæfer and Mathiesen, 1996b). The batch of PEG 3000 powder used in the high shear mixer experiments was found to have a melting range identical to that shown for PEG 3000 in Table 1, and a viscosity of 165 mPas at 75°C.

2.2. Equipment

The mixer torque rheometer (Caleva Process Solutions, UK) uses the same measuring system, data collection, and analysis concepts and techniques as those previously described (Parker et al., 1990a). The instrument is similar to the one described by Rowe (1996), but has been modified and equipped with a heating jacket system in order to control product temperatures in the mixer bowl between ambient temperature and approximately 120°C.

The Pellmix PL 1/8 laboratory scale high shear mixer (Niro A/S, Denmark) (Schæfer et al., 1993) was used for a few melt agglomeration experiments.

2.3. Mixing procedures

2.3.1. Mixing procedure in mixer torque rheometer

The mixer bowl was preheated to 50°C, and 30 g of the lactose were dry mixed with differing amounts of solid PEG at an impeller speed of 52 rev min^{-1}. After 5 min of mixing, the temperature was raised to 75°C. The start of the massing time was defined as this point. The product temperature reached 75°C after approximately 20 min of massing. Massing continued for the predetermined time, while data were collected at fixed intervals. The PEG concentrations given are in percent (m/m) of the amount of lactose.

Table 1
Physical properties of the PEGs

PEG (flakes)	Melting range (°C)	Viscosity (mPas at 75°C)
2000	42–53	88
3000	48–59	195
6000	52–62	815
8000	54–63	1408
10 000	57–64	4074
20 000	53–66	22 607

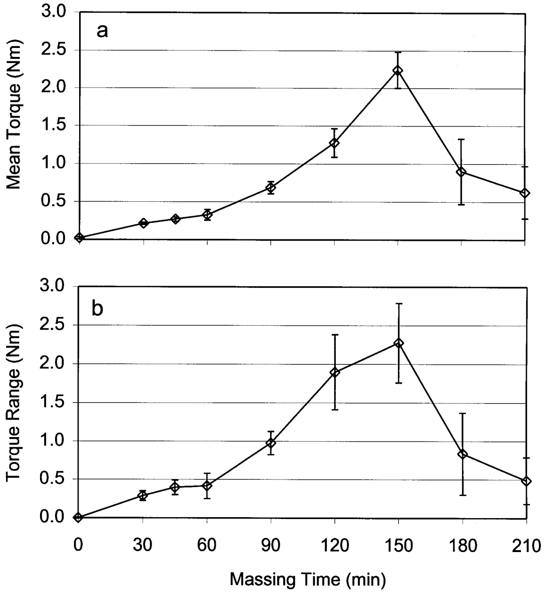

Fig. 1. Effect of massing time for PEG 3000 (powder) on mean torque (a) and torque range (b). Binder concentration, 28%.

The consistencies of the agglomerates prepared in the high shear mixer were measured in the mixer torque rheometer at 52 rev min^{-1} for 5 min in the mixer bowl preheated to 75°C.

All experiments were performed in duplicate in a randomised order. The measured torque less the torque recorded with the empty mixer was calculated. The experimental points shown in the figures are mean values. The error bars in the figures represent the standard deviation of the mean when the mean value is based on more than two repetitions (Fig. 1), and represent the range, i.e. the difference between the results, in case of two repetitions (Figs. 2–5).

2.3.2. Mixing procedure in high shear mixer

The heating jacket was preheated to 50°C. A total of 1000 g of lactose and 240 g of PEG 3000 powder was dry mixed at an impeller speed of 1300 rev min^{-1}. Because of formation of frictional heat caused by the impeller rotation, the product temperature increased during mixing to a temperature exceeding the melting point of the PEG. The melting point was observed as an inflection point on the recorded product temperature curve. This inflection point was defined as the start of massing time. Two minutes after the melting point was observed on the temperature curve, the impeller speed was lowered to 700 rev min^{-1}. Four experiments were performed with massing times of 2, 8, 14, and 20 min. The maximum product temperature was found to be 82°C.

At the end of each experiment, the agglomerates were sieved on a 4-mm Jel-Fix 50 vibration sieve (J. Engelsmann, Germany) for about 10 s, until the fraction finer than 4 mm had passed. Two 30-g samples of agglomerates were drawn from the fraction finer than 4 mm and stored in a Termaks type TS 4057 oven (Lytzen Lab, Denmark) at 75°C until the mixer torque rheometer consistency measurement could be performed (within 30–60 min). The remaining agglomerates were spread out in thin layers on trays allowing them to cool at ambient temperature.

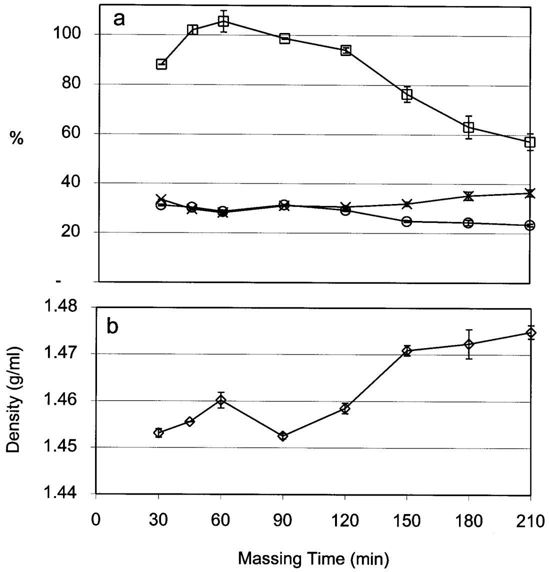

Fig. 2. Effect of massing time on (a) porosity (×), liquid saturation (□), and PEG concentration (○) and on (b) true density (◇) of the agglomerates in Fig. 1.

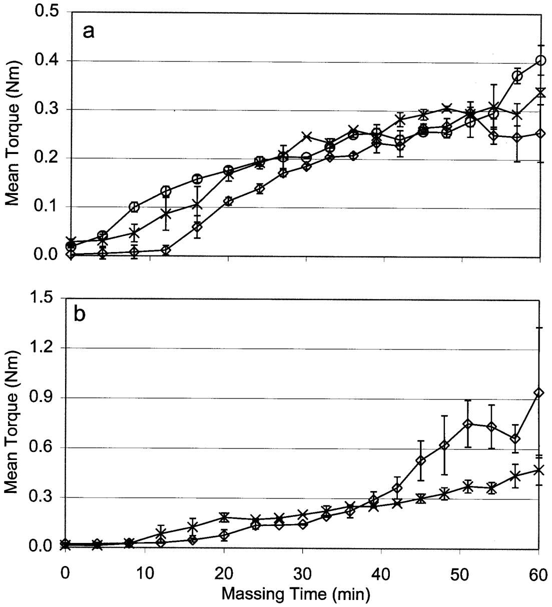

Fig. 3. Effect of binder particle size on mean torque for PEG 3000 (a) and PEG 20 000 (b). Binder concentration, 28%. Binder particle size, flakes (◇); powder (×); fine powder (○).

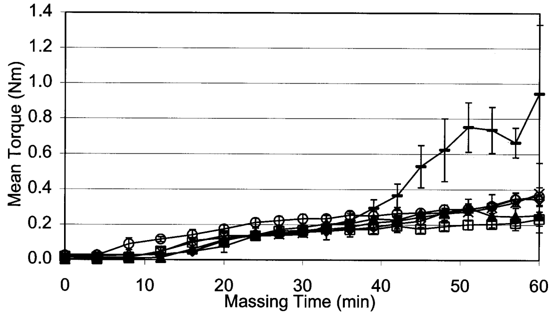

Fig. 4. Effect of type of PEG (flakes) on mean torque. Binder concentration, 28%. PEG type, 2000 (○); 3000 (▲); 6000 (□); 8000 (×); 10 000 (◇); 20 000 (–).

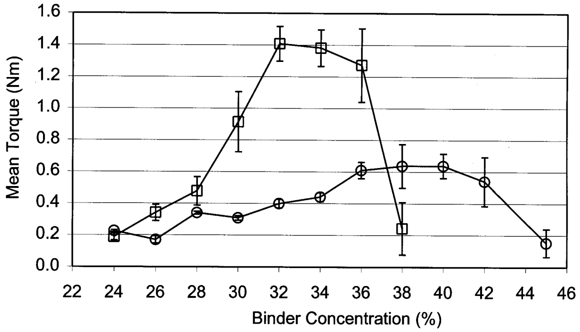

Fig. 5. Effect of binder concentration on mean torque for PEG 3000 powder (○) and PEG 20 000 powder (□). Massing time, 60 min.

2.4. Agglomerate characterization

2.4.1. Characterization of agglomerates prepared in mixer torque rheometer

The intragranular porosity was estimated by a mercury immersion method (Schæfer et al., 1992a), and the liquid saturation was calculated as described by Eliasen et al. (1998). The porosity values were corrected for the volume of solidified binder within the intragranular pores and voids. This corrected porosity reflects the porosity of the wet granules in the agglomeration phase in which the molten binder acts like a liquid (Schæfer et al., 1990).

The true density of the milled agglomerates was measured by an Accupyc 1330 gas displacement pycnometer (Micromeritics, USA) using helium purge. All porosity and density analyses were performed in duplicate.

2.4.2. Characterization of agglomerates prepared in high shear mixer

The size distributions of the agglomerates prepared in the high shear mixer were estimated by sieve analysis of a sample drawn by scooping approximately 100 g from the cooled fraction finer than 4 mm. A series of 12 ASTM standard sieves in the range of 180–2000 μm was vibrated by a Fritsch analysette 3 vibrator (Fritsch, Germany) for 10 min, and the geometric-weight mean diameter, $\bar{d}_{gw}$, and the geometric standard deviation, s_g, were calculated.

The porosity and the liquid saturation of the agglomerates were estimated as described in Section 2.4.1.

3. Results and discussion

3.1. Agglomeration experiments in mixer torque rheometer

3.1.1. Effects of massing time

Experiments were performed in order to establish the massing time needed to reach an equilibrium torque response (Hancock et al., 1992) with lactose agglomerated with PEG in the mixer torque rheometer. The resulting mean torque and torque range profiles are shown in Fig. 1, which presents the results of 16 experiments. Experiments were terminated at the eight different massing times shown in Fig. 1 in order to get samples for further analyses. Since the experiments were carried out in duplicate, the error bars at massing times 30, 45, 60, 90, 120, 150, 180, and 210 min represent the standard deviation of the mean of 16, 14, 12, ten, eight, six, four, and two repetitions, respectively. The reproducibility is seen to decrease at prolonged massing. An equilibrium torque profile cannot be expected until after approximately 20 min of massing where temperature equilibrium in the powder mass is obtained. The shape of the torque range versus massing time profiles determined in Fig. 1b, as well as in the following experiments, resembled those of the corresponding mean torque (Fig. 1a). The measurements of the mean torque are seen to be more reproducible than the measurements of the torque range.

In the experiments in Fig. 1a, the mean torque response is seen to rise with increasing massing time up to a peak at 150 min, after which the torque response declines with continued massing. Visual inspection of the mass revealed an increasing growth of agglomerates until 150 min of massing where a size reduction began to dominate. Continued massing resulted in further comminution of the mass into a fine powder. Visual inspection also revealed an ascending amount of adhesion of the mass to mixer blades and bowl.

Fig. 2 shows the changes in the porosity, the liquid saturation, and the true density of the lactose agglomerates with massing time. Furthermore, the actual PEG concentrations of the samples are calculated from the density data (Schæfer and Mathiesen, 1996b). The rise in density after approximately 120 min of massing expresses a fall in the PEG concentration of the mass with massing time. The porosity and liquid saturation values illustrated in Fig. 2a have been corrected for this change in binder concentration. During the first 60 min of massing, the agglomerates undergo a densification leading to a fall in porosity and a rise in liquid saturation. At 60 min of massing, a minimum in the porosity is reached (Fig. 2a) indicating that the densification is completed. The high binder viscosity combined with the rather low shearing forces in the mixer torque rheometer is assumed to cause this long densification time. At 60 min, the maximum liquid saturation is reached, after which it decreases for the rest of the massing time. An explanation for this behaviour could be that as the liquid saturation passes 100%, the excess of binder adheres to the mixer blades and the bowl, thus reducing the PEG concentration in the moving mass. This results in a lower liquid saturation and reduces the agglomerate strength, leading to comminution and a simultaneous formation and growth of new agglomerates with a higher porosity. The slight increase in porosity seen after 60 min indicates that the shearing forces make the saturated mass more dilated. This will increase the deformability of the mass and might explain the increase in torque seen from 60 to 150 min of massing (Fig. 1). After 150 min of massing, a sudden fall in torque is observed. At this point, the agglomerate mass has turned into a powder, presumably because at this point the amount of binder present in the moving mass is insufficient to form new agglomerates.

The results presented in Fig. 1 show that an equilibrium torque response for 28% PEG in lactose is not reached within 3.5 h of massing in the mixer torque rheometer. On the basis of these experiments, a massing time of 60 min was chosen in the following experiments since the minimum in the porosity (Fig. 2a) indicates that the densification of agglomerates has been completed at this point.

3.1.2. Effects of binder particle size

In previous melt agglomeration experiments in a high shear mixer, the particle size of the PEG was found to have an effect on agglomerate formation and growth, and this effect was found to interact with binder viscosity (Schæfer and Mathiesen, 1996b). Experiments were performed in the mixer torque rheometer in order to investigate whether the rheological properties of the mass were affected by changes in binder particle size. Fig. 3 compares the mean torque versus massing time profiles of agglomerates produced with PEG 3000 and PEG 20 000 in three and two different particle sizes, respectively. For both binder types, the initial rise in mean torque is seen to be most rapid with the smallest binder particle size. This is most likely due to the easier distribution and faster melting of the smaller particles. At prolonged massing, the difference in torque from the different particle sizes becomes levelled out when regarding the lowest viscosity binder (Fig. 3a). However, for the PEG 20 000 (Fig. 3b), a rapid mean torque increase during the end of massing is observed for the flakes. This might be due to a larger agglomerate size since the dominant mechanism of agglomerate formation will be immersion instead of distribution with a larger particle size of a highly viscous binder (Schæfer and Mathiesen, 1996b). A similar effect of the particle size of PEG 20 000 on the power consumption of the impeller motor was seen in experiments in a high shear mixer (Schæfer and Mathiesen, 1996b). The variation between repeated experiments is seen to become higher during the end of massing for PEG 20 000 as flakes (Fig. 3b). This is probably due to the combination of the very high viscosity of the binder and the large particle size, leading to a heterogeneous mass and therefore large fluctuations in the mean torque.

3.1.3. Effects of binder viscosity

An investigation was carried out as to whether the differences in the viscosities of the molten PEGs (Table 1) could be distinguished in the mixer torque rheometer. The experiments had to be carried out with flakes of PEG since the PEG 2000 was available as flakes only. The resulting mean torque profiles are shown in Fig. 4. The PEG types 3000 through 10 000 all have a similar mean torque profile. However, the PEG 2000 shows a faster initial increase in mean torque, and this is most likely due to the lower melting temperature range.

The PEG 20 000 shows a different and rapid increase in torque during the end of massing. This is ascribed to the very high viscosity of the PEG 20 000 causing the viscous contribution to the force of the liquid bridges within the agglomerates to be dominating, thus giving rise to a higher torque value. Experiments with the highest viscosity binder, PEG 20 000, showed a poor reproducibility during the end of massing compared to the other PEGs.

Table 2 shows the porosities and the liquid saturations of the final agglomerates. The PEG types 2000 through 10 000 all have similar porosities and liquid saturation values close to 100%. The highest liquid saturations are obtained with PEG 3000 and PEG 6000 which seem to cause a slightly lower mean torque at the end of massing. The PEG 20 000 results in a slightly higher porosity and a lower liquid saturation, implying that, even after 60 min of massing, the densification has not been completed. Accordingly, it was found that a high binder viscosity delayed the initial binder distribution and agglomerate densification in a high shear mixer (Schæfer and Mathiesen, 1996a).

Table 2
Effect of binder viscosity on the porosity and the liquid saturation of agglomerates prepared in the mixer torque rheometer[a]

PEG type (flakes)	Porosity (%)	Liquid saturation (%)
2000	29 (±0.35)	98 (±1.65)
3000	28 (±0.71)	105 (±3.70)
6000	27 (±0.38)	107 (±2.06)
8000	29 (±0.21)	99 (±1.03)
10 000	29 (±0.15)	98 (±0.72)
20 000	32 (±0.04)	85 (±0.17)

[a] Massing time, 60 min; binder concentration, 28%. The range of two determinations is given in parentheses.

In previous experiments in a mixer torque rheometer, an increasing binder viscosity was shown to produce a greater maximum torque (Parker et al., 1990b, 1991). In the present experiments, the binder viscosities are higher making the agglomerates less deformable. This might explain why the torque value is less sensitive to variations in binder viscosity in the present experiments.

3.1.4. Effects of binder concentration

Fig. 5 shows the mean torque after 60 min of massing in experiments with different binder concentrations of PEG 3000 or PEG 20 000. An increase in the mean torque with rising binder concentration until a maximum torque level is recognized for both binders. For PEG 3000, this maximum torque is reached at a concentration of 36–42%, and for PEG 20 000 the maximum appears at 32–36%. The mean torque profiles can most likely be related to the changes in agglomerate saturation states. A rise in binder concentration causes a higher mean torque because of a rise in the liquid saturation. When the highest torque values are reached, it suggests the liquid bridges in the agglomerates to be in the capillary state (Hancock, 1991). The torque values decrease at a higher binder concentration, because the agglomerates become overwetted and enter the droplet state.

The difference in the behaviours of the torque profiles for the two PEGs is distinct. For PEG 3000, the binder concentration can be varied within a wide range resulting in only minor changes in mean torque, whereas for PEG 20 000 smaller changes in concentration cause larger changes in torque values. For both PEG types, experiments with binder concentrations right before and at the maximum torque gave rise to an increase in the range of the duplicate determinations (Fig. 5). For the highest binder concentrations, resulting in a slurry and a decreasing torque, the reproducibility is seen to be poor. In previous work (Hancock, 1991), some of the higher liquid saturations also showed larger fluctuations in torque due to the production of heterogeneous wet masses.

Table 3
Effect of binder concentration on the porosity and the liquid saturation of agglomerates from the mixer torque rheometer experiments in Fig. 5[a]

	PEG 3000 P Binder concentration		PEG 20 000 P Binder concentration	
	28%	40%	28%	34%
Porosity (%)	28 (±0.84)	37 (±0.04)	31 (±0.04)	33 (±0.46)
Liquid saturation (%)	105 (±4.40)	99 (±0.16)	89 (±0.16)	99 (±2.08)

[a] Massing time, 60 min. The range of two determinations is given in parentheses.

The porosity and liquid saturation data from selected concentrations of the two binder types (Table 3) might explain the different sensitivity to changes in binder concentration. For PEG 3000, the liquid saturation of the agglomerates is found to be close to 100%, and nearly unaffected by an increase in binder concentration, because the porosity becomes correspondingly increased. A similar effect has been described in a ram extrusion process, where an increased moisture content increased the porosity, but did not affect the degree of liquid saturation (Jerwanska et al., 1995). This suggests that the processing of the mass in the mixer torque rheometer is related to the forces encountered in extrusion processes. In the mixer torque rheometer, therefore, the porosity of the mass becomes corrected for changes in binder concentration within a rather wide range, thus keeping the liquid saturation constant at about 100%. However, this is not true for PEG 20 000, where the high viscosity impedes the densification of agglomerates, thus resisting this correction of porosity. The effect of binder concentration on porosity and liquid saturation observed in the mixer torque rheometer is different from that seen in high shear mixers, where a higher binder concentration promotes the densification of the agglomerates (Schæfer et al., 1990). Consequently, a melt agglomeration process in a high shear mixer is much more sensitive to changes in binder concentration, typically allowing variations of approximately 2% (Schæfer et al., 1992b).

3.2. Agglomeration experiments in high shear mixer

In the present work, the consistencies of agglomerates produced in a high shear mixer with different massing times were measured in the mixer torque rheometer. A PEG 3000 concentration of 24% had to be chosen for the high shear mixer experiments in order to avoid overwetting of the agglomerates. This is markedly lower than the optimum binder concentration of 36–42% predicted from the maximum torque response in the mixer torque rheometer experiments (cf. Fig. 5).

Table 4 shows that a longer massing time gives rise to an increase in the mean granule size and to a narrower size distribution in accordance with previous results (Schæfer et al., 1993). No clear effect of massing time on the porosity and the liquid saturation of the agglomerates is seen. This implies that after about 2 min of massing, the densification of agglomerates is finished, and the agglomerates are saturated with binder liquid. Thus, the agglomerate densification is completed a lot faster in the high shear mixer than in the mixer torque rheometer, because of the much higher shear forces involved in the former.

When measured in the mixer torque rheometer, no difference in the consistency of the agglomerates with massing time is seen. Accordingly, the power consumption of the impeller motor, which is assumed to reflect the rheological properties of the mass in the high shear mixer (Schæfer et al., 1992b), did not change with massing time in the present experiments. The torque values obtained are seen (Table 4) to be much lower than the

Table 4
Effect of massing time in a high shear mixer on the agglomerate properties and on the rheological consistency estimated in the mixer torque rheometer[a]

Massing time (min)	(d_{gw} (μm)	s_g	Porosity (%)	Liquid saturation (%)	Mean torque (mNm)	Torque range (mNm)
2	557	2.26	25 (±0.05)	105 (±0.20)	19 (±0.5)	2 (±0.0)
8	647	1.46	24 (±0.15)	109 (±0.90)	18 (±1.0)	1 (±0.0)
14	814	1.39	24 (±0.10)	108 (±0.45)	16 (±4.5)	0 (±0.0)
20	867	1.34	24 (±0.10)	109 (±0.45)	15 (±6.0)	1 (±2.5)

[a] Binder, PEG 3000 powder; binder concentration, 24%. The range of two determinations is given in parentheses.

values obtained when agglomerating directly in the mixer torque rheometer. The agglomerates from the high shear mixer have a lower porosity as a result of the higher shear forces experienced in that mixer and, therefore, are less susceptible to deformation in the mixer torque rheometer.

4. Conclusions

The mixer torque rheometer has been found to be able to measure effects of massing time, binder particle size, binder viscosity, and binder concentration on the rheological properties of agglomerates produced by melt agglomeration with PEGs. Further, it has been shown that the rheological properties measured by the mixer torque rheometer are related to the liquid saturation of the agglomerates. The reproducibility of the measurements in the mixer torque rheometer was found to be poor, especially at very high viscosities or binder concentrations. This gives some limitations in the applicability of the mixer torque rheometer since differences in rheological properties have to be rather large in order to distinguish between them.

The melt agglomeration properties of PEGs in a high shear mixer cannot be predicted from experiments in a mixer torque rheometer. The optimum binder concentration estimated with the mixer torque rheometer is much higher than that being the optimum in a high shear mixer, and the massing time has to be much longer in the mixer torque rheometer than in the high shear mixer. This is primarily due to a noticeably lower densification rate of the agglomerates in the mixer torque rheometer because of the markedly lower shear forces.

The high viscosities of the molten PEGs will resist the densification, and the shear forces, therefore, are more important in the present experiments than in previous experiments with aqueous binder solutions of lower viscosities. This explains why the mixer torque rheometer has been found to be more suitable for a prediction of agglomeration properties in formulations with aqueous binder solutions. Accordingly, the mixer torque rheometer is assumed to be more useful in predicting agglomeration properties of meltable binders with viscosities lower than those of the PEGs, e.g. the hydrophobic binders used by Thomsen et al. (1994).

The increase in mean granule size with massing time obtained in melt agglomeration experiments with PEG 3000 in a high shear mixer could not be reflected in the rheological properties of the samples when measured in the mixer torque rheometer. This indicates that measurements with a mixer torque rheometer cannot be used for an estimation of the end point of melt agglomeration processes in high shear mixers.

Generally, the present experiments indicate that the mixer torque rheometer will be more useful in predicting agglomeration properties in a low shear equipment like an extruder or a low shear mixer than in a high shear mixer.

Acknowledgements

The authors wish to thank Clariant GmbH, Germany, for supplying the PEGs.

References

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

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

Hancock, B.C., 1991. Material Interactions and Surface Phenomena in Size Enlargement Processes. Ph.D. Thesis, University of Bradford, School of Pharmacy, UK.

Hancock, B.C., York, P., Rowe, R.C., Parker, M.D., 1991. Characterization of wet masses using a mixer torque rheometer: 1. Effect of instrument geometry. Int. J. Pharm. 76, 239–245.

Hancock, B.C., York, P., Rowe, R.C., 1992. Characterization of wet masses using a mixer torque rheometer: 2. Mixing kinetics. Int. J. Pharm. 83, 147–153.

Hancock, B.C., York, P., Rowe, R.C., 1994. An assessment of substrate-binder interactions in model wet masses. 1: Mixer torque rheometry. Int. J. Pharm. 102, 167–176.

Hoechst Aktiengesellschaft, 1992. Polyethylenglykole. Product information, Hoechst, Frankfurt am Main.

Janin, V., Parker, M.D., Rowe, R.C., 1990. Monitoring production scale granulation processes using an instrumented mixer torque rheometer. STP Pharma 6, 233–237.

Jerwanska, E., Alderborn, G., Newton, J.M., Nyström, C., 1995. The effect of water content on the porosity and liquid saturation of extruded cylinders. Int. J. Pharm. 121, 65–71.

Landin, M., York, P., Cliff, M.J., Rowe, R.C., Wigmore, A.J., 1996a. Scale-up of a pharmaceutical granulation in fixed bowl mixer-granulators. Int. J. Pharm. 133, 127–131.

Landin, M., York, P., Cliff, M.J., Rowe, R.C., Wigmore, A.J., 1996b. The effect of batch size on scale-up of a pharmaceutical granulation in a fixed bowl mixer granulator. Int. J. Pharm. 134, 243–246.

Parker, M.D., Rowe, R.C., Upjohn, N.G., 1990a. Mixer torque rheometry: a method for quantifying the consistency of wet granulations. Pharm. Technol. Int. 2 (9), 50–64.

Parker, M.D., York, P., Rowe, R.C., 1990b. Binder-substrate interactions in wet granulation. 1: The effect of binder characteristics. Int. J. Pharm. 64, 207–216.

Parker, M.D., York, P., Rowe, R.C., 1991. Binder-substrate interactions in wet granulation. 2: The effect of binder molecular weight. Int. J. Pharm. 72, 243–249.

Rowe, R.C., 1996. Mixer torque rheometry—further advances. Pharm. Technol. Eur. 8 (8), 38–48.

Rowe, R.C., Parker, M.D., 1994. Mixer torque rheometry—an update. Pharm. Technol. Eur. 6 (3), 27–36.

Rowe, R.C., Sadeghnejad, G.R., 1987. The rheology of microcrystalline cellulose powder/water mixes-measurement using a mixer torque rheometer. Int. J. Pharm. 38, 227–229.

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

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

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

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

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

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

Souto, C., Alvarez, L., Duro, R., Concheiro, A., Gómez-Amoza, J. L., Martínez-Pacheco, R., 1998. Versatility of mixer torque rheometry predictions in extrusion-spheronization. Proc. World Meet. Pharm. Biopharm. Pharm. Technol. 2nd, Paris, pp. 447–448.

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

York, P., Rowe, R.C., 1994. Monitoring Granulation Size Enlargement Processes Using Mixer Torque Rheometry. Proc. Int. Part. Technol. Forum 1st, Denver, CO, Part I, pp. 225–230.