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Characterization of wet masses using a mixer torque rheometer: 1. Effect of instrument geometry

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Summary

Two laboratory-scale, instrumented mixer torque rheometers have been used to monitor the rheological behaviour of a model wet mass. The two instruments differed in the arrangement and gearing of their mixing blades and the results obtained from each were not identical. In both rheometers liquid distribution was identified as being responsible for the initial variation in the rheology of the wet mass and the mechanism of that distribution process depended upon the level of liquid saturation. The rate of liquid distribution was different in each of the two rheometers and this has been attributed to the different mixing intensities of the two instruments. Equilibrium data showed similar trends, thus indicating a means by which different mixing processes could be compared. A cumulative energy of mixing term was derived to describe the energy input during the mixing process.

Introduction

Wet granulation is an important step in determining the processability and final quality of many pharmaceutical products. Previous workers have attempted to study the rheology of wet massed materials as a means of characterizing this process (e.g. Kay and Record, 1978; Leuenberger, 1982). Direct measurement of the mixing torque is thought to provide a more accurate assessment of the properties of the wet mass than either electrical or probe methods (Kristensen and Schaefer, 1987) and results from several reports support this view (e.g. Seager et al., 1976; Lindberg et al., 1982).

It is well known that the rheological behaviour of many materials is highly dependent upon the test conditions employed. Sensitivity to these conditions will vary according to the material under consideration. To minimize these problems it has been suggested that instruments for measuring rheological properties should be designed to match the final process conditions as closely as possible (Cheng, 1989).

A mixer torque rheometer for measuring mixing torque in pharmaceutical wet granulation processes has recently been described by Parker

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et al. (1990a). The instrument is based on a pharmaceutical sigma blade mixer and has been shown to be useful in solving a variety of formulation and processing problems. This study has employed the same mixer torque rheometer and a second very similar instrument to assess the effect of different test conditions on rheological measurements in a simple wet massed system.

Materials and Methods

A simple two-component solid-liquid mixture was chosen as a model system for investigation. The solid component was microcrystalline cellulose (Avicel PH101, FMC Corp., Co. Cork, Eire), a widely used excipient and granulation component with negligible aqueous solubility. The liquid component was single distilled water. This was evenly distributed over the surface of the powder bed using a syringe at the start of each experiment.

Two mixer torque rheometers were used to study the wet granulation process. Each rheometer consisted of an instrumented horizontal bench top mixer of 250 ml capacity. The reaction of the mixing bowl during wet massing was monitored continually via a torque arm linked to a dynamometer. Two torque parameters were calculated from the dynamometer output (Parker et al., 1990a). These torque parameters were monitored over the first 10–12 min of mixing after which equilibrium values were usually attained.

The two rheometers differed in the arrangement and gearing of their mixing blades (Fig. 1). There are two mixing blades (A and B) of different profiles designed to mesh together when moving at different speeds. In rheometer 1 (R1) (previously used by Parker et al., 1990a) blade A is driven by the motor at 52 rpm. Blade B is then driven from blade A with a gear ratio of 1:2. In rheometer 2 (previously used by Rowe and Sadeghnejad (1987) and Parker et al. (1990b)) the two mixing blades are reversed so that blade B is now driven by the motor at 52 rpm and blade A is driven from blade B at a ratio of 2:1. The net effect is of a constant drive speed but with the total blade speed in R1 being twice that in R2.

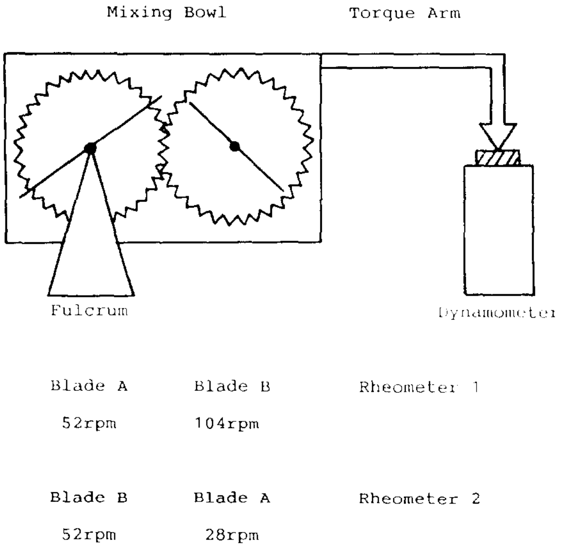

Fig. 1. Diagram of mixing blade geometries in rheometers 1 and 2.

The wet massing experiments were performed in parallel and under identical conditions at I.C.I. Pharmaceuticals (R1) and at the University of Bradford (R2).

Results and Discussion

The mixer torque rheometer can be used to determine two different torque parameters. These were described previously by Parker et al. (1990a) as the amplitude of the oscillations and the mean torque increase from the baseline. For convenience they will be referred to as the 'torque range' and 'torque mean', respectively. The variation of both of these torque parameters with changes in the mixing conditions was investigated.

Equilibrium torque results

The variation of the equilibrium torque parameters with saturation of the wet mass is shown in Fig. 2a and b. In rheometer 1 (R1) both the torque values varied in a similar manner with changing saturation of the wet mass but the torque mean response was significantly larger than the torque range response (Fig. 2a). A very similar

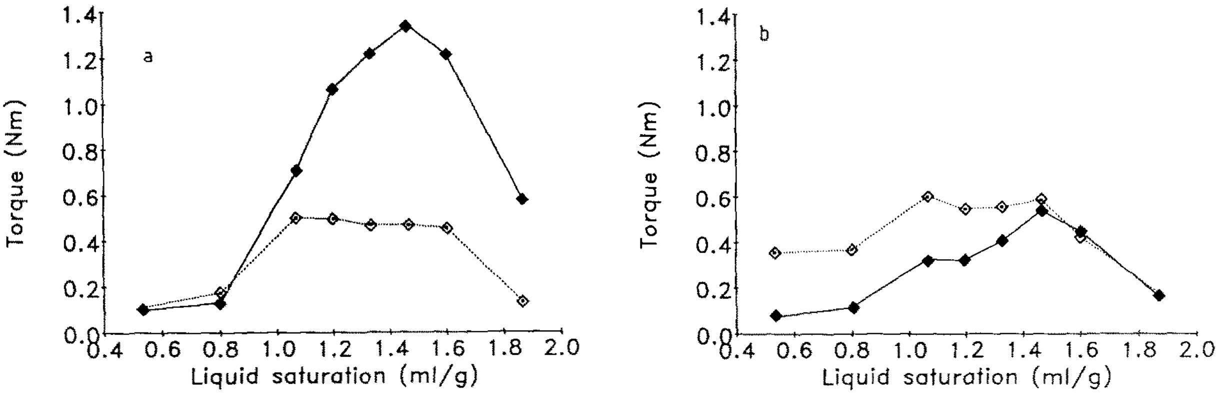

Fig. 2. (a) Equilibrium torque profiles from rheometer 1. (♦) Torque mean; (◇) torque range. (b) Equilibrium torque profiles from rheometer 2. (♦) Torque mean; (◇) torque range.

variation of the torque parameters with liquid saturation was seen in rheometer 2 (R2), however, in this case both the torque parameters were of a magnitude comparable to the torque range response in R1 (Fig. 2b).

The form of the equilibrium torque profiles was very similar in both rheometers. There was an increase in the measured torque as liquid saturation increased, up to a peak. At the peak the wet mass was smooth and pasty and any further addition of liquid caused overwetting. A slurry was then produced accompanied by a rapid fall in the torque response. Typical pharmaceutical granules were formed at liquid saturations immediately prior to the torque peak and these saturations were thought to correspond to the funicular saturation state described by Newitt and Conway-Jones (1958).

Alleva (1984) measured the rheology of microcrystalline cellulose-water wet masses in a modified shear cell apparatus and observed very similar equilibrium torque vs liquid saturation profiles. Thus, the form of the equilibrium torque profiles appears to be independent of the design of the rheometer. This allows the comparison of similar equilibrium wet masses with different processing histories and confirms the usefulness of the equilibrium torque profiles used by Rowe and Sadeghnejad (1987) and Parker et al. (1990b) in characterizing the properties of a wet mass.

A comparison of the results from R1 and R2 indicated that the torque mean was more sensi-

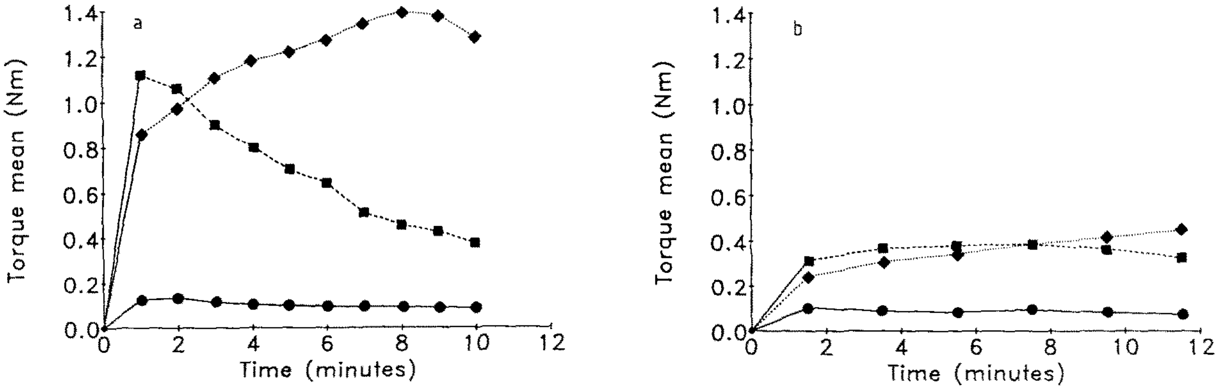

Fig. 3. (a) Torque mean variation in rheometer 1. (●) 0.5 ml/g, (■) 1.1 ml/g, (♦) 1.6 ml/g. (b) Torque mean variation in rheometer 2. (●) 0.5 ml/g, (■) 1.1 ml/g, (♦) 1.6 ml/g.

tive to differences in the geometries of the two rheometers than the torque range. The reason for this was not clear, however, it was observed that the time required to reach equilibrium was also different for each rheometer. It is possible that final rheological behaviour of the wet mass will depend upon the conditions under which equilibrium is achieved. To investigate this the variation of both torque parameters up to equilibrium was examined.

Non-equilibrium torque results

Torque mean. The variation of the torque mean over the first 10–12 min of mixing is shown in Fig. 3a and b. The torque mean response is significantly greater in R1 than in R2 at all times up to equilibrium. The major difference between the two rheometers that might account for this is their intensities of mixing. The speed of the main driven blade is identical in both rheometers but the second blade is rotating at an increased speed in R1 and at a decreased speed in R2. In terms of the combined speeds of the mixing blades R1 mixes with twice the intensity of R2. This may account for the observed differences in the torque mean responses and also the non-identical equilibration rates in the two rheometers. To test this hypothesis, the axes in Fig. 3a and b were rescaled according to the relative speed of the mixing blades in the two rheometers. This produced Fig. 4a and b where the y-axes are in a ratio of 2:1 and the x-axes are in a ratio of 1:2, since the rate and time are inversely related. The similarity of these normalized torque-time plots suggests that both the torque mean response and the rate of equilibration are directly related to the intensity of mixing. The torque is a measure of the force transmitted from the mixing blades to the mixing bowl by the wet mass and therefore an increased intensity of mixing would be expected to cause a direct increase in the measured torque. Similarly, an increase in the intensity of mixing might also be expected to reduce the time (and increase the rate) in which equilibration is attained.

The normalized torque-time plots indicate that in both rheometers the consistency of the wet mass varies significantly with mixing time. The nature of this variation in each rheometer depends upon the liquid saturation of the wet mass. At low liquid saturation an equilibrium state is reached relatively rapidly. At higher liquid saturations the system takes somewhat longer to equilibrate. Alleva (1984) observed similar behaviour with a peak resistance to shearing just after the addition of the granulating liquid. This was accompanied by an increase in granule size. It was proposed that initially a few large agglomerates were formed that offered high resistance to mixing and these were rapidly broken down as the liquid was distributed. The time required for this liquid distribution process is likely to depend upon the quantity of liquid present and this is reflected in Fig. 4a and b.

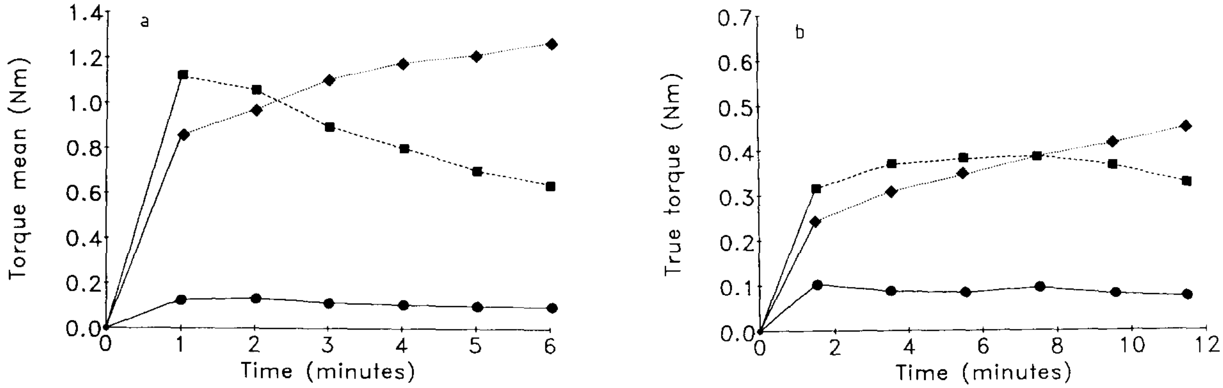

Fig. 4. (a) Re-scaled torque mean variation in rheometer 1. (●) 0.5 ml/g, (■) 1.1 ml/g, (◆) 1.6 ml/g. (b) Re-scaled torque mean variation in rheometer 2. (●) 0.5 ml/g, (■) 1.1 ml/g, (◆) 1.6 ml/g.

The normalized rheological profiles also show that the route by which equilibrium is reached was different at each saturation level. This suggests that there may be more than one mechanism of liquid distribution in this solid-liquid system.

The equilibration behaviour of the microcrystalline cellulose in this work can be compared with torque-time data previously presented for a lactose-based placebo formulation (Parker et al., 1990a). At low and intermediate liquid saturations the torque gradually increased to an equilibrium value over the first 5 min of mixing. At higher liquid saturation an initial peak was reached after which the torque dropped rapidly as the mass was over-wetted. This rheological behaviour is different from that observed with the microcrystalline cellulose where overwetting with prolonged mixing was not observed. Schildcrout (1984) studied the granulation of a lactose-based placebo with a starch-polyvinyl-pyrrolidone binder system in a similar mixer torque rheometer. The torque-time profiles in this work showed double peaks and these were attributed to different rates of distribution for each binder component.

Torque range. The variation of the torque range with mixing time was considered in an identical manner to the torque mean. The rate of torque range equilibration was also found to be directly related to the intensity of mixing. However, the magnitude of the torque range was not significantly affected by differences in mixing intensity at any time. The different effect of mixing intensity on the magnitude of the torque mean and torque range indicates that the two torque parameters must be measuring different qualities of the wet mass. A knowledge of these differences would enable a more detailed characterization of the wet mass and a greater understanding of wet granulation processes.

Variations in the route and rate of equilibration under different processing conditions emphasize the need for further rheological studies on pharmaceutical systems. Wet granulation processes will be dependent on the nature of any interactions at the solid-liquid interface. Initially, there will be wetting and spreading by the liquid phase and this will be followed by absorption, adsorption, dissolution or hydration depending on the solid-liquid system under consideration. In the case of multi-component pharmaceutical formulations the interactions occurring are likely to be highly complex and delicately balanced. Thorough preliminary mixing studies will be required to achieve robust processing procedures.

Energy of mixing

The importance of mixing intensity in the measurement of rheological properties is clear and the normalized torque-time profiles have helped to provide a qualitative comparison of these effects. However, a quantitative assessment of the energy input will be required when accurate comparison of different mixing regimens is necessary,

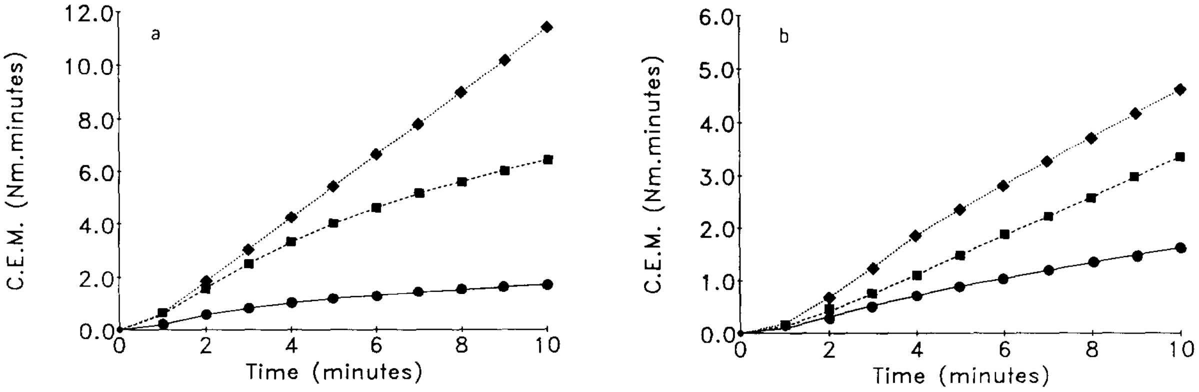

Fig. 5. (a) Cumulative energy of mixing (C.E.M.) variation in rheometer 1. (●) 0.8 ml/g, (■) 1.1 ml/g, (◆) 1.3 ml/g. (b) Cumulative energy of mixing (C.E.M.) variation in rheometer 2. (●) 0.8 ml/g, (■) 1.1 ml/g, (◆) 1.3 ml/g.

for example, during scale-up operations. In the mixer torque rheometer the measured torque at any time point provides a measure of the strength of the wet mass and of the energy required to shear that mass at that time. The integral of the torque-time profile will therefore indicate the total amount of energy that has been input into the system at any time. Holm et al. (1985) used a similar approach to relate power consumption in a high-speed mixer to temperature rises in the wet mass.

Fig. 5a and b shows the variation of the 'cumulative energy of mixing (CEM)' with mixing time for the microcrystalline cellulose-water systems at three liquid saturations. After an initial lag period of about 3–5 min the CEM varies in a linear manner ($R > 0.999$) with mixing time at each liquid saturation and in both rheometers. It seems that once the liquid has been distributed a constant amount of energy is required to continue shearing the wet mass.

The CEM was observed to increase with increasing liquid saturation up to a peak as for the torque range and torque mean (see Fig. 2a and b). This was due to the increased frequency of liquid bridges between particles at higher liquid saturations. For a fixed liquid saturation the rate of energy input (gradients in Fig. 5a and b) was approximately doubled in R1 compared to R2. This is because the mixing intensity (or rate of energy input) in R1 is twice that in R2.

Table 1 shows the CEM and the mean torque compared to the total mixing speed, mixing time and product of mixing speed and time in microcrystalline cellulose-water systems of moderate liquid saturations where typical pharmaceutical granules are produced. Mixing for 5 min at 78 rpm exposes the wet mass to 390 turns of the mixing blades. This energy input can be doubled by a 2-fold increase in either the mixing time or the mixing speed. Doubling both the time and speed of mixing results in a 4-fold increase in the energy input. Energy losses due to friction will be slightly different at each speed and time. The torque mean results show no clear relationship to mixing speed, mixing time or their product. However, the CEM varies directly with the product of mixing time and speed. That is, the integral of the torque mean-time profile reflects the total energy input into the system at any mixing intensity and over any time in similar mixers. The CEM parameter thus directly measures the energy input under any mixing conditions. This is important for pharmaceutical scale-up procedures where mixers of different intensities are commonly employed. The process end-point could be defined in terms of the total energy input and measured as the cumulative energy of mixing. A very similar approach has been applied successfully to the manufacture of bread dough (Chamberlin et al., 1962).

Conclusions

The use of two mixer torque rheometers with carefully controlled geometries has shown the importance of instrument design and assembly in the rheological characterization of wet powder masses.

The two rheological parameters (torque mean

TABLE 1

Variation of torque parameters and mixing variables at two intermediate liquid saturations (relative magnitudes in parentheses)

	Mixing speed (rpm)	Mixing time (min)	Speed × time (revolutions)	Torque mean (N m)		Cumulative energy of (N m min)	
				1.1 ml/g	1.3 ml/g	1.1 ml/g	1.3 ml/g
Rheometer 1	156 (2)	10 (2)	1560 (4)	0.38 (1)	1.20 (2.6)	6.45 (4.3)	11.37 (4.8)
	156 (2)	5 (1)	780 (2)	0.70 (1.9)	1.22 (2.6)	4.01 (2.7)	5.42 (2.3)
Rheometer 2	78 (1)	10 (2)	780 (2)	0.33 (0.9)	0.41 (0.9)	3.35 (2.2)	4.60 (1.9)
	78 (1)	5 (1)	390 (1)	0.38 (1.0)	0.46 (1.0)	1.49 (1.0)	2.36 (1.0)

and torque range) measured in this study were affected differently by changes in the rheometer construction indicating that they were measuring different properties of the wet mass. These differences may allow a more detailed assessment of the properties of pharmaceutical wet masses in the future.

Both the rheological parameters varied considerably with mixing intensity and liquid saturation. The variations were most significant at the liquid saturations typically used to produce pharmaceutical granules. In the initial stages of mixing the distribution of the liquid phase was critical and this is likely to be controlled by wetting, spreading and adhesion at the solid-liquid interface. The rate of liquid distribution was directly dependent upon the intensity of mixing and in a simple microcrystalline cellulose-water system under low shear conditions equilibrium was attained within 12 min at all liquid saturations.

The form of the equilibrium torque profiles was found to be independent of the conditions under which equilibrium was attained. Therefore, equilibrium torque profiles generated by different instruments can be compared. A cumulative energy of mixing (CEM) term was developed to quantify the energy input during mixing and this term allows different mixing procedures to be compared in terms of their total energy input.

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