Characterization of wet masses using a mixer torque rheometer: 2. Mixing kinetics

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Summary

An instrumented, laboratory-scale mixer torque rheometer has been used to measure the rheological properties of a range of model and typical pharmaceutical wet massed systems. The mixing torque was monitored as a function of the mixing time from the point of liquid addition until an equilibrium rheological state had been attained. In each system the mechanisms and kinetics of mixing varied according to the saturation of the wet mass and the identity of the substrate and binder components. Although the torque variation was different for each wet massed system an equilibrium rheological state was eventually attained in each case. Measurement of this equilibrium torque response should allow the comparison of different wet masses irrespective of their processing histories.

Introduction

In previous papers, it has been demonstrated that the rheological properties of wet powder masses can be successfully monitored using a technique known as mixer torque rheometry (Rowe and Sadeghnejad, 1987; Parker et al., 1990a,b; Hancock et al., 1991). This approach has enabled the effects of substrate source, binder concentration and mixer design to be studied. All of the investigations reported to date have concentrated on the rheological properties of the wet powder mass after a fixed period of mixing and have assumed that at this time an equilibrium rheological state has been achieved. The purpose of this study was to determine whether mixer torque rheometry could be used to monitor the variation of the rheological properties of wet masses with mixing time. If successful, this approach should provide vital information about the mechanisms and kinetics of wet massing processes.

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Materials and Methods

Glass ballotini (Englass Ltd, Leicester, U.K.) were selected as a model powder for use in the

wet massing studies. Glass ballotini have previously been used in similar studies with some success (e.g., Dingwall and Ismail, 1977). In addition to the model substrate, four typical pharmaceutical powders were selected for study. These were chosen to represent the range of materials normally encountered during pharmaceutical wet granulation processes. Griseofulvin (ICI Pharmaceuticals, Macclesfield, U.K.) was selected as a synthetic, high-dose active ingredient usually processed by wet granulation (Harwood and Pilpel, 1968). A calcitic form of calcium carbonate, Sturcal-L (J.E. Sturge Ltd, Birmingham, U.K.), was selected as a representative inorganic excipient. Two microcrystalline celluloses from different manufacturing sources were also chosen. These were Avicel PH101, the original and most widely used source (FMC International, Co. Cork, Ireland), and Unimac MG100, a direct competitor for Avicel PH101 (Unitika Rayon Ltd, Osaka, Japan). The model and typical pharmaceutical substrates were wet massed with distilled water and 5% w/v aqueous solutions of two commonly used pharmaceutical binding agents – polyvinylpyrrolidone (PVP) (Kollidon K90, BASF, Chea-

TABLE 1

Physical characteristics of the powdered substrates

Substrate	Morphology [a]	Particle size [b] Median (10–90th percentile) (μm)	Specific surface area [c] ($m^2 g^{-1}$)
Glass ballotini	spherical	11 (5–23)	0.61
Avicel PH101	irregular, porous	35 (14–55)	1.15
Unimac MG100	fibrous	33 (16–50)	1.19
Sturcal-L	agglomerated, needles	10 (5–20)	2.80
Griseofulvin	agglomerated, needles	3 [d] (1.3–8.5)	2.59

[a] Scanning electron microscopy.
[b] Coulter counter.
[c] Nitrogen sorption.
[d] From Matthews and Rhodes (1967).

TABLE 2

Physical characteristics of the liquid binders

Binder	Dynamic viscosity [a] ($g\,m^{-1}\,s^{-1}$)	Surface tension [b] ($mN\,m^{-1}$)
Distilled	1.00	71.5
5% w/v PVP	42.61	66.3
5% w/v HPMC	39.24	46.5

[a] Capillary viscometry.
[b] Wilhelmy plate.

dle, U.K.) and hydroxypropylmethylcellulose (HPMC) (Pharmacoat 606, Shin-Etsu Chemical Co., Tokyo, Japan). The physical properties of the substrates and binders are listed in Tables 1 and 2.

The mixer torque rheometer used was very similar to that described by Rowe and Sadeghnejad (1987) and Parker et al. (1990a). This type of instrument has previously been shown to measure the true rheological character of wet powder masses (Parker et al., 1990a). The rheometer was used to measure two different torque parameters, described by Parker et al. (1990a) as the amplitude of the oscillations and the mean torque increase from the baseline. For convenience these parameters will be referred to as the 'torque range' and the 'mean torque' respectively.

A fixed quantity of each substrate was used for the wet massing experiments. The capacity of the rheometer bowl was approx. 250 ml and a sufficient quantity of substrate was required to cover the mixing blades at all times. Each substrate was dry mixed in the rheometer for 1–2 min to obtain a stable baseline response prior to adding the liquid binder.

The wet massing behaviour of the single substrates was studied following the bolus addition of the granulating liquid. The required quantity of binder was drawn up into a glass syringe and evenly distributed over the surface of the mixed powder bed at the beginning of each experiment. This method of liquid binder addition should provide useful information regarding the kinetics and mechanisms of granule formation (Alleva, 1984). By repeating the same experiment at a range of liquid volumes the effect of changing

liquid saturation can also be studied. In this paper, the ratio of the liquid true volume to the total solid and liquid true volume is used to describe the liquid content of the wet masses. This ratio is comparable with the void space calculated from bulk density measurements and allows the direct comparison of substrates with different true and bulk densities.

All the wet massing experiments were performed in duplicate and a mean torque value calculated. Torque results typically varied by less than 10% of the mean and the data presented represent the mean results. In each figure, plots are shown at three representative liquid contents, namely, 60, 100 and 110% of the liquid volume required to produce the maximum equilibrium torque response.

Results and Discussion

The baseline torque response obtained by dry mixing each of the substrates was identical to that for running the rheometer empty. When the liquid binder was added to the substrate a granular material was produced over a range of liquid saturations. This formation of granules was accompanied by an increase in both torque responses.

Glass ballotini

The variation of the mean torque response with mixing time for the model substrate granu-
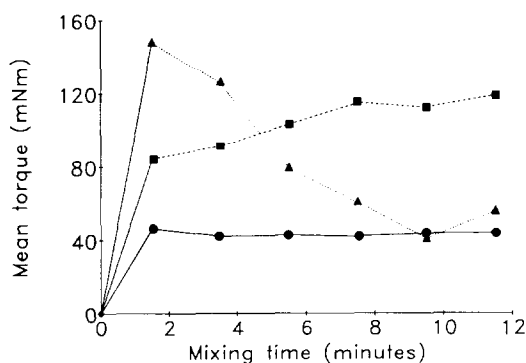

Fig. 1. Mean torque variation with mixing time for glass ballotini and water at three different liquid contents: (●) 24.8, (■) 37.7 and (▲) 39.7% v/v.
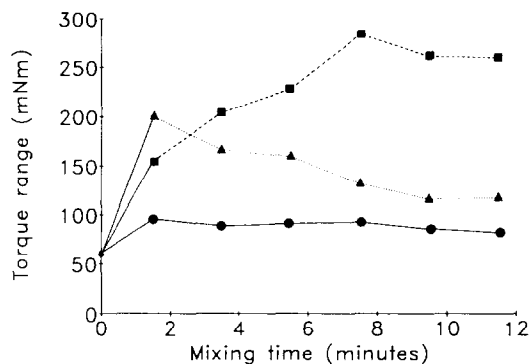

Fig. 2. Torque range variation with mixing time for glass ballotini and PVP at three different liquid contents: (●) 24.8, (■) 33.1 and (▲) 35.5% v/v.

lated with distilled water is shown in Fig. 1. At each liquid saturation, the addition of the binder to the substrate produced a measurable increase in the mean torque response within 1.5 min and a steady state or equilibrium level was attained within 12 min. A rise in the liquid content of the wet mass resulted in an increase in the torque response, up to a peak. Beyond the peak an overwet mass was formed and the torque response was reduced. Prolonged mixing at elevated liquid levels led to increased densification of the wet mass and an exacerbation of the overwetting process. This resulted in a gradual decline in the mean torque response to the equilibrium value.

The variation of the torque range with mixing time closely resembled that of the mean torque (Fig. 2). An increase in the torque range occurred almost immediately after the addition of the granulating liquid and an equilibrium torque range value was attained after about 10 min mixing. The torque range response rose with increasing liquid content up to a peak and overwet masses showed a gradually declining torque range response with continued mixing.

The mean torque and torque range vs mixing time profiles determined with the three liquid binders were all of a similar form (cf. Figs 1–4, for example). The magnitude of the torque response was slightly greater when using the polymer binder solutions as the granulating liquid and
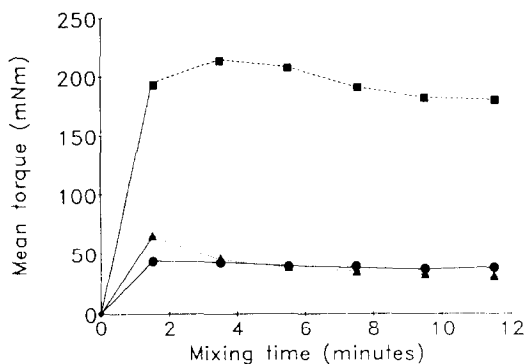
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Fig. 3. Mean torque variation with mixing time for glass ballotini and PVP at three different liquid contents: (●) 24.8, (■) 35.5 and (▲) 37.7% v/v.

Fig. 5. Mean torque variation with mixing time for griseofulvin and PVP at three different liquid contents: (●) 34.3, (■) 36.7 and (▲) 39.0% v/v.

this was attributed to the greater viscosity of the interparticle liquid binder bridges in these systems. There was no statistically significant effect on the magnitude or form of either torque response due to the different surface tensions of the equiviscous polymer binder solutions.

Griseofulvin

A representative mean torque vs mixing time plot for griseofulvin is illustrated in Fig. 5. Comparable mixing kinetics were observed with all three binders and for both torque parameters. At low and intermediate liquid contents, there was a gradual rise to a stable torque response over the first 8 min of mixing. At elevated liquid contents an overwet mass was formed and the torque fell
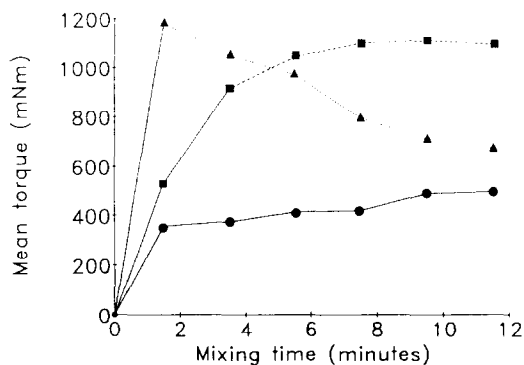
with continued mixing. The magnitude of the torque responses was much greater for the griseofulvin wet masses than for the model wet masses, although with both substrates the torque responses were slightly greater when using the polymer binder solutions rather than water as the granulating liquid. Overall, the mixing kinetics of griseofulvin closely resembled those of the model substrate (cf. Figs 1–5).

Sturcal-L

The typical mean torque variation with mixing time for Sturcal-L is depicted in Fig. 6. Identical patterns of behaviour were observed with all three binders and for the torque range measurements. At low liquid saturations, a small equilibrium
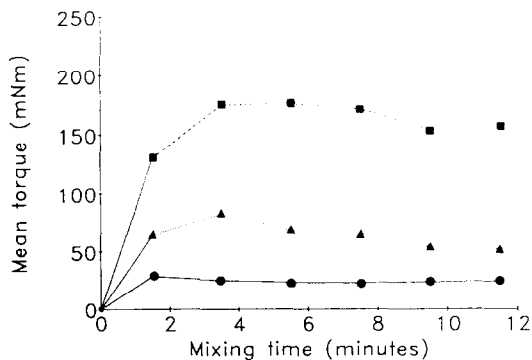

Fig. 4. Mean torque variation with mixing time for glass ballotini and HPMC at three different liquid contents: (●) 24.8, (■) 37.7 and (▲) 39.7% v/v.
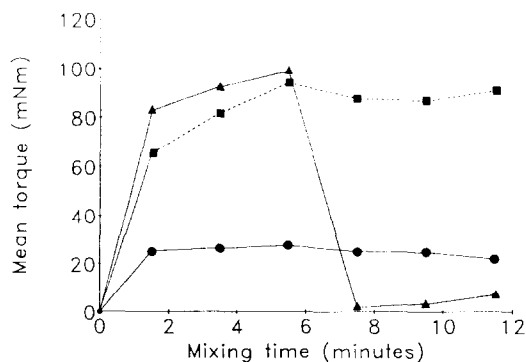

Fig. 6. Mean torque variation with mixing time for Sturcal-L and water at three different liquid contents: (●) 28.9, (■) 50.4 and (▲) 54.9% v/v.
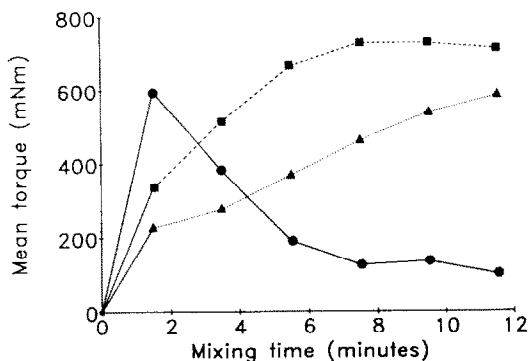
Fig. 7. Mean torque variation with mixing time for Avicel PH101 and HPMC at three different liquid contents: (●) 55.5, (■) 69.6 and (▲) 71.4% v/v.

torque response was attained with continued mixing. At higher liquid saturations similar but larger torque responses were observed. At very high liquid saturations overwetting occurred and this gave rise to a much reduced torque response. In each case, an equilibrium torque response was attained after about 8 min of mixing. This substrate exhibited mixing kinetics similar to those of the model substrate and griseofulvin (cf. Figs 1–6) despite having significantly different particulate properties (Table 1).

Avicel PH101

The typical mean torque variation with mixing time for Avicel PH101 at three different liquid contents is shown in Fig. 7. Equivalent torque profiles were produced with each of the liquid binders. The mixing kinetics of the Avicel PH101 systems were noticeably different from those of the model substrate, griseofulvin and calcium carbonate (e.g., Figs 1–6). In the Avicel PH101 systems at low liquid saturations, there was an initial torque peak followed by a gradual fall to an equilibrium response. In the other substrate systems no initial torque peak was observed. At intermediate liquid levels with all the substrates the mean torque response rose slowly to reach a plateau. With an overwet Avicel PH101 mass the torque response rose at a constant rate with continued mixing whereas with the other overwet masses the mean torque response declined gradually.

Alleva (1984) used a modified shear cell to study the rheology of Avicel PH101-water wet masses and obtained similar force-time profiles to those shown in Fig. 7. The initial force peak observed at low to intermediate liquid contents was attributed to the uneven distribution of the granulating liquid and the consequent formation of large unstable agglomerates. The major factor thought to be responsible for this phenomenon was the irregular morphology of the microcrystalline cellulose particles.

The variation of the torque range response with mixing time for the Avicel PH101 systems followed an identical pattern to that described for the torque mean. Parker (1989) also studied the variation of the torque range with mixing time in an Avicel PH101-water system. The results obtained were comparable at low, intermediate and high liquid contents and equilibrium torque values were attained after about 8 min of mixing. In another similar system, Rowe and Sadeghnejad (1987) noted that steady-state torque range conditions were attained after 3–5 min of mixing.

Avicel PH101 will probably undergo complex physicochemical interactions with the aqueous binder systems (Hollenbeck, 1977; Parker, 1989). Wet massed Avicel PH101 will contain tightly bound structural water, loosely bound water and free water within its semi-crystalline structure (Zografi et al., 1984). This water may plasticise the particles and agglomerates and may induce swelling or rupture of the intermolecular hydrogen bonds (Khan et al., 1988). Each of these processes will occur at different rates and may influence the mixing kinetics of the wet massed Avicel PH101 systems.

Unimac MG100

The variation of mean torque with mixing time for the Unimac MG100-HPMC system is illustrated in Fig. 8. The mean torque and torque range results both varied in a very similar manner with each of the three liquid binders. The mixing kinetics of the Unimac MG100 systems were different from those of the glass ballotini, griseofulvin and Sturcal-L but similar to those of the Avicel PH101 systems.
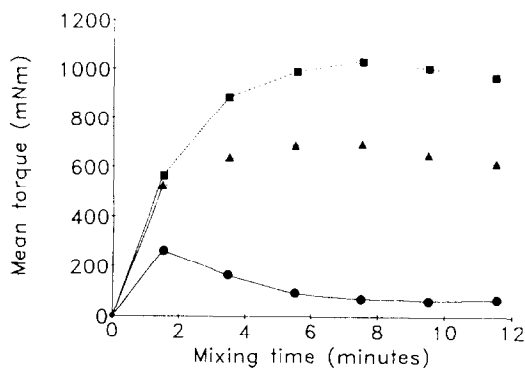
Fig. 8. Mean torque variation with mixing time for Unimac MG100 and HPMC at three different liquid contents: (●) 45.4, (■) 59.3 and (▲) 62.5% v/v.

At low liquid levels the initial peak in the torque response with Unimac MG100 was less marked than with Avicel PH101. At higher liquid levels, the torque response with Unimac MG100 did not change significantly with continued mixing. In general, the whole process of equilibration appeared to be slightly more rapid with Unimac MG100 than with Avicel PH101. These results indicate that the mixing kinetics of microcrystalline cellulose wet masses are influenced by the manufacturing source of the substrate. The physical properties of these two microcrystalline celluloses (in particular their particle morphologies; Table 1) are more disparate than their chemical properties and probably account for the differences in their wet massing behaviour. The practical implications of such differences have been discussed previously by Parker (1989).

General discussion

In each of the wet massed systems considered in this study, the major factor determining the form and magnitude of the torque responses was the identity of the substrate. This is in agreement with the results reported in previous work (Holm et al., 1985; Ghanta et al., 1986; Usteri and Leuenberger, 1989). There was no constant effect on the form or magnitude of either torque response due to the substrate particle size, the substrate-specific surface area or the binder surface tension. However, for each substrate there was a small overall increase in the magnitude of

the torque responses with increasing liquid binder viscosity.

The critical liquid requirement of the different wet massed systems varied between 33 and 70% of the true volume of the wet mass and was unique to the particular substrate-binder combination under consideration. In general, the critical liquid requirement was greater for the pharmaceutical substrates than for the model substrate. This was probably due to the pharmaceutical substrates having more irregular particles than the model substrate and thereby providing a greater intra- and inter-particulate void space. The critical liquid requirement did not appear to be directly linked to the surface area of the substrate as has been suggested previously (Usteri and Leuenberger, 1989).

The wet massing kinetics of the different substrate-binder systems showed some important similarities. In each case, there was an initial rapid change in both torque responses followed by the gradual attainment of equilibrium values with continued mixing. The rate of equilibration was characteristic of the substrate-binder combination under consideration and the liquid saturation of the wet mass. The torque mean and the torque range responses both varied in similar ways despite the fact that they are thought to be measuring slightly different properties of the wet masses (Hancock et al., 1991).

It has previously been shown that the rate of equilibration is partially dependent upon the intensity of the mixing process (Hancock et al., 1991). The torque vs mixing time profiles obtained with Avicel PH101 and water in a similar mixer running at twice the speed were of a similar form to those shown in Fig. 7. However, the equilibrium torque responses were achieved almost twice as quickly. It can be concluded that equilibrium torque responses will be attained in all mixers provided sufficient mixing has taken place. The rate of equilibration will vary according to the type of mixer, the choice of operating conditions and the solid-liquid system under consideration.

For all the substrate-binder combinations considered in this study the torque data were used to provide tri-axial surface plots of torque vs mixing
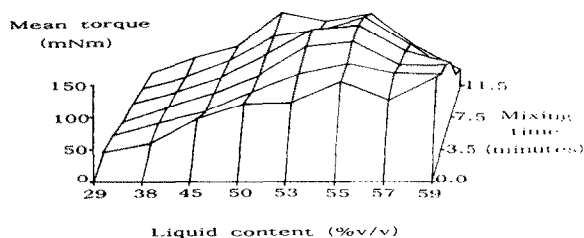
Fig. 9. Mean torque variation with mixing time and liquid content for Sturcal-L and HPMC.

time vs liquid content (e.g., Fig. 9). This representation of the mixing rheology data allowed the combined effects of mixing time and liquid content to be studied. Although the kinetics of mixing were slightly different in all the substrate-binder combinations, an equilibrium rheological state was always attained. This enabled the direct comparison of all the different wet massed systems and confirmed the usefulness of the 'equilibrium' torque profiles used previously by Rowe and Sadeghnejad (1987) and Parker et al. (1990a,b). The use of equilibrium torque profiles for the detailed characterisation and comparison of the model and typical pharmaceutical wet masses will be the subject of a future paper.

Conclusions

The technique of mixer torque rheometry has been used to monitor variations in the rheology of wet powder masses with mixing time. It was able to cope with a wide variety of materials and could differentiate between the rheological properties of very similar wet masses. Under a fixed set of mixing conditions, the most important variables affecting the kinetics of the mixing process were the substrate and binder identities and the liquid content of the wet mass. Despite the slightly different kinetics of mixing in each solid-liquid system, equilibrium torque readings were always attained after a fixed period of mixing. This equilibrium torque response should provide a means of comparing the rheological properties of a wide range of wet massed systems.

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