An assessment of substrate-binder interactions in model wet masses. 1: Mixer torque rheometry

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Summary

Recent work has shown the importance of physical interactions between materials during size enlargement processes (e.g., wet granulation). In this study several model substrates and binder solutions were selected, their particulate, solution and energetic properties determined and the potential physical interactions of the solid and liquid phases assessed. Considerable differences were noted in the wetting, spreading and adhesion tendencies of the various substrate-binder combinations. The rheological properties of the wet massed solid-liquid systems were then measured using an instrumented mixer torque rheometer. The results confirmed that solid-liquid physical interactions (especially spreading) are important in determining wet massing behaviour. The most important influences appeared to be on the stability of the wet masses at elevated liquid levels and theories were developed to explain this observation in terms of the accepted models of wet granule structure.

Introduction

Whenever materials are mixed there is potential for them to interact. This interaction may be chemical, resulting in the creation of a new species, or physical, resulting in the formation of attractive or repulsive forces. Chemical interactions between materials during pharmaceutical size enlargement processes are usually avoided by the careful selection of the formulation compo-

nents. However, physical interactions are unavoidable and have been identified in a large number of situations including wet granulation (Hancock, 1991). The exact nature of the physical interactions occurring during wet granulation will depend upon the physical, chemical and energetic properties of the granulation components (Krycer et al., 1983). The initial interaction will be wetting of the substrate by the binder and this may be followed by spreading, adhesion and/or swelling. Previous studies have shown that it is possible to predict the physical interactions between components of a wet granulation formulation from a consideration of their surface energetic properties (Rowe, 1989a,b; Zajic and Buckton, 1990). In addition, it has been shown that the effects of

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such interactions can be directly measured using instrumented mixing apparatus (Parker et al., 1990a). The aim of this study was to determine whether the substrate-binder interactions predicted for a series of simple two component model wet masses could be directly reconciled with the rheological properties of those wet masses.

Interaction prediction

The approach used for predicting substrate-binder interactions was based on that originally developed by Wu (1982) for estimating physical interactions in polymer melts. The same method has previously been used by several authors for predicting the interactions occurring during pharmaceutical wet granulation processes (Rowe, 1989a,b; Parker et al., 1990a; Zajic and Buckton, 1990). The surface free energy (γ) and polarity (x_p) of the substrate and binder components are determined (see Materials and Methods) and then used to calculate the works of cohesion (W_c), the work of adhesion (W_a) and an interaction parameter (ϕ) (Eqns 1-4).

$$W_{cs} = 2\gamma_s \tag{1}$$

$$W_{cb} = 2\gamma_b \tag{2}$$

$$W_a = 4\left[\frac{\gamma_{sd} \cdot \gamma_{bd}}{\gamma_{sd} + \gamma_{bd}} + \frac{\gamma_{sp} \cdot \gamma_{bp}}{\gamma_{sp} \cdot \gamma_{bp}}\right] \tag{3}$$

$$\phi = 2\left[\frac{x_{sd} \cdot x_{bd}}{g_s \cdot x_{sd} + g_b \cdot x_{bd}} + \frac{x_{sp} \cdot x_{bp}}{g_s \cdot x_{sp} + g_b \cdot x_{bp}}\right] \tag{4}$$

where W_c is the work of cohesion, W_a denotes the work of adhesion, γ is the surface or interfacial free energy, s indicates the substrate phase, b represents the binder phase, p indicates the polar component, d corresponds to the non-polar or dispersion component, and

$$x_d = \left[\frac{\gamma_d}{(\gamma_d + \gamma_p)}\right] \qquad x_p = \left[\frac{\gamma_p}{(\gamma_d + \gamma_p)}\right]$$

$$g_s = \left[\frac{\gamma_s}{\gamma_b}\right]^{0.5} \qquad g_b = \left[\frac{\gamma_b}{\gamma_s}\right]^{0.5}$$

The work of cohesion is the work done in separating unit area of the substrate or binder from itself and the work of adhesion is the work done in separating unit area of the two adhering materials. The interaction parameter indicates the likely mode of failure at the substrate-binder interface. A value of unity for the interaction parameter implies that substrate-binder adhesion is good and any failure should occur in the weaker component (usually the binder).

The works of cohesion and adhesion are then normalised to produce three spreading coefficients – λ_{bs}, λ_{sb} and λ_r (Eqns 5–7):

$$\lambda_{bs} = W_a - W_{cb} \tag{5}$$

$$\lambda_{sb} = W_a - W_{cs} \tag{6}$$

$$\lambda_r = W_a / W_{cb} \tag{7}$$

λ_{bs} expresses the tendency for the binder to spread over the substrate and λ_{sb} indicates the tendency for the substrate to spread over the binder. A positive value for each of these parameters implies that spreading will occur. λ_r indicates whether binder film formation is likely and a value of unity implies good film formation.

Granulation rheology

The measurement of the torque required to shear a wet mass equates with a rheological characterisation of that system and it has been suggested that such measurements are vital to the analysis of physical interactions in solid-liquid systems (Wu, 1982). In previous papers (Rowe and Sadeghnejad, 1987; Parker et al., 1990a,b; Hancock et al., 1991, 1992; Parker and Rowe, 1991) it has been demonstrated that the rheological properties of wet powder masses can be successfully monitored using a technique known as mixer torque rheometry. Similar measurements have also been used to measure the compatibility of molten polymer blends (Jurado et al., 1987) and to assess material interactions during the production of fertilisers (Kuwabara et al., 1977). In this study mixer torque rheometry was chosen to assess the effects of substrate-binder interactions in a series of model wet massed systems.

Materials and Methods

Materials

Glass ballotini (Englass Ltd, Leicester, U.K.; solvent washed) were chosen as a model substrate. A small size grade (nominally 1–20 μm) was selected to minimise attrition of the particles during mixing and to maximise the surface area available for interaction. Glass has a hydrophilic nature which can be modified using a 'silanising agent' to produce a hydrophobic surface. Both hydrophilic and hydrophobic model substrates were utilised to enable the effect of substrate surface character on wet granulation behaviour to be assessed. The substrates were wet massed with 5% w/v aqueous solutions of two commonly used pharmaceutical binding agents – polyvinylpyrrolidone (PVP) (Kollidon K90, BASF, Cheadle, U.K.) and hydroxypropylmethylcellulose (HPMC) (Pharmacoat 606, Shin-Etsu Chemical Co., Tokyo, Japan).

Material characterisation

The particle size and true density of the substrates were determined using laser diffraction size analysis (Malvern 2600, Malvern Instruments, U.K.) and air pycnometry (Beckman 930, Beckman Instruments, U.K.), respectively. The two polymer binder solutions exhibited Newtonian rheology (Parker, 1989) and were therefore characterised by a single point viscosity determination (Cannon Ubbelohde capillary viscometer; Poulton, Self and Lee Ltd, Wickford, U.K.). The dynamic viscosity of each solution was calculated as the product of its kinematic viscosity and solution density.

Newitt and Conway-Jones (1958) proposed that settled density measurements would be an accurate way of estimating the voids within a wet massed system and therefore a settled density determination was devised for use in this study. A known mass of each substrate was placed in a 100 ml stoppered measuring cylinder with 50.0 ml of an aqueous surfactant solution (1% w/v sodium dodecyl sulphate; BDH Ltd, Poole, U.K.). The solids were suspended by vigorous shaking and allowed to settle out until a constant solid volume was achieved (approx. 120 h). The final volume of

the settled solids was noted and the settled bulk density determined.

The surface energetic properties of the substrates and binders were determined using dynamic contact angle analysis. The Wilhelmy plate method (Cahn DCA 312, Cahn Instruments Inc., Cerritos, U.S.A.) was selected as it was thought to best model the dynamic wetting process occurring during wet granulation. The reference liquids were distilled water and diiodomethane (Aldrich Chemical Co., 99% pure) and the reference solids were glass and polytetrafluoroethylene. Hydrophilic and hydrophobic glass microscope coverslips were used as the model substrate specimens.

Granulation rheology

A laboratory scale mixer torque rheometer was used to measure the rheological properties of the wet massed substrate-binder systems. The instrument was identical to that described previously (Rowe and Sadeghnejad, 1987; Parker et al., 1990a,b; Hancock et al., 1991, 1992; Parker and Rowe, 1991). The capacity of the rheometer bowl was approx. 250 ml and the two mixing blades were arranged in a sigma configuration and driven at a speed of 52 rpm. The effect of changing the arrangement of the mixing blades and the drive speed has been described previously (Hancock et al., 1991, 1992).

A fixed quantity of substrate (sufficient to completely cover the mixing blades) was used for each wet massing experiment. Initially the substrate was dry mixed in the rheometer for 1–2 min to obtain a baseline response which reflected the strength of the cohesive forces between the dry particles and any interaction with the rheometer blades and walls. In all cases this baseline response was practically identical to that obtained when running the rheometer empty. After several minutes of dry mixing the required quantity of binder solution was drawn up into a glass syringe and evenly and rapidly distributed over the surface of the mixed powder bed. Mixing was continued until a stable rheological response was attained (usually 5–10 min). By repeating the same experiment with a range of liquid volumes the effect of changing liquid content was studied.

All the wet massing experiments were performed in duplicate and mean equilibrium torque values calculated. The results typically varied by less than 10% of the mean and the data presented are the mean results. The rheometer measured two different torque parameters which have previously been described as the 'amplitude of the oscillations' and the 'mean torque increase from the baseline' (Parker et al., 1990b). For convenience these parameters will hereafter be referred to as the 'torque range' and the 'mean torque', respectively.

Note: 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.

Results and Discussion

Material characterisation

The physical properties of the substrates and the polymer binders are listed in Tables 1–3. Both the model substrates consisted of non-porous, smooth surfaced, spherical particles with a median diameter of 12 μm (range 1–30 μm; equivalent area diameter). There were no significant differences in the morphology, size distribution or true density of the ballotini before and

TABLE 1

The physical properties of the model substrates

Substrate	Morphology [a]	Particle size [b] Median (10–90th percentile) (μm)	True density [c] (Mg m^{-3})	Settled voidage (%)
Hydrophilic ballotini	spherical, non-porous	12 (5–25)	2.50	38
Hydrophobic ballotini	spherical, non-porous	12 (7–25)	2.44	33

[a] Scanning electron microscopy. [b] Laser diffraction analysis; equivalent area diameter. [c] Air pycnometry.

TABLE 2

The physical properties of the polymer binder solutions

Material	Density of solution (Mg m^{-3})	Kinematic viscosity [a] (m^2 s^{-1}) ($\times 10^{-6}$)	Dynamic viscosity (g m^{-1} s^{-1})
PVP	1.0076	42.29	42.61
HPMC	1.0088	38.90	39.24

[a] Capillary viscometry.

after silanising. The settled voidage of both model substrates corresponded to that typically found in a randomly packed bed of spherical particles (German, 1989) and was similar to that obtained previously for slightly larger glass ballotini (Butensky and Hyman, 1971; Palmer and Rowe, 1974; Holm et al., 1985). The packing of the hydrophobic ballotini was slightly more efficient than that of the hydrophilic ballotini although the reason for this was not clear. The hydrophilic glass surfaces were of a relatively high surface free energy and polarity, whereas the hydrophobic glass surfaces were of a low surface free energy and polarity. The two polymer binder solutions had very similar kinematic and dynamic viscosities and solution densities. The surface free energies and polarities obtained for the polymer binder solutions were quite different from one another but consistent with those reported in the literature (Harwood and Pilpel, 1968; Krycer et al., 1983; Wells and Walker, 1983; Johnson and Zografi, 1986; Van Oss and Good, 1989; D'Alonzo

TABLE 3

Surface free energy and polarity of the model substrates and the polymer binder solutions

Material	Surface free energy (γ) (mN m^{-1})	Fractional polarity (x_p)
Hydrophilic glass	71.7	0.67
Hydrophobic glass	24.6	0.12
PVP	66.3	0.44
HPMC	46.5	0.69

et al., 1990; Parker et al., 1990a; Zajic and Buckton, 1990).

Interaction prediction

The interaction parameters and spreading coefficients calculated for the various substrate-binder pairs are listed in Table 4. The values obtained are very similar to those calculated using literature values for the substrate and binder surface free energies and polarities (Rowe, 1989b). These data indicate that the two polymer binder solutions will behave quite differently when mixed with the model glass substrates. With the hydrophilic substrate adhesion and binder film formation will occur with both binders ($\phi \approx 1$; $\lambda_r \approx 1$), only the HPMC will spread over the surface of the substrate ($\lambda_{bs} \approx +ve$) and substrate spreading will not be favoured in either system ($\lambda_{sb} \approx -ve$). With the hydrophobic glass adhesion and film formation will be very poor with both binders ($\phi < 1$; $\lambda_r < 1$), binder spreading will also be very unlikely ($\lambda_{bs} \approx -ve$) but substrate spreading should occur with the PVP ($\lambda_{sb} \approx +ve$). As a consequence of these different interactions each of the substrate-binder combinations is likely to form moist agglomerates in different ways. Both binder adhesion and film formation are thought to be necessary for the formation of conventional granules (Krycer et al., 1983) and these processes will only occur with the hydrophilic glass. There will probably also be differences in granule structure due to the differ-
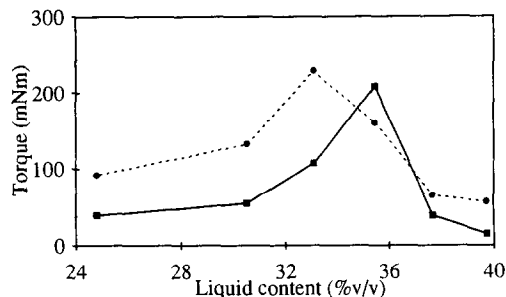

Fig. 1. Equilibrium torque variation with liquid content for the hydrophilic glass wet massed with the PVP solution. (Continuous line) Mean torque; (broken line) torque range.

ent spreading tendencies of the two binders (Rowe, 1989a,b; Zajic and Buckton, 1990).

Granulation rheology

General   Fig. 1 shows typical equilibrium mean torque and torque range profiles obtained with the model substrate-binder wet masses. The torque responses recorded when mixing the wet masses were several orders of magnitude greater than those recorded when mixing any of the substrates or binder solutions separately. Therefore, it was assumed that these torque measurements primarily reflected the strength of the interactions occurring between the components of the wet masses rather than any interactions with the mixer blades or walls. The cohesiveness of all the equilibrium wet masses rose with increasing liquid content up to a maximum. At this maximum the masses were smooth and pasty. Any further increase in the liquid content caused overwetting and a rapid reduction in the measured torque. Similar equilibrium rheological profiles have previously been reported for wet masses of microcrystalline cellulose (Alleva, 1984; Rowe and Sadeghnejad, 1987; Parker et al., 1990b; Hancock et al., 1991; Parker and Rowe, 1991), lactose, calcium phosphate, mannitol and starch (Alleva, 1984) and for a series of industrial fertiliser formulations (Kuwabara et al., 1977).

Alleva (1984) and Rowe and Sadeghnejad (1987) proposed a link between the form of such equilibrium torque profiles and the theoretical agglomerate saturation states proposed by Newitt and Conway-Jones (1958) and Barlow (1968). This

TABLE 4

Interaction parameters and spreading coefficients calculated for the model substrate-binder systems

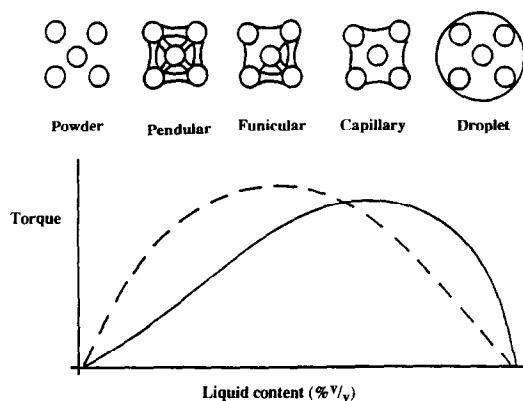| Material	ϕ	λ_r	λ_{bs} (mN m^{-1})	λ_{sb} (mN m^{-1})
Hydrophilic glass-PVP	0.95	0.98	− 2.19	− 12.99
Hydrophilic glass-HPMC	0.98	1.21	19.78	− 30.62
Hydrophobic glass-PVP	0.81	0.49	− 67.18	16.22
Hydrophobic glass-HPMC	0.67	0.49	− 47.57	− 3.77

Fig. 2. Equilibrium torque variation with liquid content. (Continuous line) Mean torque; (broken line) torque range.

Fig. 3. Schematic of shearing a wet granule in the mixer torque rheometer.

approach can be used to explain the equilibrium rheological profiles obtained with the model substrate systems. The addition of binder to the dry substrate causes liquid bridges to be created between the solid particles and initially pendular agglomerates are formed (Fig. 2). These agglomerates provide a greater resistance to shearing than the dry powder and a positive torque response is recorded. As the binder content is increased the number and extent of the liquid bridges increases and the funicular state is reached. This is accompanied by a rise in the measured torque. The further addition of binder fills all the interparticulate voids and the agglomerates are held together by strong capillary forces. At this point the torque reaches a maximum. The addition of any more binder causes overwetting and this is accompanied by a rapid reduction in the torque response.

Comparison of the torque mean and torque range results (Fig. 1 and Table 5) shows one major difference – the torque range peaks all occur at slightly lower liquid saturations than the corresponding torque mean peaks. As this difference occurs in all the substrate-binder pairs it can be attributed to the way in which the two torque parameters are derived. Fig. 3 shows the typical path that a mixing blade takes as it shears through a wet agglomerate. Provided the substrate particles are small compared to the mixing blade the blade will deflect the solid particles and shear the voids and the liquid bridges. From earlier work (Parker et al., 1990b) it is known that the torque range is a measure of the range of forces encountered by the mixing blade as it shears through the wet mass whereas the mean torque is the average of those forces. The range of forces is likely to be greatest when both voids and capillary liquid bridges are being sheared and this corresponds to the funicular granule state (Fig. 2). The mean force is likely to be maximal when there are the

TABLE 5

Summary of the equilibrium torque peak locations and magnitudes in the model substrate-binder systems

Material	Settled voidage (% v/v)	Binder	Mean torque peak		Torque range peak	
			L (% v/v)	M (mN m)	L (% v/v)	M (mN m)
Hydrophilic glass	38	PVP	35	208	33	228
		HPMC	38	176	31	220
Hydrophobic glass	33	PVP	33	156	30	231
		HPMC	30	125	27	346

L, location (liquid content); M, magnitude.

18%   25%   31%   33%   36%   38%

Liquid content (%ᵛ/ᵥ)

Hydrophilic glass - PVP
10mm

18%   25%   31%   33%   36%   38%

Liquid content (%ᵛ/ᵥ)
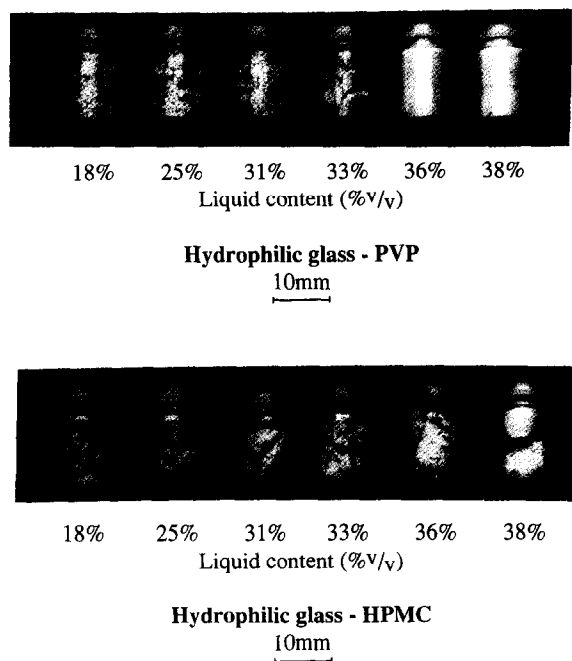
Hydrophilic glass - HPMC
10mm

Fig. 4. Photograph of the wet masses produced by mixing the hydrophilic glass with the PVP and HPMC solutions.

greatest number of capillary bridges being sheared and this corresponds to the capillary state. Thus, the torque range peak should occur at a lower liquid level than mean torque peak. This occurred in all the model substrate granulations (Fig. 1 and Table 5) and consideration of data in the literature (Parker et al., 1990b) shows that this type of behaviour also occurs in 'real' wet massed systems. The torque range and the mean torque can thus be used to provide different information about the qualities of a wet mass and from these two parameters it should be possible to obtain a detailed and meaningful characterisation of many wet massed systems.

Peak torque location Although the model substrate-binder systems all showed similar patterns of equilibrium rheological behaviour there were also some important differences. The most striking difference was that within each substrate system overwetting took place at a different liquid content with the two polymer binders (Fig. 4) (Table 5). With the hydrophilic model substrate overwetting occurred at a lower liquid content

with the PVP whereas with the hydrophobic model substrate it occurred at a lower liquid content with the HPMC. Since all the apparatus, operational and product variables that are known to affect wet granulation behaviour (e.g., binder viscosity, substrate particle size, mixing speed) were kept constant this response can be attributed to the different substrate-binder interactions occurring in each wet mass (see earlier and Table 4).

With the hydrophilic model substrate both polymer binders will adhere to the substrate and form a film around the particles enabling strong dense granules to be formed. However, the two polymer binders differ in their relative spreading tendencies. The HPMC spreads spontaneously over this substrate whereas the PVP does not. This spontaneous spreading of HPMC appears to allow stable granules to be formed at elevated liquid contents and notably the position of the mean torque peak in this system corresponds to the total filling of the substrate void space (estimated from settled density determinations) (Table 5). With the PVP an absence of spontaneous spreading results in the formation of unstable granules at elevated liquid contents and premature overwetting takes place.

With the hydrophobic model substrate film formation, adhesion and spreading are very poor with both binders and substrate spreading only occurs spontaneously with the PVP. As before the spreading of one phase over the other appears to stabilise the granules formed at elevated liquid levels and the peak location in the spreading system corresponds to total filling of the substrate void space. With the HPMC an absence of substrate spreading results in the formation of an unstable wet mass and overwetting occurs at a reduced liquid content.

The behaviour of the model substrates during wet massing thus appears to be strongly influenced by the spreading tendencies of the substrate and binder components. The theories of agglomerate structure proposed by Newitt and Conway-Jones (1958) and Barlow (1968) (Fig. 2) assume perfect wetting and spreading within the agglomerates and clearly this does not always occur in practice. It is therefore necessary to

consider how substrate-binder interaction differences might affect wet granule structure.

In a substrate-binder system where spreading can occur the pendular agglomerate state will be readily formed when the liquid binder is mixed with the substrate. As the liquid content increases the binder will be accommodated by the spreading of the substrate or binder over the other component. This will eventually lead to the total filling of the interparticulate voids by the granulating liquid and the formation of the capillary saturation state (Fig. 2). The greatest resistance to mixing (i.e. the mean torque peak) will usually occur at this point and the greatest heterogeneity (i.e., the torque range peak) will occur at a slightly lower liquid content (i.e., the funicular state) as described previously. In a system where spreading does not take place spontaneously the pendular state will still be formed initially since spreading is probably not essential for the formation of the lenticular liquid bridges. However, as the liquid content is increased air will become trapped between the non-spreading liquid bridges preventing the formation of the true capillary state (Fig. 5). Instead a weak 'pseudo-droplet' state will be formed where the interparticulate voids are not completely filled with binder. In this situation the mean torque peak will probably occur at a lower liquid content than in the spreading system, closer to the region of maximum heterogeneity (i.e., the torque range peak). This is what was observed experimentally.
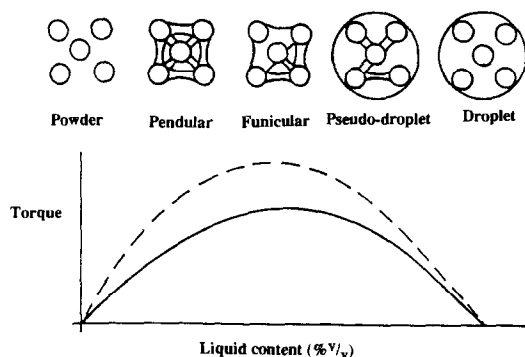

Fig. 5. Equilibrium torque variation with liquid content in a non-spreading system. (Continuous line) Mean torque; (broken line) torque range.

Thus it appears that the saturation states of Newitt and Conway-Jones (1958) and Barlow (1968) can be modified to account for the different interactions occurring between the substrate and binder components of any wet mass. This treatment is consistent with the observed rheological properties of the model wet masses and may enable a more precise and detailed characterisation of wet massed systems encountered in practice.

Peak torque magnitude It was shown earlier that the two torque parameters measured in these experiments quantify slightly different properties of the model wet masses. Whilst the locations of these parameter peaks have been considered it is also relevant to examine their magnitudes since these data may provide some additional information about the substrate-binder interactions occurring within the model wet masses.

In theory, the magnitude of the torque mean and range peaks will depend upon the strength of the cohesive and adhesive forces within the wet mass and the degree of interaction at the interface (e.g., wetting and spreading). From previous suppositions the magnitude of the torque mean peak should be largest when the strength and the degree of substrate-binder interaction are both high and the torque range response should be maximal when the interactions are strong but heterogeneously distributed. In addition Rowe (1988, 1989a,b, 1990, 1992) forecast that where adhesion, film formation and spreading processes are all favoured granules will be formed whose maximum strength will be determined by the work of cohesion of the binder. Where these interactions are less extensive granules will be formed whose strength will be primarily dependent upon the work of adhesion.

The works of cohesion and adhesion calculated for model substrate-binder pairs are presented in Table 6. The equilibrium mean torque peaks for both substrates were greater in the PVP systems than in the HPMC systems (Table 5) and the works of cohesion and adhesion were also greater in these systems so the mean torque peak magnitudes follow the expected trend. The mean torque peaks were also higher for the hydrophilic substrate than for the hydrophobic substrate un-

TABLE 6

Works of adhesion (W_a) *and cohesion* (W_c) *in the model substrate-binder pairs* $(mN\ m^{-1})$

Material		PVP $(W_c = 132.6)$	HPMC $(W_c = 93.0)$
Hydrophilic glass	$(W_c = 143.4)$	130.4	112.8
Hydrophobic glass	$(W_c = 49.2)$	65.4	45.4

der any given conditions and this is consistent with the predictions of Rowe (1988, 1989a,b, 1990, 1992) with the works of cohesion of the two polymer binders being much larger than the works of adhesion in the hydrophobic substrate systems. The torque range responses were also very slightly higher in the hydrophobic model substrate systems and this correlates with the production of a more heterogeneous wet mass in these poorly interacting systems. The equilibrium torque range peaks for the model substrates were all larger than the corresponding mean torque peaks due to the choice of mixing speed and blade configuration used in this study (Hancock et al., 1992) and there was no obvious relationship between the magnitude of either torque parameter and the degree of substrate or binder spreading. Thus, overall, the mean torque and torque range peak magnitudes for the model substrate systems follow the trends expected from the predicted substrate-binder interaction phenomena and provide further support for the mechanisms of granule growth and structure proposed earlier.

Conclusions

The use of mixer torque rheometry to study the wet massing rheology of model substrate-binder systems has provided a valuable insight into the mechanisms of wet granule formation and growth. In all of the systems considered the wet massing rheology was controlled by a complex balance of physical interactions at the substrate-binder interface. At the liquid contents where typical pharmaceutical granules are produced (around the funicular state) the integrity of the granules was most strongly influenced by spread-

ing of the binder or substrate phases. Poor spreading produced unstable granules and precipitated overwetting whereas good spreading enabled stable granules to be formed even at elevated liquid contents. By reconsidering the theoretical agglomerate structures proposed by Newitt and Conway-Jones (1958) and Barlow (1968) it was possible to expand the theories of wet granulation to take into account the most likely interaction differences and explain the observed variations in wet massing behaviour. The location of the peak torque in the model wet masses was determined not only by the packing density of the particles but also by the ability of the granulating liquid to fill the void space. This may explain the apparently anomalous results in the literature regarding the optimum liquid requirement for wet granulation processes. For the materials used in this study a good estimate of the intragranular void space was obtained from settled density determinations.

Overall the importance of substrate-binder interactions in wet granulation has been demonstrated, with the location and magnitude of the mean torque and torque range responses in the mixer torque rheometer providing valuable information about the degree of substrate-binder interaction occurring in the wet mass. It is concluded that the surface properties and physical interactions of the substrate and binder phases require careful consideration prior to development of any commercial wet granulation process.

References

Alleva, D.S., The wet granulation process: kinetics and mechanisms of granule formation. Ph.D. Thesis, Philadelphia College of Pharmacy and Science, U.S.A. (1984).

Barlow, C.E., The granulation of powders. *Chem. Eng.*, July/August (1968) 196–201.

Butensky, M. and Hyman, D., Study of the factors affecting granule size. *Ind. Eng. Chem. Fundam.*, 10 (1971) 212–219.

D'Alonzo, G.D., O'Connor, R.E. and Schwartz, J.B., Effect of binder concentration and method of addition on granule growth in a high intensity mixer. *Drug Dev. Ind. Pharm.*, 16 (1990) 1931–1944.

German, R.M., *Particle Packing Characteristics*, Metal Powder Industries Federation, NJ (1989).

Hancock, B.C., Ph.D. Thesis, University of Bradford, U.K. (1991).

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

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

Harwood, C.F. and Pilpel, N., Granulation of griseofulvin. *J. Pharm. Sci.*, 57 (1968) 478–481.

Holm, P., Schaefer, T. and Kristensen, H.G., Granulation in high speed mixers: 5. Power consumption and temperature changes during granulation. *Powder Technol.*, 43 (1985) 213–223.

Johnson, B.A. and Zografi, G., Adhesion of hydroxypropyl cellulose films to low energy solid substrates. *J. Pharm. Sci.*, 75 (1986) 529–533.

Jurado, M.J., Mondragon, I. and Nazabal, J., A study of the compatibility of polymer mixtures by the observation of mixing torque. *Rev. Plasticos Modernos*, 370 (1987) 487–489.

Krycer, I., Pope, D.G. and Hersey, J.A., An evaluation of tablet binding agents: 1. Solution binders. *Powder Technol.*, 34 (1983) 39–51.

Kuwabara, M., Hayamizu, S. and Hatakeyama, A., Trends in urea based granular compound fertiliser technology. In Proceedings of *Granular Fertilisers and their Production*, Conference, 14–15th November (1977) 125–147.

Newitt, D.M. and Conway-Jones, J.M., A contribution to the theory and practice of granulation. *Trans. Inst. Chem. Eng.*, 36 (1958) 422–442.

Palmer, H.K. and Rowe, R.C., The application of mercury porosimetry to porous polymer powders. *Powder Technol.*, 9 (1974) 181–186.

Parker, M.D., Solid-liquid interactions in the wet massing phase of pharmaceutical wet granulation. Ph.D. Thesis, University of Bradford, U.K. (1989).

Parker, M.D. and Rowe, R.C., Source variation in the wet massing (granulation) of some microcrystalline celluloses. *Powder Technol.*, 65 (1991) 273–282.

Parker, M.D., Rowe, R.C. and Upjohn, N.G., Mixer torque rheometry – a method for quantifying the consistency of wet granulations. *Pharm. Technol. Int.*, 2(8) (1990) 50–64.

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

Rowe, R.C., Binder substrate interactions in tablets: a theoretical approach based on solubility parameters. *Acta Pharm. Technol.*, 34 (1988) 144–146.

Rowe, R.C., Binder-substrate interactions in granulation: a theoretical approach based on surface free energy and polarity. *Int. J. Pharm.*, 52 (1989a) 149–154.

Rowe, R.C., Surface free energy and polarity effects in the granulation of a model system. *Int. J. Pharm.*, 53 (1989b) 75–78.

Rowe, R.C., Correlation between predicted binder spreading coefficients and measured granule and tablet properties in the granulation of paracetamol. *Int. J. Pharm.*, 58 (1990) 209–213.

Rowe, R.C., Interactions in powders and granules – a reappraisal. *Int. J. Pharm.*, 79 (1992) 257–261.

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

Van Oss, C.J. and Good, R.J., Surface tension and the solubility of polymers and biopolymers: the role of polar and apolar interfacial free energies. *J. Macromol. Sci. Chem.*, A26 (1989) 1183–1203.

Wells, J.I. and Walker, C.V., The influence of granulation fluids upon granule and tablet properties: the role of secondary binding. *Int. J. Pharm.*, 15 (1983) 97–111.

Wu, S., *Polymer Interface and Adhesion*, Dekker, New York, 1982.

Zajic, L. and Buckton, Z., The use of surface free energy values to predict optimum binder selection for granulations. *Int. J. Pharm.*, 59 (1990) 155–164.