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Binder-substrate interactions in wet granulation. 1: The effect of binder characteristics

M.D. Parker [1]*, P. York [1] and R.C. Rowe [2]

[1] *Postgraduate studies in Pharmaceutical Technology, The School of Pharmacy, University of Bradford, Bradford BD7 1DP (U.K.)*
and [2] *ICI Pharmaceuticals, Alderley Park, Macclesfield SK10 2TG (U.K.)*

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Summary

A laboratory-scale, instrumented mixer torque rheometer has been used to examine the interactions of microcrystalline cellulose with aqueous solutions of two polymer binders. The rheological behaviour indicated differences, at equivalent viscosity, between the two polymers, which were explained by theories relating binder surface tension to granule properties. The measured surface tension values were then used to calculate the surface free energies, interfacial works of cohesion and adhesion and spreading coefficients for the interaction between the materials used in this study. These data indicated a different degree of interaction between the two polymers and the cellulose substrate, which was probed further using a series of experiments to examine polymer adsorption phenomena. These combined data were used to propose a pattern of behaviour based on consideration of 'intra-granular viscosity' which helped to explain the observed rheological behaviour.

Introduction

Owing to their wide-ranging physicochemical and mechanical properties, pharmaceutical powders and their blends frequently exhibit poor flow and compaction behaviour (Krycer et al., 1983). Thus, an intermediate step — granulation — is usually required in solid dose manufacture to produce a free-flowing material with good compression characteristics.

The process of wet granulation occurs by complex interactions of several parameters, each of which will affect the final product performance. A knowledge of the effect of each of these parameters is therefore necessary if the granulation process is to be adequately controlled (Kristensen and Schaefer, 1987).

Examination of the literature reveals numerous instances where final granule properties have been related to binder physical properties (Opakunle and Spring, 1976; Jaiyoba and Spring, 1979; Wells and Walker, 1983; Ritala et al., 1986, 1988). While this approach is undoubtedly of value in predicting the relative influences of solid and liquid components of a formulation, it fails to take into

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Correspondence (present address): M.D. Parker, ICI Pharmaceuticals, Alderley Park, Macclesfield, Cheshire SK10 2TG, U.K.

account the interaction phenomena which have been shown to occur at many solid/liquid interfaces (Kellaway and Najib, 1980). These molecular interactions may well influence the final granule properties and hence the final product performance.

Rowe (1988, 1989a, b, c) has recently proposed that inconsistency in the literature regarding the choice of binder for granulation purposes can be explained by consideration of the relative influence of the thermodynamic works of cohesion and adhesion, based on a knowledge of either the solubility parameters (Rowe, 1988) or the surface free energy components (Rowe, 1989a) of substrates and binders. From these data, statements regarding film formation, granule morphology and granule strength could be made (Rowe, 1989b).

The objective of this study was to use a granulation monitoring technique to examine the interactions occurring during the wet massing stage of the granulation process. The literature reveals a variety of techniques which have been suggested as monitoring methods. These include electrical methods such as ammeters for motor current and power consumption meters (Bier et al., 1979; Leuenberger et al., 1979; Holm et al., 1985), machine characteristics such as torque measurements (Lindberg et al., 1977, 1982), and mass properties such as temperature changes (Holm et al., 1985), moisture content (Fry, 1984) and probes inserted into the mass (Kay and Record, 1978; Staniforth et al., 1986). It has been suggested (Kristensen and Schaefer, 1987), that the measurement of torque should provide the most reliable control method, since it is proportional to the resistance of the mass, and thus directly monitors changes in cohesiveness. According to Voisey (1971), the most accurate torque measurement technique is to measure the reaction of the mixing bowl, rather than the torque on the shafts of the blades, because the bowl is generally stationary, and the frictional effects within the mechanism driving the blades are therefore eliminated.

We have used a specially designed mixer torque rheometer (Rowe and Sadeghnejad, 1987) to monitor the rheological changes occurring during the wet massing of a commonly used tabletting excipient (microcrystalline cellulose), with aqueous solutions of two polymer binders. Possible correlations can then be explored between the observed rheological behaviour, measured binder physical characteristics, such as viscosity and surface tension, and possible binder/substrate interactions.

Materials and Methods

Materials

Microcrystalline cellulose (MCC: Avicel PH 101, FMC Corp., Co. Cork, Eire) with a nominal particle size of 50 μm was used as received, with a moisture content of 4.5% measured using thermogravimetry (Du Pont 1090 thermal analyser, Du Pont Ltd, Stevenage, U.K.). Polyvinylpyrrolidone (PVP: Kollidon 25, BASF (U.K.) Ltd, Cheadle, Cheshire, U.K.) and hydroxypropyl methylcellulose (HPMC: Pharmacoat 603, Shin-Etsu Chemical Co., Tokyo, Japan) were selected as representative polymer binders for which both physical characterisation, and granulation performance data were available in the literature (Wells and Walker, 1983; Cutt et al., 1986; Ritala et al., 1986, 1988).

Methods

Binder characterisation

Aqueous solutions of varying concentrations of each binder was prepared by dissolving an appropriate quantity of powder, accurately weighed into 100 ml of distilled water.

Viscosity The dynamic viscosity (cP) was determined for each solution using capillary viscometry at a temperature of 20°C. The necessary solution density was determined using a hand-held, digital density meter (DMA 35, Anton Paar K.C., Austria).

Surface tension The surface tension of aqueous solutions of varying concentration of each binder was determined after equilibration at 20°C for 1 h, using a Du Nuöy tensiometer fitted with a 4 cm circumference platinum ring.

G.P.C. analysis The molecular weight distributions were determined for each polymer using a

Waters gel permeation chromatography system (model GPC 510, Waters Associates, U.S.A.), incorporating a TSK gel column and a Waters differential refractometer detector (model 410). The column was calibrated using a series of 13 dextrans of varying molecular weight. The mobile phase was distilled water containing 0.02% sodium azide as a bacteriostat. 1% HPMC and 3% PVP samples were injected into the system via a 45 μm membrane filter to remove any particulate matter. From the resultant chromatograms, the weight average (M_w) and number average (M_n) molecular weights could be determined for each polymer.

In order to investigate possible adsorption of polymer molecules onto excipient surfaces, the GPC system was used to obtain molecular weight distributions of the polymer solutions following agitation with a known quantity of microcrystalline cellulose. Examination of these distribution profiles and molecular weight data can then yield information regarding possible adsorption phenomena.

Wet massing studies

For this investigation a specially constructed mixer torque rheometer was employed. The rheometer was similar to that of the commercially available instrument (Plasti-corder, rotational torque rheometer) used by Schildcrout (1984), and was identical to that designed and reported by Rowe and Sadeghnejad (1987). For the experimental procedure, a steady baseline torque value was initially generated by starting the empty mixer and chart recorder for a short period (usually 20–30 s). 15 g of powdered material, the quantity of material which just covered the mixer blades when dry, was added to the mixing bowl followed by a measured volume of binder or water in a single addition, using a syringe to aid binder distribution. The mixer was then left to run until 'steady-state' conditions were reached, as determined by the chart recorder trace. Preliminary experiments indicated that 'steady-state' conditions were usually attained within 5 min. The equilibrium torque value, reflecting the rheology of the wet mass, was then determined by measuring the mean amplitude of the oscillation in torque over 10 successive cycles, at and around the five min point on the chart recorder trace. The final value was then obtained from a calibration curve after subtraction of the baseline value from the empty mixer. The experimental procedure was repeated three times for each volume of binder. From this data rheological profiles of torque against proportion of binder could be generated for different concentrations of each binder.

Results and Discussion

Viscosity and surface tension

Wells and Walker (1983) suggested that the process of granulation will depend on the surface tension and viscosity of the binder, since these will influence the strength of the liquid bridges formed between particles, and the distribution of the binder during the wet massing stage.

The viscosity and surface tension data for the different concentrations of each binder are presented in Table 1. In general, the viscosity results agree with those presented in the manufacturer's literature, and illustrate a non-linear relationship between viscosity and concentration. From the surface tension results it can be seen that at low concentration, the presence of the polymers causes a decrease in surface tension of the solution. As

TABLE 1

Experimental data for polymer binders

Binder (% w/v)	Viscosity (cP)	Surface tension (mN m^{-1})	Maximum torque (N m)
Water	1.0	72.00	0.5280 (0.0107)
PVP			
1% K25	1.19	58.48	0.4988 (0.0345)
3% K25	1.58	56.43	0.4887 (0.0023)
5% K25	2.25	55.14	0.5345 (0.0178)
8.24% K25	3.82	–	0.6186 (0.0076)
12.78% K25	6.87	–	0.6427 (0.0115)
HPMC			
0.1% 603	–	49.30	– –
0.5% 603	–	48.50	– –
1.3% 603	2.26	48.00	0.4299 (0.0216)
3% 603	5.41	47.57	0.5596 (0.0233)
5% 603	12.56	47.53	0.6839 (0.0128)

Values in parentheses represent standard deviations ($n = 3$).

the concentration increases, the surface tension then levels out to approximately constant values. The marked reduction in the surface tension values of HPMC solutions may well influence the ease of distribution of the binder during wet massing, and hence the observed rheological behaviour. From these results it was concluded that changes in surface tension with concentration would have a minimal effect on differences in behaviour observed during the wet massing studies, since the values would remain almost constant throughout the range of concentrations to be studied, except at low concentrations of PVP where the limiting values appear not to have been reached.

Wet massing studies

Figs 1 and 2 show the rheological profiles for Avicel PH 101 using 1, 3 and 5% w/v aqueous solutions of PVP K25 and HPMC 603. The error bars represent the standard deviation of the mean and demonstrate the good reproducibility of the experimental technique. Figs 1 and 2 show there is an increase in torque with increasing liquid content, rising to a maximum, then decreasing as larger volumes of binder are used. Rowe and Sadeghnejad (1987) have suggested that this pattern is consistent with the different states of liquid saturation in agglomeration as defined by Newitt and Conway-Jones (1958). The pendular and funicular states are characterised by a progressively increasing network of liquid bridges. Both these stages will cause an increase in cohesiveness of the powder mass, and hence an increased torque on the mixer. The capillary state which is reached when all the air spaces in the granular material are filled with liquid, occurs at the maximum on the curve. With further addition of liquid the torque decreases as a slurry of particles dispersed in liquid is formed. For the PVP systems both the peak torque and the volume of liquid added at the peak are similar to that observed by Rowe and Sadeghnejad (1987) using water as the binder. For the HPMC system it can be seen that increasing the binder concentration and hence its viscosity, produces a greater maximum torque and also a reduced liquid requirement at the maximum. The maximum torque values are also listed in Table 1.

In order to examine the effect of binder viscosity on torque development, the data from Table 1

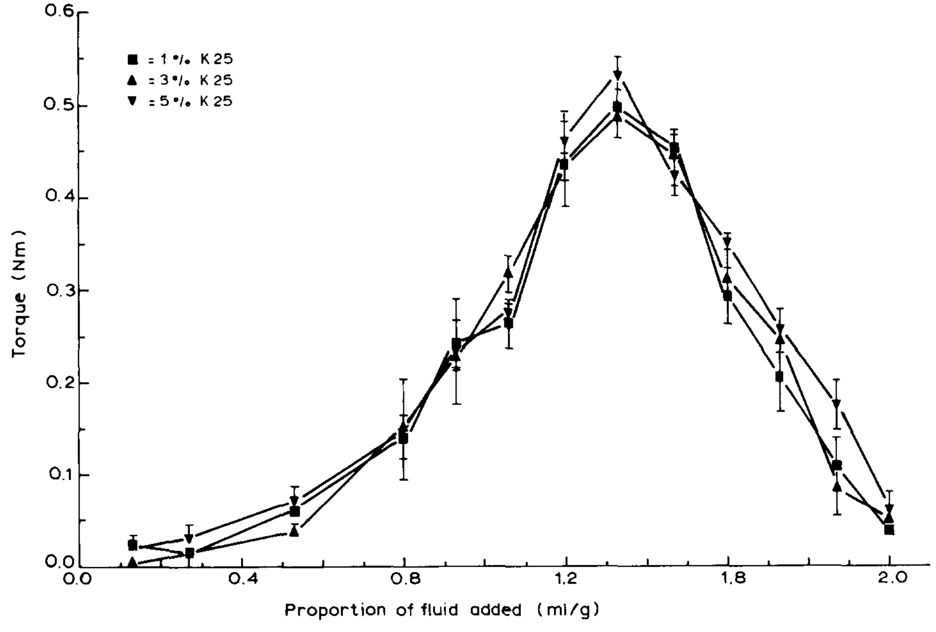

Fig. 1. Rheological profiles for Avicel PH 101 wet massed with aqueous solutions of PVP K25.

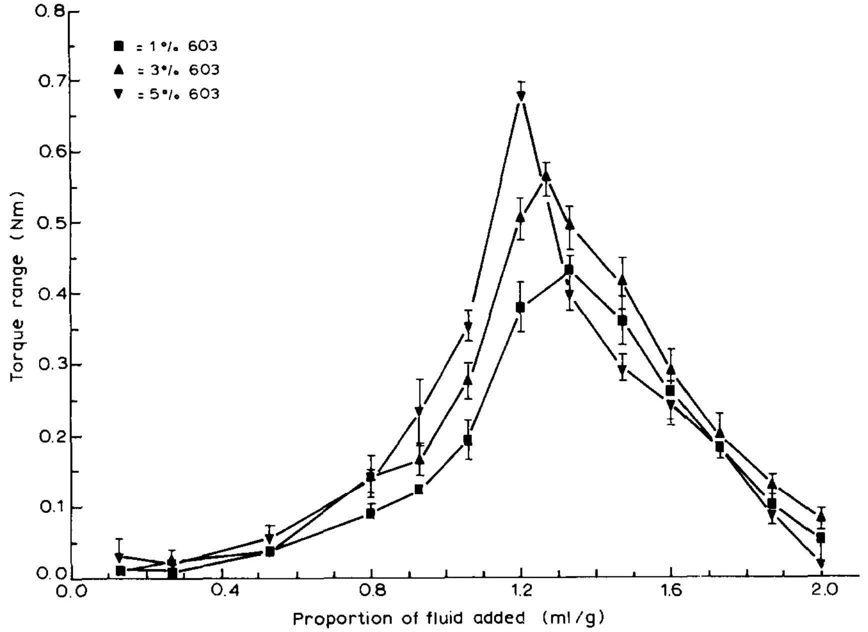

Fig. 2. Rheological profiles for Avicel PH 101 wet massed with aqueous solutions of HPMC 603.

were plotted in the form of graphs of maximum torque against binder viscosity (Fig. 3). From Fig. 3 it can be seen that the two polymer systems exhibit a similar pattern of behaviour. In both systems the curve passes through a minimum followed by a positive slope as the dynamic viscosity increases. Another interesting feature of these derived curves is that the torque values obtained from the Avicel/PVP system are generally higher than those from the Avicel/HPMC system. It is therefore appropriate to discuss the factors which may contribute to this observed pattern of behaviour.

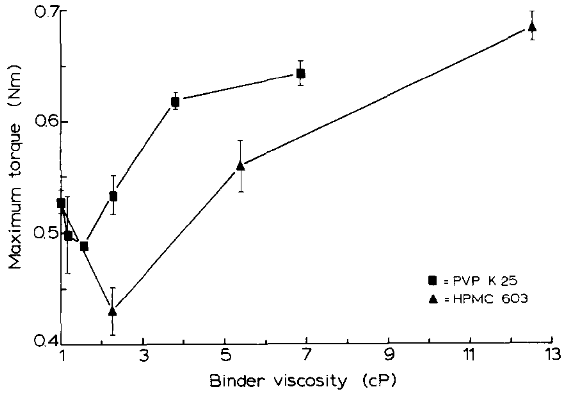

Fig. 3. Effect of binder viscosity on maximum torque for experimental materials.

As described above, the torque values are obtained by measuring the mean amplitude of the oscillation in torque. It is proposed that this torque amplitude represents the shearing force required to drive the blades through the damp mass as they reach the position of closest proximity. The data in Fig. 3 illustrate the effect of viscosity on the maximum torque, and this maximum torque has been linked to the capillary state in granulation. Fig. 4 illustrates the path of the mixer blades through a portion of the wet powder mass in the capillary state. From this diagram it can be seen that any changes imposed on the binder, for example, in concentration or surface tension, are likely to be important factors influencing torque development.

When considering the effect of binder viscosity, various authors have observed that increasing binder concentration, and thereby viscosity, results in stronger granules (Chalmers and Elworthy, 1976; Cutt et al., 1986). Cutt et al. (1986) suggest

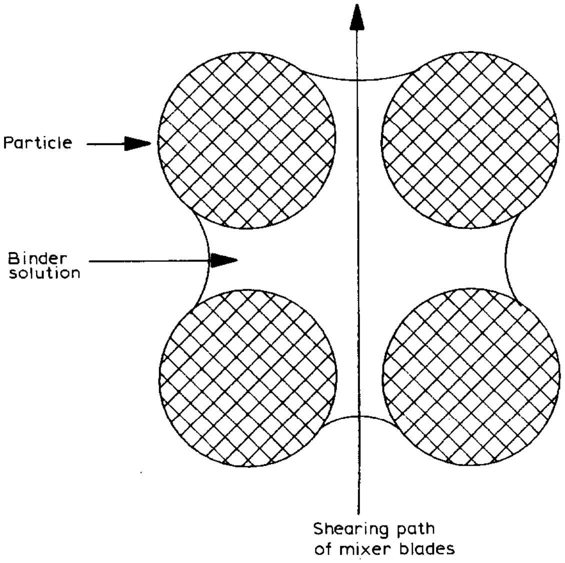

Fig. 4. Shearing path of mixer blades through wet mass at capillary state.

this is due to the increased amount of binder per bond, increasing the bond strength. In contrast to these observations, Ritala et al. (1986) found that binder concentration only had a minor effect on granule growth during the liquid addition phase in a high shear mixer, and that densification of the material dictated the granule properties to a greater extent. These authors in fact observed an apparent decrease in power consumption with increasing binder concentration. This was attributed to a lubrication effect of the binder. A different interpretation is of the increased binder concentration and hence viscosity resulting in poorer binder distribution and therefore a reduced power consumption when compared with the more easily distributed, lower viscosity binder.

In terms of the development of torque within the mixer used for this study, it is reasonable to suggest that as the binder viscosity increases, so the torque developed within the mixer also increases due to the changes in shearing force required to drive the blades through the damp mass. The data in Fig. 3 support this hypothesis and show the general trend for both systems that increasing binder viscosity gives increased maximum torque values. This simple pattern of behaviour does not, however, explain the initial dip in the curves for both systems, or why, at equivalent viscosity, the two binders produce different torque values.

Ritala et al. (1986, 1988) concluded that different binders alter granule strength by their influence on the intragranular porosity. It was also suggested that the high surface tension of PVP solutions caused the moist agglomerates to have the lowest porosity values, thus increasing the mean strength of the granules through the effect on liquid saturation. In testing this hypothesis by the addition of a surfactant to PVP binder solutions, it was found that increasing the surfactant reduced the binder surface tension, resulting in a greater liquid requirement and the formation of more porous granules. In contrast to these findings, Usteri and Leuenberger (1989) have found that the liquid requirement during granulation in a high shear mixer is significantly reduced when surfactant solutions are used in comparison with granulation using water. It was also found that the liquid requirement decreased as the surfactant concentration increased. Initial correlations were made between the liquid requirement and the surface tension of the surfactant solution; however, the liquid requirement continued to decrease at surfactant concentrations above the CMC, although the surface tension of these solutions remained constant. This behaviour could therefore not be explained purely on the basis of decreases in surface tension resulting in improved wetting of the substrate. A more complex pattern of interaction was suggested involving possible adsorption phenomena.

Examination of the data from this study in Table 1 reveals that aqueous solutions of both polymer binders have lower surface tensions in comparison with that of water. For the low viscosity solutions this reduced surface tension may lead to the formation of more porous, lower strength granules in the manner suggested by Ritala et al. (1986, 1988). As a result, less shearing force would be required to drive the mixer blades through the damp mass, compared with granulations prepared using water as the binder. This behaviour may explain the initial drop in peak torque values below that of water. As the binder viscosity increases, the influence it has on torque development begins to dominate over the effects of reduced surface tension, and so the torque values for both binder systems increase to levels above that observed with water. As discussed above, the data in Table 1 also reveal consistently lower surface tension values for the HPMC solutions compared with those of the PVP solutions. It can also be observed from Fig. 3 that the maximum torque values for the HPMC solution are generally lower than those of the PVP solutions. Thus, it is possible that the correlation suggested by Ritala et al. (1986, 1988) between binder surface tension and the strength of moist agglomerates can be further demonstrated in this study by the apparently similar relationship between torque development and binder surface tension.

Interaction phenomena and binder spreading

As discussed above, much of the research into granulation processes has been concerned with the effects of material and binder physical properties on subsequent granule and tablet properties. However, there has been relatively little discussion on the possible interactions between binder and substrate within granulation systems. Based on the work carried out by Rowe (1988, 1989a, b, c), it is possible, by using a surface free energy approach, to examine the inter-relationships between binder/binder and binder/substrate adhesive/cohesive interactions occurring within the systems examined in this study.

If γ_B and γ_S are the surface free energies of the binder and substrate respectively, then it is possible to calculate the work of cohesion (Wc) of each of the two components, and the work of adhesion (Wa) between the binder and the substrate (Wu, 1973; Rowe, 1989a):

$$\mathrm{Wc_B} = 2\gamma_B \tag{1}$$

$$\mathrm{Wc_S} = 2\gamma_S \tag{2}$$

$$\mathrm{Wa} = 4\left[\frac{\gamma_B^d \cdot \gamma_S^d}{\gamma_B^d + \gamma_S^d} + \frac{\gamma_B^p \cdot \gamma_S^p}{\gamma_B^p + \gamma_S^p}\right] \tag{3}$$

where γ^d and γ^p are the respective polar and nonpolar components of the surface free energy of the binder and substrate.

From the above derived data, the spreading coefficients λ_{12} (binder over substrate), λ_{21} (substrate over binder) and λ_R (reduced) can be calculated for each binder/substrate combination:

$$\lambda_{12} = \mathrm{Wa} - \mathrm{Wc_B} \tag{4}$$

$$\lambda_{21} = \mathrm{Wa} - \mathrm{Wc_S} \tag{5}$$

$$\lambda_R = \frac{\mathrm{Wa}}{\mathrm{Wc_B}} \tag{6}$$

The dimensionless parameter of reduced spreading coefficient defines the ease of film formation of the polymer binder over the substrate, and thus the production of strong granules (Rowe, 1989c). In the context of this study, the spreading coefficients provide comparative information on the degree of interaction between the binder and the substrate.

The intensity of the adhesive and cohesive interactions between microcrystalline cellulose and the two polymer binders has been calculated using surface free energy data for Avicel PH 101 reported by Lee and Luner (1972) and fractional polarity data for the polymer binders given by Rowe (1989a). The total surface free energy data for the binders were estimated in a similar manner to that used by Rowe (1989a) from the surface tension values of 5% aqueous solutions. At this concentration the surface tension is in the range of concentration independence, and is considered to represent the surface free energy of the polymer. The results are presented in Table 2.

Examination of the data in Table 2 shows there is a greater work of adhesion with the microcrystalline cellulose, and a greater binder/binder work of cohesion for the PVP binder. Consideration of the spreading coefficients for the two binder/substrate systems reveals positive values for λ_{12} and negative values for λ_{21}. According to Wu (1973) and Rowe (1989a), this indicates energetically favourable spreading of the binder over the substrate, leading to the formation of strong, dense granules. These data also indicate that the value for the spreading of HPMC over the cellulose substrate is 82% higher than that of PVP, resulting

TABLE 2

Surface free energy and adhesion/cohesion data for experimental materials

	PVP	HPMC	MCC
Surface free energy components (mN m^{-1})			
γ	55.1	47.5	63.9
γ^d	29.2	18.1	29.1
Fractional polarity			
x^p	0.47	0.62	0.54
Work of cohesion			
Wc (mN m^{-1})	110.3	95.1	–
Work of adhesion			
Wa (mN m^{-1})	117.5	108.2	–
Spreading coefficients			
λ_{12} (mN m^{-1})	+7.2	+13.1	–
λ_{21} (mN m^{-1})	−10.3	−19.6	–
λ_R	1.07	1.14	–

in a larger reduced spreading coefficient for the Avicel/HPMC system compared with the PVP system.

The data in Table 2 have therefore indicated that there is a different degree of interaction between MCC and the two polymer binders. Similar thermodynamic parameters of cohesion and adhesion have been generated using a cohesion/solubility parameter approach (Rowe, 1988). This approach yields data indicating a 49% stronger adhesive interaction between HPMC and microcrystalline cellulose, and also a stronger binder/binder cohesive interaction for the HPMC polymer. This then results in a much greater reduced spreading coefficient for the HPMC/MCC system. Thus it appears that the degree of interaction follows the same rank order, independent of the approach used to calculate the parameters.

Excipient / binder adsorption

Consideration of polymer/substrate interactions plays an important role in many pharmaceutical systems. It has recently been suggested (Usteri and Leuenberger, 1989) that the adsorption of polymer molecules onto excipient substrates could be responsible for the observed power consumption changes during granulation with surfactant solutions. A survey of the literature indicates that the adsorption of PVP molecules occurs with a number of solid substrates (Kellaway and Najib, 1980; Cohen-Stuart et al., 1982) including cellulose in the form of wood pulp (Ishimaru and Lindstrom, 1984). These workers further demonstrated that cellulose derivatives (hydroxypropyl cellulose) are also adsorbed onto cellulose fibres. It is therefore appropriate to examine whether adsorption processes could occur within the wet granulation systems used in this study, and the role this could have in explaining the observed rheological behaviour during the wet massing studies.

Table 3 presents the GPC analysis data for different concentrations of each binder, before and after equilibration with MCC.

From Table 3 it can be seen that the results for the PVP solutions are generally inconclusive. The weight average molecular weight values (M_w) show no change after equilibration with the Avicel substrate. There is also no apparent effect on increasing the binder solution concentration. The number average molecular weight values (M_n) are rather variable, showing no clear pattern. It is interesting, however, to note that the values for the peak molecular weight are lower for the samples equilibrated with MCC than for the control sample, possibly indicating a degree of adsorption.

The results for the HPMC experiments give a stronger indication that adsorption of polymer is occurring at the excipient/binder interface (an

TABLE 3

GPC results for polymer samples

Sample	M_w ($\times 10^3$)	M_n ($\times 10^3$)	Peak mol. wt ($\times 10^3$)
PVP			
3% K25 (control)	30	3.6	24.9
3% K25/Avicel	29	1.0	22.7
8% K25/Avicel	30	4.3	22.7
HPMC			
1% 603 (control)	45	3.5	33.3
1% 603/Avicel	48	3.8	36.4
5% 603/Avicel	40	2.0	25.0

M_w difference of > 1000 at $M_w = 40000$ is usually considered significant). Table 3 shows reductions in all three measured parameters for the equilibrated samples at the 5% level when compared with the control, indicating adsorption of perhaps the high molecular weight component. The apparent rise in the measured values for the 1% equilibrated sample is perhaps an artefact due to an observed peak splitting problem in the high molecular weight portion of the chromatogram for the control sample, leading to artificially low values for this sample.

In general these results indicate that polymer adsorption can occur within the systems examined in this study. Although literature evidence demonstrates the adsorption of PVP onto cellulose substrates, no firm supporting conclusions can be drawn regarding PVP adsorption from this study. However, the data for HPMC indicate that a degree of adsorption does occur, possibly related to the polymer concentration. This study therefore also supports the hypothesis obtained from surface free energy considerations that for the two polymers studied there is a greater attraction between HPMC and MCC than between PVP and MCC.

It has been proposed above that any changes imposed on the binder, for example, in concentration, are likely to be important factors influencing torque development within the mixer. From Fig. 4 it can be seen that such changes in concentration etc will have a corresponding effect on the viscosity of the binder in the void spaces between the particles within the granule, i.e. the effect will be an alteration of the 'intra-granular' viscosity. Therefore, as the binder concentration increases so the intra-granular viscosity increases, and a greater shearing force is required to drive the mixer blades through the damp mass. It is proposed that any differences in rheological behaviour caused by adsorption phenomena or binder/substrate interactions are mediated through an effect on the intra-granular viscosity. Any adsorption of polymer molecules within the granule would lead to a reduction in the intra-granular viscosity, as the molecules are effectively removed from the solution. This would therefore reduce the required shearing force on the mixer blades and hence produce a lower torque value.

From the binder/substrate interaction and polymer adsorption data it was concluded that for MCC there is generally a greater degree of interaction with HPMC than with PVP, with evidence of adsorption of HPMC molecules. From these conclusions it can be suggested that the maximum torque values obtained with PVP as the binder will generally be higher than those with HPMC, since there will be a greater attraction, and therefore greater adsorption of HPMC molecules, resulting in a lower intra-granular viscosity.

Conclusions

While traditional methods of using binder physical properties to predict the influence of the binder on the granulation process and final granule properties are undoubtedly of value, an understanding of the fundamental molecular interactions occurring between components of a formulation during wet granulation is becoming increasingly important in order to achieve accurate control of the granulation process. The instrumented mixer torque rheometer has been successfully used to examine the changes in rheological behaviour which occur when aqueous polymer solutions replace water as the binder in wet granulation processes. The results have shown that different polymers behave differently in the wet massing process. Examination of excipient/binder interactions at the solid/liquid interface, together with traditionally considered binder physical properties has been used to describe and explain the observed rheological behaviour. The theoretical and experimental data presented here clearly show the possible role of solid/liquid interactions in governing the rheological behaviour during wet massing and therefore predicting final product performance.

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