International Journal of Pharmaceutics, 72 (1991) 243–249

ADONIS 037851739100232M

IJP 02426

Binder-substrate interactions in wet granulation. 2: The effect of binder molecular weight

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, Cheshire SK10 2TG (U.K.)*

(Received 8 November 1990)
(Modified version received 4 February 1991)
(Accepted 17 February 1991)

Key words: Granulation; Polymer binder; Torque rheometry; Interaction; Microcrystalline cellulose

Summary

The interactions during wet granulation between microcrystalline cellulose and aqueous solutions of two molecular weight grades of two polymer binders, have been monitored using an instrumented mixer torque rheometer. The rheological behaviour indicated that different molecular weight grades of the same polymer exhibited different behaviour at equivalent viscosity. This observation could only partly be explained using traditionally considered theories relating binder surface tension to granule strength. An examination of polymer adsorption phenomena gave results consistent with earlier data indicating a different degree of interaction between the two polymer types, and possible preferential adsorption of high molecular weight molecules. A model to describe particle : binder behaviour during wet massing has been suggested to explain the observed differences in rheological behaviour.

Introduction

The role of the binder in wet granulation processes is to assist bond formation between particles through the formation of solid bridges after drying. The properties and behaviour of the binder have profound effects on the granule properties, and hence the choice of binder for a particular formulation may be critical in determining final product performance.

While traditional methods of using binder physical properties to predict the influence of the binder on the granulation process and final granule properties (Opakunle and Spring, 1976; Wells and Walker, 1983; Ritala et al., 1986) are undoubtedly of value, they fail to take into account the interaction phenomena which have been shown to occur at many solid/liquid interfaces (Kellaway and Najib, 1980).

An instrumented mixer torque rheometer has recently been used to examine the rheological behaviour of wet masses, granulated with different concentrations of two aqueous polymer binders (Parker et al., 1990a). The results indicated that different polymers behave differently during the wet massing process. These differences could only be partly explained by current theories relating

---

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

fundamental material properties such as binder viscosity and surface tension to final granule properties. Examination of possible excipient/binder interactions gave theoretical and experimental data which indicated the role of solid/liquid interactions in governing the rheological behaviour during wet massing, and therefore predicting final product behaviour.

The objective of this study was to extend this approach in order to examine the effects of changes in the binder grade on the subsequent rheological behaviour of the wet mass. Microcrystalline cellulose was used as the excipient, and the rheological behaviour with aqueous solutions of two molecular weight grades of each of two polymer binders was examined using the mixer torque rheometer (Rowe and Sadeghnejad, 1987; Parker et al., 1990a). Correlations could then be explored between the observed rheological behaviour, binder physical properties and excipient/binder interactions.

Materials and Methods

Materials

Microcrystalline cellulose (MCC: Avicel PH 101, FMC Corp., Co. Cork, Ireland) 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 and Kollidon 90, BASF (U.K.), Ltd, Cheadle, Cheshire, U.K.) and hydroxypropyl methylcellulose (HPMC: Pharmacoat 603 and Pharmacoat 606, Shin-Etsu Chemical Co., Tokyo, Japan) were used as the representative polymer binders.

Methods

Binder characterisation Aqueous solutions of varying concentrations of each binder were prepared by dissolving an appropriate quantity of powder, accurately weighed, into 100 ml of distilled water. The dynamic viscosity and surface tension of each binder solution were then determined using capillary viscometry and a Du Nuoy tensiometer respectively, as described by Parker et al. (1990a).

The molecular weight distributions of each polymer, together with possible interaction phenomena, were investigated using a gel-permeation chromatography technique (GPC) described elsewhere (Parker et al., 1990a). From the resultant chromatograms, the weight average (M_w) and number average (M_n) molecular weights could be determined for each polymer, together with information regarding the possible adsorption of polymer molecules onto the excipient surface.

Wet massing studies The rheology of the wet mass was monitored using an instrumented mixer torque rheometer technique described elsewhere

TABLE 1

Experimental data for PVP grades

Binder (% w/v)	Viscosity (cP)	Surface tension (mN m^{-1})	Max. torque (Nm)	Liquid content at max. torque (ml/g)
Water	1.0	72.00	0.5280 (0.0107)	1.33
1% K25	1.19	58.48	0.4988 (0.0345)	1.33
3% K25	1.58	56.43	0.4887 (0.0023)	1.33
5% K25	2.25	55.14	0.5345 (0.0178)	1.33
8.24% K25	3.82	-	0.6186 (0.0076)	1.33
12.78% K25	6.87	-	0.6427 (0.0115)	1.20
0.3% K90	1.54	-	0.5756 (0.0425)	1.20
1% K90	3.82	65.47	0.5826 (0.0142)	1.27
3% K90	16.49	65.50	0.6336 (0.0088)	1.20
5% K90	41.95	65.53	0.6723 (0.0391)	1.20

Figures in parentheses represent standard deviations.

(Rowe and Sadeghnejad, 1987; Parker et al., 1990a, b). The equilibrium torque value, reflecting the rheology of the wet mass, was determined three times for each volume of binder. From these data, rheological profiles of torque against proportion of binder were generated for different concentrations of each binder.

Results and Discussion

Binder characterisation

The viscosity and surface tension data for each binder are presented in Tables 1 and 2. The data in Table 1 indicate that solutions of the two PVP molecular weight grades have slightly different surface tension, with the K25 grade reducing the surface tension to a greater degree than that of the K90 grade. For the HPMC solutions (Table 2), it can be seen that the two molecular weight grades have similar effects on the surface tensions of their aqueous solutions. Both grades cause a sharp reduction in the surface tension at low concentration, while at the concentrations to be used in the wet massing studies, the values remain almost constant.

It can also be seen that the PVP K90 grade has a similar viscosity profile to the HPMC 606 grade despite the fact that it has a tenfold larger weight average molecular weight. This may be due to the lower intramolecular interaction between the PVP molecules in solution. Rubinstein (1975) suggested that with increasing concentration PVP molecules aggregate to form spheres so that a minimum interparticulate contact area exists. Furthermore, as the concentration continues to rise, the size of the aggregates increases whilst the number remains about the same, thus maintaining a minimal contact area.

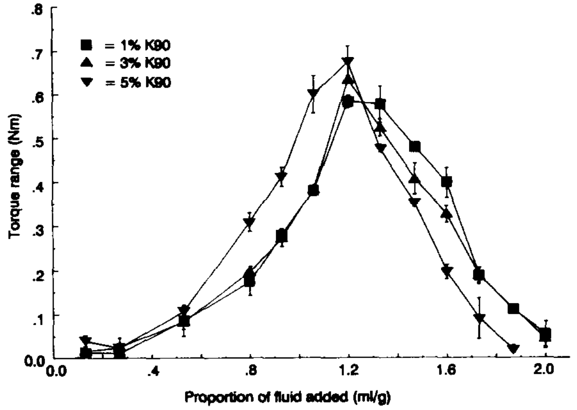

Fig. 1. Rheological profiles for Avicel PH 101 wet massed with aqueous solutions of PVP K90.

Wet massing studies

In a previous communication (Parker et al., 1990a), rheological profiles of torque against proportion of binder added were presented for the Avicel PH 101/PVP K25 and Avicel PH 101/HPMC 603 systems, Figs 1 and 2 show the rheological profiles for Avicel PH 101 using 1, 3 and 5% w/v solutions of PVP K90 and HPMC

TABLE 2

Experimental data for HPMC grades

Binder (% w/v)	Viscosity (cP)	Surface tension (mN m^{-1})	Max. torque (Nm)	Liquid content at max. torque (ml/g)
Water	1.0	72.00	0.5280 (0.0107)	1.33
0.1% 603	–	49.30	–	–
0.5% 603	–	48.50	–	–
1.3% 603	2.26	48.00	0.4299 (0.0216)	1.33
3% 603	5.41	47.57	0.5596 (0.0233)	1.27
5% 603	12.56	47.54	0.6839 (0.0128)	1.20
1% 606	2.71	48.23	0.4990 (0.0365)	1.33
3% 606	12.24	48.00	0.5671 (0.0610)	1.20
5% 606	39.27	48.07	0.7954 (0.0691)	1.27

Figures in parentheses represent standard deviations.

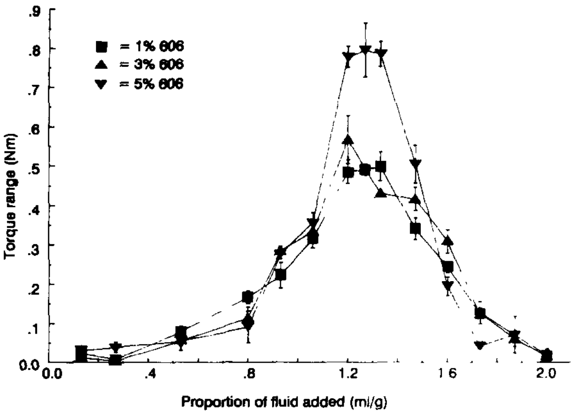

Fig. 2. Rheological profiles for Avicel PH 101 wet massed with aqueous solutions of HPMC 603.

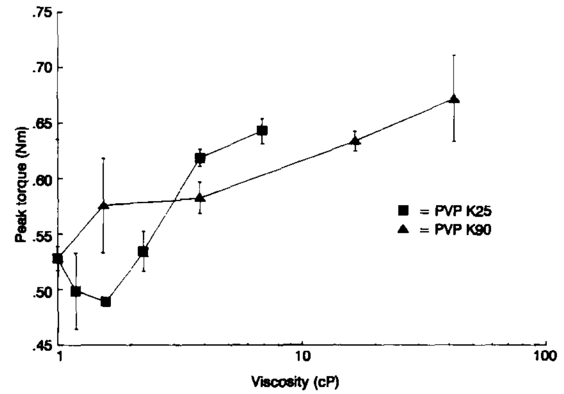

Fig. 3. Relationship between binder viscosity and maximum torque for Avicel/PVP systems.

606. The shape of the profiles is consistent with that reported elsewhere (Rowe and Sadeghnejad, 1987; Parker et al., 1990a). Each combination exhibits an increase in torque with increasing binder content rising to a maximum, thereafter decreasing as a slurry was produced. It has been suggested that the peak occurs at the capillary state in agglomeration (Rowe and Sadeghnejad, 1987), the torque subsequently decreasing rapidly as excess water is added.

It has recently been proposed (Parker et al., 1990a) that the maximum torque represents the shearing force required to drive the mixer blades through the damp mass at the capillary state in agglomeration. Therefore any changes in viscosity or surface tension of the binder, in what is essentially a two phase system, will influence torque development. For both systems it can be seen that increasing the binder concentration, and hence the viscosity, produces an increase in the maximum torque, and for the PVP K90 system, reduced liquid requirement at the maximum. The maximum torque values for all systems are presented in Tables 1 and 2.

Figs 3 and 4 show the relationship between binder viscosity (on a log scale) and the maximum torque for the four binder/substrate combinations. From these figures it can be seen that a similar pattern of behaviour is exhibited by the two polymer systems studied. In both systems the curve for the low molecular weight grade passes through a minimum, followed by a positive slope until the curve crosses that of the higher molecular weight grade. The previously observed differences in behaviour between the two low molecular weight systems (Parker et al., 1990a) is repeated for the higher molecular weight grades, where the torque values for the Avicel/PVP system are generally higher than those of the Avicel/HPMC system (except at the highest viscosity solutions where the trend is reversed). It is also interesting to note that for both systems, the different grades of the same material exhibit different behaviour at equivalent viscosity.

For the Avicel/PVP mixes, the surface tension values for the K25 grade are generally lower than those for the K90 grade. The lower surface tension

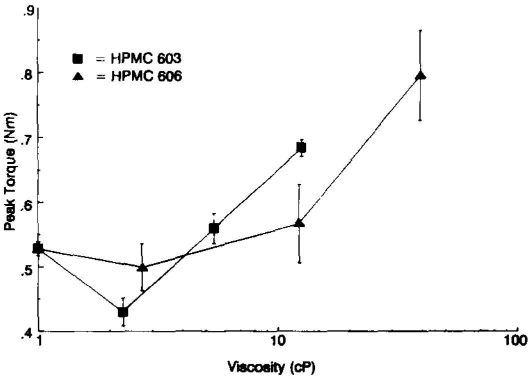

Fig. 4. Relationship between binder viscosity and maximum torque for Avicel/HPMC systems.

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. It is therefore possible that the initial minimum in the K25 torque curve (Fig. 3) below that of both water and the K90 curve may be due to the difference in the surface tensions of the binder solutions.

The results for the K90 solutions also show that the maximum torque occurs with lower binder volumes when compared to that of the K25 solutions. This trend is also consistent with the hypothesis put forward by Ritala et al. (1986, 1988), that the higher surface tension of the K90 solutions reduces the intragranule porosity and therefore increases the liquid saturation. The liquid requirement is consequently reduced, resulting in the peak torque occurring at lower binder concentrations.

For the Avicel/HPMC mixes (Fig. 4 and Table 2) the presence of the polymer considerably reduces the surface tensions of the aqueous solutions. This may affect both the wetting of the powder and the distribution of the binder over the excipient, and may in turn explain the drop in the peak torque values below that of water. Whilst the surface tension values for the two grades are very similar, an initial minimum is still observed in Fig. 4 for the 603 grade curve which is not present in the curve for the 606 grade. Thus surface tension cannot be assumed to be wholly responsible for the behaviour of the HPMC grades at low viscosity.

Additionally for both systems, the peak torque increases as the concentration of the lower molecular weight material increases. This takes place to such an extent that the torque developed at any given viscosity is greater for the lower grade material than for the higher molecular weight grade, even though constant relationships exist between the surface tensions of the different molecular weight grades with increasing concentration. Thus it would appear that either the influence of surface tension effects in producing torque differences is small, or that a 'functional balance' with the solution viscosity takes place, i.e. as the solution viscosity increases, the influence it has on the torque values dominates over the surface tension effects at low viscosity.

Increasing the concentration and hence the viscosity of the higher molecular weight grade polymers results in an increase in the maximum torque developed. This supports the hypothesis that increasing binder viscosity results in an increase in the shearing force required to drive the mixer blades through the wet mass, and hence an increase in the developed torque (Parker et al., 1990a). Since this viscosity induced behaviour does not explain why at equivalent viscosities the different grades of the same material produce different torque values, it is proposed that a more complex balance of several interactions is occurring within the granulation system.

Binder / excipient adsorption

An analysis of possible adsorption phenomena between Avicel PH 101 and the low molecular weight grades of PVP and HPMC using GPC (Parker et al., 1990a), gave results which indicated the adsorption of HPMC molecules onto the cellulose substrate.

It has been found (Kellaway and Najib, 1980; Cohen-Stuart et al., 1982) that polymer adsorption increases with increasing molecular weight, although the increase in adsorption is not proportional to the molecular weight increase, and is dependent on the characteristics of the polymer.

Regarding the effects of polydispersity on adsorption, experimental evidence shows that high molecular weight macromolecules adsorb preferentially to low molecular weight molecules (Felter and Ray, 1970; Vander Linden and Leemput, 1978). Stromberg (1967) suggested that in a mixture of molecular weights, low molecular weight material is adsorbed first, but is subsequently replaced by the high molecular weight material which is actually preferentially adsorbed.

Table 3 presents the GPC analysis data for the high molecular weight polymers, before and after equilibration with Avicel PH 101.

The PVP K90 samples tended to elute at the void volume of the column, and consequently the results may be of limited value. It can be seen however, that there is a reduction in the weight average molecular weight (M_w) values for all the

TABLE 3

GPC results for polymer samples

Sample	Weight average molecular wt. (M_w) ($\times 10^3$)	Number average molecular wt. (M_n) ($\times 10^3$)	Peak mol. wt
PVP			
1% K90 (control)	2250	174	809.8
0.3% K90/Avicel	1890	166	959.0
1% K90/Avicel	2020	206	589.3
2.5% K90/Avicel	1930	136	589.3
HPMC			
1% 606 (control)	93	11.0	51.6
1% 606/Avicel	94	11.0	56.1
3% 606/Avicel	88	14.0	43.4

equilibrated samples, accompanied, in two out of three cases, by a reduction in the peak molecular weight values. This perhaps gives an indication that some adsorption is taking place, the drop in the peak molecular weight value suggesting that this may be of the high molecular weight component.

Examination of the HPMC 606 results in Table 3, also indicates that polymer adsorption is taking place at the excipient/binder interface. There is a reduction in the average molecular weight (M_w) and peak molecular weight for the equilibrated samples at the 3% level when compared with the control.

In general these results demonstrate that adsorption can occur within the high molecular weight systems in a similar manner to that observed earlier for the low molecular weight systems (Parker et al., 1990a).

Binder/excipient interactions and observed rheological behaviour

It has been proposed (Parker et al., 1990a) that any differences in rheological behaviour between the systems examined using the mixer torque rheometer are mediated through an effect on the ‘intra-granular viscosity’. It is now possible to link the interaction and adsorption phenomena, together with the surface tension and viscosity parameters, in order to explain the shapes of the derived curves in Figs 3 and 4. At low concentration, and hence viscosity, the surface tension differences between the PVP K25 and K90 solutions causes a reduction in the observed peak torque values for the K25 solutions below that of the K90 samples. As the concentration, and hence viscosity, increases, the effect of reduced surface tension becomes less significant and so the peak torque values for the K25 samples increase. At this point the adsorption of the high molecular weight K90 molecules causes a greater reduction in the intra-granular viscosity than that caused by any adsorption of the low molecular weight K25 molecules. As a result lower peak torque values for the higher molecular weight polymer are obtained.

The peak torque results for the HPMC grades presented in Fig. 4 show a similar pattern of behaviour to that seen for the PVP results. However, in this case the curves for both grades of polymer initially exhibit a minimum below the peak torque value obtained with water as the binder. It is suggested that this is due to the reduced surface tension of both grades of HPMC compared to that of water, causing an effect on the granule strength in a manner similar to that suggested by Ritala et al. (1986, 1988). It can also be seen that the minimum in the curve for the low molecular weight material is again below that of the higher molecular weight grade. Considering the effects on intra-granular viscosity, preferential adsorption of high molecular weight molecules would result in the peak torque against viscosity curve for the 606 grade dropping below that of the 603 grade in a similar manner to that proposed for the PVP system. However, due to the large degree of overlap in the molecular weight distributions of these two polymer grades (Rowe, 1976), this effect may not be apparent until higher binder concentrations are reached, where the high molecular weight adsorption is greatest. The observed differences in solution viscosity of the two HPMC grades are due to the presence of the high molecular weight component in the 606 material. At low concentration, the adsorption of the high molecular weight component of the 606 grade may well reduce the intra-granular viscosity. However, adsorption of the high molecular weight components of the 603 grade may still result in a lower intra-granular viscosity for this material over that of the

606 grade. As the concentration increases, the effects of adsorption of the increased numbers of high molecular weight molecules present in the 606 material, which are responsible for the observed solution viscosity differences, may result in a greater lowering of the intra-granular viscosity than caused by the adsorption of the 603 molecules.

Based on surface free energy data (Parker et al., 1990a) it was proposed that for the two polymers studied, HPMC has a greater interaction potential with microcrystalline cellulose than PVP. Therefore the peak torque values for HPMC should generally be lower than those for PVP. The polymer adsorption data supports this hypothesis, in that it gives a clear indication that adsorption of HPMC molecules can occur. From the peak torque data it was observed that the values for the HPMC grades are generally lower than those for the PVP grades, where the trend is reversed. A possible explanation for the reversal in the trend for the highest viscosity solutions may involve consideration of the reduced spreading coefficients for the two systems (Parker et al., 1990a). At high binder viscosity even distribution of the binder throughout the mass becomes more difficult, and this may influence torque development. The theoretical spreading coefficient data indicate that HPMC has a greater capacity for spreading over the surface of microcrystalline cellulose than does PVP. This would result in a better distribution of the HPMC throughout the damp mass. A greater shearing force will then be required to drive the mixer blades through the wet mass containing HPMC than through the mass containing the less well distributed PVP.

References

Cohen-Stuart, M.A., Fleer, G.J. and Bijsterbosch, B.H., The adsorption of poly(vinyl pyrrolidone) onto silica. I. Amount adsorbed. *J. Coll. Interface. Sci.*, 90 (1982) 310–320.

Felter, R.E. and Ray, L.N., Polymer adsorption studies at the solid-liquid interface using gel permeation chromatography I. molecular weight distribution along the adsorption isotherm. *J. Coll. Interface. Sci.*, 32 (1970) 349–360.

Kellaway, I.W. and Najib, N.M., The adsorption of hydrophilic polymers at the polystyrene-water Interface. *Int. J. Pharm.*, 6 (1980) 285–294.

Opakunle, W.O. and Spring, M.S., The granulation of binary mixtures: The effects of the composition of the granulating solution and the initial particle size of one component on granule properties. *J. Pharm. Pharmacol.*, 28 (1976) 806–809.

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 (1990a) 207–216.

Parker, M.D., Rowe, R.C. and Upjohn, N.G., Mixer torque rheometry: A technique for characterising wet powder masses. *Pharm. Tech. Int.*, 2 (1990b) 52–64.

Ritala, M., Holm, P., Schaefer, T. and Kristensen, H.G., A comparison between binders in the wet phase of granulation in a high shear mixer. *Drug Dev. Ind. Pharm.*, 12 (1986) 1685–1700.

Ritala, M., Holm, P., Schaefer, T. and Kristensen, H.G., Influence of liquid bonding strength on power consumption during granulation in a high shear mixer. *Drug Dev. Ind. Pharm.*, 14 (1988) 1041–1060.

Rowe, R.C., The molecular weight and molecular weight distribution of hydroxypropyl methylcellulose used in the film coating of tablets. *J. Pharm. Pharmacol.* 32 (1976) 116–119.

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.

Rubinstein, M.H., Viscosity, vapour pressure and electron-microscope studies of aqueous solutions of polyvinylpyrrolidone. *J. Pharm. Pharmacol.*, 27 (1975) 776–777.

Stromberg, R.R., Adsorption of polymers. In Patrick, R.L. (Ed.), Treatise on Adhesion and Adhesives, Dekker, New York, 1967, pp. 92–115.

Vander Linden, C. and Van Leemput, R., Adsorption studies of polystyrene on silica. I. Monodisperse adsorbate. *J. Coll. Interface. Sci.*, 67 (1978) 48–62.

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