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Study of effect of excipient source variation on rheological behavior of diltiazem HCl-HPMC wet masses using a mixer torque rheometer

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Abstract

In the wet massing of powders and powder blends, the rheological behavior of the wet powder masses not only plays a critical role in the unit process but also influences the attributes of the product. The physical properties of the powder excipients, such as particle size and size distribution, shape, surface area, bulk and tapped density and surface morphology, are a major source of variability in the rheological behavior of wet powder masses and the quality attributes of the final product. The objective of the present investigations was to study the rheological behavior of wet masses containing hydroxypropyl methylcellulose (HPMC) obtained from two sources (Methocel® from Dow and Pharmacoat® from Shin-Etsu) using a mixer torque rheometer. In order to simulate a real formulation, diltiazem HCl (DTZ) (40% loading) was used as part of the substrate powder mass. Hydroxypropyl cellulose (HPC) was used as the binder. Since HPMC is water-soluble, isopropyl alcohol (IPA) was used as the wet massing liquid. The rheological behavior of the wet powder masses was studied as a function of mixing time and amount of wet massing liquid (IPA). The rheological profiles obtained for DTZ-Methocel and DTZ-Pharmacoat exhibited same magnitude for mean torque, however, for DTZ-Pharmacoat the peak was more extended than that for DTZ-Methocel. The extended peak for DTZ-Pharmacoat indicated that the wet mass will stay suitable during the process for larger quantities of the wet massing liquid before turning into paste and becoming unsuitable for the process as compared with the DTZ-Methocel system. The mixing kinetics of the two powder systems appeared to be quite different. These differences in the rheological behavior of the wet masses may be attributed to the difference in the particulate and surface properties of the two HPMCs. Some of the properties of the two HPMCs, such as particle size and size distribution, surface area, surface morphology and DSC thermograms, explain the difference observed in their rheological behavior. The difference in the rheological profiles of the two DTZ-HPMC systems indicated superiority of Pharmacoat over Methocel considering their wet massing behavior.

Keywords: Mixer torque rheometer; Excipient source variation; Diltiazem HCl; Hydroxypropyl methylcellulose; Methocel; Pharmacoat; Hydroxypropyl cellulose; Substrate–binder interaction

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1. Introduction

The majority of solid dosage forms are produced by formulation of powders and powder blends, the processing of which often involves wet massing. The wet massing process and the attributes of the final product are largely governed by the physico-chemical properties of the powder actives and excipients and the rheological behavior of the wet powder masses.

Since physico-chemical properties of the powder excipients play a critical role in the formulation, processing, in vitro and in vivo performance of the finished dosage forms (Doelker et al., 1987; Whiteman and Yarwood, 1988; Parker and Rowe, 1991; Landin et al., 1992, 1993a,b,c; Newton et al., 1993), their characterization is vital to obtaining the product with desired and reproducible attributes. The physico-chemical properties may show inter-vendor, and even inter-lot, variability. Sometimes physical characterization of powder excipients indicates that the materials are identical, however, their behavior during processing and in the finished product may vary. This is due to the fact that the process and the product are sensitive to the physico-chemical and morphological variation of the excipient that can not be detected by routine physical characterization. Therefore, spectral and thermal analyses become necessary to support the inferences drawn on the basis of physical characterization.

The rheological behavior of wet powder masses is known to be influenced by physico-chemical and mechanical properties of the substrate being wet massed and excipient variability, therefore, rheological characterization of the wet masses has become increasingly necessary for excipient evaluation. In recent years, mixer torque rheometer has gained popularity in characterizing the behavior of powder materials used for wet granulation and other specialized applications, such as pelletization by extrusion/spheronization. Several studies investigating the effect of excipient source variation (Rowe and Sadeghnejad, 1987; Parker et al., 1992), substrate–binder interaction (Hancock et al., 1992, 1993a,b, 1994; Parker et al., 1990b, 1991, 1992), mixer geometry (Hancock et al., 1991), mixer blade orientation (Rowe, 1996), mixer shaft speed and sample weight (Landin et al., 1995) and formulation scale-up (Parker et al., 1990a) have been reported. In most of these studies, microcrystalline cellulose was used as the model excipient because of its widespread use in the solid dosage formulations. In general, water was used as the wet massing liquid alone or in combination with binders in all the reported studies.

There are drugs and drug/excipient blends that are more suitably wet-massed using a non-aqueous liquid. In an earlier report, a study of the wet massing behavior of powder blends containing hydroxypropyl methylcellulose and hydroxyethyl cellulose with isopropyl alcohol using a mixer torque rheometer was presented (Chatlapalli and Rohera, 1998b). In the reported study, microcrystalline cellulose was used as a reference material for comparison purposes. The results of the study indicated that the rheological profiles as a function of mixing time as well as wet massing liquid level for microcrystalline cellulose and hydroxyethyl cellulose were similar, however, the profiles for hydroxypropyl methylcellulose were different.

The objectives of the present study were to characterize hydroxypropyl methylcellulose obtained from two widely used sources, namely Methocel and Pharmacoat, for their physico-chemical properties, to investigate their wet massing behavior and to determine the effect of their physico-chemical properties on their rheological behavior. In order to simulate a real formulation, diltiazem HCl was included as a model drug as part of the powder blends so that the information generated can be extrapolated to the pharmaceutical processes, such as wet granulation and extrusion/spheronization.

2. Materials and methods

2.1. Materials

Hydroxypropyl methylcellulose (HPMC) was obtained from two widely used sources, namely Methocel® E6P from Dow Chemical Co., Midland, MI and Pharmacoat® 606 from Shin-Etsu

Chemical Co., Tokyo, Japan. Diltiazem HCl (DTZ) (Plantex Corp., Engelwood Cliffs, NJ) was used as a model drug (40% loading) in all powder blends with the two hydroxypropyl methylcelluloses (HPMCs). Hydroxypropyl cellulose (HPC) (Klucel® EXF, Aqualon Company, Wilmington, DE) was used as a binder and isopropyl alcohol, USP (IPA) (Union Carbide Co., Danbury, CT) was used as the wet massing liquid.

2.2. Material characterization

The drug and cellulosic excipients were characterized for their particle size and size distribution, surface area, and bulk and tapped density. The surface morphology of the two HPMCs was examined by scanning electron micrographs. Hausner's flowability (Hausner, 1967) and Carr's compressibility (Carr, 1970) indices were derived from the bulk and tapped density data. The details of the characterization of powder materials have been given in an earlier report (Chatlapalli and Rohera, 1998a). Also, since IPA was used as the wet massing liquid for DTZ-HPMC blends, solubility of the two HPMCs in IPA was determined by mechanically shaking excess of HPMC in IPA at room temperature for 48 h or until equilibrium solubility was achieved. The material characterization data are summarized in Table 1.

In addition, infrared and X-ray diffraction patterns of the two HPMCs were determined and also differential scanning calorimetric analysis was performed in order to explain the difference in the rheological behavior of their wet masses and substrate–binder interaction.

The infrared spectra were obtained by KBr pellet method using an IR spectrophotometer (model 1600, Perkin–Elmer, Norwalk, CT). The spectra were recorded over a range of 400–4000 cm^{-1}. The powder X-ray diffraction analysis was carried out using a automated powder diffractometer (Siemens D500, Madison, WI) equipped with a graphic monochromator using Cu^{++} radiation, and X-ray source operating at 50 kV and 40 mA. The thermal analysis was carried out using a differential scanning calorimeter (model SSC 5200, Seiko Instruments Inc., Horsham, PA). The instrument was calibrated with an indium standard. The thermal runs were conducted over a temperature range of 30–250 °C at a heating rate of 10 °C/min under nitrogen gas flowing at the rate of 50 ml/min.

2.3. Wet massing studies using a mixer torque rheometer

The details of mixer torque rheometer, equipment settings and process conditions used for wet massing, rheological parameters obtained, and data acquisition and their analyses have been given in an earlier report (Chatlapalli and Rohera, 1998b).

In the present investigations, the rheological behavior of the wet powder masses was characterized by variable mixing time and incremental (multiple) liquid addition techniques. In both the

Table 1
Physical properties of Diltiazem HCl, Methocel and Pharmacoat

	Diltiazem HCl	Methocel	Pharmacoat
Solubility in IPA (mg/ml)		0.313 ± 0.021	0.668 ± 0.024
Particle size (μm)			
50 percentile	18.68 ± 0.4	64.4 ± 0.30	69.6 ± 0.34
90 percentile	72.50 ± 3.03	158.2 ± 0.64	175.5 ± 4.94
10 percentile	3.44 ± 0.09	24.4 ± 0.79	22.3 ± 0.64
Surface area (m^2/g)	0.528 ± 0.038	0.267 ± 0.001	0.448 ± 0.021
Bulk/tapped density (g/cc)	0.48/0.72	0.44/0.60	0.34/0.51
Hausner's ratio	1.50	1.36	1.50
Carr's compressibility index (%)	33.3	26.7	33.3

$\pm$ values indicate standard deviation ($n \geq 3$).

studies, the quantity and the composition of the powder masses were the same and were as follows: 8 g of DTZ, 11 g of Methocel or Pharmacoat and 1 g of binder (HPC). Thus, the quantity of the substrate was fixed at 20 g, and the only variable was the amount of wet massing liquid. In a part of the study, binder was excluded from the formulation to obtain the rheological profile of the two DTZ-HPMC blends without binder for reference. Since HPMC is a water-soluble cellulose, IPA was used as the wet massing liquid. The binder was added to the powder blend as a solution in IPA.

In the variable mixing time studies, the IPA levels studied were 9.0, 12.7, 16.3 and 23.6 g (i.e. 12.3, 17.4, 22.3 and 32.3 ml) in the 20 g dry powder mass. These IPA levels corresponded to 31.0, 38.8, 44.9 and 54.1% w/w of the wet powder mass. IPA was added with the help of a burette positioned over the access port in the safety cover above the mixing bowl. A steady baseline torque was generated by running the empty mixer and logging-in the data for 15 s. The DTZ-HPMC blend was then transferred to the mixer bowl and dry-mixed for 45 s and the torque data were logged-in for 15 s. The mixer torque rheometer was programmed to have 45-s mixing and 15-s data acquisition sequences (Chatlapalli and Rohera, 1998b). The pre-determined quantity of IPA (with binder dissolved in it) was added evenly over the substrate in a single addition and the mixing/data acquisition program was initiated. The variable mixing time studies were carried out in duplicate. The results varied by less than 10% of the mean values. The rheological parameters plotted represent the mean values.

In the incremental (multiple) liquid addition studies, a steady baseline was obtained for the mixer with the dry DTZ-HPMC blend by logging-in the torque data for 15 s after mixing for 45 s. Nine grams of IPA (with binder dissolved in it) was added in a single addition and mixed for 180 s before logging-in the torque data. Thereafter, the rheometer was programmed to have 45-s mixing and 15-s data acquisition sequences similar to the ones used in the variable mixing time studies. However, each mixing/log-in cycle was followed by addition of 3.66 g (5 ml) of IPA until the powder mass became over-wetted resulting in the torque to approach the baseline. These studies were carried out in triplicate. The rheological data presented are the mean of three determinations.

2.4. Statistical analysis

The rheological parameters of the wet masses of DTZ-Methocel and DTZ-Pharmacoat systems were compared using *repeated measures design* (Neter et al., 1990; Chatlapalli and Rohera, 1998b). In the present studies, the DTZ-HPMC blends are the subjects and the wet massing liquid (IPA) levels form the treatments. The effects of subjects are considered random and the effects of treatments are considered fixed. All the data were analyzed by analysis of variance (ANOVA) ($\alpha = 0.05$) using a SAS statistical package (SAS Institute Inc., Cary, NC).

3. Results

3.1. Material characterization

The characterization revealed some minor differences in the physico-chemical properties of the two HPMCs (Table 1). The median particle size of Methocel was slightly smaller than that of Pharmacoat. Although from the size distribution profiles it appeared that Methocel had higher percentage of particles at the peak, the value of 90 percentile for Methocel and Pharmacoat was 158.2 and 175.5 μm, respectively. The surface area of Pharmacoat was more than one and a half times (≈ 1.66 times) that of Methocel. The correlation coefficient for each determination was 0.999 or better indicating validity of the test method.

Methocel exhibited higher bulk and tapped density as compared with Pharmacoat. In contrast, Pharmacoat yielded higher compressibility and higher flowability indices than those of Methocel indicating higher degree of densification and consolidation but relatively poor flowability as compared with Methocel (Table 1). The bulk and tapped density data of the two HPMCs are in agreement with the reported values (Wade and Weller, 1994).

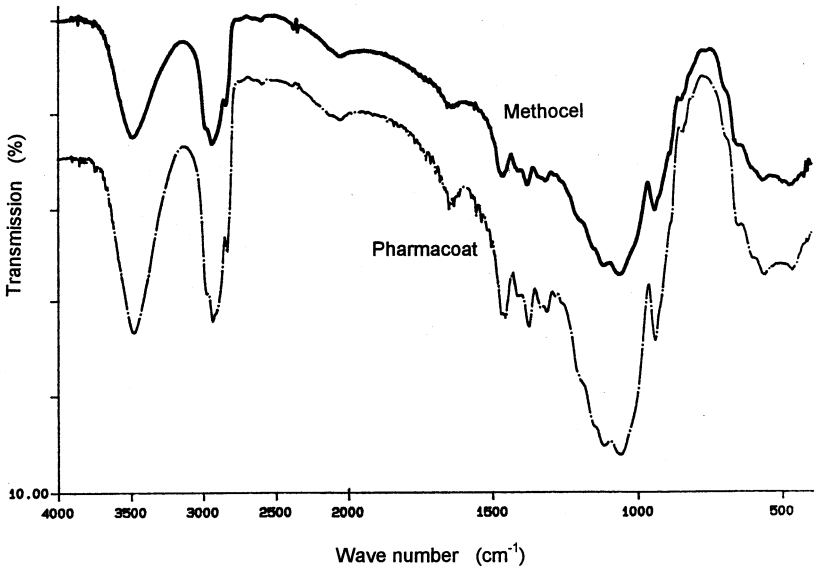

Fig. 1. Infrared spectra of Methocel and Pharmacoat.

Typically IR spectroscopy is employed for the identification of a molecular entity because each functional group in the molecule has a characteristic absorption frequency. The IR spectra for both HPMCs show vibrational groups at the same frequency indicating presence of identical chemical entity (Fig. 1). The X-ray diffraction profiles of the two HPMCs are grossly similar with respect to the relative peak height and the position indicating no significant difference in the degree of their crystallinity, and the major part of both HPMCs being amorphous (Fig. 2).

The DSC thermograms of the two HPMCs are shown in Fig. 3. Usually, the presence of water in a substance manifests itself as a broad endotherm during scanning. For both the HPMCs, an initial endothermic peak is observed at a temperature close to 100 °C. This peak corresponds to the temperature at which water begins to evaporate. The water endotherms for Methocel and Pharmacoat occurred at 80.7 and 94.4 °C, respectively. The endotherm for Methocel at a temperature much lower than that for Pharmacoat indicates relatively weaker molecular attraction or binding between Methocel and water as compared with that between Pharmacoat and water. In other words, Pharmacoat has a higher tendency to hold water and, consequently, needs relatively more energy to make the transition to occur as compared with Methocel. A second endothermic peak is observed at a temperature close to 180 °C which agrees with the observations reported in the literature (Sakellariou et al., 1985). This peak corresponds to the glass transition temperature, T_g, of HPMC. The glass transition temperature for Methocel was 184.7 °C and that for Pharmacoat was 187.1 °C (Fig. 3). This difference may be due to the difference in the structure and orientation of the polymer molecules, residual monomer content and polarity (i.e. relative hydrophilicity) of the polymer molecules.

Scanning electron micrographs of the two HPMCs are shown in Fig. 4. These micrographs show typical morphological characteristics of the cellulose ethers exhibiting fibrous or granular elongated particles. Although there is gross similarity between the mean particle size of Methocel and Pharmacoat, the photomicrographs reveal difference in the surface morphology of the two HPMCs.

3.2. Rheological characterization

3.2.1. Variable mixing time studies

The mean torque obtained for dry powder mixing for both the DTZ-HPMC systems corresponded to the baseline. As the mixing was continued following addition of the predetermined quantity of IPA, the torque started to build up reaching an equilibrium. The torque in each case exhibited a gradual increase with mixing time before plateauing, although the increase was dramatic in the case of DTZ-Pharmacoat as compared with DTZ-Methocel. The rheological profiles of DTZ-Methocel and DTZ-Pharmacoat at four IPA levels, i.e. 31, 38.8, 44.9 and 54.1%, are presented in Figs. 5 and 6, respectively. As evident from the figures, the torque profiles for DTZ-Methocel were significantly different from those for DTZ-Pharmacoat at 38.8, 44.9 and 54.1% IPA levels. At 31% IPA level, the mean torque profile and the equilibrium mean torque for both DTZ-Methocel and DTZ-Pharmacoat were similar and almost of the same magnitude. At 38.8, 44.9 and 54.1% IPA levels, however, the profiles were different. In general, the equilibrium mean torque for DTZ-Methocel was much less than that observed for DTZ-Pharmacoat at 38.8, 44.9 and 54.1% IPA levels. In the case of DTZ-Methocel, the equilibrium mean torque for the four IPA levels was in the range of 0.1–0.25 Nm whereas that for DTZ-Pharmacoat, the torque ranged between 0.1 and 0.6 Nm. For 38.8, 44.9 and 54.1% IPA levels, the mean torque at equilibrium was about 1.5–2.5 times higher for DTZ-Pharmacoat than that for DTZ-Methocel. Overall, both the DTZ-HPMC powder systems exhibited similar trend in the mean torque response as a function of IPA level, the torque at 38.8% IPA level being higher than that at 31, 44.9 and 54.1% IPA levels. At 54.1% IPA level, DTZ-HPMC systems exhibited lower equilibrium torque as compared with that at 38.8 and 44.9% IPA levels indicating overwetting of the powder systems. Analysis of the data by *repeated measures design* indicated that there was statistically significant difference in the mean torque across 38.8 and 44.9% IPA levels for the two DTZ-HPMC systems studied. However, the difference across 31 and 54.1% IPA levels was statistically not significant. The analysis also indicated that the difference in mean torque across different levels of IPA (31, 38.8, 44.9 and 54.1%) was significant ($P = 0.01$) for the DTZ-Pharmacoat system. However, for DTZ-Methocel system, this difference was not significant.

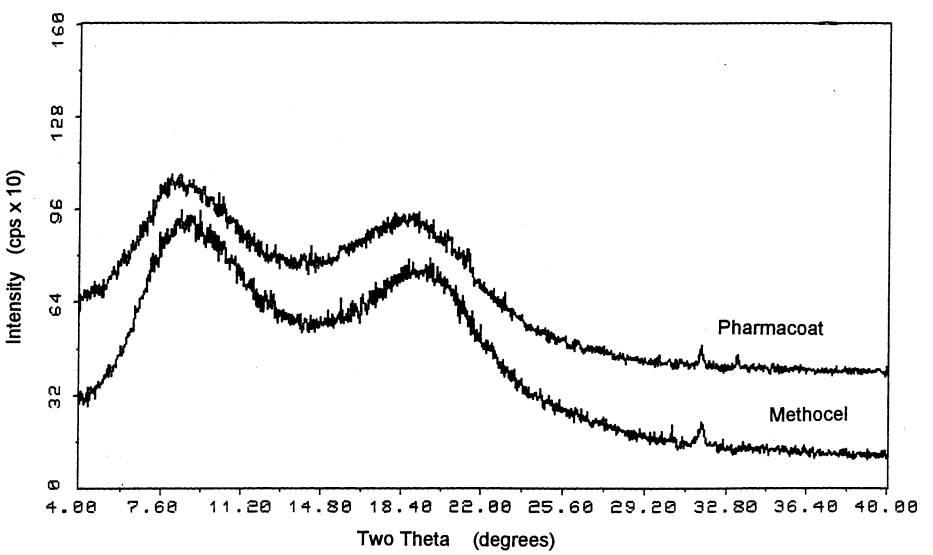

Fig. 2. X-ray diffraction profiles of Methocel and Pharmacoat.

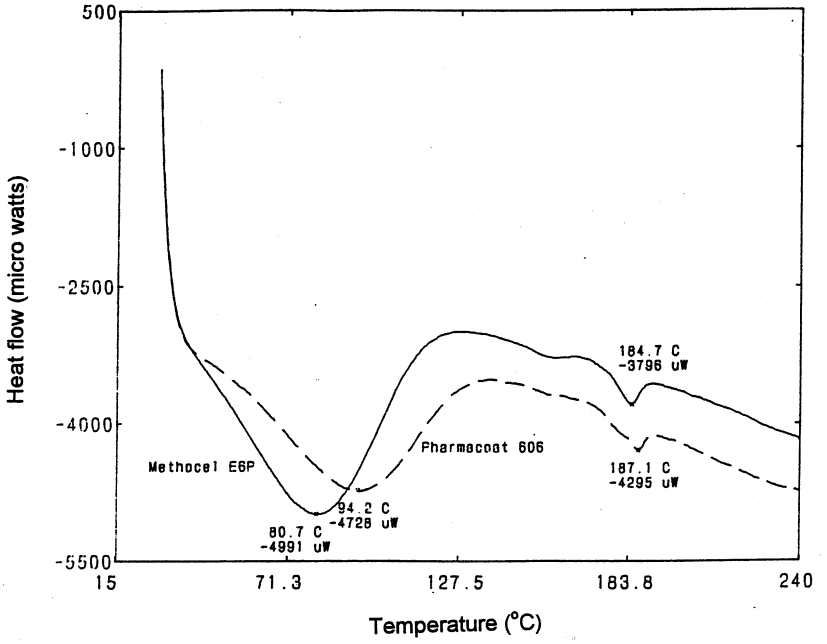

Fig. 3. DSC thermograms of Methocel and Pharmacoat.

3.2.2. Incremental (multiple) liquid addition studies

The rheological profiles of DTZ-Methocel and DTZ-Pharmacoat showing mean torque as a function of incremental (multiple) IPA addition are illustrated in Fig. 7. In both the powder systems, as IPA was added to the powder system, the torque started to build up reaching an equilibrium. In general, the rheological profiles obtained for DTZ-HPMC blends were significantly different from a typical profile of a pharmaceutical material which normally yields a sharp peak for mean torque followed by a drop in the torque as liquid addition continues (Chatlapalli and Rohera, 1998b). Instead of exhibiting a sharp peak, the DTZ-HPMC systems yielded mean torque which increased to a maximum and stayed at that level for a considerable amount of IPA addition and mixing before turning into paste-like consistency and losing the torque. At this stage, the powder mass was over-wetted. It can be observed from Fig. 7 that the two DTZ-HPMC systems had almost the same magnitude of mean torque reaching at approximately the same level of liquid saturation. Analysis of the data by *repeated measures design* indicated that there was statistically no significant difference in the mean torque for the wet masses of both the DTZ-HPMC systems. However, the magnitude of the mean torque was slightly more extended for DTZ-Pharmacoat than that for DTZ-Methocel.

4. Discussion

There are several differences observed in the physico-chemical characteristics of Methocel and Pharmacoat. These differences include particle size and size distribution, surface area, bulk and tapped density, surface morphology and DSC thermograms of the two HPMCs. With DTZ being common component in both powder systems, the differences observed in the particulate properties of the two HPMCs partly explain the difference observed in the wet massing behavior of the two powder systems.

An examination of the particle size and size distribution data indicates that both 90 and 50

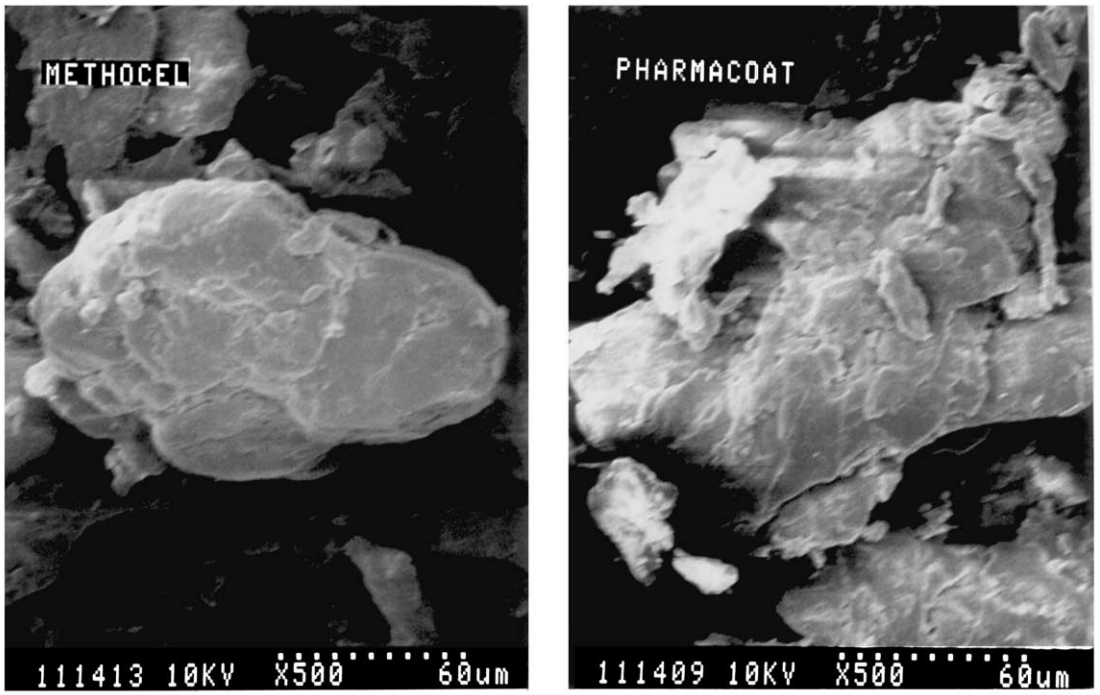

Fig. 4. Scanning electron micrographs of Methocel and Pharmacoat.

percentile (median) sizes for Pharmacoat were slightly higher than those of Methocel. Based on this difference, Pharmacoat should have relatively smaller surface area as compared with Methocel. In contrast, the surface area of Pharmacoat was observed to be approximately 1.66 times larger than that of Methocel (Table 1). This discrepancy in the relationship between particle size and surface area might be due to variability in the shape, surface morphology and porosity of the two HPMCs. The surface area of a powder material is a critical variable in the wet massing process, and the liquid requirement of a powder mass is directly proportional to its surface area. The difference in the surface area may influence the critical liquid requirement of the material during the wet massing process. Since Pharmacoat has larger surface area compared with Methocel, it may result in higher critical liquid requirement of Pharmacoat as compared with Methocel during the wet massing process. As evident from the photomicrographs (Fig. 4), Methocel particles appear to have relatively smoother surface as compared with Pharmacoat which partly contributed to its lower surface area. The slightly extended mean torque peak and the additional liquid requirement for DTZ-Pharmacoat may be attributed to the larger surface area of Pharmacoat as compared with that of Methocel.

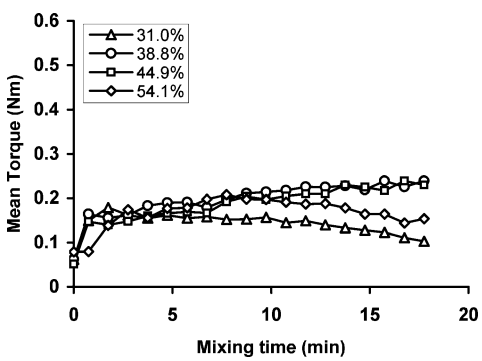

Fig. 5. Plot of mean torque as a function of mixing time for DTZ-Methocel system at 31, 38.8, 44.9 and 54.1% wet massing liquid (IPA) levels.

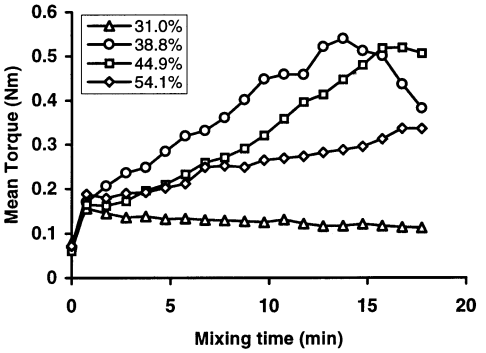

Fig. 6. Plot of mean torque as a function of mixing time for DTZ-Pharmacoat system at 31, 38.8, 44.9 and 54.1% wet massing liquid (IPA) levels.

The difference observed in the compressibility index of the two HPMCs might not have a significant impact on the rheological behavior of the wet powder masses. However, this might be of interest in specialized applications, such as pelletization by extrusion/spheronization, where the higher compressibility would be an added advantage since this will yield denser pellets with lower friability which is desirable for the coating applications. An examination of the bulk and tapped density of the two HPMCs indicates that Methocel has higher bulk and tapped density as compared with Pharmacoat. The values of bulk and tapped density of Methocel are 0.44 and 0.60 g/cc, respectively, and those of Pharmacoat are 0.34 and 0.51 g/cc, respectively. The difference in the densities appears to be significant. The higher bulk and tapped density of Methocel points towards the smoother particle surface morphology as evident from the photomicrographs. As a general rule, smoother the particle surface, higher is the bulk and tapped density. The difference in the densities can also be correlated with the liquid requirement in a wet massing process. The liquid required to reach a specific torque in the case of denser material will be lower because of faster consolidation of the material due to relatively smoother surface morphology of the particles. On the other hand, a low density material will need a larger quantity of wet massing liquid to reach the same specific torque. It has been reported that the liquid requirement in a granulation process is a function of the densification of the powder blend (Kristensen et al., 1984). Therefore, Pharmacoat which has lower bulk and tapped density and much larger surface area as compared with Methocel required larger amount of IPA and exhibited an extended torque over the period of IPA addition and mixing in incremental (multiple) liquid addition studies. Pharmacoat has relatively higher solubility in IPA (0.668 mg/ml) as compared with Methocel (0.313 mg/ml) which may contribute in the binding and result in higher torque. However, the significant difference in their torque values can hardly be attributed to the difference in their solubility.

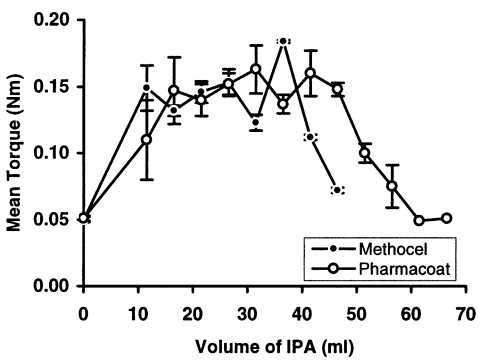

Fig. 7. Plot of mean torque as a function of wet massing liquid (IPA) level for DTZ-Methocel and DTZ-Pharmacoat systems.

There was an increase in the equilibrium torque with an increase in the wet massing liquid (IPA), rising to a maximum, for both DTZ-Methocel and DTZ-Pharmacoat systems (Figs. 5 and 6). This was due to increasing number of liquid bridges forming between the powder particles with increasing liquid content, up to a maximum, resulting in increased torque. At this maximum, the powder masses were pasty. Further IPA addition resulted in slurry and loss of torque. Similar observations have been reported for wet masses of microcrystalline cellulose (Alleva, 1984; Rowe and Sadeghnejad, 1987; Parker et al., 1990b; Hancock et al., 1991, 1993b; Parker and Rowe, 1991), lactose, calcium phosphate, mannitol and starch (Alleva, 1984) and for a series of industrial fertilizer formulations (Kuwabara et al., 1977). The mean torque ranged between 0.1 and 0.25 Nm for DTZ-Methocel and between 0.1 and 0.6 Nm for DTZ-Pharmacoat for the four IPA levels studied.

At 31% IPA level, the mean torque was low and was similar for both the powder systems. This stage corresponds to the pendular stage of the wet agglomeration process where discrete, lens-shaped rings of liquid are formed at the points of contact of particles (Parker et al., 1990a). As more IPA was added, the mean torque increased which resulted from increased liquid bridges representing funicular and capillary stages of granulation process. Further IPA addition resulted in the formation of slurry with a decrease in the torque. An increase in the mean torque for DTZ-Pharmacoat at stages corresponding to funicular and capillary states was much higher than that for DTZ-Methocel possibly because of its larger surface area and, therefore, higher degree of substrate–binder interaction. With DTZ being a common component in both the powder systems, the critical liquid requirement of the two powder masses and the resultant torque were dependent on the physical properties of the two HPMCs and the nature of physical interaction between the substrate and the liquid, e.g. wetting followed by spreading and adhesion (Hancock et al., 1993a). Krycer et al. (1983) have shown that the exact nature of physical interaction during wet massing depends upon physical and chemical properties as well as surface energetics of the wet massing components.

In the case of incremental (multiple) liquid addition studies, the two DTZ-HPMC systems exhibited a peak for the three rheological parameters, i.e. mean torque, torque amplitude and peak torque (Figs. 8 and 9). According to Rowe and Parker (1994), the degree of liquid spreading and wetting, as well as the substrate–binder interaction will determine the relative positions of the peak values of mean torque and torque amplitude. The peak values of the two parameters will be farthest apart for a system exhibiting perfect spreading and wetting, and will be close to each other when there is poor liquid spreading and powder wetting. The relative positions of the mean torque and the torque amplitude in the case of both the DTZ-HPMC systems were initially very close indicating the presence of a heterogeneous system that is associated with poor liquid spreading and substrate wetting. As more of IPA was added and mixing continued, the two rheological parameters separated which indicates better liquid spreading, better substrate wetting, and a higher degree of substrate–binder interaction (Rowe and Parker, 1994). However, both the mean torque and the torque amplitude remained at peak for a slightly longer period of time for DTZ-Pharmacoat system compared with DTZ-Methocel system during liquid addition and mixing. These differences in the amount of liquid and mixing time needed to reach the end-point in the rheological curve may again be attributed to the difference in the physico-chemical properties of the two HPMCs and the nature and magnitude of physical interaction between the wet massing components. In general, the existence of the mean

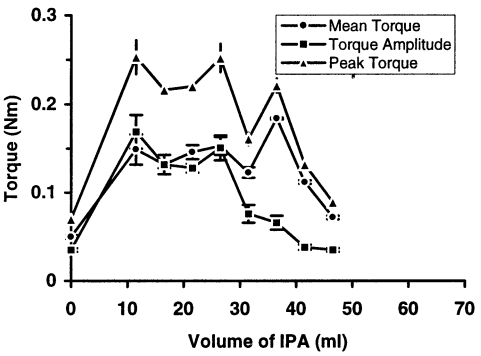

Fig. 8. Plot of mean torque, torque amplitude and peak torque as a function of wet massing liquid (IPA) level for DTZ-Methocel system.

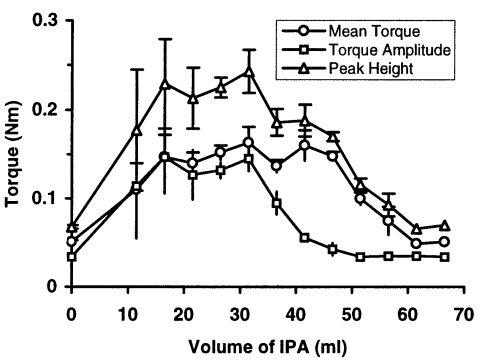

Fig. 9. Plot of mean torque, torque amplitude and peak torque as a function of wet massing liquid (IPA) level for DTZ-Pharmacoat system.

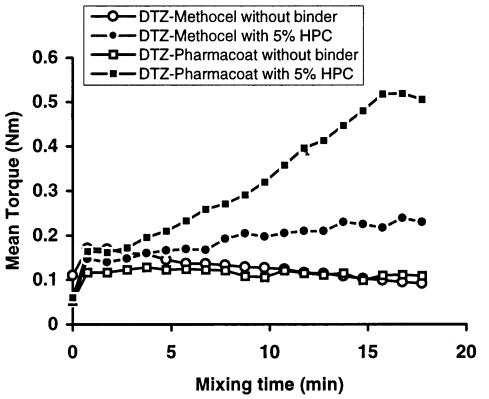

Fig. 10. Plot of mean torque as a function of mixing time for DTZ-Methocel and DTZ-Pharmacoat systems with and without binder.

torque at peak even after the wet mass became homogenous indicates a strong substrate–binder interaction for both the DTZ-HPMC systems. It has been reported earlier that HPMC can retain a relatively larger quantity of wet massing liquid (Chatlapalli and Rohera, 1998b). This behavior is analogous to the water retaining ability of microcrystalline cellulose. Microcrystalline cellulose acts like a molecular sponge for water, physically retaining very high quantities of water within itself and allowing its removal by evaporation to take place easily (Fielden et al., 1988). The flat and extended peak observed for the DTZ-HPMC systems indicates that HPMC has much better IPA retention capability and will be suitable for wet kneading process and specialized applications, such as extrusion/spheronization, for much larger quantities of the wet massing liquid (IPA) before turning into paste and becoming unsuitable for the process.

In the present study, there was no or little increase in the mean torque for both DTZ-Methocel and DTZ-Pharmacoat systems without binder indicating that the substrate-wet massing liquid (IPA) interaction was of the same magnitude for both the systems (Fig. 10). However, when binder (HPC) was used, a significant difference in the development of torque was observed for these systems. This clearly indicates that the torque is a function of substrate-binder interaction. From the torque values, one can infer that the substrate–binder interaction is higher in the case of DTZ-Pharmacoat as compared with that in DTZ-Methocel system. This higher interaction might result from the difference in the physico-chemical properties of the two HPMCs, such as particle size, size distribution and surface area. The larger surface area, which added to the lower bulk and tapped density of Pharmacoat, might be the reason for the difference observed in the rheological behavior of the two HPMCs. At the same time, the influence of surface energetics of the components can not be ignored. The importance of surface energetics in the wet massing of powders has been well documented in the literature (Rowe, 1989a,b, 1990; Zajic and Buckton, 1990; Hancock et al., 1993a).

The substrate–binder interaction and adsorption are common phenomena in many of the pharmaceutical systems. Hancock et al. (1993a), in the wet granulation studies of hydrophilic and hydrophobic glass ballotini using two binding agents, attributed the difference in the substrate-binder interaction to the physico-chemical properties as well as surface energetics of the components. It has also been suggested that cellulose derivatives, such as HPC, are adsorbed on to cellulose fibers (Ishimaru and Lindstorm, 1984). The findings in the present study may partly be explained based on the inference drawn by Parker et al. (1990b) in their studies. Methocel and Pharmacoat might have different adsorption capacities for the adsorbate molecules, i.e. HPC, due to difference in the nature and magnitude of substrate–binder interaction. Methocel particles might be adsorbing more of HPC leading to a decrease in the HPC molecules in the solution, thereby, resulting in a reduction in the intra-granular viscosity. The decrease in the intra-granular viscosity might have finally led to a decrease in the shearing force in the mixer and therefore, lower torque value. On the other hand, HPC might be getting adsorbed to a lesser extent on to the Pharmacoat particles resulting in higher viscosity of the wet mass and, consequently, in higher torque value. This explanation appears to be reasonable based on the findings of Parker et al. (1990b), however, it needs to be confirmed by appropriate analytical techniques.

The rheological behavior of the two powder systems containing HPMCs from two different sources (Methocel and Pharmacoat) is clearly different as seen from the studies in the mixer torque rheometer at various IPA levels. This difference arises mainly from the difference in the physical properties and the affinity of the two HPMCs for water as evidenced by DSC thermograms. From the thermal analysis data, it can be inferred that Pharmacoat has relatively stronger interaction with water as compared with Methocel. It is well established that the water endotherms are a function of hydrophilicity of the polymer. Sakellariou et al. (1985), in studying the glass transition temperatures of cellulose derivatives, reported that the water endotherms for HPMC, HPC, hydroxypropyl methylcellulose phthalate (HPMCP) and cellulose acetate phthalate (CAP) were observed between 85 and 100 °C temperatures whereas that for ethylcellulose, which is less hydrophilic than the other celluloses studied, occurred at some 10 °C lower. The relatively higher hydrophilicity of Pharmacoat may have contributed to the slightly extended mean torque in the mixer torque rheometer studies. In addition, it is also a strong possibility that the surface energetics of the two HPMCs resulting from the method of preparation or pretreatment during the manufacture may also be playing an important role in dictating the rheological behavior of their wet masses.

5. Conclusions

The rheological characterization of wet masses of HPMCs obtained from two different sources using a mixer torque rheometer suggests distinct difference between the two HPMCs. The difference in the rheological behavior and the mixing kinetics of the wet powder masses containing two HPMCs can be attributed mainly to the difference in their particulate and surface properties and partly to the type and degree of physical interaction at the surface between the substrate and the binder molecules. This is similar to the inference of Parker et al. (1992) for microcrystalline cellulose obtained from different sources where the difference in the rheological behavior was attributed primarily to the extensive difference in the particulate properties of the material. These findings suggest that rheological evaluation of the excipients for solid dosage forms must be added to the routine evaluation of alternate sources of excipients. The information obtained might form a valuable tool not only in the traditional wet granulation process but also for specialized pharmaceutical processes, such as pelletization by extrusion/spheronization.

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