

Rheological characterization of diltiazem HCl/cellulose wet masses using a mixer torque rheometer

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Abstract

The objective of the present investigations was to study the rheological behavior of wet powder masses containing two commonly used cellulose ethers, hydroxypropyl methylcellulose (HPMC) and hydroxyethyl cellulose (HEC), 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 both the cellulose ethers used for the study are water soluble, isopropyl alcohol (IPA) was used as the wet massing liquid. For comparison purposes, microcrystalline cellulose (MCC) was used as a reference material. In addition, pelletization studies of these powder formulations were carried out to establish a critical window of the wet massing liquid needed for successful extrusion/spheronization. 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 of wet masses of DTZ–MCC and DTZ–HEC systems were similar and indicated poor liquid spreading, poor substrate wetting and weak substrate/binder interaction, and exhibited a narrow window of tolerance for the wet massing liquid. In contrast, the rheological profiles of DTZ–HPMC system indicated that this powder system has relatively better liquid spreading, better substrate wetting and higher degree of substrate/binder interaction, and higher liquid retention capability. During pelletization, in contrast to the other two powder systems, the DTZ–HPMC system could be extruded/spheronized using a relatively wider range of IPA level in Nica[®] extruder/spheronizer without becoming over-wet, which concurs with the observations made from the mixer torque rheometer studies. The study concludes that with DTZ being the common component in the three powder systems, the critical liquid requirement of the three powder systems is a function of the individual cellulosic component of the system. Of the three cellulosic excipients, HPMC exhibited a relatively higher affinity for IPA and the ability to be extruded/spheronized successfully with a wider range of the liquid. © 1998 Published by Elsevier Science B.V. All rights reserved.

Keywords: Mixer torque rheometer; Diltiazem HCl; Hydroxypropyl methylcellulose; Hydroxyethyl cellulose; Microcrystalline cellulose; Mixing kinetics; Substrate–binder interaction; Pelletization

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1. Introduction

In solid dosage form technology, wet granulation and extrusion/spheronization are important unit processes which require wet massing of powders and powder blends. Since the interaction of several complex parameters dictate these processes, a study of each of these parameters is necessary to understand these processes and to obtain the product with desired attributes. One of the parameters which not only plays a critical role in the unit processes but also influences the attributes of the product is the rheological behavior of the wet powder masses.

During wet massing process, the growing cohesiveness of powder particles with an increase in the liquid causes higher resistance and thereby higher torque on the mixer blade or mixer bowl. Consequently, more energy (e.g. power) is consumed to complete the process. The wet massing process and the energy utilized depend on the physico-chemical and mechanical properties of the substrate being wet massed. Thus an inter-relationship among the physico-chemical and mechanical properties of the substrate, rheological behavior of the wet powder mass, and power consumption or torque exists. There are several methods reported in the literature that have been used to study the rheological behavior of wet powder masses in pharmaceutical wet massing processes. A number of studies have been based on the power consumption of the mixer and torque measurement on the mixer blade or mixer bowl. Capillary rheometry has been used to characterize the rheological behavior of wet powder masses with special reference to the extrusion/spheronization process (Harrison et al., 1984, 1985a,b, 1987). Recently, Delalonde et al. (1996) developed an instrument called compresso-rheometer to characterize the rheology of small quantities of wet powder masses and attempted to establish a correlation between the physical characteristics of raw materials, the rheological behavior of their wet masses and the quality of the finished product.

In the recent years, the mixer torque rheometer has gained popularity in characterizing the behavior of powder materials used for wet granulation

and other specialized applications, such as extrusion/spheronization. It can be used to identify the critical window of the wet massing stage in which granules and pellets having desired characteristics can be produced. Several studies investigating substrate/binder interaction (Parker et al., 1990a, 1991, 1992), excipient source variation (Parker et al., 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., 1990b) have been reported. The rheological behavior of the wet masses can be determined from either mean torque, torque amplitude or peak torque. Parker et al. (1990b) and Rowe and Parker (1994) have summarized the use and applications of mixer torque rheometer in characterizing the rheological behavior and consistency of wet powder masses in two review articles.

In a majority of the reports published on the rheological behavior of wet powder masses, microcrystalline cellulose has been studied using the mixer torque rheometer because of its wide acceptance in the formulation of solid dosage forms using wet granulation and other specialized applications, such as extrusion/spheronization (Rowe and Sadeghnejad, 1987; Parker et al., 1990a, 1991, 1992; Hancock et al., 1991, 1992; Landin et al., 1995). It is the excipient of choice for the preparation of pellets by extrusion/spheronization because of its unique properties and desirable rheological properties when wetted with water.

In solid dosage formulations, an organic liquid may have to be used instead of water for wet massing due to the reasons of stability and ease of wet massing. In some cases, it may be necessary to develop a product formulation where complete water solubility of all the formulation excipients is desired. Therefore, it is necessary to study the wet massing behavior of water-soluble excipients using a non-aqueous wet massing liquid. With this objective in mind, the rheological behavior of wet powder masses containing two most commonly used cellulose ethers, hydroxypropyl methylcellulose and hydroxyethyl cellulose, was investigated. In order to simulate a real formulation, diltiazem HCl was used as part of the substrate system. Microcrystalline cellulose, also in combination

Table 1
Physical properties of the materials studied in the mixer torque rheometer

| | Diltiazem HCl | MCC | HEC | HPMC |
|----------------------------------|---------------|---------------|---------------|---------------|
| Moisture content (%) | 0.30 ± 0.01 | 4.06 ± 0.04 | 4.46 ± 0.06 | 1.64 ± 0.02 |
| Median particle size (μm) | 18.68 ± 0.4 | 64.6 ± 0.5 | 110.1 ± 3.2 | 64.4 ± 0.3 |
| Surface area (m ² /g) | 0.528 ± 0.038 | 1.044 ± 0.023 | 0.071 ± 0.001 | 0.267 ± 0.001 |
| Bulk/tapped density (g/cc) | 0.48/0.72 | 0.35/0.48 | 0.51/0.68 | 0.44/0.60 |
| Carr's compressibility index | 33.3 | 27.1 | 25.0 | 26.7 |

± values indicate S.D. (*n* = 3).

with diltiazem HCl, was used as a reference material for comparison purposes.

In addition, studies were carried out on these powder masses to establish a critical window of the wet massing liquid needed to achieve the consistency of the powder mass suitable for extrusion/spheronization.

2. Materials and methods

2.1. Materials

Two cellulose ethers, hydroxypropyl methylcellulose (HPMC) (Methocel[®] E6P, Dow, Midland, MI) and hydroxyethyl cellulose (HEC) (Natrosol[®] 250 HHX, Aqualon, Wilmington, DE) and microcrystalline cellulose (MCC) (Avicel[®] PH 101, FMC, Philadelphia, PA) were used as excipients for the rheological studies. Diltiazem HCl (DTZ) (Plantex, Engelwood Cliffs, NJ) was used as the model drug in all powder blends with the cellulosic excipients. Hydroxypropyl cellulose (HPC) (Klucel[®] EXF, Aqualon) was used as a binder and isopropyl alcohol, USP (Union Carbide, Danbury, CT) (IPA) was used as the wet massing liquid.

2.2. Physical characterization

The drug and cellulosic excipients were characterized for their moisture content, particle size and size distribution, surface area, and bulk and tapped density. Carr's compressibility index (Carr, 1970) was derived from the bulk and tapped density data. The details of the characterization of the powder materials have been described elsewhere (Chatlapalli and Rohera, 1998). The mate-

rial characterization data are summarized in Table 1.

2.3. Wet massing studies using a mixer torque rheometer

The mixer torque rheometer used in the present study consists of a 135-ml capacity stainless steel bowl equipped with two mixing blades with rotational speed ranging between 20–150 rpm (G.B. Caleva, Sturminster Newton, UK, marketed by GEI Processing, Towaco, NJ). Depending on the bulk density, a sample of 15–30 g of dry powder material is sufficient to cover the mixer blades. The torque is measured directly on the mixer bowl with the help of a torque arm connected from the main body of the mixer to a calibrated load transducer. The following equipment settings were used for all the studies: mixer speed, 52 rpm; sampling rate at which data were captured during logging periods, 100 Hz; smoothing factor, 5; and sensitivity factor, 2. The data acquisition and analyses were carried out by a personal computer using data acquisition system and software package supplied by the equipment manufacturer.

The mixer torque rheometer provides three rheological parameters, i.e. mean torque, torque amplitude and peak torque. The mean torque is the average torque exerted on the mixer bowl by the wet powder mass at any measurement (log-in) period during mixing. The torque amplitude or torque range is the average of the range of oscillations of torque exerted by the wet mass on the mixer bowl during any measurement period during mixing. The peak or maximum torque is the mean of maximum torque observed during any log-in period.

Table 2

Formulation composition used for wet massing in variable mixing time and incremental (multiple) liquid addition studies

| | Variable mixing time studies | Multiple (incremental) liquid addition studies |
|----------------------|---|--|
| Diltiazem HCl (g) | 8 | 8 |
| MCC, HEC or HPMC (g) | 11 | 11 |
| HPC (g) | 1 | 1 |
| IPA | Four levels (i.e. 9.0, 12.7, 16.3 and 23.6 g) | Initially 9 g, with incremental addition of 1.83 g (2.5 ml) following each mixing/log-in cycle |

In the present investigations, the rheological behavior of the wet powder masses was characterized as a function of variable mixing time and incremental (multiple) liquid addition. In both the studies, the quantity and the composition of the powder masses were the same and were as follows: 8 g of DTZ, 11 g of cellulosic excipient (MCC, HEC or HPMC) 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 the wet massing liquid (Table 2). Since HPMC and HEC are water-soluble celluloses, IPA was used as the wet massing liquid. Although MCC is a water-insoluble material and is generally wet massed with water, it also was wet massed using IPA for the reasons of consistency and comparison. HPC was added to the powder blend as a solution in IPA. During the wet massing studies, no significant sticking of the wet powder mass on the mixer bowl surface was observed.

In the variable mixing time studies, the wet massing liquid levels studied were 9.0, 12.7 and 16.3 g (i.e. 12.3, 17.4 and 22.3 ml) in the 20 g dry powder mass (Table 2). These IPA levels correspond to 31.0, 38.8, and 44.9% (w/w) of the wet powder mass. Since the DTZ–HPMC system could retain relatively higher quantity of IPA before becoming over-wet, an additional liquid level, 23.6 g (i.e. 32.3 ml) of IPA, corresponding to 54.1% (w/w) of the wet powder mass was also studied for this powder system. 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 seconds. The drug-cellulose powder blend was then transferred to the mixer bowl and dry-

mixed for 45 seconds and the torque data were logged-in for 15 seconds. The mixer torque rheometer was programmed to have 45-second mixing and 15-second data acquisition sequences (Table 3). The pre-determined quantity of the wet massing liquid (with HPC 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 rheological data plotted represent the mean values (Figs. 1–3).

In the incremental (multiple) liquid addition studies, a steady baseline was obtained for the mixer without and with the dry drug–cellulose blend. It was done by logging-in the torque data for 15 seconds after mixing for 45 seconds. Nine grams of IPA (with HPC dissolved in it) was added in a single addition and mixed for 180 seconds before logging-in the torque data. Thereafter, the rheometer was programmed to have 45-second mixing and 15-second data acquisition sequences similar to the ones used in the variable mixing time studies (Table 3). However, each mixing/log-in cycle was followed by the addition of 1.83 g (2.5 ml) of IPA (Table 2) 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 (Figs. 4–7).

2.4. Statistical analysis

The rheological parameters of the wet masses of DTZ–MCC, DTZ–HEC and DTZ–HPMC systems were compared using repeated measures design (Neter et al., 1990). Repeated measures

Table 3

Wet massing liquid addition, mixing and data acquisition sequences in the mixer torque rheometer studies

| Study | Mixing/log-in for dry powder blend (sec) | Mixing/log-in after first addition of liquid (sec) | Subsequent mixing/log-in sequences (sec) | Amount of liquid added before each mixing/log-in sequence | Total mixing/log-in time (min) |
|--|--|--|--|---|--------------------------------|
| Variable mixing time | 45/15 | 45/15 | 45/15 | None | 18 |
| Incremental (multiple liquid addition) | 45/15 | 180/15 | 45/15 | 2.5 ml | Variable (max. 18 min) |

designs employ the same subject (e.g. powder substrate) for each of the treatments (e.g. wet massing liquid level) under study. A repeated measures analysis may sometimes involve several treatments, or only a single treatment that is evaluated at different points in time, especially when the interest is in evaluating the effect of a treatment, such as wet massing liquid level. The main advantage of these designs is that they offer high precision for comparing treatments because all sources of variability between subjects are excluded from the experimental error. The subjects serve as their own controls because the experimental error term includes just the intra-subject variation.

The model used for the single-factor repeated-measures design, when treatment effects are fixed, is an additive type and is as follows:

$$Y_{ij} = \mu + \rho_i + \tau_j + \epsilon_{(ij)}$$

where μ is a constant, ρ_i are independent $N(0, \sigma_p^2)$, τ_j are constants subject to $\sum \tau_j = 0$, $\epsilon_{(ij)}$ are independent $N(0, \sigma_p^2)$, ρ_i and $\epsilon_{(ij)}$ are independent, $i = 1, \dots, n$ and $j = 1, \dots, r$.

In the present study, the drug–cellulose powder systems 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 rheological data were analyzed by analysis of variance (ANOVA) ($\alpha = 0.05$) using a SAS statistical package (SAS Institute, Cary, NC).

2.5. Pellet preparation

The composition of the pellet formulations was similar to the powder blends studied in the mixer

torque rheometer and was as follows: DTZ (40%), MCC, HEC or HPMC (55%) and HPC (5%). IPA was used for the wet massing of the powder blends. The batch size was 500 g.

The 475 g drug–cellulose blends were dry mixed and wet massed initially with a binder solution consisting of 25 g of HPC dissolved in 225 g (308 ml) of IPA in a planetary mixer (Hobart® N-50, Hobart, North York, Ont., Canada) followed by additional IPA as needed to achieve the consistency of the wet mass suitable for extrusion/spheronization. The additional IPA required for the DTZ–MCC and DTZ–HEC blends was in the range of 150–200 ml (110–146 g) and in the range of 250–500 ml (183–365 g) for the DTZ–HPMC blend. The wet mass was immediately passed through a radial basket type extruder (Nica®, model E-140, Niro-Aeromatic, Columbia, MD) using a 1-mm screen and processed in a spheronizer (Nica®, model S-320, Niro-Aeromatic). The speeds of the feeder and the extruder were 120 and 100 rpm, respectively. The spheronizer speed was 600 rpm and the residence time was 6 min. The pellets were dried in a forced air-circulation oven at 40°C to a moisture content of less than 3%.

3. Results

3.1. Variable mixing time studies

The mean torque obtained for the empty mixer and for dry powder mixing corresponded to the baseline. At 31.0 and 38.8% IPA levels for DTZ–MCC and DTZ–HEC systems and at 38.8, 44.9 and 54.1% for the DTZ–HPMC system, the mean

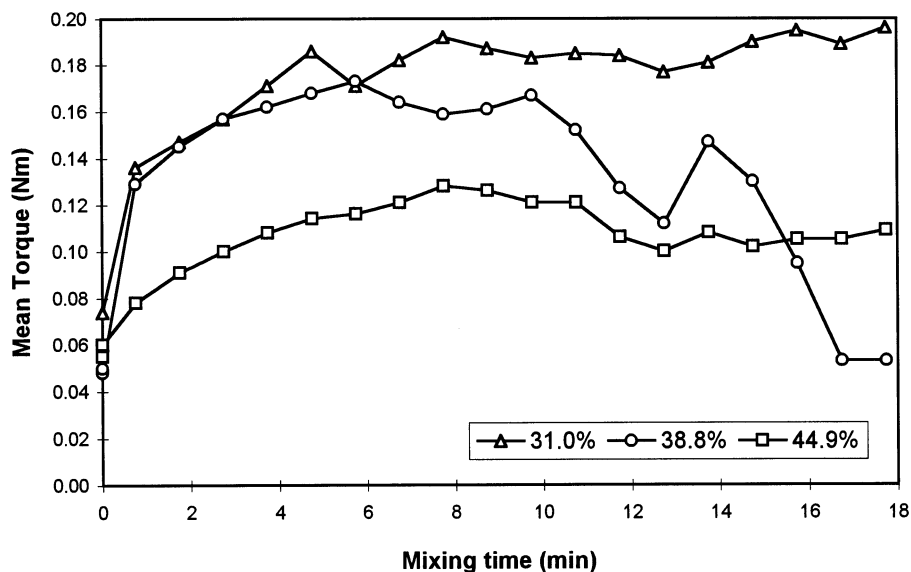


Fig. 1. Plot of mean torque as a function of mixing time for DTZ–MCC system at 31, 38.8 and 44.9% wet massing liquid (IPA) levels.

torque values were much higher indicating strong substrate/binder interaction. However, at higher liquid saturation levels for the three powder blends, the torque was very low indicating a very low torque and/or a weak substrate/binder interaction. The analysis of the data by repeated measures design indicated that there were statistically significant differences in the mean torque across 38.8 and 44.9% IPA levels for all the three powder systems studied. However, the difference across 31% IPA level was statistically not significant.

Fig. 1 shows the mean torque plotted as a function of mixing time at 31, 38.8 and 44.9% IPA levels for the DTZ–MCC system. As evident from the figure, the equilibrium mean torque was attained within 4–8 min of mixing for the three IPA levels studied. At 31% IPA level, the torque increased to a peak in about 5 min of mixing, which stayed at steady state equilibrium on further mixing for up to 18 min. An increase in the IPA level to 38.8% led to an increase in the torque value to a peak similar to that observed in the case of 31% IPA level. However, continued mixing led to precipitation of the excess liquid and over-wetting of the powder mass which eventually resulted in the loss of torque. At 44.9% IPA level,

there was very small increase in the torque as compared to the baseline torque. The peak torque was less than that observed in the case of 31 and 38.8% IPA levels indicating that the powder mass was over-wetted at this liquid level.

The rheological profile of the DTZ–HEC system (Fig. 2) was comparable to the one observed in the case of DTZ–MCC system (Fig. 1). The equilibrium torque was attained within 4–7 min of mixing which decreased with an increase in the liquid level for the three IPA levels studied. At 31% IPA level, the torque rapidly increased to a peak and remained at equilibrium over the entire period of mixing. At 38.8% IPA level, the torque exhibited a gradual increase requiring a longer period of time to reach the equilibrium. The peak torque was, however, less than that observed for 31% IPA level. Eventually, on prolonged mixing, the excess liquid was precipitated and powder mass was over-wetted which resulted in decrease in the torque approaching baseline. At 44.9% IPA level, the powder mass immediately turned into paste-like consistency without developing any appreciable torque. In general, the rheological profile and the magnitude of mean torque for the DTZ–HEC system were comparable to those of

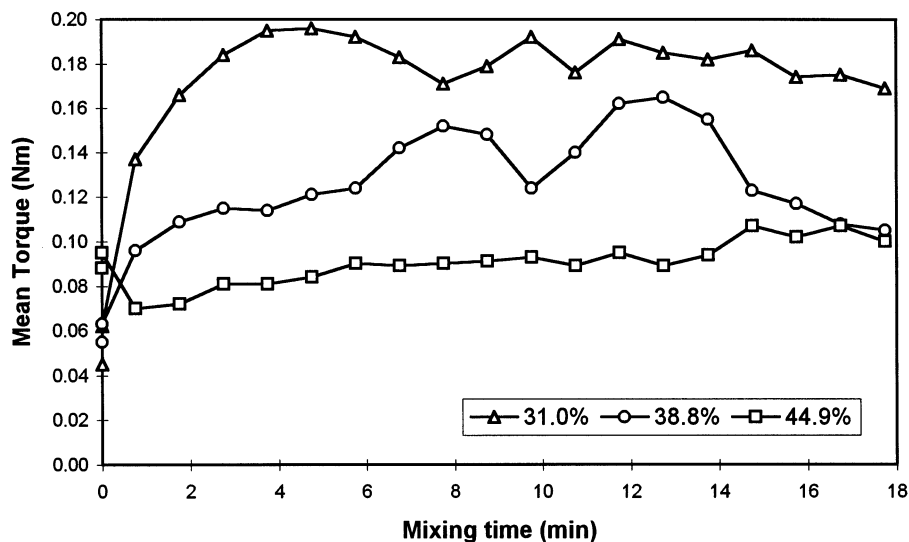


Fig. 2. Plot of mean torque as a function of mixing time for DTZ–HEC system at 31, 38.8 and 44.9% wet massing liquid (IPA) levels.

the DTZ–MCC system at the three IPA levels studied.

In the case of DTZ–HPMC system, the mean torque profile (Fig. 3) appeared to be different from those observed for the DTZ–MCC and DTZ–HEC systems (Figs. 1 and 2). The equilibrium torque was attained within 2–8 min of mixing, taking longer time with higher IPA levels. However, the torque plateaued in a narrow range for all the IPA levels studied for this system, i.e. 31, 38.8, 44.9 and 54.1%. At 31% IPA level, a low peak torque was observed which gradually declined. At 38.8 and 44.9% IPA levels, the torque value initially increased at the same rate as observed for 31% IPA level and eventually attained equilibrium. At 54.1% IPA level, however, the powder mass appeared to be over-wetted. The torque for the over-wet mass increased at a slower rate as compared to 31, 38.8 and 44.9% IPA levels and attained equilibrium. It then showed a gradual decline on continued mixing indicating loss of torque because of precipitation of the excess liquid and over-wetting of the powder mass.

3.2. Incremental (multiple) liquid addition studies

The rheological profiles showing mean torque as a function of incremental IPA addition for the three powder systems are illustrated in Fig. 4. Analysis of the data by repeated-measures design indicated that there were statistically significant differences in the mean torque for the wet masses of the three systems. The amount of IPA at which the peak torque was attained was different for each of the three systems; the DTZ–HEC blend required the minimum, whereas the DTZ–HPMC blend required the maximum quantity of IPA of the three powder systems. The DTZ–MCC and DTZ–HEC systems exhibited a sharp but short peak torque with a sharp decline as the IPA level was increased, whereas the DTZ–HPMC system yielded a flat and extended peak which sustained for much higher IPA level as compared to the other two powder systems (Fig. 4). In general, the torque reached its peak at a lower liquid level for the DTZ–HEC system followed by that for DTZ–MCC and DTZ–HPMC systems.

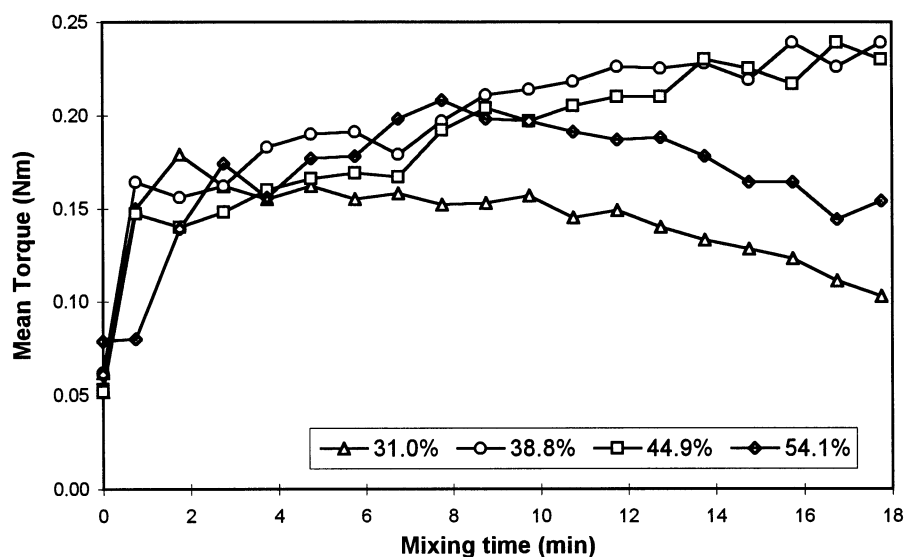


Fig. 3. Plot of mean torque as a function of mixing time for DTZ–HPMC system at 31, 38.8, 44.9 and 54.1% wet massing liquid (IPA) levels.

The three rheological parameters, i.e. mean torque, torque amplitude and peak torque, as a function of incremental IPA addition for DTZ–MCC, DTZ–HEC and DTZ–HPMC systems are shown in Figs. 5–7, respectively. Although the profiles of the three rheological parameters were comparable for the DTZ–MCC and DTZ–HEC systems (Figs. 5 and 6), they were different for the DTZ–HPMC system (Fig. 7).

4. Discussion

The critical liquid requirement of the three powder systems appeared to vary between 31 and 54% (w/w) (Figs. 1–3) and, with diltiazem HCl and binder (HPC) being common in all the three systems, appears to be dependent on the individual cellulosic excipient. The critical liquid requirement of a powder mass is a function of the physical properties of the substrate, such as particle size, size distribution, surface area, bulk and tapped density, and physicochemical properties, such as surface energetics, wetting phenomenon, etc. The physical properties of the drug and the cellulosic excipients under study are listed in Table 1. The bulk and tapped density data for the

three celluloses, MCC, HEC and HPMC, are in good conformity with those reported in the literature (Wade and Weller, 1994). Also the surface area of MCC determined agrees with that reported in the literature (Nakai et al., 1977; Zografis et al., 1984). The derived parameter, i.e. Carr's compressibility index, for the three cellulosic materials is very close (Table 1). The difference in the densification and consolidation behavior of powder materials is known to influence their critical liquid requirement during wet massing process (Parker et al., 1992). However, since the compressibility index of MCC, HEC and HPMC is comparable, it may be concluded that the difference in their critical liquid requirement is not a function of their densification and consolidation behavior.

Although the median particle size of MCC and HPMC was determined to be nearly identical, the surface area of MCC was almost four times larger than that of HPMC (Table 1). The higher surface area of MCC may be attributed to its higher porosity resulting from the manufacturing process (Wallace, 1990). 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.

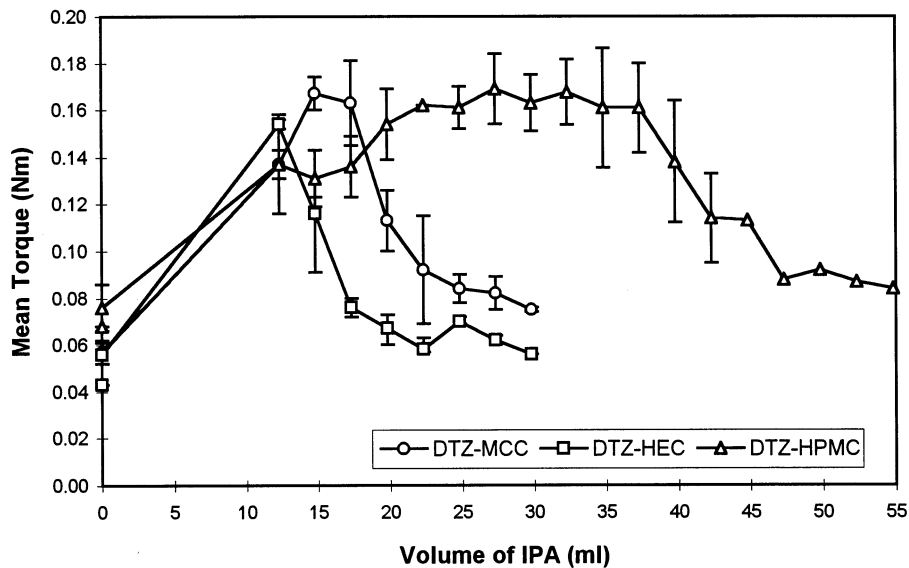


Fig. 4. Plot of mean torque as a function of wet massing liquid (IPA) level for DTZ–MCC, DTZ–HEC and DTZ–HPMC systems.

However, the critical wet massing liquid requirement deduced from the present studies cannot be correlated with the surface area of the powder substrates; MCC which has much larger surface area than HEC and HPMC did not exhibit higher critical liquid requirement. These observations agree with the findings of Hancock et al. (1992). The difference in the rheological behavior of HPMC and MCC can not be explained entirely on the basis of their physical properties. The difference may possibly be attributed to the surface properties of the materials, such as surface energetics, wetting phenomenon, etc. It appears that the cellulosic excipients studied were more sensitive to surface variation than the more commonly accepted physical properties, such as particle size, surface area, bulk and tapped density, etc. (Buckton, 1995). The importance of surface energetics in wet massing has been well documented by Rowe (1989a,b, 1990), and it has been shown that selection of the best binder in a formulation is dependent on the spreading coefficient of the binder liquid over the substrate.

In the case of incremental (multiple) liquid addition studies, all of the powder systems exhibited a peak for the three rheological parameters, i.e. mean torque, torque amplitude and peak torque

(Figs. 5–7). This is in confirmation of the observations of other researchers with MCC (Parker et al., 1990a, 1991, 1992; Hancock et al., 1992). An increase in the mean torque with an increase in the IPA level exhibiting either a sharp or an extended peak followed by a drop in the torque as over-wetting of the powder mass occurred (Fig. 4) is consistent with the stages observed in a typical wet massing process, i.e. pendicular, funicular, capillary and slurry formation.

For the DTZ–MCC and DTZ–HEC systems, both the mean torque and torque amplitude initially showed an increase and then a gradual decrease with an increase in the amount of wet massing liquid (Figs. 5 and 6). The peaks for the two rheological parameters for both the powder blends were very close, and the profiles of these parameters almost overlapped throughout the mixing process. 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

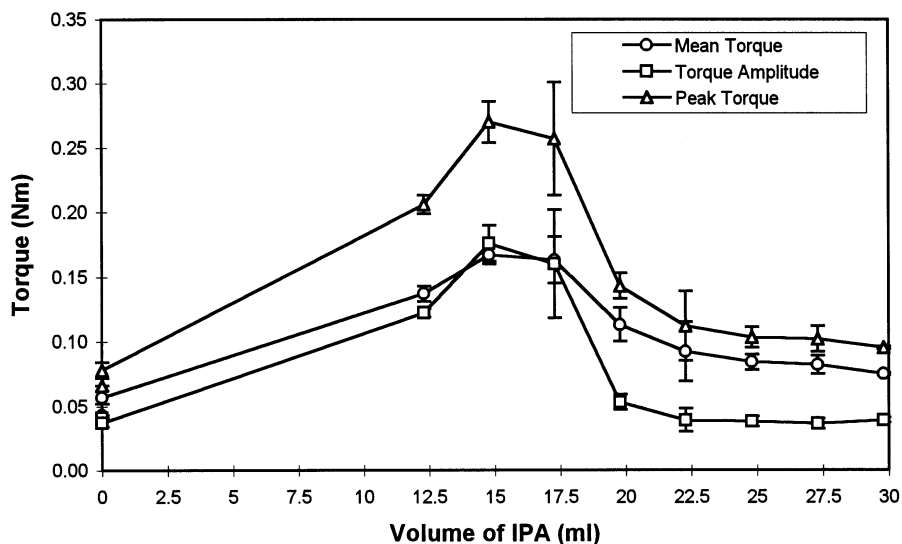


Fig. 5. Plot of mean torque, torque amplitude and peak torque as a function of wet massing liquid (IPA) level for DTZ–MCC system.

rheological profiles of the DTZ–MCC and DTZ–HEC systems, therefore, indicate poor liquid spreading, poor substrate wetting, and weak substrate/binder interaction. The magnitude of torque for the DTZ–MCC system was not as high in the present studies as that reported where water was used as the wet-massing liquid (Parker et al., 1992). This may possibly be due to better interaction of MCC with water which has been discussed thoroughly in the literature (Hollenbeck et al., 1978; Zografis et al., 1984; Sadeghnejad et al., 1985; Khan and Pilpel, 1986; Fielden et al., 1988). Extensive hydrogen bonding, large surface area and mechanical interlocking of the irregular particles have been suggested to be the factors responsible for the excellent binding property of MCC (Sixsmith, 1977). The hydroxyl groups in the cellulose chains form intra- and intermolecular hydrogen bonds and are likely hydrogen bonded with water molecules. However, IPA being less polar than water may not interact with MCC in the same fashion as water, i.e. it may not form hydrogen bonding to the same extent as water, and MCC may not behave like a molecular sponge for IPA as it does for water. Instead IPA, being an organic solvent, may weaken or even disrupt the hydrogen bonds, replace the free and

loosely bound water, and even make the surface of MCC relatively less polar.

In contrast, the relative positions of the mean torque and the torque amplitude in the case of DTZ–HPMC system 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 (Fig. 7) which indicates better liquid spreading, better substrate wetting, and a higher degree of substrate/binder interaction. The mean torque remained at peak for a longer period of time during liquid addition and mixing, and the peak was more extended than the torque amplitude peak (Fig. 7). The existence of the mean torque at peak, even after the wet mass became homogenous, indicates that there was a strong substrate/binder interaction in the case of the DTZ–HPMC system in contrast to the DTZ–MCC and DTZ–HEC systems.

The flat and extended peak observed for the DTZ–HPMC system 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

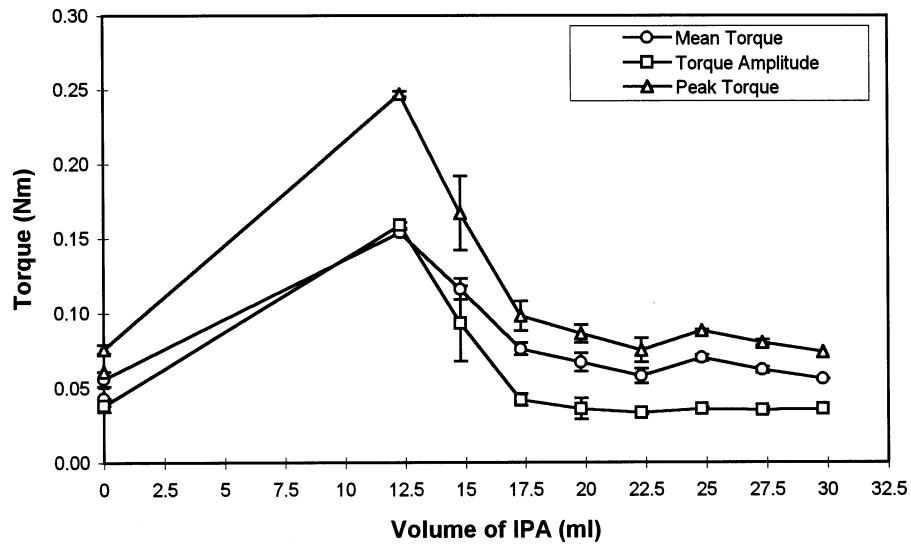


Fig. 6. Plot of mean torque, torque amplitude and peak torque as a function of wet massing liquid (IPA) level for DTZ-HEC system.

(IPA) before turning into paste and becoming unsuitable for the process. However, this was not observed in the case of DTZ-MCC and DTZ-HEC systems.

During extrusion/spheronization studies, the wet mass was able to be extruded and spheronized

over a wider range of IPA levels for the DTZ-HPMC system concurring with the observations made from mixer torque rheometer studies; although increasing amounts of IPA resulted in larger pellets as compared to the pellets made with lower IPA levels. The window of critical

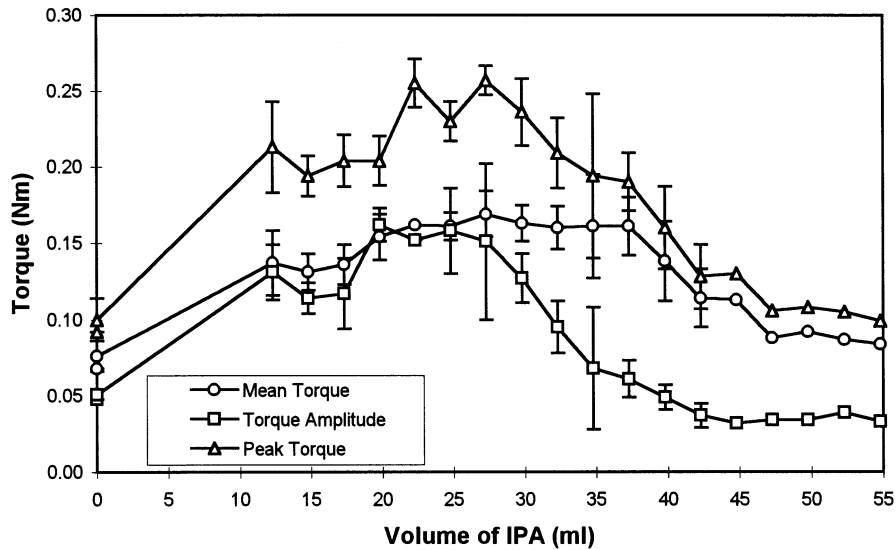


Fig. 7. Plot of mean torque, torque amplitude and peak torque as a function of wet massing liquid (IPA) level for DTZ-HPMC system.

liquid requirement to produce acceptable pellets for the DTZ–MCC and DTZ–HEC systems was much narrower as compared to the DTZ–HPMC system. The typical liquid requirement for the DTZ–MCC and the DTZ–HEC system was in the range of 335–370 g (458–508 ml), whereas for the DTZ–HPMC system, it was in the range of 408–590 g (558–800 ml) for a 500 g batch. The wider liquid range for the DTZ–HPMC system appears to correlate with the flat and extended mean torque peak observed over a larger quantity of IPA in the mixer torque rheometer studies. On the other hand, the narrower liquid range (458–508 ml) corresponds to the sharp and short peak torque for the DTZ–MCC and DTZ–HEC systems. It appears that the window of critical liquid requirement for wet massing processes, i.e. wet granulation and extrusion/spheronization, can be deduced from the observations of the mixer torque rheometer studies. Similar observations have been reported in the literature for MCC using water as the wet massing liquid. Rowe and Sadeghnejad (1987) have correlated the amount of water required by MCC at the maximum torque in their study with the amount of water required for the production of optimum spheroids during spheronization in another study reported by Miyake et al. (1973).

5. Conclusions

Mixer torque rheometer is an excellent tool for the characterization of rheological behavior during wet massing of the powders and powder blends. In the present study, the magnitude of mean torque and the rate to reach the peak were found to be a function of the wet massing liquid level, mixing time, and the type of substrate. The rheological profiles of the DTZ–MCC and DTZ–HEC systems were similar and indicated poor liquid spreading, poor substrate wetting and weak substrate/binder interaction, and exhibited a narrow window of tolerance for the wet massing liquid. In contrast, the rheological profile of the DTZ–HPMC system indicated that this powder system has relatively better liquid spreading, better substrate wetting and a higher degree of substrate/binder interaction, and better liquid retention

capability. During pelletization, the DTZ–MCC and DTZ–HEC systems could be wet massed for extrusion/spheronization purposes using a narrow window of wet massing liquid. A slight excess of IPA rendered over-wet mass unsuitable for the process. In contrast, the DTZ–HPMC system could be extruded/spheronized using a relatively wider range of IPA level which concurs with the observations made from mixer torque rheometer studies; although larger quantities of the wet massing liquid yielded larger pellets. The results led to the conclusion that in the three powder systems, with diltiazem HCl being the common component, their critical liquid requirement was a function of the individual cellulose in the system. Among the three celluloses, HPMC exhibited better affinity for IPA and ability to be successfully extruded/spheronized with relatively wider range of the liquid. These observations make HPMC a better cellulosic excipient as compared to HEC and MCC when IPA, and possibly any other organic liquid, is the wet massing liquid of choice.

In addition, it may also be concluded from the observations that the rheological profile, rather than a single torque reading, gives better insight into the substrate/binder interaction.

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