Assessment of Polymer-Polymer Interactions in Blends of HPMC and Film Forming Polymers by Modulated Temperature Differential Scanning Calorimetry

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Purpose. To assess the miscibility and phase behavior of binary blends of hydroxypropylmethyl cellulose (HPMC) with hydroxypropyl cellulose (HPC), methylcellulose (MC), and polyvinylpyrrolidone (PVP).
Methods. Polymer-polymer miscibility was assessed by measurement of the glass transition temperature (Tg) and the width of the glass transition temperature (W-Tg), using modulated temperature differential scanning calorimetry (MTDSC).
Results. HPMC K4M/PVP and HPMC E5/MC blends were miscible as evidenced by a single, composition dependent, Tg throughout the entire composition range. HPMC/HPC blends were immiscible at all compositions. For the miscible blends, the variation in Tg with blend composition was compared to the values predicted by the Fox and Couchman-Karasz equations. At intermediate blend compositions, HPMC K4M/PVP blends exhibited negative deviations from ideal behavior. The Tg of the HPMC E5/MC blends was found to follow the Fox equation. The W-Tg measurements of the miscible blends gave evidence of phase separation at certain compositions.
Conclusions. MTDSC was shown to be a useful technique in characterizing the interactions between some commonly used pharmaceutical polymers.

KEY WORDS: polymer blends; polymer-polymer interactions; glass transition temperature; modulated differential scanning calorimetry.

INTRODUCTION

Polymeric blends are often used to improve or combine polymer properties without markedly altering the structure and function of the individual polymers. Hydroxypropyl methylcellulose (HPMC) has been added to ethylcellulose (EC) to modulate the release properties of EC films, while polymers such as polyethylene glycol and polyvinyl alcohol have been used as plasticizers to reduce the brittleness of polymeric films (1). In addition to their use in film coating, polymers are widely used as excipients in the formulation of dosage forms. Polymeric blends have been used for the delivery of proteins (2), vaccines (3), and for ocular drug delivery (4). The end-use properties of polymeric film coatings or dosage forms are dependent on the physical and chemical properties of the polymers used as well as the interactions that occur between these polymers.

Several methods can be used to study interactions in polymeric blends including, thermoanalytical techniques, microscopy, light scattering, small-angle neutron scattering, inverse gas chromatography, rheology, and spectroscopic techniques (5). A commonly used approach in studying the behavior of these systems is by measurement of the glass transition temperature (Tg) (1,6). The glass transition is a fundamental property of an amorphous material that determines its end-use properties, such as mechanical properties, thermal properties, and permeability. At the Tg, an amorphous polymer softens, undergoing a transformation from a glassy state to a rubbery state as a result of increased segmental molecular mobility. Depending on the nature of the interactions between the individual components, polymeric blends may be miscible (single phase), partially miscible, or immiscible (phase separated). Miscible blends will exhibit a single Tg at an intermediate value, between the Tgs of the individual components (7). In immiscible blends, the Tgs of the individual components will remain unchanged. Partial miscibility occurs when the solubility limit of one of the polymers in a miscible blend is exceeded, resulting in phase separation, and an additional Tg corresponding to the polymer in excess. The final properties of the blend will be determined by the miscibility and the phase behavior of the blend (7).

The aim of this study was to assess the behavior of blends of HPMC and some commonly used film forming polymers using modulated temperature differential scanning calorimetry (MTDSC). MTDSC differs from conventional differential scanning calorimetry (DSC) in that in MTDSC, a sinusoidal heating profile is overlaid on the conventional linear heating ramp. This more complex heating profile allows the total heat flow signal to be separated into heat capacity dependent and kinetic components, as shown in equation 1,

$$\frac{dQ}{dt} = Cp\,\frac{dT}{dt} + f(t, T) \tag{1}$$

where dQ/dt is the total heat flow, Cp is the heat capacity, dT/dt is the heating rate and $f(t, T)$ represents the heat flow from events which are a function of time and absolute temperature (kinetic events). The $Cp\ dT/dt$ term is also known as the reversing heat flow while the $f(t, T)$ term is also referred to as the non-reversing heat flow (8). Conventional DSC only measures the total heat flow, which is the sum of the reversing and non-reversing components. The ability of MTDSC to separate the total heat flow into heat capacity and kinetic components is a significant advantage over conventional DSC because it permits the separation of overlapping transitions that show different responses to the imposed heating profile (9). Furthermore, the sinusoidal modulation results in a fast instantaneous heating rate, which provides sensitivity while the slow underlying heating rate used provides resolution. The Tg (a heat capacity dependent event) will be observed in the reversing heat flow and will be enhanced as a result of: 1) the separation of overlapping transitions (e.g. enthalpic relaxation) and 2) the fast instantaneous heating rate that results from the sinusoidal modulation. More details of MTDSC have been discussed by Reading *et al.* (9). Coleman and Craig have reviewed the application of this technique to pharmaceutical systems (10).

HPMC, hydroxypropyl cellulose (HPC), methylcellulose (MC), and polyvinylpyrrolidone (PVP) are widely used excipients in pharmaceutical formulations, with applications in film coating and as binders for solid dosage forms. HPMC, HPC, and MC are cellulose ethers that share a common cellulosic

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backbone, but have different substituent groups. These polymers are produced by partial or total etherification of the three hydroxyl groups present on the anhydroglucose repeat unit of the cellulose chain (11). Intra- and intermolecular interactions can occur between unsubstituted hydroxyl groups, ether oxygen groups, and hydroxyls introduced by the substituent groups (1). Given their similar structure, we were interested in determining the behavior of these polymers in multi-component systems. Since pharmaceutical formulations often include different polymeric components, an understanding of the fundamental interactions that occur in these systems provides a basis by which the properties of the formulation can be characterized and predicted. While recent studies have shown the utility of MTDSC in characterizing glass transitions and miscibility in polymeric blends (6,12), the number of systems that have been studied by this technique is limited and it has not yet been used to characterize blends of pharmaceutical polymers. In this paper, MTDSC was used to study the miscibility of binary blends of HPMC and HPC, and HPMC and MC. For comparison, blends of HPMC and a non-cellulosic polymer, PVP, were also studied. The benefits of MTDSC to the study of polymeric blends are also discussed.

MATERIALS

Hydroxypropyl methylcellulose (Methocel K4M and Methocel E5) and methylcellulose (Methocel A4M) were obtained from Dow Chemical Company (Midland, MI). The number average molecular ($\overline{M}$n) weights given by the manufacturer for HPMC K4M, HPMC E5, and MC A4M were, 86 000, 10 000, and 86 000, respectively. Hydroxypropyl cellulose (Klucel EXF), with a weight average molecular weight ($\overline{M}$w) of 80 000 was obtained from Hercules Inc., (Wilmington, DE). Polyvinylpyrrolidone (PVP K-30), with a $\overline{M}$n of 10 000, was obtained from International Specialty Products (Wayne, NJ).

METHODS

Films of the polymeric blends were cast from aqueous solutions. The films were oven-dried at 70°C to a constant weight and stored in a dessicator. Three binary systems were studied: HPMC E5/HPC blends, HPMC E5/MC blends, and HPMC K4M/PVP blends.

Modulated temperature differential scanning calorimetry experiments were performed using a MDSC 2920 (TA Instruments, New Castle, DE). Nitrogen was used as the purge gas at a flow rate of 50 ml/min for the DSC cell and 150 ml/min for the refrigerated cooling system. The calorimeter was calibrated for temperature and cell constant using indium (melting point 156.61°C, enthalpy of fusion 28.71 J/g). Heat capacity calibration was performed using a standard sapphire sample. All experiments were performed using non-hermetic aluminum pans. The MTDSC parameters were a heating rate of 2.5°C/min, an amplitude of ±1°C, and a period of 60 seconds. Prior to the start of the MTDSC run, an equilibration step at 120°C for 10 minutes was included to remove any residual moisture in the samples. The quality of the modulated heat flow signal was used to assess the ability of the sample to follow the heating program. For all experiments, the Tg was determined from the derivative of the reversing heat flow signal. Experiments were performed in duplicate.

RESULTS AND DISCUSSION

MTDSC Considerations

While the Tg of PVP was readily determinable using conventional DSC, the small change in heat capacity at the Tg of HPMC K4M, HPMC E5, and MC presented difficulties in distinguishing the Tg from baseline noise which necessitated the use of MTDSC for accurate measurements, especially in polymeric blends in which there were low weight fractions of one component. Furthermore, the detection of such small transitions by conventional DSC required the use of high heating rates leading to decreased resolution, which became a problem since the differences between the Tgs of the polymers studied were relatively small. MTDSC allowed the determination of these Tgs without sacrificing the desired resolution.

An important requirement for MTDSC experiments is that the entire sample must be capable of following the imposed temperature modulation. Furthermore, the choice of heating rate and period should allow for at least four to six cycles across the width of the thermal transition. The ability of the sample to follow the imposed temperature modulation was assessed by observing the quality of the modulated heat flow signal. In all cases, a smooth sine wave was observed indicating that the sample could follow the heating program. The heating rate and period used were chosen so as to allow for a sufficient number of cycles across the width of the transition. Thin flat, low mass samples were used to minimize thermal gradients within the sample. In addition to reducing the ability of the sample to follow the temperature modulation, thermal gradients can lead to the broadening of thermal transitions.

The Tg can be reported as the onset, midpoint (1/2 × change in heat capacity at the Tg), or the endset (offset) of the glass transition. We used the peak of the derivative of the reversing heat flow signal to determine the Tg. Unlike the usual method of determining the Tg, this method is uninfluenced by the placement of tangent lines and permits an easier determination of the Tg for weak transitions, which are seen as slight endothermic shifts in the baseline. It is often recommended when taking Tg measurements to first heat the sample above its Tg, so as to erase the effects of the sample's thermal history, cool it down to a temperature well below the Tg and then determine the Tg on the second heating. It was noticed though that HPMC K4M, HPMC E5, and PVP films turned slightly darker after heating. However, second scans of the films had similar Tgs (to within a few degrees) to the unheated samples. Nonetheless, given the possibility that changes in the integrity and composition of the sample may have occurred during heating, and since MTDSC permits separation of accompanying enthalpic relaxation events, it was decided to use the first scans for the Tg measurements. Another reason for using the first scans is that it is possible, since miscibility is influenced by temperature, that heating the blends above the Tg could have induced changes in the phase behavior of the components. Therefore, even in the absence of sample decomposition, it could have been possible that the second scans may not have reflected the phase behavior of the original blend. This highlights an important advantage of MTDSC, since measurement of the Tg using conventional DSC may have required heating and cooling the sample to remove any accompanying enthalpic relaxation events.

Individual Polymers

The MTDSC curves for the individual polymers are shown in Fig. 1A, where the reversing heat flow curve is used to illustrate the Tg. At the Tg, an endothermic step change in the reversing heat flow occurs, reflecting the transition from the glassy to the rubbery state. With the exception of HPC, a Tg was detected for all the polymers. The Tgs determined in this study are shown in Table I and compared to some reported Tg values in the literature. The Tgs of HPMC E5 and PVP are consistent with previously reported values (13,14,15). The Tg of MC was a few degrees lower than the value reported by Doelker (11). The Tg determined for HPMC K4M was higher than the literature reported values (11,16). Such discrepancies in Tg values may result from differences in experimental technique, molecular weight, sample heating rate, sample cooling rate, thermal history, enthalpic relaxation, residual solvent, presence of additives, method of reporting the Tg, and sample preparation. HPC showed a reproducible endothermic transition above 180°C, which is believed to be due to either melting of the crystalline phase or a liquid crystal isotropic transition (17). Kararli *et al.*, using dynamic mechanical analysis, were also unable to determine a Tg for HPC (Klucel EF) (18). The complex morphological structure of HPC, perhaps accounts for the difficulties in determining a Tg for this compound and the wide range of Tg values (19,20,21) that have been reported in the literature (Table I).

Table I. Glass Transition Temperatures for Individual Polymers

Polymer	Tg (°C)	Literature values
HPMC K4M	191	184[a], 188[b]
HPMC E5	154	154[c], 155[d]
HPC	—	19 [e], 25[f], 30[g], 124[h]
MC A4M	191	196[i]
PVP K-30	163	162[j]

[a] BY DSC (Ref. 11).
[b] BY DSC (Ref. 16).
[c] BY DSC (Ref. 13).
[d] BY DSC (Ref. 14).
[e] HPC Klucel L ($\overline{M}w \sim 95\ 000$) by DSC and DMA (Ref. 17).
[f] HPC ($\overline{M}w \sim 93\ 000$) by DMA (Ref. 19).
[g] HPC Klucel LF ($\overline{M}w \sim 95\ 000$) by DSC and DMA (Ref. 20).
[h] HPC Klucel L by TBA (Ref. 21).
[i] By DSC (Ref. 11).
[j] By DSC (Ref. 15). Abbreviations: DSC - differential scanning calorimetry, DMA - dynamic mechanical analysis, TBA - torsional braid analysis.

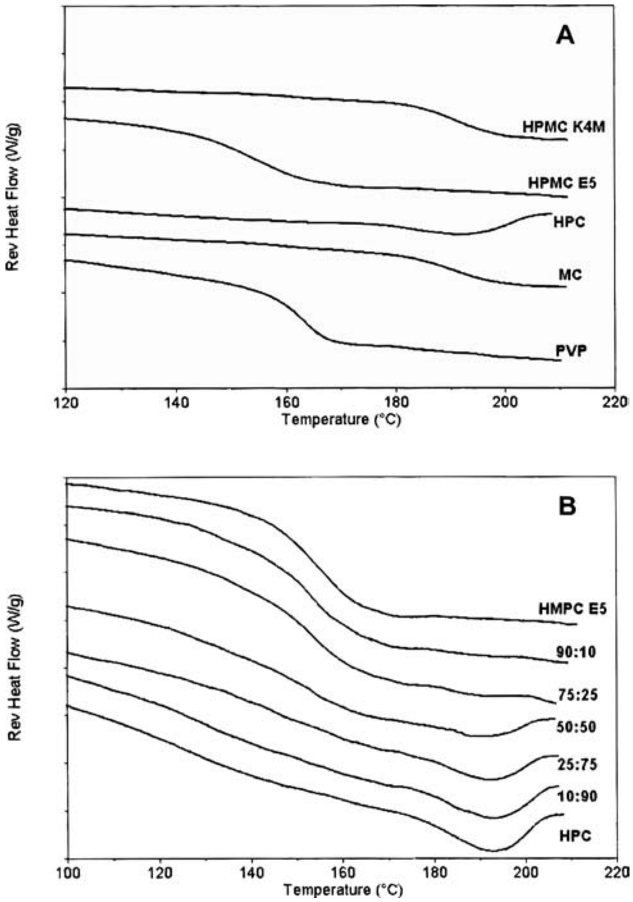

Fig. 1. (A) MTDSC reversing heat flow curves of the individual polymers. (B) MTDSC reversing heat flow curves of HPMC E5/HPC blends.

HPMC/HPC Blends

The MTDSC curves of the HPMC E5/HPC blends are shown in Fig. 1B. Although a Tg was not determined for HPC, the results show that the Tg of HPMC E5 in the HPMC E5/HPC blends is not altered by the addition of HPC up to a 0.25 weight fraction of the latter, suggesting that these blends are immiscible. At a HPC weight fraction of 0.5 the Tg of HPMC E5 is just barely detectable, but although the glass transition event is considerably broader, the Tg is unchanged. At higher HPC weight fractions, a Tg for HPMC E5 was not detected, even when the sample mass was increased to well above the sensitivity limits of the instrument. However, the absence of any changes in the temperature at which the HPC endothermic event occurred in these blends, provides additional evidence in favor of the immiscibility of these polymers. Although HPC has the same basic cellulosic backbone as HPMC, it lacks methoxyl substituent groups and has a considerably higher amount of hydroxypropyl groups. In spite of the similarities in the chemical structure of these two polymers, the results suggest that HPMC E5/HPC blends will exhibit phase separation due to the absence of favorable interactions between the polymers. In phase separated polymer blends, the properties of the interfacial regions are important in determining the characteristics of the blend (5).

HPMC/PVP Blends

MTDSC curves for the HPMC K4M/PVP blends are shown in Fig. 2A. For all blend compositions, one Tg is clearly seen between the Tgs of the HPMC K4M and PVP indicating that these systems are miscible. As the amount of PVP in the blend is increased, the Tg of the blend decreases, indicating that PVP plasticizes HPMC K4M. The Tgs for the HPMC K4M/PVP blends are shown in Table II. Interestingly PVP, which has a very different structure than HPC, is miscible with HPMC. The ability of polymers to form compatible blends requires that favorable intermolecular interactions occur

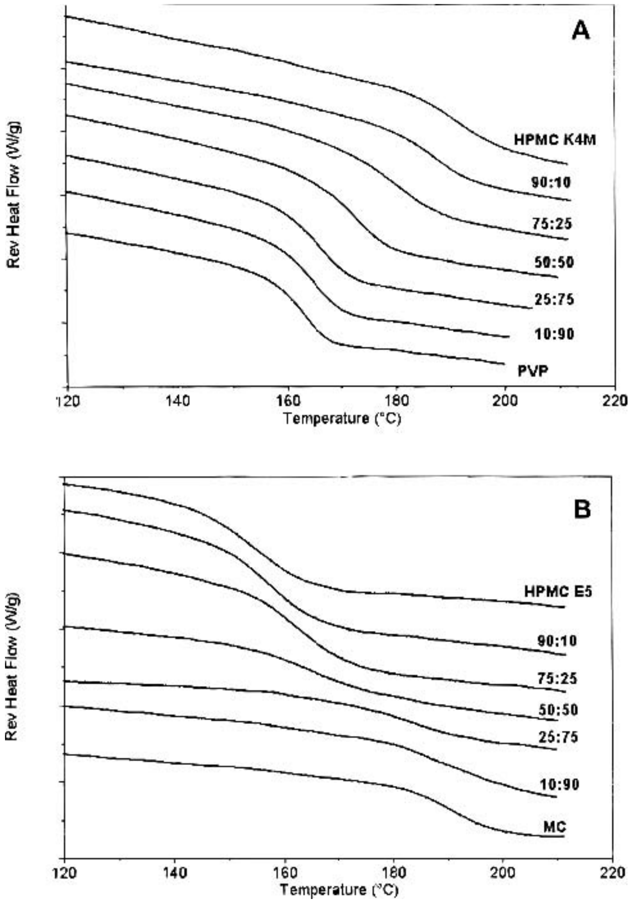

Fig. 2. (A) MTDSC reversing heat flow curves of HPMC K4M/PVP blends. (B) MTDSC reversing heat flow curves of HPMC E5/MC blends.

Table II. Glass Transition Temperatures for HPMC K4M/PVP and HPMC E5/MC Blends

Polymeric blend	Tg(°C)
HPMC K4M/PVP	
90/10	188.0
75/25	181.5
50/50	172.9
25/75	166.6
10/90	165.2
HPMC E5/MC	
90/10	157.7
75/25	161.4
50/50	171.1
25/75	182.8
10/90	185.7

between the different polymer chains. Thermodynamically, a negative free energy of mixing is a necessary condition for polymer-polymer miscibility (7). The free energy of mixing is given by Eq. 2,

$$\Delta G_M = \Delta H_M - T\Delta S_M \tag{2}$$

where ΔG_M is the free energy of mixing, ΔH_M is the enthalpy of mixing, T is the absolute temperature, and ΔS_M is the entropy of mixing. Due to the small entropy of mixing in polymeric blends, the enthalpy of mixing is the primary factor determining whether the components are miscible (7). Since most polymeric blends have a positive (endothermic) enthalpy of mixing, these systems are usually immiscible and exhibit phase separation. A negative (exothermic) enthalpy of mixing is therefore, generally, considered a requirement for two polymers to be miscible and form a single phase system (7). Specific interactions between the constituent polymers, such as hydrogen bonding, which produce a negative enthalpy of mixing are therefore usually necessary for miscibility to occur (1). Taylor and Zografi have reported that hydrogen bond interactions can occur in mixtures of amorphous oligosaccharides and PVP between the sugar hydroxyl groups and the polymer carbonyl group (22). Since HPMC is a partially substituted polysaccharide and given the presence of unsubstituted hydroxyl groups on the cellulose chain as well on the hydroxypropyl substituent groups, it seems reasonable to conclude that this polymer may interact with PVP in a similar manner.

HPMC/MC Blends

MTDSC curves for the HPMC E5/MC blends are shown in Fig. 2B. All blend compositions exhibit a single Tg indicating that these systems are miscible. Increasing the relative amount of MC increases the Tg of the blend, indicting that the addition of MC restricts the molecular mobility of HPMC E5. The Tgs for the HPMC E5/MC blends are shown in Table II. The properties of the substituent groups as well as the degree of substitution are important factors influencing the nature of the molecular interactions in cellulosic polymers (11). MC differs from HPMC E5 in that it lacks hydroxypropyl substituent groups, although it has a similar substitution level of methoxyl groups (30%) to that of HPMC E5 (29%) (23). Non-specific hydrogen bonding between unsubstituted hydroxyl groups would be appear to be the most probable reason for the miscibility of HPMC E5 and MC. In addition to the methoxyl groups, HPMC E5 also has hydroxypropyl substituent groups (8.5%) (23), which account for the different physicochemical properties of this polymer compared to MC. In HPC however, a considerably greater proportion of hydroxyls on the cellulose chain have been substituted by hydroxypropyl groups (24). The greater miscibility of HPMC E5 with MC than HPC suggests that the lower degree of hydroxyl substitution and therefore the higher amount of unsubstituted hydroxyls on the cellulose chain, is an important factor for the ability of these polymers to interact. The high degree of hydroxypropyl substitution in HPC, which leads to significant intramolecular hydrogen bonding (25), may limit its ability to interact with chemically similar molecules such as HPMC. HPMC E5 and MC both have a lower degree of substituent groups, which results in more unsubstituted hydroxyl groups are available for intermolecular interactions. It is believed that most of the primary hydroxyls in HPC have been substituted and the remaining reactive groups are secondary hydroxyls present on the hydroxypropyl substituent groups (26). It is unclear whether the unsubstituted primary hydroxyls on the cellulose chain play a greater role in intermolecular interactions than the secondary hydroxyl groups.

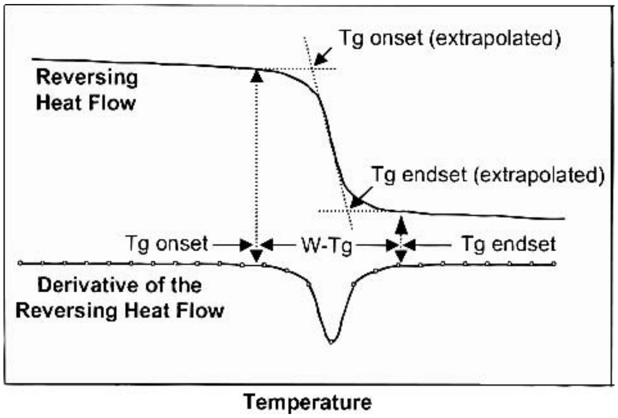

Fig. 3. Illustration of two methods for determining W-Tg.

W-Tg Measurements

The width of W-Tg [i.e., difference between the onset and endset (offset) of the glass transition] can provide useful information on the miscibility and phase behavior of polymeric blends (6,7). Partially miscible and heterogeneous blends, exhibit broader W-Tg values, relative to that of the constituent polymers or homogenous blends (6,7). The onset and endset of the glass transition can be determined, either from the intersection of the extrapolated tangents (Fig. 3) or from the temperatures at the very beginning and the end of the 'step' change, using the derivative of the reversing heat flow. In this study, we determined W-Tg from the derivative of the reversing heat flow, as indicated in Fig. 3. Figs. 4A and 4B, show a plot of W-Tg as a function of blend composition for the HPMC K4M/PVP and HPMC E5/MC blends, respectively. It can be seen that W-Tg increases in most of the blends, relative to that of the pure polymers, although to varying degrees. While most of the HPMC K4M/PVP blends, have a W-Tg that is a few degrees higher than the average W-Tg of the individual polymers, the 75:25 blend shows a considerably higher W-Tg. Similarly, in the HPMC E5/MC system, the 50:50 and 75:25 blends display a notably higher W-Tg than that of the other blend compositions. This may indicate that these blends exhibit partial miscibility as the solubility limit of one of the polymers is exceeded. When this solubility limit is exceeded, the Tg of polymer in excess is seen, but is not resolved from the Tg of the blend because of the proximity the Tgs. Broadening the glass transition event in miscible polymer blends has also been attributed to small scale compositional fluctuations (27), and each of the components in the blend experiencing a different Tg from the blend Tg as a result of being preferentially surrounded by its own species (28).

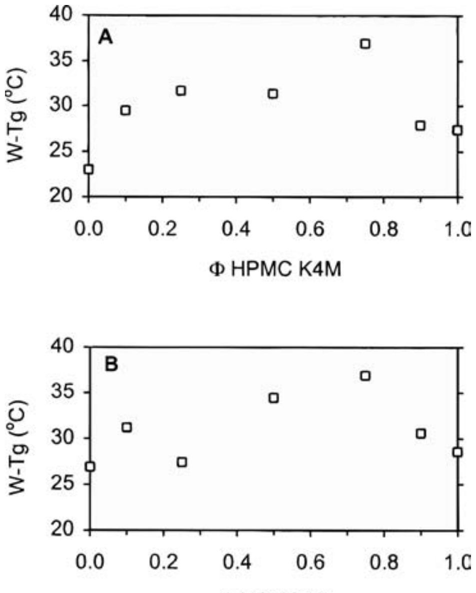

Fig. 4. (A) W-Tg as a function of composition for HPMC K4M/PVP blends. Φ - weight fraction. (B) W-Tg as a function of composition for HPMC E5/MC blends. Φ - weight fraction.

Tg-Composition Relationships

Several equations have been developed that relate the dependence of the Tg of a miscible polymeric blend to its composition. The simplest of these is the Fox equation (29),

$$\frac{1}{Tg} = \frac{W_1}{Tg_1} + \frac{W_2}{Tg_2} \tag{3}$$

where Tg is the glass transition temperature of the blend, Tg_1 and Tg_2 are the glass transition temperatures of the individual polymers, and W_1 and W_2 are the weight fractions of the individual polymers. The Fox equation does not account for intermolecular interactions between the components and assumes that the volume fractions of the individual polymers are additive. Another widely used equation is the Couchman-Karasz equation,

$$Tg = \frac{W_1 Tg_1 + (\Delta Cp_2/\Delta Cp_1) W_2 Tg_2}{W_1 + (\Delta Cp_2/\Delta Cp_1) W_2} \tag{4}$$

where ΔCp_1 and ΔCp_2 are the change in heat capacity at the glass transition, for the individual polymers (30). The Couchman-Karasz equation was derived with the assumption that the entropy of mixing is continuous at the Tg. If $\Delta Cp_1 \approx \Delta Cp_2$, then equation 4 reduces to the Fox equation. The experimental data for the HPMC K4M/PVP blend were compared to the Tg values predicted by these equations (Fig. 5A). While both these equations show a close fit to the experimentally determined Tg values as the blend composition approaches limiting values, at intermediate compositions, a negative deviation from ideal behavior is clearly apparent. The negative departure from ideal behavior reflects the specific interactions that occur between the components and the non-additivity of free volumes in these blends.

In Fig. 5B, the Tg of the HPMC E5/MC blends is shown as a function composition along with the values predicted by the Fox and the Couchman-Karasz equations. As illustrated in Fig. 5B, the experimental data are well fitted by the Fox equation, implying ideal mixing behavior. The Couchman-Karasz equation also shows a reasonably good fit to the experimental data, but with slight deviations at some intermediate blend compositions. Ideal mixing behavior is characterized by similar forces between the like and unlike molecules, giving rise to random mixing and additivity of free volumes. The apparent ideal mixing behavior of the HPMC E5/MC blends may be

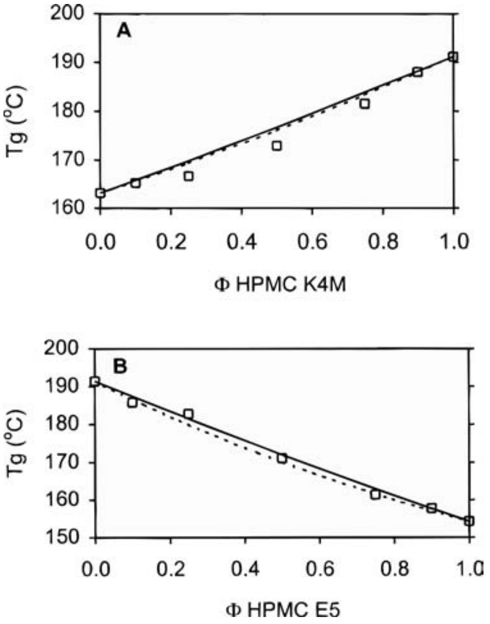

Fig. 5. (A) Tg as a function of composition for HPMC K4M/PVP blends. Squares - experimental data. Solid line - Tg predicted by Fox equation. Broken line - Tg predicted by Couchman-Karasz equation. Φ - weight fraction. (B) Tg as a function of composition for HPMC E5/MC blends. Squares - experimental data. Solid line - Tg predicted by Fox equation. Broken line - Tg predicted by Couchman-Karasz equation. Φ - weight fraction.

due to the non-specificity of the interactions between the polymeric components.

It is also important to note that MTDSC allowed accurate heat capacity determinations (used for the Couchman-Karasz equation) on single sample runs, unlike conventional DSC, which would have required several scans to obtain similar results.

CONCLUSIONS

MTDSC was shown to be a useful technique in assessing the interaction between HPMC and other film-forming polymers. In general, HPMC K4M/PVP and HPMC E5/MC blends were miscible as evidenced by a single Tg. The W-Tg measurements for these blends gave evidence of some heterogeneity at certain intermediate blend compositions. HPMC and HPC blends were immiscible, resulting in phase separation. The greater sensitivity of MTDSC relative to conventional DSC is especially important when characterizing polymeric blends in which there are low weight fractions of one component, since 'dilution' by the component that is present in greater amounts will diminish the change in heat capacity at the Tg of the former. In such a situation, the absence of sufficient sensitivity may prevent the detection of a second Tg, leading to the conclusion that the components are completely miscible, while in reality the components may only be partially miscible. MTDSC is also useful in assessing polymer-polymer miscibility when only the first scans of the sample can be used due to degradation of one or both of the components on heating above the Tg. In these cases, the Tg can be determined without accompanying enthalpic relaxation events.

Given the ability of MTDSC to combine sensitivity and resolution as well its capability to separate overlapping transitions, this technique should prove to be a valuable tool in the characterization of pharmaceutical polymeric blends. Knowledge of the phase behavior and interactions that occur in these systems provides a rational basis for their design and formulation based on fundamental material properties.

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