

Interactions in poly(ethylene oxide)–hydroxypropyl methylcellulose blends

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Abstract

Blends of poly(ethylene oxide) and hydroxypropyl methylcellulose in the form of free films are examined for evidence of specific polymer:polymer interactions. Such interactions might affect the drug release behaviour of compressed matrices incorporating these polymers. The effect of HPMC on the crystallisation of PEO during casting is investigated using differential scanning calorimetry (DSC) and wide-angle X-ray diffraction. Fourier transform infra-red (FT-IR) and Raman spectroscopies are used to examine the possibility of a complex between the two polymers. Thermodynamic interaction parameters are calculated for films cast from water and *N,N*-dimethylacetamide (DMAc) using the Flory–Huggins theory of mixing. The interaction parameter calculated is negative, indicating a miscible blend, and a hydrogen bonding interaction is detected. This hydrogen bonding is less likely to occur in films cast from water than in films cast from DMAc perhaps because residual water can shield the interaction sites.

Finally, a transition involving a sharp reduction in heat capacity at high temperatures is reported. This transition is characterised using DSC and FT-IR and Raman spectroscopies, and is interpreted as a further complexing of the polymers. © 2001 Elsevier Science Ltd. All rights reserved.

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1. Introduction

Hydrophilic polymers are used extensively to formulate matrix tablets for controlled drug delivery. The combination of hydroxypropyl methylcellulose (HPMC) and poly(ethylene oxide) (PEO), two non-ionic polymers, has been shown to give a novel matrix tablet system that allows modification of the rate of drug release compared with pure HPMC. For example, the HPMC/PEO system can be used to increase the release rate at later times [1]. A possible mechanism by which drug release is modified is via a direct polymer:polymer interaction. Studies by Kondo et al. have established that the primary hydroxyl group on cellulose and methylcelluloses can form a hydrogen bond to the ether oxygen in PEO [2,3]. This opens up the possibility of a similar interaction between PEO and the hydroxyl groups on hydroxypropyl methylcellulose. This study aims to find the nature and extent of any interactions between these polymers, and is a natural extension of the work of Kondo et al. and Nishio et al. [2–4].

Films have been studied because any polymer:polymer interaction which occurs in compressed matrix tablets will be exaggerated in a more intimately mixed system. Two different solvents have been used for film casting: DMAc in order to allow a direct comparison with previous studies on similar systems; and water because drug release occurs via penetration of aqueous fluid ingress into the system.

Films are studied, both in the ‘as cast’ state, in which significant amounts of bound and unbound solvent may be present, and, for interaction parameter analysis, after annealing at elevated temperature. Such annealing might be expected to remove some residual solvent. The possible effects of residual solvent on the nature of the polymer:polymer interactions are discussed.

2. Experimental

2.1. Materials

HPMC K4M Premium grade was purchased from Dow. The nominal molecular weight of this grade is 88,000 and the degrees of substitution for CH₃ and CH₂CHOHCH₃ are 4.12 and 19.24%, respectively. PEO with a nominal

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molecular weight of 200,000 was purchased from Union Carbide Corporation. HPLC-grade *N,N*-dimethylacetamide (DMAc) and HPLC-grade water were both supplied by Aldrich Chemical Co. Distilled water was supplied by the Department of Materials Science and Metallurgy. All materials were used without further purification.

2.2. Preparation of samples

Separate solutions of 0.8 wt% HPMC and 1.3 wt% PEO were prepared. Aqueous solutions were made by heating two thirds of the water to approximately 85°C, stirring on a magnetic hot plate stirrer, adding the polymer powder to the vortex in a steady stream, then adding the remaining water at room temperature. These solutions were then left to cool, and stirred for 3 days before mixing in the relevant quantities and stirring for a further 3 days. DMAc solutions were made in a similar manner without heating the liquid prior to adding the polymer. The relative amounts (w/w) of the two polymers in the final solutions were 100/0, 67/33, 50/50, 34/66 and 0/100 (HPMC/PEO). Samples will be referred to in terms of their PEO content in per cent. After mixing, the solutions were poured into Petri-dishes and dried at 50°C in air for 3 days followed by 3 days at 50°C under vacuum. Samples were then stored in vacuum desiccators.

2.3. Measurements

Differential scanning calorimetry was carried out on a Perkin Elmer DSC-7 in a nitrogen atmosphere. The instrument was calibrated with an indium standard. The thermal behaviour of the samples was examined by applying controlled heating and cooling regimes. Melting temperature was taken as the peak of the melting endotherm. The error in each measurement was estimated to be $\pm 0.5^\circ\text{C}$. Where measurements were repeated the error given is the standard deviation divided by the number of measurements minus one.

Wide-angle X-ray diffraction patterns were obtained using a Philips Diffractometer. Samples were placed on a silicon substrate to carry out the scans, and each sample was measured in duplicate to ensure reproducibility. $\text{CuK}\alpha$ radiation was produced by a Philips X-Ray generator.

Raman Spectra were recorded using a 780 nm diode laser on a Renishaw Ramascope 1000. Spectra were measured in two or three places on each sample and representative data are shown. Infra-red spectra were recorded using attenuated total reflectance on a Perkin Elmer Infrared Fourier Transform Spectrometer.

3. Results and discussion

3.1. Characterisation of as-cast films

In this section, the behaviour of as-cast films is considered. These films are likely to have small but significant

quantities of residual solvent which may be bound to the polymer. Since bound solvent could reduce the extent of specific polymer:polymer interactions by occupying interaction sites, the nature of the solvent used in casting may have an effect on the final properties of the film.

The films were examined under a polarised, transmitted light microscope and similar structural features were observed in films cast from DMAc and water. Pure PEO has a spherulitic morphology with spherulites measuring approximately 0.05 mm in diameter in water-cast, and 0.5 mm in DMAc-cast films. This difference reflects a difference in the balance of spherulite nucleation and growth rates in films cast from the two solvents, which could be due to different levels of impurities or different solvent evaporation rates. All the films cast from blends have a much finer scale structure with very small (non-spherulitic) crystalline domains measuring less than 0.01 mm across and no evidence of gross phase separation in the amorphous phase. It is possible that there was a degree of phase separation in the solutions, which could have led to some residual phase separation in the amorphous phase of the as-cast films, although none is detectable by the techniques used in this study.

3.1.1. Melt behaviour

DSC traces of HPMC/PEO blends heated to 90°C at $10^\circ\text{C min}^{-1}$ reveal that the PEO melt temperature decreased with increasing HPMC content, as illustrated in Fig. 1. The error bars represent the standard deviation divided by the number of repeats minus one. The decrease was similar for blends obtained from DMAc and water, but films cast from DMAc gave lower melting points across the complete composition range. This lower melting temperature in DMAc-cast films could indicate increased miscibility in the amorphous regions of these blends compared with the water-cast blends, although since the effect is also seen (albeit to a lesser extent) in the pure PEO film, this cannot account for the full difference. It would appear that even in pure PEO, more stable crystals result from casting from water, possibly due to differences in solvent evaporation rates or different levels of impurities in each solvent.

The quantity of PEO melting, as indicated by the melting enthalpy, also decreased with increasing HPMC content, again with DMAc giving lower values across the complete composition range, although the values for pure PEO in this case are very similar. Films cast from both solvents give non-zero intercepts on the %PEO axis of the plot of melting enthalpy vs. %PEO in Fig. 1, indicating that PEO is unable to crystallise below a certain concentration in HPMC. The intercept for blends cast from DMAc is at a higher PEO concentration than for blends cast from water.

The melting enthalpy data indicate that HPMC hinders the crystallisation of PEO in binary blends cast from either solution. This effect is more pronounced for blends cast from DMAc than from water.

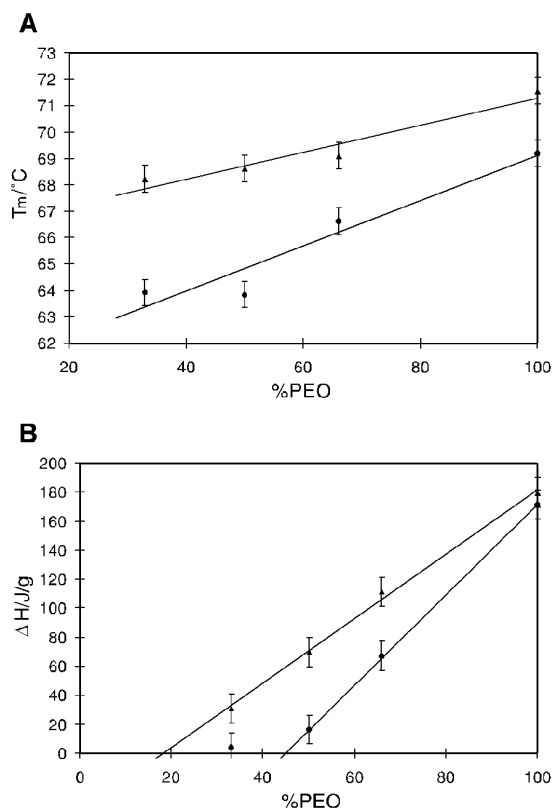


Fig. 1. (A) Peak melting temperature vs. PEO content and (B) melting enthalpy vs. PEO content for as-cast films cast from water (▲) and DMAc (●).

3.1.2. Crystallinity

Measurement of crystallinity was carried out by calculating the areas under wide-angle X-ray diffractometer scans. The results were compared with crystallinities calculated from DSC. Examples of the X-ray data used to calculate crystallinity are shown in Fig. 2. The formula used to calculate crystallinity was:

$$\text{crystalline fraction} = \frac{\text{total area} - \text{area of amorphous halo}}{\text{total area}} \quad (1)$$

This calculation assumes that the scatter from each molecule is the same. Melting enthalpies (ΔH), measured using first heat DSC data, were converted into crystallinities by dividing ΔH by the melting enthalpy of 100% crystalline PEO (197 J g^{-1}) [5].

The dependence on solvent suggests that water prevents, to some degree, the interactions between PEO and HPMC. In the absence of water, the polymers interact more strongly and PEO is less able to crystallise during casting. This effect may be due to water interacting with the two polymers, preventing them from interacting with

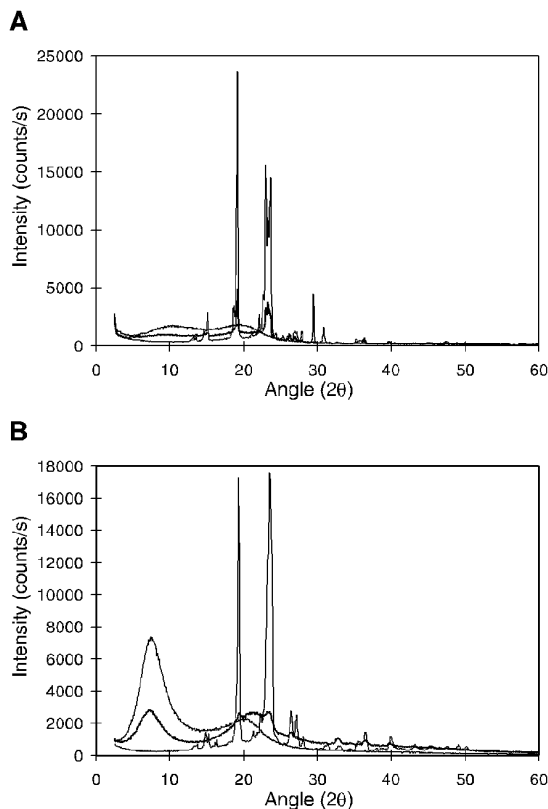


Fig. 2. Examples of the X-ray diffractometer scans used to calculate degrees of crystallinity: (A) water-cast; (B) DMAc-cast. Thin line = 0% PEO; thick line = 50% PEO; medium line = 100% PEO.

each other, be this on a molecular level, or by a greater degree of phase separation in the casting solution. Alternatively, this effect could be due to differences in impurity levels affecting nucleation rates, or a difference in solvent evaporation rates; with DMAc evaporating more quickly than water, there may be insufficient time for PEO to crystallise as fully as it could with a more slowly evaporating solvent.

Fig. 3 shows the crystallinities of the HPMC/PEO blends calculated from WAXS and DSC data. The crystallinity decreases linearly with decreasing PEO content for films cast from both DMAc and water. This relationship is expected because the content of crystallisable polymer is decreasing linearly. Both plots show non-zero intercepts on the %PEO axes indicating that PEO does not crystallise above a certain HPMC content; the effect is more pronounced for films cast from DMAc, the intercept occurring at about 40% PEO compared to 20% PEO for films cast from water. The DSC and WAXS data are in good agreement and demonstrate the differences between the films cast from water and from DMAc, that is, the PEO in the blend is more able to crystallise when the film is cast from water.

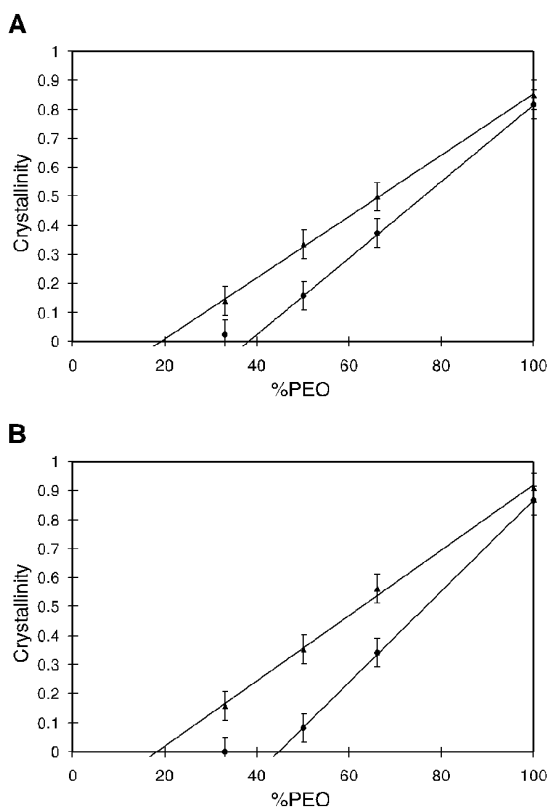


Fig. 3. Crystallinity vs. PEO content measured by (A) wide-angle X-ray diffraction and (B) DSC for as-cast films cast from water (▲) and DMAc (●).

3.1.3. Vibrational spectroscopy

Fourier transform infra-red (FT-IR) and Raman spectroscopy of as-cast films were carried out in order to detect any peak shifts that could be attributed to weak interactions between the two polymers, such as hydrogen bonding or complexation.

The IR peak of interest is the C–O–C asymmetric stretch at 1100 cm^{-1} [6]. This peak in the PEO spectrum has been shown to shift due to hydrogen bonding to methylcellulose [2,3]. The spectra obtained for blends are shown in Fig. 4. There were no detectable peak shifts for water-cast films, but there was a 5 cm^{-1} shift to higher wavenumber for blends cast from DMAc compared with pure PEO cast from DMAc. This strongly supports the idea that a hydrogen bond can form between PEO and HPMC. The absence of a peak shift in the water-cast films may be because water bonds to the interaction sites, thus preventing the interaction with HPMC and allowing PEO to crystallise more readily. In addition, there could be a greater degree of microphase separation in the amorphous regions of blends cast from water compared with those cast from DMAc, which would also prevent the polymers from interacting.

The region of the Raman spectra of particular interest is

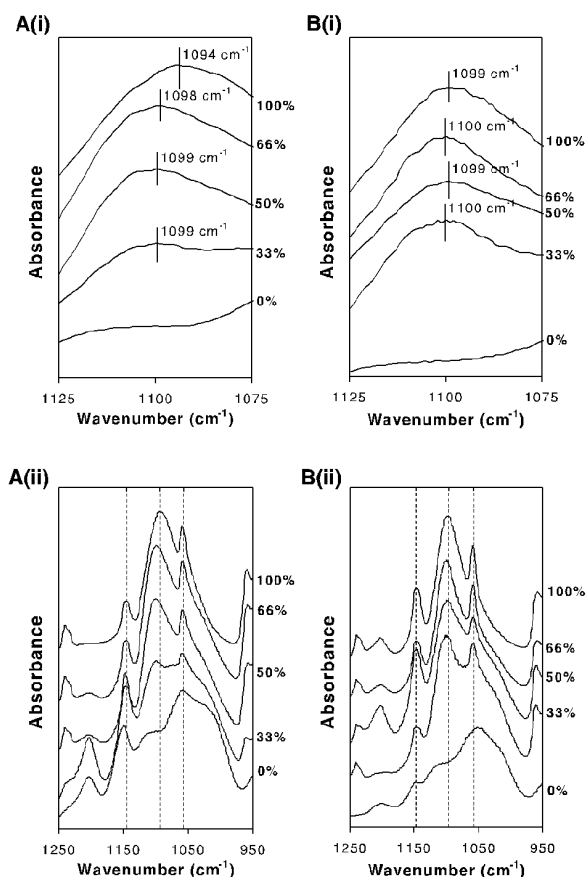


Fig. 4. IR spectra of PEO from films cast from (A) water and (B) DMAc, showing (i) the range $1075\text{--}1125\text{ cm}^{-3}$ and (ii) the range $950\text{--}1250\text{ cm}^{-3}$. The percentages refer to the amount of PEO in each blend. The relevant proportion of the pure HPMC spectrum has been subtracted from the blend spectra to obtain these traces.

$100\text{--}600\text{ cm}^{-1}$. This region contains peaks attributed to PEO backbone vibrations (e.g. C–C–O, C–O–C bends and C–C, C–O internal rotations) [7]. Once again, if a hydrogen bond is formed to the ether oxygen in PEO then these vibrations will be affected. There are no significant peaks in the HPMC spectra.

Fig. 5 shows Raman spectra from as-cast films. The measured spectra for the blends are compared with theoretical spectra for mechanical mixtures of the two polymers. Theoretical spectra were calculated by adding the appropriate fractions (in terms of mass) of the PEO and HPMC spectra. In general, the measured spectra show less intense peaks across the range of wavenumbers indicating that the PEO backbone is being prevented from vibrating. This effect is more pronounced for the DMAc-cast films. This shows that there is a strong possibility that hydrogen bonds have been formed between the hydroxyl groups of HPMC and ether oxygens of PEO, and that water prevents this interaction to some extent.

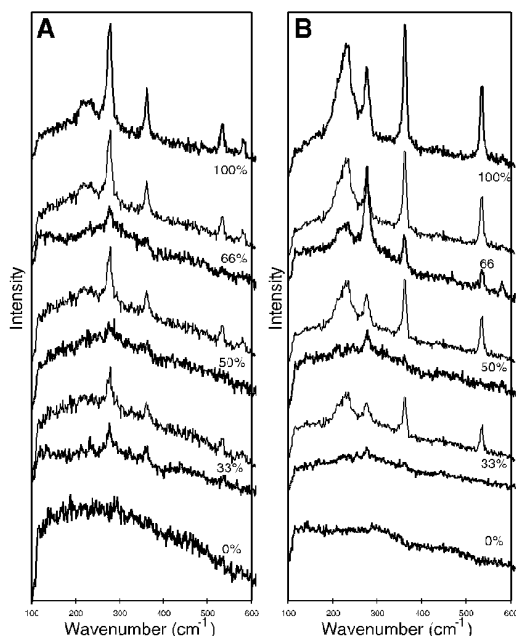


Fig. 5. Raman spectra from films cast from (A) water and (B) DMAc; the upper of each pair (thinner line) is calculated from the measured spectra for pure HPMC and pure PEO and the lower of each pair is the measured spectrum for that blend.

It is clear that the solvent used to cast films is important in determining the degree of interaction between the two polymers in the as-cast state. Water has been seen to prevent the interaction to some extent, possibly because it can bond to the interaction sites on PEO and HPMC. All the evidence presented here strongly suggests that the two polymers can hydrogen bond to each other in a similar way to PEO and 2,3-di-*O*-methylcellulose [2,3], but that the interaction is less likely to occur in films cast from water.

3.2. Flory–Huggins analysis of annealed films

An attempt to quantify the interaction between the PEO and HPMC cast from DMAc and from water was made using the method reported by Kondo et al. [3]. Samples were heated in the DSC to 90°C at 10°C min⁻¹ and held for 10 min before quenching at 200°C min⁻¹ to the isothermal crystallisation temperature, T_{ic} . The samples were monitored and held at this temperature for at least 10 min after complete crystallisation. The samples were then cooled to 20°C at 10°C min⁻¹, held for 2 min then heated to 90°C at 10°C min⁻¹ to measure the subsequent melting temperature, T_m .

The thermal profile applied by the DSC first subjects the as-cast film to an annealing treatment at an elevated temperature, to allow full interaction of the polymers in the amorphous phase before controlled crystallisation. Since the annealing temperature of 90°C is considerably

higher than the casting temperature of 50°C, it is likely that further residual solvent is driven from the films in this stage. However, it is still possible that some solvent remains bound to the polymer molecules. One might, therefore still expect there to be differences in the behaviour of films originally cast from the different solvents, if the quality of the residual solvent has an effect.

It is important to note here that samples were annealed at a temperature below the T_g of HPMC. Ideally, the blends would be annealed at a temperature above the glass transition temperatures of both constituents to allow the amorphous phase to interact fully. However, thermal degradation occurs if the blends are heated above the glass transition temperature of HPMC, invalidating the results. Kondo et al. [3] also encounter this problem, and adopt a similar solution. By following their method, and annealing at 90°C, we enable our results to be directly compared with theirs on PEO blends with cellulose and methylcellulose. Furthermore, we observed an unpredictable transition in the blends studied here at around 130°C, which is discussed later. Annealing at 90°C has the additional advantage of avoiding the complication of this transition occurring in some samples but not others.

The concept of melting point depression to measure the interaction parameter is used because the blends consist of a crystalline and an amorphous polymer. However, morphological effects must also be considered because the degree of perfection and size of polymer crystallites, as well as any interaction between the polymers, affect the melting point of isothermally crystallised polymers. A true Flory–Huggins interaction parameter may only be calculated if morphology is independent of PEO concentration, that is, melting point depression is solely a result of polymer:polymer interactions.

3.2.1. Hoffman–Weeks plots

If morphology is independent of PEO concentration, then the stability parameter, ϕ , which is a function of crystal thickness, will also be independent of PEO concentration. In order to find out the stability, and the equilibrium melting temperature of the PEO crystals in the blends, the observed melting temperatures, T_m , of isothermally crystallised PEO were plotted against T_{ic} , the isothermal crystallisation temperature for each blend composition. These plots are known as *Hoffman–Weeks* [8] plots and are shown in Fig. 6. The lines are lines of best fit calculated by the least squares method. Although there is some scatter in the data there is a general increase in T_m with T_{ic} . Each data set was fitted to the following equation to estimate a value for stability parameter, ϕ (ϕ being equal to the gradient of the line):

$$T_m^{eq} - T_m = \phi(T_m^{eq} - T_{ic}) \quad 0 \leq \phi \leq 1 \quad (2)$$

T_m^{eq} is the equilibrium melting point and ϕ , the stability parameter which depends on the crystal thickness. The

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