

The Interactions and Partitioning of Low Molecular Weight Polyethylene Glycols and Diethyl Phthalate in Ethylcellulose / Hydroxypropyl Methylcellulose Blends

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Synopsis

The interactions and partitioning of diethyl phthalate and low molecular weight polyethylene glycols in blends of ethylcellulose/hydroxypropyl methylcellulose have been studied. Both plasticizers were shown to diffuse in both phases according to the overall volume composition. The plasticizers interacted preferentially with one polymer component of the blend as predicted from studies of the individual polymers. Diethyl phthalate, a preferential plasticizer for ethylcellulose, demonstrated increased partitioning in the ethylcellulose-rich phase only at 80/20 w/w ethylcellulose/hydroxypropyl methylcellulose compositions. Polyethylene glycols, PEG200 and PEG400, preferential plasticizers for hydroxypropyl methylcellulose, showed increased partitioning in the hydroxypropyl-methylcellulose-rich phase also in blends containing 80% w/w ethylcellulose. The general effect of the mechanism and kinetics of the phase separation of the blend on the plasticizer partitioning has also been discussed.

INTRODUCTION

Blends of ethylcellulose together with water-soluble and pH-dependent soluble cellulose derivatives are widely used in the formulation of delayed or sustained release film coatings.^{1,2} The water-insoluble ethylcellulose is usually chosen as the matrix with the water-soluble component, for instance, hydroxypropyl methylcellulose, constituting the minor phase, the drug being released through the pores created in the film coating by the dissolution of the dispersed phase. A knowledge of the phase separation and the resulting morphology of the blends is of prime importance for the understanding of the movement of substances through the film coating. Recent research on the dynamic mechanical behavior of blends of ethylcellulose with hydroxypropyl methylcellulose showed that, despite the presence of interactions between the polymer chains, the two polymers are incompatible all through the blend composition range.³

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It is apparent that the integrity of the film coating and the absence of cracks and flaws are essential in controlling the release of the drug from such a preparation. Plasticizers are added to the formulations to improve the flexibility, increase the strength, toughness, tear, and impact resistance of the coatings and thus minimize the incidence of flaws.¹ Plasticizers tend to affect the release of the drug through the matrix,⁴ and, therefore, it is generally desirable to use the least amount of such materials. Recent data on the most common plasticizers for cellulose-derivative film coatings, dialkyl phthalates and polyethylene glycols, reported the variation of their plasticization efficiency with respect to the plasticizer content in films of ethylcellulose and hydroxypropyl methylcellulose.^{5,6} Incorporation of a plasticizer into a phase-separated system with preferential interactions for one of the components of the blend raises an important question as to its partitioning into the two polymer phases.

In this study we report on the effect of diethyl phthalate and low molecular weight polyethylene glycols (PEG200 and PEG400) on the dynamic mechanical behavior of blends of ethylcellulose and hydroxypropyl methylcellulose. The variation of the glass transition temperatures of the plasticized blend components as compared to the behavior of the plasticized homopolymers has been used to provide information on the partitioning of the plasticizer in the phase-separated system.

EXPERIMENTAL

Materials

The film formers used were hydroxypropyl methylcellulose (HMPC-Pharmacoat 606, Shin-Etsu Chemical Co., Tokyo, Japan) and ethylcellulose (EC-Grade N50, Hercules Inc., Wilmington, DE). The plasticizers were diethyl phthalate (DEP) and polyethylene glycols (PEG200 and PEG400, BDH, UK). Methanol and dichloromethane, used as solvents, were commercial reagents (BDH, UK). All materials were used as received.

Methods

The method employed to study the dynamic mechanical behavior of the unmodified and plasticized blends was torsional braid analysis (TBA). This is a sensitive torsional pendulum which monitors the response of the polymer-impregnated multifilament glass braid to a sinusoidal stress with temperature at a relatively constant frequency. The instrument used has been fully described elsewhere.⁷ The dynamic mechanical behavior of the samples at ca. 1 Hz was recorded over the temperature range from 20 to 200 °C at a heating rate of 1 °C min⁻¹. The 85-mm-long glass braids used consisted of two heat-cleaned glass yarns doubled to produce about 2½ turns per inch and trapped between two butt-type clamps.

The samples were prepared by impregnating the braids with 15% w/v solutions of the formulation in a solvent mixture consisting of equal parts by volume of methanol and dichloromethane for at least 3 hrs. The solvents were removed by drying the samples at 45 to 80 °C to constant weight in an air oven while taking special precautions to ensure that the samples remained

straight. The dynamic mechanical spectra were recorded as the logarithmic decrement (Δ) and relative rigidity ($1/P^2$) variation with temperature. Only the logarithmic decrement curves are reported here as the relative rigidity curves provided similar information.

RESULTS AND DISCUSSION

Plasticization of Ethylcellulose and Hydroxypropyl Methylcellulose

The variation of the glass transition temperature of ethylcellulose and hydroxypropyl methylcellulose with the concentration of diethyl phthalate (DEP) is shown in Figure 1. Diethyl phthalate preferentially plasticizes ethylcellulose, leaving hydroxypropyl methylcellulose almost unaffected. The behavior of the ethylcellulose/diethyl phthalate system in this study compares very well with the data recorded for the same system cast from 80/20 v/v toluene/ethanol mixtures.⁶

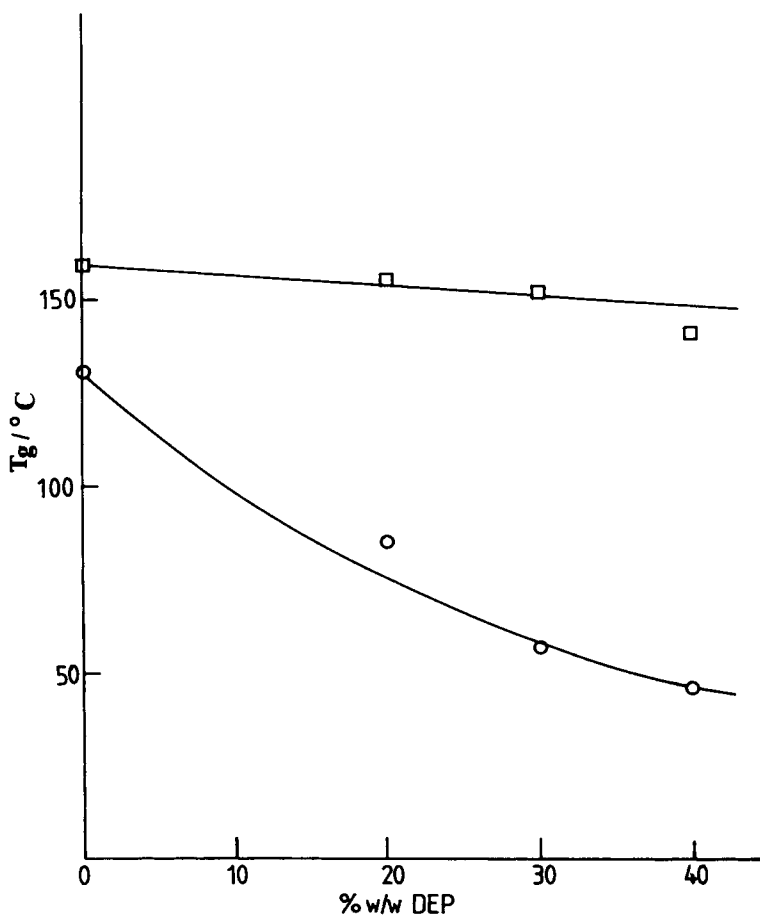


Fig. 1. Variation of the glass transition temperature of ethylcellulose (○) and hydroxypropyl methylcellulose (□) with diethyl phthalate concentration.

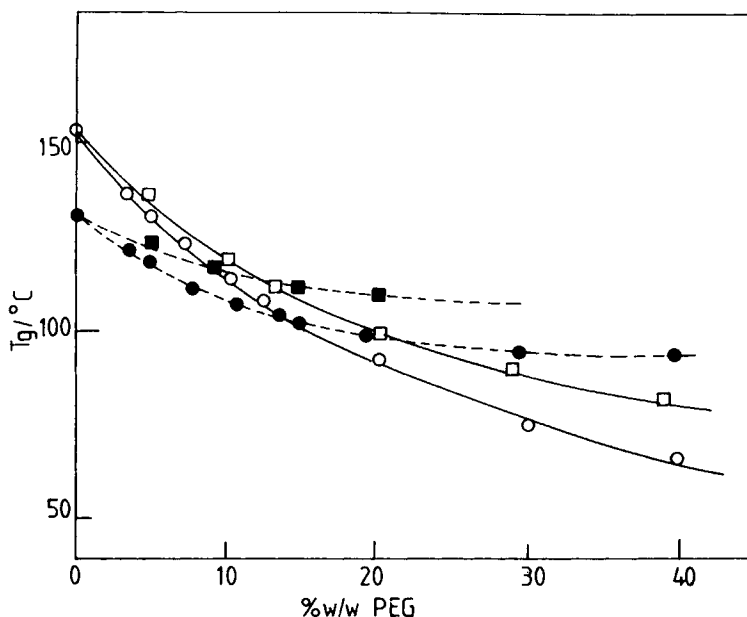


Fig. 2. Variation of the glass transition temperature of ethylcellulose (■, ●) and hydroxypropyl methylcellulose (□, ○) with the concentration of PEG200 (○, ●) and PEG400 (□, ■).

The effect of the low molecular weight polyethylene glycols on ethylcellulose and hydroxypropyl methylcellulose has been discussed in detail in a previous publication.⁵ For comparative purposes we summarize, in Figure 2 the behavior of the individual film formers with added PEG200 and PEG400. Both polyethylene glycol grades preferentially plasticize the hydroxypropyl methylcellulose with the plasticizing efficiency increasing with decreasing molecular weight of the plasticizer. Furthermore, polyethylene glycols phase separate in ethylcellulose at all concentrations and in hydroxypropyl methylcellulose above a critical concentration. This is manifested as a plateau at about 60° in the dynamic mechanical spectra of both plasticized film formers. Although the position of this plateau does not alter with the concentration and molecular weight of the polyethylene glycols, its intensity varies proportionally with the polyethylene glycol content.⁵

Plasticization of Ethylcellulose / Hydroxypropyl Methylcellulose Blends with Diethyl Phthalate

The behavior of ethylcellulose/hydroxypropyl methylcellulose blends plasticized with diethyl phthalate as compared to the behavior of the corresponding homopolymers is summarized in Figure 3. Two relaxations were recorded all through the blend composition range. Diethyl phthalate preferentially plasticizes ethylcellulose while having a negligible effect on hydroxypropyl methylcellulose.

The behavior of the hydroxypropyl methylcellulose-rich phase compares very well with the behavior of the plasticized individual homopolymer, as shown in Figure 6. The ethylcellulose-rich phase shows deviations from the

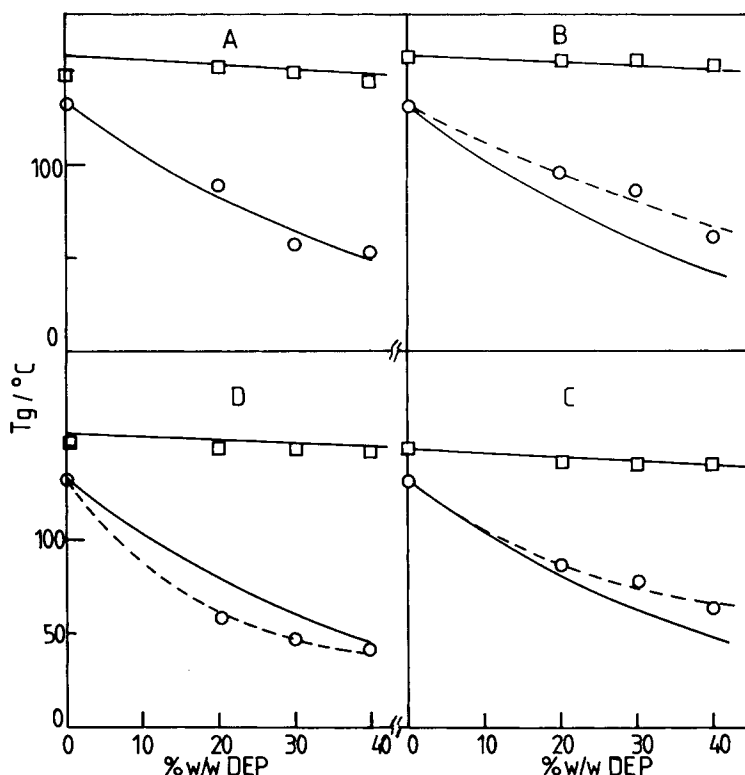


Fig. 3. Variation of the glass transition temperatures of ethylcellulose/hydroxypropyl methylcellulose blends with blend composition and diethyl phthalate concentration: (A) 20/80, (B) 40/60, (C) 60/40, and (D) 20/80 w/w ethylcellulose/hydroxypropyl methylcellulose. (\square) T_g of hydroxypropyl methylcellulose-rich phase; (\circ) T_g of ethylcellulose-rich phase. Continuous lines represent the behavior of the individual polymers.

behavior of the plasticized homopolymer with both blend composition and plasticizer concentration. The glass transition of this phase is shifted to lower temperatures for blends containing 80% w/w ethylcellulose. This is thought to occur due to increased partitioning of diethyl phthalate into this phase. When the concentration of hydroxypropyl methylcellulose exceeds 20% by weight, the glass transition temperatures of the ethylcellulose-rich phase either compares well or is higher than the values recorded for the diethyl phthalate/ethylcellulose systems. This seems to suggest that considerable amounts of the component with the unfavorable interactions with the plasticizer imposes barriers to any preferential diffusion of the plasticizer into the other phase.

High plasticizer concentrations also demonstrate negative effect on the plasticizer efficiency to depress the glass transition temperatures of the ethylcellulose-rich phase. This is thought to be due to the presence of the hydroxypropyl methylcellulose in the blend which shows poor interactions with diethyl phthalate. Increased amounts of diethyl phthalate tend to phase-separate into the hydroxypropyl methylcellulose-rich phase.

To minimize the complications associated with the presence of excessive amounts of plasticizers in the systems, and particularly in view of the intense

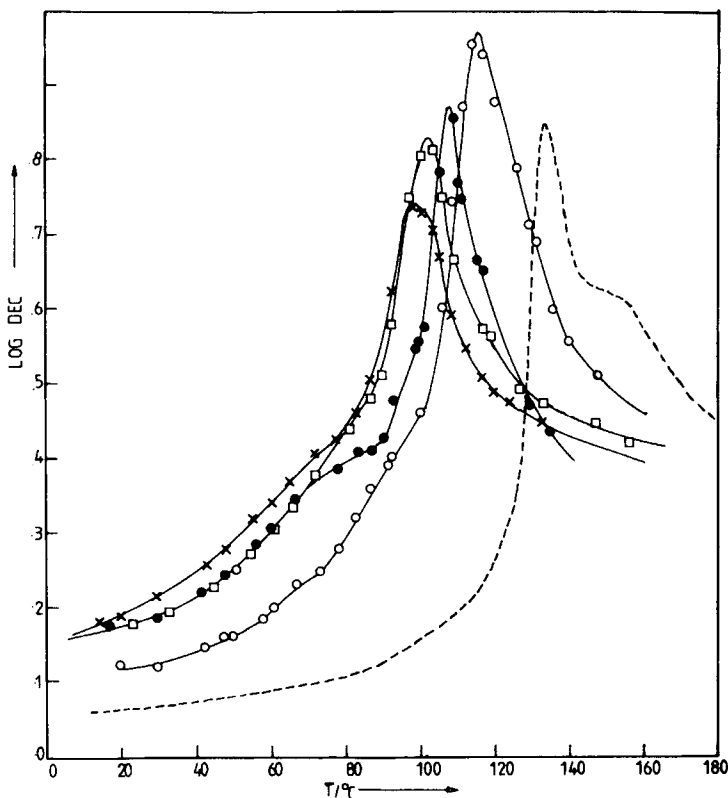


Fig. 4(A). Effect of PEG200 on the dynamic mechanical behavior of 80/20 w/w ethylcellulose/hydroxypropyl methylcellulose blends; w/w PEG200: (○) 5; (●) 10; (□) 15; (×) 20. (---) Original blend.

phase separation of the polyethylene glycols in the homopolymers at such concentrations, the study of the ethylcellulose/hydroxypropyl methylcellulose system was limited to plasticizer contents below 20% by weight.

Plasticization of Ethylcellulose / Hydroxypropyl Methylcellulose Blends with Polyethylene Glycols

The effect of PEG200 and PEG400 on 80/20 w/w ethylcellulose/hydroxypropyl methylcellulose blends is illustrated in Figures 4(A) and 4(B). In both cases only one glass relaxation is recorded in contrast to the two relaxations resolved in the dynamic mechanical spectra of the unmodified blend.

The variation of the glass transition temperature of the plasticized blends with polyethylene glycol concentration follows the behavior of the plasticized ethylcellulose component as shown in Figures 5 and 6. The recorded glass transition can, therefore, be assigned to the plasticized matrix of the blend, with the second peak due to the hydroxypropyl methylcellulose-rich phase being merged into the main relaxation. Although merging of the two transitions renders the interpretation of the data with respect to plasticizer partitioning very difficult, the absence of a second glass transition peak towards higher temperatures at polyethylene glycol concentrations below 6% w/w indicates that an excess of plasticizer has been partitioned into the hydroxypropyl-

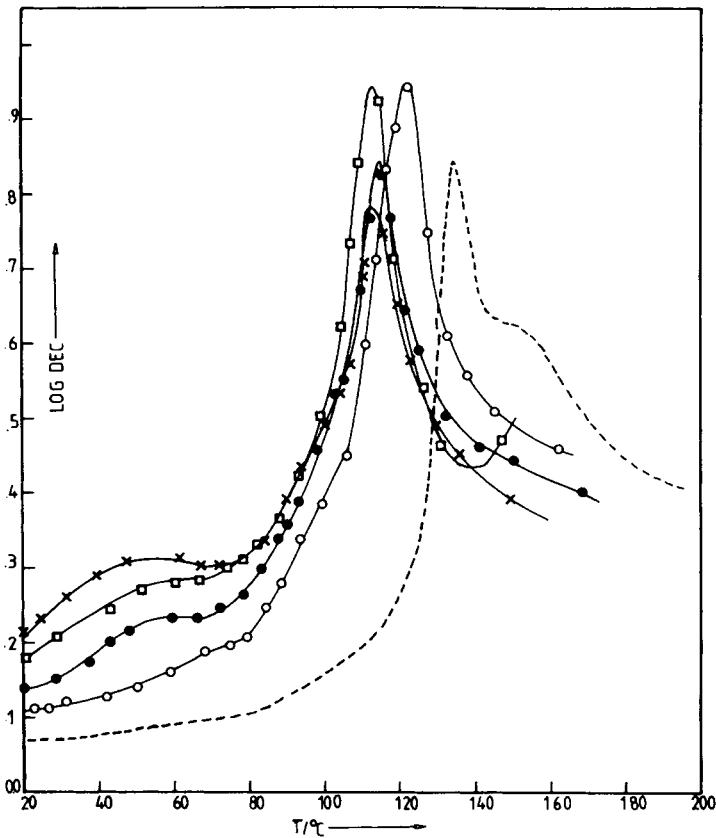


Fig. 4(B). Effect of PEG400 on the dynamic mechanical behavior of 80/20 w/w ethylcellulose/hydroxypropyl methylcellulose blends; w/w PEG400: (○) 5; (●) 10; (□) 16; (×) 20. (---) Original blend.

methylcellulose-rich phase shifting the glass transition peak to lower temperatures than expected (Figs. 5 and 6). Since the hydroxypropyl methylcellulose/polyethylene glycol 200 and 400 systems did not exhibit any phase separation at polyethylene glycol concentration below ca. 30% w/w, the plateau recorded in the plasticized blends must be associated with the phase separation of the polyethylene glycols in the ethylcellulose-rich phase. These relaxations can thus provide additional evidence on the polyethylene glycol partitioning in the blend. Comparison between the dynamic mechanical spectra shown in Figures 4(A) and 4(B) reveals that these relaxations have been reduced to a broadening of the glass transition for the systems containing PEG200, whereas they retained their original intensity and breadth for the systems with PEG400. This is thought to be due to an increased dispersion of PEG200 into the hydroxypropyl methylcellulose-rich domains, thus limiting its phase separation into the ethylcellulose rich matrix.

Theoretical predictions on polymer/polymer and polymer/plasticizer compatibility can be obtained from the solubility parameter maps.¹² A three-dimensional plot of the dispersion or van der Waals component (δ_d), polar component (δ_p), and hydrogen bonding component (δ_h) of the solubility parameter of the solvents which dissolve each polymer defines a characteristic

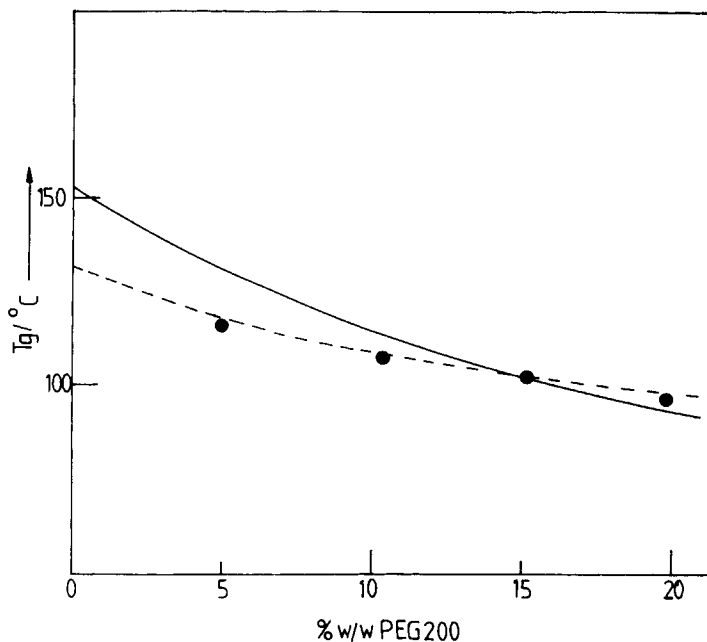


Fig. 5. Variation of the glass transition temperature of 80/20 w/w of ethylcellulose/hydroxypropyl methylcellulose blends (●), ethylcellulose (---), and hydroxypropyl methylcellulose (____) with the concentration of PEG200.

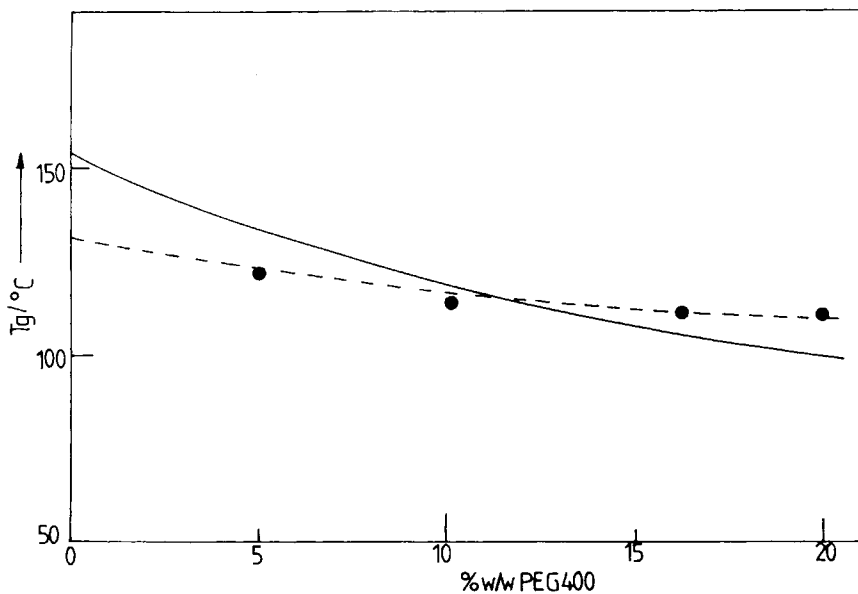


Fig. 6. Variation of the glass transition temperature of 80/20 w/w ethylcellulose/hydroxypropyl methylcellulose blend (●) ethylcellulose (---), and hydroxypropyl methylcellulose (____) with the concentration of PEG-400.

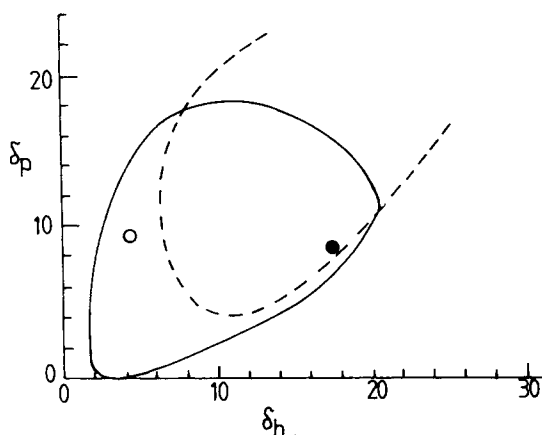


Fig. 7. Solubility parameter maps for ethylcellulose, (—), hydroxypropyl methylcellulose (---), and positions of hexaethylene glycol (●) and diethyl phthalate (○).

volume for that polymer. The degree of overlap between the characteristic volumes for the two polymers and the relative positions of the plasticizers provide information on their compatibility. Two-dimensional plots of δ_h and δ_p have more generally been used for practical reasons.

The experimental data presented in this work are consistent with the theoretical predictions based on the solubility parameter maps of the two film formers and the plasticizers as shown in Figure 7. The solubility parameter maps for the particular systems used in this work were constructed using δ values available in the literature.¹⁰⁻¹² The figure demonstrates clearly that ethylcellulose and hydroxypropyl methylcellulose are incompatible with a limited degree of miscibility. The position of the plasticizers with respect to the solubility maps of the two polymers indicates a preferential solubility of diethyl phthalate in ethylcellulose and polyethylene glycol in hydroxypropyl methylcellulose. Furthermore, the solubility parameter of diethyl phthalate is shown to be situated clearly outside the solubility area of hydroxypropyl methylcellulose, complying with the rather poor plasticization action on that polymer observed experimentally. On the other hand, low molecular weight polyethylene glycols could be expected to show minor effect on ethylcellulose since they are situated at the boundaries of the solubility map of this film former. This is also confirmed by the dynamic mechanical spectra in Figure 2.

Although no data are available on the thermodynamics and kinetics of the phase separation of the present system, an approximate qualitative picture on the general process can be outlined based on data from simpler systems.⁸ For the purposes of this preliminary analysis the solvent mixture will be considered as a single solvent. At the initial high dilution state, the system is homogeneous, and the plasticizer is distributed uniformly in the solution. As the solvent is removed and when the system crosses the binodal, phase separation occurs by nucleation and growth of the minor phase, creating droplets rich in this polymer dispersed in the matrix of the major component. At this stage the plasticizer is basically distributed according to the volume composition of the two phases in the system. With the further growth of the domains and due to the preferential interaction of the plasticizer with one

component an additional amount will diffuse into the phase rich in this component. However, as the phase separation process is a nonequilibrium situation, and particularly because of the rather fast casting procedure, it is rather unlikely that all the possible amount of plasticizer will be partitioned preferentially into the corresponding phase. In the case of 80:20 w/w ethylcellulose/hydroxypropyl methylcellulose system containing 10% w/w overall polyethylene glycol, this process would produce ethylcellulose-rich matrix with ca. 8% w/w plasticizer and hydroxypropyl methylcellulose-rich dispersions with ca. 16% w/w plasticizer. Such a composition would explain the shift in the relaxation due to the matrix as well as the presence of the plateau at lower temperatures, even at very low plasticizer contents. The solid state morphology of this system will comprise three phases: ethylcellulose-rich matrix containing phase-separated polyethylene glycol droplets and plasticized hydroxypropyl methylcellulose-rich domains. The fact that evidence for a preferential partition of both diethyl phthalate and polyethylene glycols was recorded for the same blend composition indicates involvement of the mechanism and kinetics of the phase separation on the plasticizer partitioning in the phase separated system.

In conclusion, the present data demonstrate that, despite the presence of preferential interactions, the plasticizers diffuse in both phases according to the volume composition of the blend. Evidence for preferential partitioning of both plasticizers was obtained only for 80/20 w/w ethylcellulose/hydroxypropyl methylcellulose blends.

References

1. R. C. Rowe, *Pharm. Int.*, **6**, 14 (1985).
2. N. B. Shah and B. B. Sheth, *J. Pharm. Sci.*, **61**, 412 (1972).
3. P. Sakellariou, R. C. Rowe, and E. F. T. White, *Int. J. Pharm.*, **34**, 93 (1986).
4. R. C. Rowe, *Int. J. Pharm.*, **29**, 37 (1986).
5. P. Sakellariou, R. C. Rowe, and E. F. T. White, *Int. J. Pharm.*, **31**, 55 (1986).
6. R. C. Rowe, A. D. Kotaras, and E. F. T. White, *Int. J. Pharm.*, **22**, 57 (1984).
7. P. Sakellariou, R. C. Rowe, and E. F. T. White, *Br. Polym. J.*, **19**, 73 (1987).
8. T. K. Kwei and T. T. Wang, in *Polymer Blends*, D. R. Paul, S. Newman, Eds., 1978, Academic, New York, Vol. 1.
9. P. Sakellariou, R. C. Rowe, and E. F. T. White, *Int. J. Pharm.*, **31**, 175 (1986).
10. A. F. M. Barton, *Handbook of Solubility Parameters and Other Cohesion Parameters*, CR Press, Florida, 1983.
11. R. C. Rowe, *J. Pharm. Pharmacol.*, **38**, 214 (1986).
12. C. M. Hansen, *J. Paint Technol.*, **39**, 104 (1967).

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