ELSEVIER

International Journal of Pharmaceutics 125 (1995) 289-296

international journal of pharmaceutics

The morphology of blends of ethylcellulose with hydroxypropyl methylcellulose as used in film coating

P. Sakellariou [a,1,*], R. C. Rowe [b]

[a] ICI Paints, Wexham Road, Slough SL5 2DS, UK
[b] Zeneca Pharmaceuticals, Pharmaceutical Department, Macclesfield SK10 2TG, UK

Received 10 February 1995; accepted 3 April 1995

Abstract

Near-equilibrium morphologies of thin films (< 0.2 μm) of ethylcellulose-rich incompatible blends of ethylcellulose (EC) with hydroxypropyl methylcellulose (HPMC) consist of HPMC-rich macroscopic polydisperse domains (3–approx. 20 μm) dispersed in an EC-rich matrix implying complete leaching of the water soluble phase. However, for thick films (> 100 μm) complete leaching was observed only for systems with above 60% w/w HPMC, whereas all other systems showed some HPMC retention. The observed HPMC leaching behaviour is attributed to deviations of the phase decomposition from equilibrium during film formation arising from the rate of viscosity increase and changes in the solvent system composition.

Keywords: Hydroxypropyl methylcellulose; Ethyl cellulose; Blend; Interaction; Leaching; Drug release; Morphology; Tablet coating; Film formation

1. Introduction

Blends of ethylcellulose with hydroxypropyl methylcellulose are widely used in the formulation of delayed or sustained drug release film coatings (Shah and Sheth, 1972; Rowe, 1985). The water insoluble ethylcellulose is usually chosen as the matrix and the water soluble hydroxypropyl methylcellulose as the minor component. The drug is released through pores created in the film coating by the dissolution of the dispersed phase. The interactions and morphology in the blend are of prime importance to the drug release profile. Ethylcellulose/hydroxypropyl methylcellulose blends have been shown to phase separate (Sakellariou et al., 1986a) with a very limited degree of mixing between the two polymers. In an earlier publication (Sakellariou et al., 1988), data were reported on the retention/leaching of water-soluble and pH-dependent-soluble cellulose derivatives and PEG6000 from blends with ethylcellulose containing 20% and 80% w/w eth-

---

[*] Corresponding author.

[1] Present address: Courtaulds Coatings Ltd, New Technology Group, Stoneygate Lane, Felling, Gateshead, Tyne and Wear NE10 0JY, UK.

SSDI 0378-5173(95)00147-6

ylcellulose. A small amount of hydroxypropyl methylcellulose is retained in blends with high (80% w/w) ethylcellulose content (Sakellariou et al., 1988).

This paper reports on the morphology of blends of ethylcellulose with hydroxypropyl methylcellulose with specific reference to the effect of film preparation.

2. Materials and methods

The hydroxypropyl methylcellulose (HPMC, Pharmacoat 606) was supplied by Shin-Etsu Chemical Co., Tokyo, Japan, and ethylcellulose (EC, Grade N50) from Hercules Powder Co., Wilmington, DE, USA. Molecular weights and degrees of substitution of the two polymers are listed in Table 1. Films were prepared by solution casting from 50:50 v/v methanol/methylene chloride.

To overcome difficulties encountered in studying the morphology of thick films of ethylcellulose/hydroxypropyl methylcellulose blends (> 100 μm), a thin film applicator was built. It consists of a thermostatted oil bath where the dilute polymer solution (2% w/v) is kept in a Pyrex glass tube. A cleaned microscope slide was suspended over the solution and in solvent vapour for 20 min, and subsequently lowered slowly into the solution where it remained for 20 min. The immersed slide was withdrawn from the polymer solution at 1 cm min^{-1} and kept suspended in the solvent vapours to dry over 2–3 h, ensuring near equilibrium solution casting of the blend. The movements of the microscope slide were controlled by a gear box equipped with a motor and power supply. The thickness of the film was controlled by the concentration of the polymer solution and the speed of slide withdrawal from the solution. Under the conditions of our experiments, films of 1000–1500 Å thickness were obtained eliminating the need for microsectioning. The coated films were collected on a clean microscope slide after floating in a water trough. Although swelling of the HPMC phases with water would enhance phase contrast (at room temperature), they did not give rise to morphological artefacts. This was confirmed by the fact that morphology remained unaltered as the temperature increased above the boiling point of water, and even at temperatures above the glass transition temperature (T_g) of both polymers.

The dynamic mechanical spectra of the blends were obtained with a torsional braid analyser (TBA) described in detail elsewhere (Sakellariou et al., 1985). Leached samples were prepared by immersing the TBA specimens in distilled water for a period of 16 h before being dried at 85°C to constant weight. The drying procedure was sufficient to remove all free moisture. The weight loss after leaching was determined by difference. Repeated measurements on selected samples confirmed the reproducibility of weight loss with a low coefficient of variation (< 2%).

Table 1
Degrees of substitution (% w/w), number average molecular weight (M_n), polydispersity index (M_w/M_n), solubility parameter (δ) and T_g of EC and HPMC

	Degrees of substitution (% w/w)			M_n ($\times 10^{-3}$) (g/mol)	M_w/M_n	δ ($\text{MPa}^{1/2}$) [a]	T_g (°C) [b]
	Ethoxy	Methoxy	Hydroxypropoxyl				
EC [c]	48–49.5	–	–	53	2.96	20.6	131.5
HPMC [d]	–	28–30	7–12	58	3.02	24.4	153.5

[a] Sakellariou et al. (1985).
[b] Sakellariou et al. (1986b).
[c] Grade N50.
[d] Pharmacoat 606.

3. Results and discussion

Optical micrographs of blends with 60 and 80% EC are shown in Figs. 1 and 2. Both systems exhibited morphologies typical to nucleation and growth mechanism of phase separation, with HPMC-rich domains dispersed in an EC-rich matrix. The size of the disperse phase was in the region from 3 to 5 μm for the blend with 80% w/w EC and 3 to approx. 20 μm for the system with 60% w/w EC. It is interesting to note that the essential morphological features of the blend films prepared under ambient conditions remained unaltered on raising the temperature from ambient to 200°C, well above the T_g of both polymers (see Table 1). This confirms that the morphologies obtained were near-equilibrium ones and that the observed polymer incompatibility was not due to the effect of the solvent system but due to thermodynamic incompatibility of the two polymers. The phase separation observed is consistent with the solubility parameters of the two polymers (see Table 1). The Flory-Huggins interaction parameter for the blend ($\chi = 1.04$) was significantly higher than the critical value for phase separation ($\chi = 0.04$) (Sakellariou and Rowe, 1995). The cause of this incompatibility has been attributed to absence of intermolecular interactions in view of the negligible contribution of the change in entropy on mixing to the free energy of mixing. Earlier work has elucidated the absence of intermolecular interactions in terms of the solubility parameter maps of the two polymers (Rowe, 1986). Only limited overlap of the solubility parameter maps of EC and HPMC was reported indicating that no significant dipole-dipole/induced dipole and hydrogen bonding interactions take place between EC and HPMC.

The phase separation in blends of EC with HPMC was also confirmed by the presence of two transitions in the TBA spectra corresponding to the glass transition temperatures of the two polymers (Sakellariou et al., 1986b). For comparative purposes Fig. 3 shows the dynamic mechani-

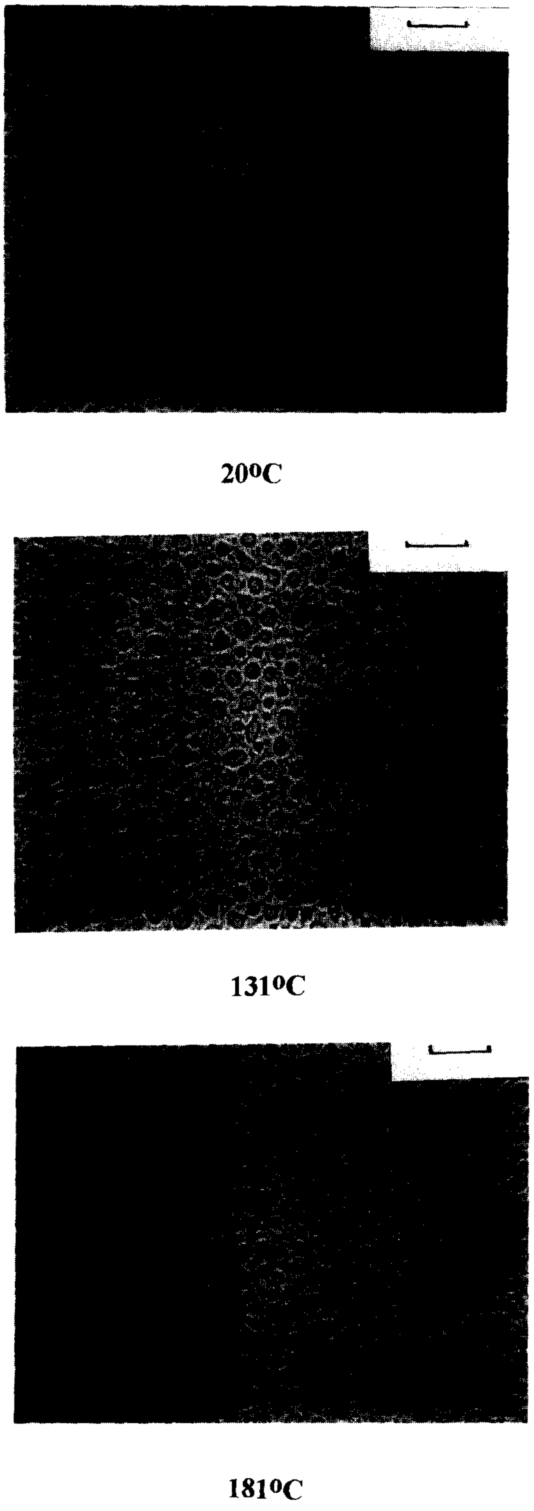
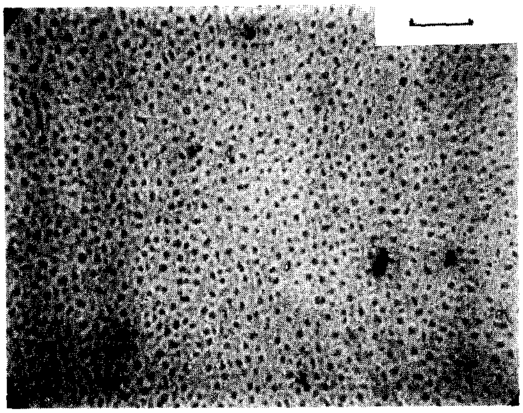


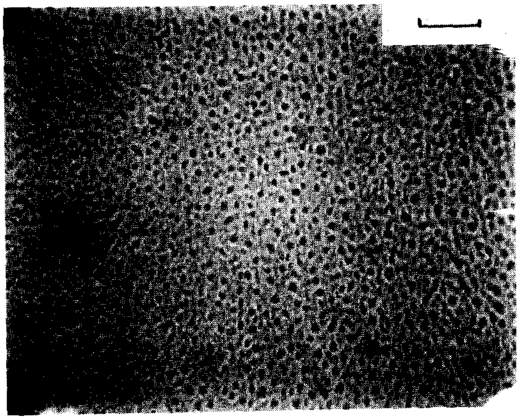
Fig. 1. Morphology of thin films of 60:40 w/w EC/HPMC blends with increasing temperature (bar 30 μm).

cal behaviour of these blends in terms of the logarithmic decrement (log dec) and relative rigidity ($1/p^2$, p = period of sinusoidal damping). Leaching of the water soluble HPMC from the blend would be expected to result in lowering the height of the glass transition peak assigned to the HPMC-rich phase; the peak would disappear completely if the whole of the HPMC-rich phase were leached out. Glass transition peaks in the dynamic mechanical spectra due to minor blend components at contents as low as 10% w/w can be detected (MacKnight et al., 1978). The dynamic mechanical spectra of EC/HPMC blends leached in distilled water are shown in Fig. 4. A single main transition at 131–133°C was recorded for all blend compositions. The temperature at which this transition occurred, together with the fact that its maximum logarithmic decrement decreased in line with EC content in the blend, suggest strongly that it is due to EC-rich phases in the blend. The height of the transition peak due to the HPMC-rich phase of the blend was reduced markedly, indicating a significant extent of HPMC leaching from the films. In blends with 20, 40 and 60% w/w HPMC it became a shoulder superimposed on the peak due to the EC-rich phase, and in the system with 80% HPMC it disappeared completely. Comparison of the dynamic mechanical spectra of the blends before and after leaching demonstrates clearly that significant fractions of HPMC have been leached away from the film, and for systems containing more than 60% w/w HPMC leaching was almost complete.

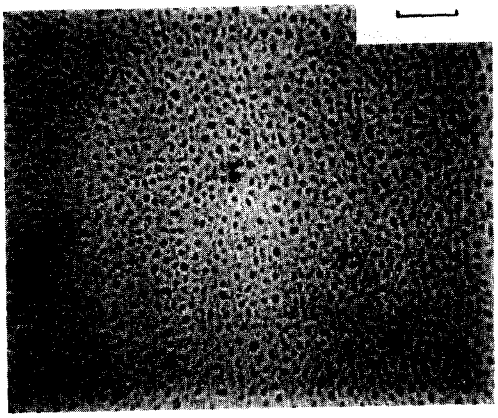
Trends observed in the dynamic mechanical spectra were corroborated by weight loss data (Fig. 5). Blends with EC as the major phase exhibited some retention of HPMC in the film. This was not the case for systems with HPMC as the major phase. It is interesting to note that the latter systems showed leaching greater than the theoretical one implying that perhaps some EC has also been leached away. From the TBA and gravimetric data it would appear that leaching of



25°C



101°C



140°C

Fig. 2. Morphology of thin films of 80:20 w/w EC/HPMC blends with increasing temperature (bar 30 μm).

HPMC from the film is related not only to the water solubility of HPMC but also to the phase morphology of the blend.

The morphologies of thin EC/HPMC blend films would suggest complete leaching of the HPMC-rich dispersed phase. On the other hand, the dynamic mechanical data and gravimetric analysis showed that, under the leaching conditions of our experiments, only for the systems containing more than 60% w/w HPMC was complete leaching achieved. HPMC retention was indicated for all systems with EC as the major component. The apparent contradiction is believed to stem from differences in the film preparation processes for the films used for dynamic mechanical analysis and morphological studies. TBA samples were thick films (> 100 μm) cast under ambient conditions leading to faster solvent evaporation (non-equilibrium conditions). In contrast, the films used in the morphological studies were thin (< 0.2 μm) and cast under near equilibrium conditions in an atmosphere of the solvent system vapours. Fig. 6a illustrates the phase separation process during solvent evaporation. Once the system concentration has crossed the binodal and exceeded a critical value, nucleation and growth leads to formation of two phases. On further solvent evaporation under equilibrium conditions, phase ripening takes place across the binodal leading to phases richer in the corre-

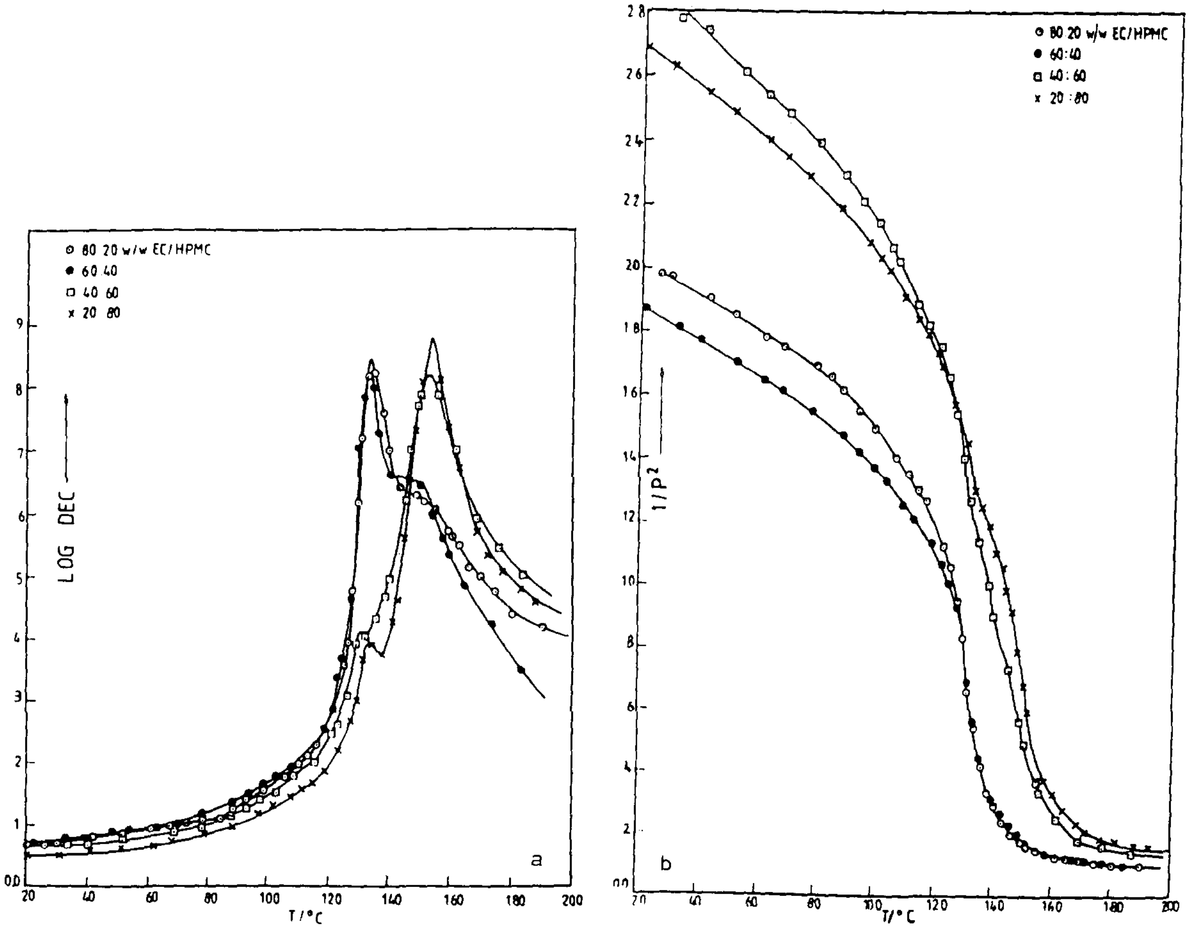


Fig. 3. Logarithmic decrement (LOG DEC) (a) and relative rigidity (b) for EC/HPMC blends before leaching.

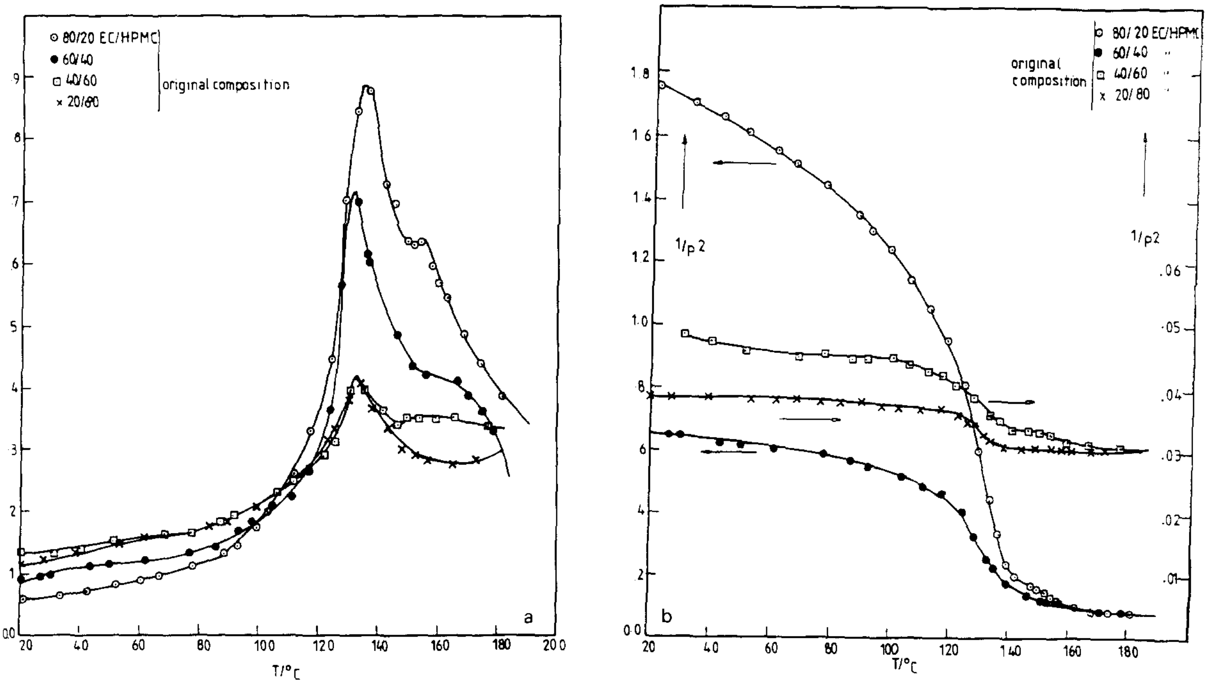


Fig. 4. Logarithmic decrement (a) and relative rigidity (b) for EC/HPMC blends after leaching in distilled water.

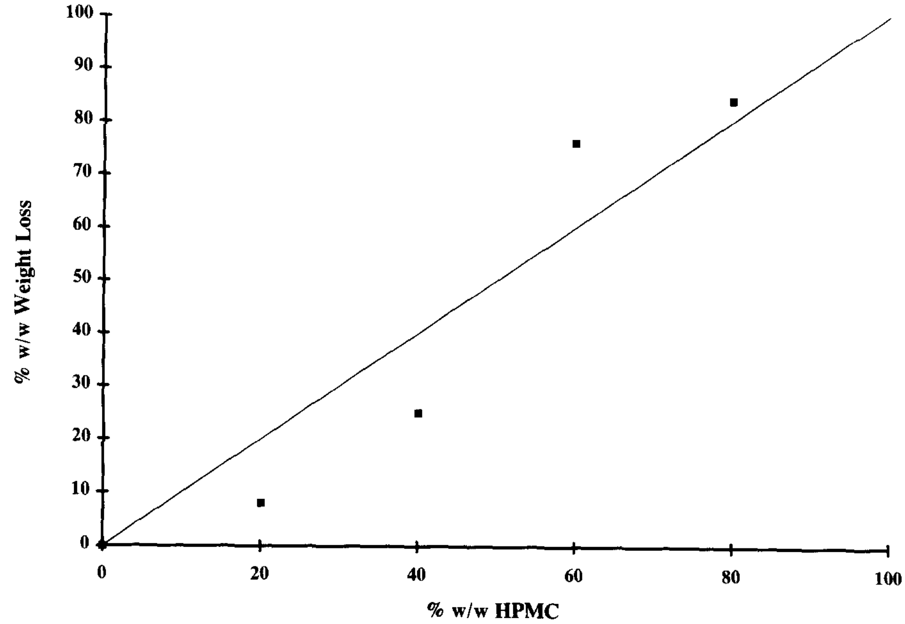


Fig. 5. Experimental weight loss against original blend composition for EC/HPMC blends. The line represents the theoretical weight loss if all HPMC were leached out.

sponding major component. This process is complicated by the rate of solvent removal and changes in the composition of the solvent system during film formation.

The effect of the rate of solvent removal can now be considered. In the case of TBA films, a point is reached when the time scale for molecular diffusion necessary for phase rearrangement becomes comparable to or slower than that for thermodynamically driven concentration changes in the system. This will lead to deviations from equilibrium binodal phase decomposition (indicated by the arrows in Fig. 6a) and give rise to relatively increased mixing in the two phases.

The interfacial tension between the two phases can be approximated by (Van Krevelen and Hoftyzer, 1976):

$$\gamma_{12} \approx \left(\gamma_1^{1/2} - \gamma_2^{1/2}\right)^2 \quad (1)$$

where γ denotes the surface energies of phases 1 and 2 which are given by (Sakellariou, 1993):

$$\gamma_1 = \varphi^1_{\mathrm{EC}}\gamma_{\mathrm{EC}} + \varphi^1_{\mathrm{HPMC}}\gamma_{\mathrm{HPMC}} \quad (2)$$

$$\gamma_2 = \varphi^2_{\mathrm{EC}}\gamma_{\mathrm{EC}} + \varphi^2_{\mathrm{HPMC}}\gamma_{\mathrm{HPMC}} \quad (3)$$

where φ is the volume fraction of EC and HPMC homopolymers; superscripts 1 and 2 denote the corresponding phases. If it is assumed that $\varphi_{\mathrm{HPMC}} > \varphi_{\mathrm{EC}}$ (justified in view of the higher polarity of the former polymer), Eq. 2 and 3 show that as $\varphi^1_{\mathrm{HPMC}}$ and φ^2_{EC} increase in the corresponding phases (increased mixing) the difference in the surface energies of the two phases also increases leading to higher interfacial tension (cf. Eq. 1). The final film morphology will, therefore, reflect a frozen-in morphology of phases with higher interfacial tension and, consequently, larger dispersions of the minor phase. The HPMC-rich domains of the TBA films will, therefore, exceed in size those prepared under equilibrium conditions. Although direct evidence of the pore size in fully formulated EC/HMPC blended film coated drug release systems is not available, Lippold et al. (1980) revealed the presence of large pores (10–100 μm) in coated depots of Carbutamide with EC/PEG1500 blended film.

The effect of changes in the solvent system composition can now be examined. Enrichment of the solvent system in the less volatile methanol will have important implications for polymer solvency, system viscosity, chain conformation and diffusion. The blend of equal volumes of methanol and methylene chloride is a non-solvent/solvent system for EC and a cosolvent system for HPMC (Sakellariou and Rowe, 1991). Solvent enrichment in methanol during film formation will contribute to deviations from the original binodal by altering the solvency of both polymers and phase rearrangement. HPMC will come out of solution first leading to purer HPMC-rich phases (Fig.

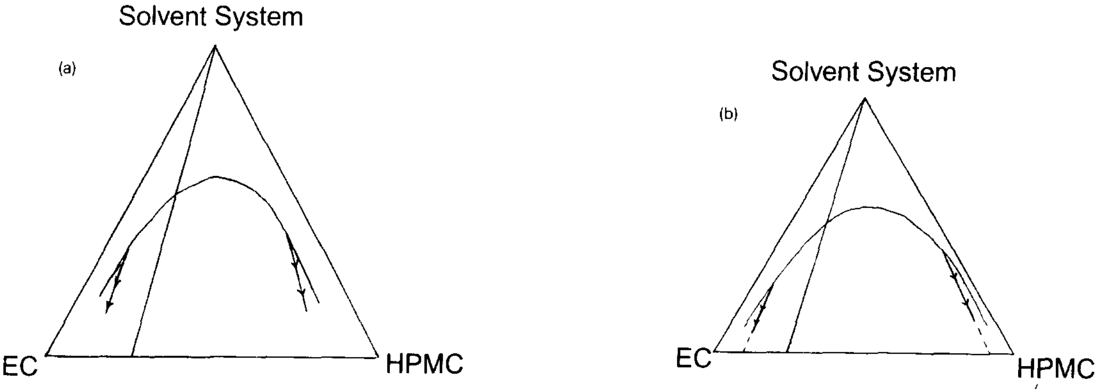


Fig. 6. (a) Schematic phase diagram of EC/HPMC/solvent system (50:50 v/v methanol/methylene chloride). (b) Schematic phase diagram of EC/HPMC/solvent system (methanol/methylene chloride) enriched in methanol (see text for explanation).

6b). A similar process will take place with EC-rich phases at later stages as the solvent system is enriched further in methanol.

Both processes have significant ramifications for drug release from spheroids or tablets coated in coating drums at 60°C. The non-equilibrium morphologies resulting from the film coating procedures will be characterised by larger HPMC-rich domains leading to larger than expected holes and relatively reduced polymer demixing reducing the leaching of HPMC form the film coating. At the same time changes in the solvent system composition would tend to produce purer phases. The final film morphology will depend on the relative rate for the two processes. The kinetically controlled phase morphology of the final film coating will inadvertently lead to complications in the reproducibility of the drug release profiles from solvent cast systems. The final product performance will depend strongly on film thickness, rate of wet film application, solvent system, temperature profile and air flow conditions of the coating process.

References

Lippold, C., Lippold, B.H. and Sgoll, G.B., Steuerung der Arnzeistoff-reisetzung aus Mikrokapseln. *Pharm. Ind.*, 42 (1980) 745-751.

MacKnight, W.J., Karasz F.E. and Fried, J.R., Solid state transition behaviour of blends. In Paul, D.R. and Newman, S. (Eds), *Polymer Blends*, Vol. 1, Academic Press, London, 1978, pp. 185-242.

Rowe, R.C., Film coating -the ideal process for the production of modified release oral dosage forms. *Pharm. Int.*, 6 (1985) 14-17.

Rowe, R.C., The prediction of compatibility/incompatibility in blends of ethylcellulose with hydroxypropyl methylcellulose or hydroxypropyl cellulose using 2-dimensional solubility parameter maps. *J. Pharm. Pharmacol.*, 38 (1986) 214-215.

Sakellariou, P., Effect of polymer compatibility on the surface enrichment in polymer blends. *Polymer*, 34 (1993) 3408-3415.

Sakellariou, P. and Rowe, R.C., Phase separation and morphology in ethylcellulose/cellulose acetate phthalate blends. *J. Appl. Polym. Sci.*, 43 (1991) 845-855.

Sakellariou, P. and Rowe, R.C, Interactions in cellulose derivative films for oral drug delivery. *Prog. Polym. Sci.*, (1995) in press.

Sakellariou, P., Rowe, R.C. and White, E.F.T., The thermomechanical properties and glass transition temperatures of some cellulose derivatives used in film coating. *Int. J. Pharm.*, 27 (1985) 267-277.

Sakellariou, P., Rowe, R.C. and White, E.F.T., Polymer/polymer interactions in blends of ethylcellulose with cellulose derivatives and polyethylene glycol 6000. *Int. J. Pharm.*, 34 (1986a) 93-103.

Sakellariou, P., Rowe, R.C. and White, E.F.T., The solubility parameters of some cellulose derivatives and polyethylene glycols used in tablet film coating. *Int. J. Pharm.*, 31 (1986b) 175-177.

Sakellariou, P., Rowe, R.C. and White, E.F.T., A study of the leaching/retention of water soluble polymers in blends with ethylcellulose using torsional braid analysis. *J. Controlled Release*, 7 (1988) 147-157.

Shah, N.B. and Sheth, B.B., A method for study of timed-release films. *J. Pharm. Sci.*, 61 (1972) 412-416.

Van Krevelen, D.W. and Hoftyzer, P.J., *Properties of Polymers: Their Estimation and Correlation with Chemical Structure*, 2nd Edn, Elsevier, Amsterdam, 1976.