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International Journal of Pharmaceutics 328 (2007) 95–98
INTERNATIONAL JOURNAL OF PHARMACEUTICS
www.elsevier.com/locate/ijpharm

Note

Mixtures of triblock copolymers $E_{62}P_{39}E_{62}$ and $E_{137}S_{18}E_{137}$ Potential for drug delivery from in situ gelling micellar formulations

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Received 16 May 2006; accepted 26 July 2006
Available online 31 July 2006

Abstract

The gelation behaviour of concentrated micellar solutions of mixtures of a block copolymer of ethylene oxide and styrene oxide ($E_{137}S_{18}E_{137}$) with one of ethylene oxide and propylene oxide ($E_{62}P_{39}E_{62}$) has been investigated. Over a wide range of compositions, up to 90 wt.% $E_{137}S_{18}E_{137}$ in the mixture, gelation resembled that of solutions of $E_{62}P_{39}E_{62}$ alone, i.e. they gelled on heating from ambient to body temperature. In related experiments, using the aromatic drug griseofulvin as a comparative standard, it was demonstrated that solubilisation efficiency of dilute micellar solutions of the mixtures with 80 wt.% or more $E_{137}S_{18}E_{137}$ approached that of solutions of $E_{137}S_{18}E_{137}$ alone. Thus it was shown that the mixed system could have both the satisfactory solubilisation capacity of micellar solutions of $E_{137}S_{18}E_{137}$ and the desirable gelation characteristics of $E_{62}P_{39}E_{62}$, and so have potential for use in drug release applications involving in situ gelation.

Keywords: Solubilisation; Block copolymers; In situ gelation

1. Introduction

Block copoly(oxyalkylene)s may self-associate to form micelles in dilute aqueous solution (Booth and Attwood, 2000; Chu and Zhou, 1996) while at higher concentrations the micelles may pack to form liquid crystal mesophases (gels) (Hamley et al., 2001; Chu and Zhou, 1996). These dilute solutions and gels, and those of other poly(oxyethylene)-based block copolymers, are of interest in a variety of pharmaceutical and related applications, particularly for the solubilisation and delivery of drugs which are poorly soluble in water (see, for example, Kwon and Kataoka, 1995; Allen et al., 1999; Kabanov et al., 2002) A feature of the gelation of solutions of certain block copoly(oxyalkylene)s is 'cold gelation', i.e. the formation of a hard gel (high-modulus gel) on heating a concentrated micellar solution from a low temperature. This effect was first recognised in solutions of triblock copolymers of ethylene oxide and propylene oxide, type $E_mP_nE_m$ (where E denotes oxyethylene, OCH_2CH_2, P denotes oxypropylene, $OCH_2CH(CH_3)$, and the subscripts denote number-average block lengths in chain units), and has been exploited in several delivery systems whereby drug-loaded micellar fluids are prepared at room temperature but gel on application at body temperature (see, for example, Schmolka, 1972; Miyazaki et al., 1992; Pisal et al., 2004). A drawback when using micellar solutions of $E_mP_nE_m$ copolymers is their poor solubilisation capacity for aromatic drugs. The use of block copolymers of ethylene oxide and styrene oxide is an obvious strategy, and the high solubilisation capacity of micellar solutions of diblock and triblock copolymers of this type for the aromatic drug griseofulvin has been demonstrated (Crothers et al., 2005). However, although concentrated solutions of these copolymers readily gel, in our experience none of them show cold gelation (Crothers et al., 2002; Yang et al., 2003).

Recently we showed that concentrated solutions of 50/50 wt.% mixtures of copolymers $E_{62}P_{39}E_{62}$ and $E_{137}S_{18}E_{137}$

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doi:10.1016/j.ijpharm.2006.07.047

(S denotes oxyphenylethylene, $OCH_2CH(C_6H_5)$) have the desirable cold gelation behaviour of solutions of copolymer $E_{62}P_{39}E_{62}$ alone (Ricardo et al., 2005). In this paper we present the results of an investigation of the effect of the composition of mixtures of these two copolymers on solubilisation of an aromatic drug in aqueous micellar solutions and gelation of concentrated micellar solutions, and demonstrate that it is possible to combine satisfactory gelation characteristics with a high solubilisation capacity.

2. Experimental

2.1. Copolymers

Copolymer $E_{62}P_{39}E_{62}$ (commercial notation F87) was a gift from ICI Surfactants, now Uniqema, and copolymer $E_{137}S_{18}E_{137}$ was prepared in our laboratory. The molecular characteristics of the copolymers are given in Table 1, i.e. the number-average molar mass (M_n) and weight fraction E (w_E) from C^{13} NMR spectroscopy, and the ratio of weight- to number-average molar mass (M_w/M_n) from gel permeation chromatography. Also listed are values of the critical micelle concentration (cmc) of the two copolymers in aqueous solution at 30 °C. Details can be found elsewhere (Yang et al., 2003; Harrison et al., 2005).

2.2. Gelation

The mobility of the solutions was determined using an inverted-tube test. Solutions (0.5 g) were enclosed in small tubes (internal diameter ca. 10 mm), and observed whilst slowly (<0.5 °C min^{-1}) heating or cooling the tube in a water bath within the range 0–95 °C. Under the conditions used, solutions are immobile in the inverted-tube test if the yield stress of the gel is greater than ca. 30 Pa (Li et al., 2003).

2.3. Solubilisation

Griseofulvin was used as a standard aromatic drug. It is a crystalline solid with a very low water solubility, approximately 10 mg dm^{-3} at 25 °C and 12 mg dm^{-3} at 37 °C (Yalkowsky and Ye, 2003). A portion of stock solution (1 or 2 wt.% copolymer) was added to finely ground griseofulvin powder and the mixture stirred at 37 °C for 3–5 days before being filtered at the same temperature to remove unsolubilised drug. The extent of solubilisation was determined by UV spectroscopy (Crothers et al., 2005).

Table 1
Copolymer characteristics

Copolymer	M_n (g mol^{-1})	w_E	M_w/M_n	cmc (30 °C, g dm^{-3})
$E_{62}P_{39}E_{62}$	7720	0.71	1.09	0.81
$E_{137}S_{18}E_{137}$	14200	0.85	1.06	0.0023

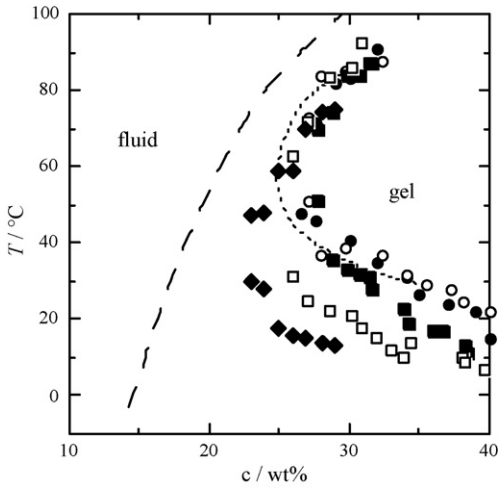

Fig. 1. Gel diagram for aqueous solutions of (dashed curve) $E_{137}S_{18}E_{137}$, (dotted curve) $E_{62}P_{39}E_{62}$ and mixtures of the two ($E_{137}S_{18}E_{137}/E_{62}P_{39}E_{62}$) in proportion (wt.%) (●) 50/50, (◯) 60/40, (■) (70/30), (□) 80/20 and (♦) 90/10. The results for the separate copolymers are taken from Yang et al. (2003) and Harrison et al. (2005).

3. Results and discussion

3.1. Gel diagrams

Hard gel boundaries established for the separate copolymers and for mixtures of the two in the range 50/50 to 90/10 wt.% $E_{137}S_{18}E_{137}/E_{62}P_{39}E_{62}$ are shown in Fig. 1. As can be seen, the gel phase of copolymer $E_{137}S_{18}E_{137}$ has no lower boundary, whereas the gel phase of $E_{62}P_{39}E_{62}$ and those of its mixtures with $E_{137}S_{18}E_{137}$, do have this desirable feature. For example, a 24 wt.% solution of the mixture containing 90 wt.% $E_{137}S_{18}E_{137}$ is fluid at 20 °C and immobile gel at 37 °C.

It has been observed that a single distribution of micelles is formed when the hydrophobic blocks of the copolymers have similar hydrophobicity, otherwise two distributions of micelles are formed (Liu et al., 1999; Harrison et al., 2005; Ricardo et al., 2006). The hydrophobicities of P and S chain units are very different: as judged from values of the critical micelle concentration (cmc in molar units) they are in approximate ratio P:S = 1:10 (Yang et al., 2003). On this basis, the hydrophobicities of the central blocks of the two copolymers are in ratio $P_{39}:S_{18} \approx 1:5$. The values of the cmc summarised in Table 1 reinforce this ranking. Accordingly two types of micelle are expected for the mixture. Even so, investigation of gels by small-angle X-ray scattering has shown that those of $E_{62}P_{39}E_{62}$ and $E_{137}S_{18}E_{137}$ separately, and that of a 50/50 wt.% mixture of the two, all have similar body-centred cubic (bcc) structures with similar lattice dimensions (Hamley et al., 2006).

In Fig. 1 it is seen that the upper boundary of the gel is similar for all the mixtures. This boundary is determined by the negative temperature coefficient of solubility of copolymers in water. The copolymers are fully micellised at this boundary, and the temperature of the gel/fluid transition on heating is determined mainly by the contraction of the E chains of the micelle corona, and the consequent reduction of the volume fraction of

micelles in the solution. The effect is similar for the coronae of both types of micelle. In contrast, the lower boundary is determined by the unimer-micelle equilibrium under the conditions prevailing in concentrated solution (Bedells et al., 1993; Nixon et al., 2004). Copolymer $E_{137}S_{18}E_{137}$ micellises much more readily than copolymer $E_{62}P_{39}E_{62}$, and will be fully micellised at a low temperature. The gel state is achieved when the proportion of $E_{62}P_{39}E_{62}$ micellised on heating is sufficient to increase the overall volume fraction of micelles in solution to the value at which they pack. Consequently, it is influenced markedly by the proportion of $E_{62}P_{39}E_{62}$ micelles in the solution.

3.2. Solubilisation capacity

The solubilisation capacity of the copolymer in solution (s_{cp}) is reported in milligrams of drug solubilised per gram of copolymer after correction for the solubility of griseofulvin in water. No systematic differences in values of s_{cp} were observed for the different copolymer concentrations used, and the values obtained were averages of several determinations. Also calculated are values of the solubilisation capacity per gram of hydrophobic component, calculated from values of s_{cp} as $s_h = s_{cp}/w_h$, where w_h is the weight fraction of the hydrophobic block (i.e. $w_h = 1 - w_E$, with weight-average values of w_E calculated for the mixtures using the values for the separate copolymers listed in Table 1). Correction was made for the small amount of griseofulvin solubilised in the micelle corona (Crothers et al., 2005). The quantity s_h gives a direct measure of the efficiency of solubilisation of griseofulvin in the micelle cores, and so is independent of copolymer composition.

In Fig. 2, solubilisation capacities measured for the separate copolymers and for the five mixtures are plotted against wt.% $E_{137}S_{18}E_{137}$. Solubilisation capacities, both s_{cp} and s_h, are similar to those of micellar solutions of copolymer $E_{137}S_{18}E_{137}$ alone when the proportion of $E_{137}S_{18}E_{137}$ in the mixture is 80 wt.% or more.

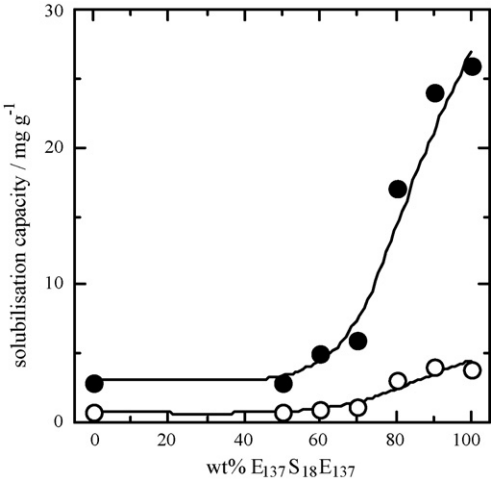

Fig. 2. The effect of the proportion of $E_{137}S_{18}E_{137}$ on the solubilisation capacities at 37 °C of griseofulvin in aqueous micellar solutions of copolymers $E_{137}S_{18}E_{137}$, $E_{62}P_{39}E_{62}$ and their mixtures: (◯) s_{cp} and (●) s_h.

4. Concluding remarks

A system has been defined which combines the superior solubilisation efficiency of micellar solutions of $E_mS_nE_m$ copolymers for aromatic drugs with the desirable gelation characteristics of micellar solutions of $E_mP_nE_m$ copolymers. The technique has been investigated using just two triblock copolymers, and has not been optimised. Results obtained for many block copolymers confirm, as would be expected, that the solubilisation capacity s_{cp} increases when the copolymers used contain a smaller proportion of E. More interestingly, it has been shown that the solubilisation capacity (whether s_{cp} or s_h) increases if triblock copolymers are replaced by comparable diblock copolymers, and can be very high if cylindrical micelles are formed (Crothers et al., 2005).

Acknowledgements

We are grateful to Dr. Zhuo Yang, Dr. Frank Heatley and Mr. Keith Nixon for the preparation and characterisation of copolymer $E_{137}S_{18}E_{137}$. The work was supported by the Brazilian Research Council CNPq and by Engineering and Physical Science Research Council, UK.

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