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Controlling the gelation of aqueous micellar solutions of ethylene-oxide-based block copoly(oxyalkylene)s

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Abstract

Micellar solutions of $E_mP_nE_m$ copolymers may be mobile at ambient temperature and form hard gels on warming to body temperature, whereas micellar solutions of $E_mS_nE_m$ copolymers do not show this effect (E denotes oxyethylene, P oxypropylene and S oxyphenylethylene, and subscripts *m* and *n* denote chain lengths). The aim of this study was to combine the desirable gelation characteristics of solutions of the $E_mP_nE_m$ copolymers with the greater solubilising capacities of solutions of the $E_mS_nE_m$ copolymers. Accordingly, the gelation characteristics in aqueous solution of binary mixtures of the triblock copolymer $E_{62}P_{39}E_{62}$ (Pluronic F87) with $E_{137}S_{18}E_{137}$, $E_{82}S_9E_{82}$ or $E_{76}S_5E_{76}$ were investigated by rheological techniques. We have shown that 50/50 wt.% mixtures of $E_{62}P_{39}E_{62}$ with either $E_{137}S_{18}E_{137}$ or $E_{82}S_9E_{82}$ at a total copolymer concentration of approximately 30 wt.% are fluids of low viscosity at temperatures below 22–25 °C and gels of high elastic modulus at body temperature. The mixed systems have potential as vehicles for the controlled delivery of solubilised drug from gels formed in situ following subcutaneous injection of a low viscosity aqueous solution.

Keywords: Solubilisation; Block copolymers; In situ gelation; Rheology

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1. Introduction

Poly(oxyalkylene) block copolymers may self associate to form micelles in dilute aqueous solution (Booth and Attwood, 2000) while at higher concentrations micelles may pack to form liquid crystal mesophases (gels) (Almgren et al., 1995; Chu and Zhou, 1996;

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Mortensen, 2000; Hamley et al., 2001). These micellar solutions and gels are of interest in a variety of pharmaceutical and related applications (Kabanov and Alakhov, 2000; Malmsten, 2000).

In recent work, we have shown that micellar solutions of block copolymers prepared with hydrophilic blocks of ethylene oxide (EO) and hydrophobic blocks of butylene oxide (BO), styrene oxide (SO) or phenyl glycidyl ether (PGE), are more efficient solubilisers of lyophilic drugs, particularly aromatic drugs, than are micellar solutions of block copolymers prepared from EO and propylene oxide (PO) (Rekatas et al., 2001; Crothers et al., 2005; Taboada et al., 2005). Considering the poorly water-soluble aromatic drug griseofulvin, values of the solubilisation capacity (s_H) expressed per unit mass of hydrophobe in the micelle cores ranks approximately in order of the hydrophobicity of the chain units, i.e.

$$P \ll B < S \approx G$$

where P denotes oxypropylene, $OCH_2CH(CH_3)$; B denotes oxybutylene, $OCH_2CH(C_2H_5)$; S (from styrene oxide) denotes oxyphenylethylene, $OCH_2CH(C_6H_5)$; G (from phenyl glycidyl ether) denotes oxy(phenyloxymethylene)ethylene, $OCH_2CH(CH_2OC_6H_5)$. The difference is significant; values of s_H for P and S cores are in approximate ratio 1:12. As discussed elsewhere (Taboada et al., 2005), micelles with poly(PGE) cores have an advantage for solubilisation compared with micelles with poly(SO) cores.

A feature of the gelation of concentrated aqueous 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 EO and PO, type $E_mP_nE_m$ (where E denotes oxyethylene, OCH_2CH_2, and the subscripts denote number-average block lengths in chain units). The potential usefulness of these systems was realised many years ago in connection with the use of aqueous gels in the treatment of burns (Schmolka, 1972). The thermally reversible gelation characteristics of the poloxamers, and in particular that of Pluronic F127 ($E_{106}P_{69}E_{106}$), have been exploited in drug delivery systems for ophthalmic (Desai and Blanchard, 1998; Edsman et al., 1998; El-Kamel, 2002), rectal (Miyazaki et al., 1986), nasal (Pisal et al., 2004) and parenteral use (Guzmán et al., 1992; Johnston et al., 1992; Miyazaki et al., 1992; Pec et al., 1992; Wang and Johnston, 1995; Katakam et al., 1997; Paavola et al., 1998). A severe limitation when using micellar solutions of $E_mP_nE_m$ copolymers is their poor solubilisation capacity for aromatic drugs, as discussed above. The use of $E_mS_nE_m$ or $E_mG_nE_m$ copolymers seems an obvious strategy. However, although concentrated solutions of these copolymers readily gel (Yang et al., 2003a; Taboada et al., 2005), as do solutions of related diblock (E_mS_n) and inverse triblock ($S_nE_mS_n$) copolymers (Mai et al., 2000; Kelarakis et al., 2001; Crothers et al., 2002; Ricardo et al., 2004), none of them, in our experience, show cold gelation.

Recently (Harrison et al., in press), we have investigated the gelation of micellar solutions formed from a 50/50 wt.% mixture of the block copolymers $E_{45}B_{14}E_{45}$ and $E_{62}P_{39}E_{62}$ (denoted commercially as F87), which have significantly different micellisation behaviour. In 1 wt.% solutions, the critical micelle temperatures of these two copolymers are 20 °C apart, i.e. approximately 40 °C ($E_{62}P_{39}E_{62}$) and 20 °C ($E_{45}B_{14}E_{45}$). A difference in micellisation behaviour carries through to more concentrated solutions (Harrison et al., in press); the temperatures at which hard gels are detected on raising the temperature of 30 wt.% solutions of the individual copolymers are approximately 39 °C ($E_{62}P_{39}E_{62}$) and 13 °C ($E_{45}B_{14}E_{45}$), consistent with the volume fraction of micelles in solution reaching a critical level for packing in a structured mesophase. This despite the fact that micellisation conditions in 30 wt.% solutions are very different from those in dilute solutions, as the solvent is no longer structured by water/water hydrogen bonds but, to an increasing extent as concentration is increased, by water/ether–oxygen hydrogen bonds (see, for example, Yu et al., 1992; Nixon et al., 2004). In dilute solution, at temperatures and concentrations when micellisation is complete, e.g. $c = 1$ wt.%, $T = 50$ °C, the mixed copolymers form two distributions of micelles (Harrison et al., in press). While it is likely that these are two distributions of mixed micelles, effectively the copolymers micellise separately in the mixture, with copolymer $E_{45}B_{14}E_{45}$ starting to micellise at a low temperature and copolymer $E_{62}P_{39}E_{62}$ forming a separate distribution of micelles at a higher temperature. Over a wide concentration range it was found that the cold gelation boundary of the mixture was identical to that of solutions of $E_{62}P_{39}E_{62}$ alone.

This is consistent with copolymer $E_{45}B_{14}E_{45}$ being fully micellised at low temperatures, and the formation of a packed micellar mesophase being determined predominantly by the extent of micellisation of the $E_{62}P_{39}E_{62}$.

In this paper, we describe a first investigation of the possible use of mixtures to combine the desirable solubilisation properties of micellar solutions of $E_mS_nE_m$ copolymers with the desirable gelation properties of $E_mP_nE_m$ copolymers. Following previous work (Harrison et al., in press), we use copolymer $E_{62}P_{39}E_{62}$ as a common component in binary mixtures with three $E_mS_nE_m$ copolymers having different micellisation properties.

2. Experimental

2.1. Copolymers

The $E_mS_nE_m$ copolymers were prepared in 30–50 g quantities by oxyanionic polymerisation of styrene oxide starting from a difunctional initiator to form the central block, followed by ethylene oxide to form the end blocks (Yang et al., 2003a). Copolymer $E_{62}P_{39}E_{62}$ (F87) was a gift from ICI Surfactants, now Uniqema. The molecular characteristics of the copolymers are summarised in Table 1. The $E_mS_nE_m$ copolymers had narrow single-peaked gel permeation (GPC) curves. Values of number-average molar mass (M_n) and wt.% E were obtained by end-group and backbone-group analysis based on ^{13}C NMR, and values of the ratio M_w/M_n (M_w: weight-average molar mass) came from GPC. As described previously (Wang et al., 1992), the GPC curve obtained for our sample of $E_{62}P_{39}E_{62}$ was also narrow but gave evidence of two components with molar masses at the peak of approximately 9000 and 4000 g mol^{-1}, the latter comprising 10 wt.% of the whole. For this copolymer, the values of M_n and wt.% E came from the formula supplied by the manufacturer, and the overall ratio M_w/M_n was obtained using GPC.

Table 1
Molecular characteristics of the triblock copolymers

Copolymer	M_n (g mol^{-1})	wt.% E	M_w/M_n
$E_{62}P_{39}E_{62}$	7720	71	1.09
$E_{137}S_{18}E_{137}$	14200	85	1.06
$E_{82}S_9E_{82}$	8300	87	1.04
$E_{76}S_5E_{76}$	7400	91	1.06

2.2. Tube inversion and rheometry

Solutions were prepared in screw-cap tubes, mixing at temperatures where the solutions were fluid, and allowing several days for equilibration before storing in a refrigerator.

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 while slowly heating the tube in a water bath within the range 0–95 °C. The heating/cooling rate was 0.5° min^{-1} or less. Inverting the tube served to characterise the solution as mobile or immobile. The solutions were closely observed and did not cloud during these tests.

The temperature and frequency dependences of modulus were determined for certain solutions by means of a Bohlin CS50 rheometer with water-bath temperature control. Couette geometry (bob, 24.5 mm diameter, 27 mm height; cup, 26.5 mm diameter, 29 mm height) was used for all the samples, with 2.5 cm^3 sample being added, if possible, to the cup in the mobile state. A solvent trap maintained a solvent-saturated atmosphere around the cell, and evaporation was not significant for the temperatures and time-scales investigated. The samples were loaded into the Couette cell and equilibrated for at least 2 h before beginning an experiment: short equilibration times gave irreproducible results. The strain amplitude was set to a low value ($A = 0.5\%$) using the autostress facility of the Bohlin software in order to keep measurements of modulus within the linear viscoelastic region. Data for solutions of low modulus, which fell outside the range for satisfactory operation of the autostress feedback were rejected.

3. Results and discussion

3.1. Separate copolymers

Results obtained in previous work for aqueous solutions of the separate copolymers are summarised in this section. Results obtained for mixtures are reported in Sections 3.2 and 3.3.

Table 2
Critical micelle concentrations and micelle association numbers for the copolymers in aqueous solution

Copolymer	cmc (30 °C, wt.%)	N_w (50 °C)
$E_{62}P_{39}E_{62}$	0.81	11
$E_{137}S_{18}E_{137}$	0.0023	36
$E_{82}S_9E_{82}$	0.019	17
$E_{76}S_5E_{76}$	0.36	10

3.1.1. *Critical micelle concentration*

Values of the critical micelle concentration (cmc) for the individual copolymers in aqueous solution at 30 °C are listed in Table 2. These are smoothed values, those for the $E_mS_nE_m$ copolymers being taken from Fig. 4 of Yang et al. (2003a), and that for $E_{62}P_{39}E_{62}$ being taken from Fig. 2 of Harrison et al. (in press). As can be seen in the table, the $E_mS_nE_m$ copolymers have a wide range of values of the cmc, covering two decades, all below that of copolymer $E_{62}P_{39}E_{62}$. It is seen that any of the three $E_mS_nE_m$ copolymers in a binary mixture with $E_{62}P_{39}E_{62}$ will micellise first when the temperature of a dilute solution is raised from a low value. As noted in Section 1, it is probable, but not necessary, that this ranking will hold in the concentrated solutions, which form gels. The effect of temperature on values of the cmc of the four copolymers is discussed in Section 3.4.

3.1.2. *Association number*

The average association number of the micelles is an important parameter in a consideration of the gelling characteristics and weight-average (N_w) values are included in Table 2 (see Yang et al., 2003a; Harrison et al., in press; Ricardo et al., in preparation). For efficient packing in a body-centred or face-centred cubic structure it is necessary that the micelles interact effectively as hard spheres, i.e. that the water-swollen E-block corona of a micelle is radially symmetrical (or almost so) and is sufficiently concentrated that, at a given radius, it effectively excludes the E-block corona of a second micelle. As described elsewhere (Yang et al., 2003b; Taboada et al., 2005), for a given value of N_w the average volume of a micelle core is readily estimated, and the corresponding spherical radius (r_c) can be compared with the half-length of the extended hydrophobic block ($l\,1/2$). With allowance made for a Poisson distribution of hydrophobic-block lengths, experience shows that spherical (or near spherical) micelles will be formed if $l\,1/2$ approximately equal to or greater than the value of r_c. The micelles of copolymers $E_{62}P_{39}E_{62}$, $E_{137}S_{18}E_{137}$ and $E_{82}S_9E_{82}$ meet this requirement, while those of $E_{76}S_5E_{76}$ fall short, and may well be elongated.

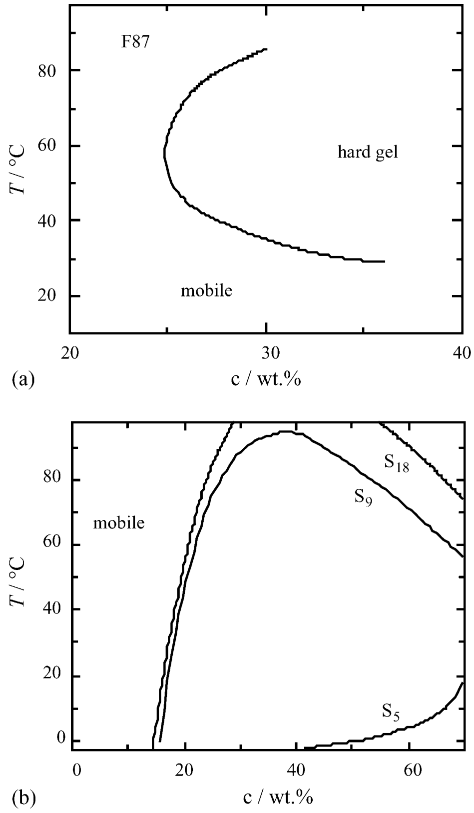

Fig. 1. Gel boundaries for the individual copolymers: (a) copolymer $E_{62}P_{39}E_{62}$ (F87) and (b) copolymers $E_{137}S_{18}E_{137}$ (S_{18}), $E_{82}S_9E_{82}$ (S_9) and $E_{76}S_5E_{76}$ (S_5), as indicated.

3.1.3. *Gel diagrams: copolymers*

Hard gel boundaries for the copolymers established in previous work (Yang et al., 2003a; Harrison et al., in press), mainly by tube inversion but confirmed by rheology, are illustrated in Fig. 1. As seen in Fig. 1a, gels of copolymer $E_{62}P_{39}E_{62}$ have a low-*T* boundary. For example, the fluid/gel transition temperature of a 35 wt.% solution is 30 °C, a convenient gelation temperature for pharmaceutical application. The gelation of another sample of copolymer F87 (from BASF Wyandotte Corp.) has been studied using rheometry (Brown et al., 1992). That sample gelled at somewhat lower concentrations than ours, but at similar temperatures. Maximum elastic moduli of the gels were high for both samples: e.g. $G' \approx 25$ kPa for a 30 wt.% gel of the ICI sample ($T \approx 40$ °C, frequency $f = 1$ Hz, strain amplitude $A = 0.5\%$) and $G' \approx 15$ kPa for a 25 wt.% gel of the BASF sample ($T \approx 50$ °C, $f = 0.05$ Hz, $A = 1\%$). Differences in gelation behaviour between batches of nominally the same commercial $E_mP_nE_m$ copolymers have been remarked upon previously (see, for example, Attwood et al., 1985). No doubt they reflect significant differences in micellisation behaviour (Yu et al., 1997).

As seen in Fig. 1b, gels of copolymers $E_{137}S_{18}E_{137}$ and $E_{82}S_9E_{82}$ first form at concentrations near 15 wt.%, and their more concentrated gels are stable up to high temperatures. Gels of copolymer $E_{76}S_5E_{76}$ form only at concentrations higher than ca. 40 wt.% ($T = -3$ °C) and are restricted to low temperatures. Recent work in our laboratory has shown that crystallisation may occur at low temperatures in solutions of concentration greater that 60 wt.%, which puts an upper limit on the concentration range for studying the gelation of this copolymer. In the concentration range 25–35 wt.% of present interest, i.e. that over which we have investigated the gelation behaviour of $E_{62}P_{39}E_{62}$, solutions of copolymer $E_{76}S_5E_{76}$ do not gel at accessible temperatures. As mentioned in Section 3.1.2, this significant difference in gelation behaviour may well originate in a difference in micelle shape.

3.2. Gel diagrams: mixtures

Aqueous solutions of three mixtures were prepared: i.e. 50/50 wt.% mixtures of $E_{62}P_{39}E_{62}$ with $E_{137}S_{18}E_{137}$ (mixture 1), $E_{82}S_9E_{82}$ (mixture 2) or $E_{76}S_5E_{76}$ (mixture 3). Gel boundaries determined by the tube inversion method are presented in this section. Many of the gelation temperatures shown in Figs. 2–4 are average values from replicate determinations. Reproducibility was ±2 °C at the low-T boundaries, and somewhat poorer, ±4 °C, at the high-T boundary. Reproducibility is discussed in Section 3.4.

The gel boundary found for aqueous solutions of mixture 1 is shown in Fig. 2. Comparison is made with the gel boundaries for the separate copolymers, these being taken from Fig. 1. It is seen that the boundary found for the mixture closely follows that established for copolymer $E_{62}P_{39}E_{62}$ alone. Approximate values of the concentration (c^*) and temperature (T^*) at which gel is first formed are listed in Table 3.

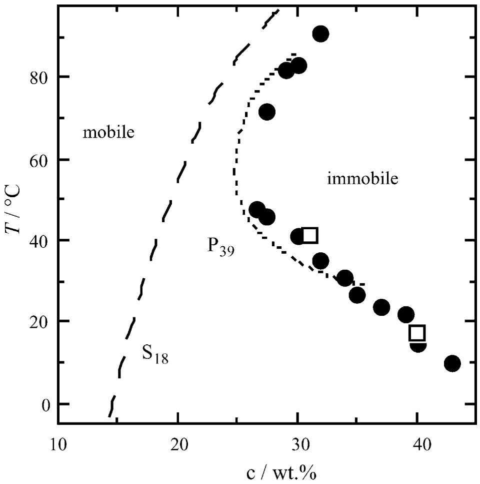

Fig. 2. Gel diagram for aqueous solutions of mixture 1: copolymers $E_{62}P_{39}E_{62}$ and $E_{137}S_{18}E_{137}$, 50/50 wt.%. The dashed curve labelled S_{18} shows the gel boundary for solutions of $E_{137}S_{18}E_{137}$ alone; the dotted curve labelled P_{39} shows that for solutions of $E_{62}P_{39}E_{62}$ alone. The filled circles are data points obtained by the tube inversion method for the mixture; the unfilled squares are data points from rheometry (see Section 3.3).

As discussed in Section 1, it can be assumed that copolymer $E_{137}S_{18}E_{137}$ is fully micellised in solutions

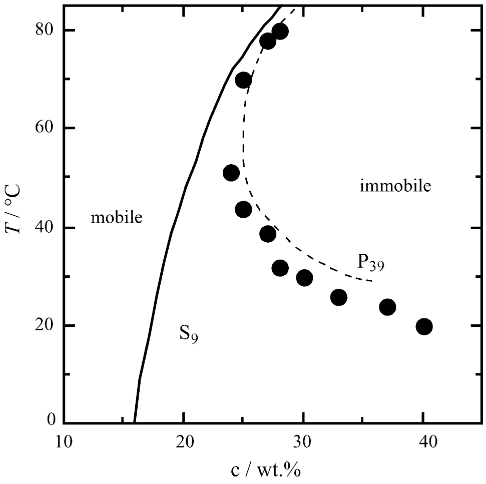

Fig. 3. Gel diagram for aqueous solutions of mixture 2: copolymers $E_{62}P_{39}E_{62}$ and $E_{82}S_9E_{82}$, 50/50 wt.%. The filled circles are data points obtained by the tube inversion method for the mixture. The full curve labelled S_9 shows the gel boundary for solutions of $E_{82}S_9E_{82}$ alone; the dotted curve labelled P_{39} shows that for solutions of $E_{62}P_{39}E_{62}$ alone.

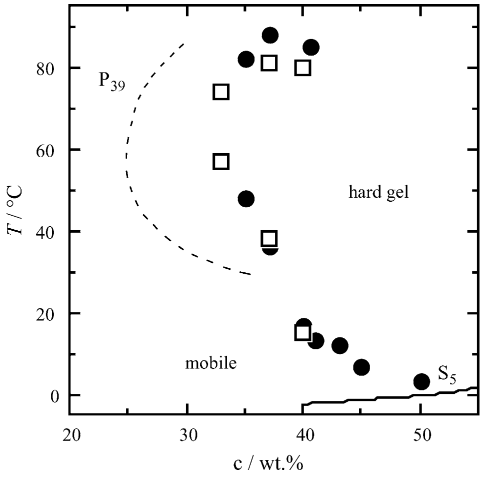

Fig. 4. Gel diagram for aqueous solutions of mixture 3: copolymers $E_{62}P_{39}E_{62}$ and $E_{76}S_5E_{76}$, 50/50 wt.%. The full curve labelled S_5 shows the gel boundary for solutions of $E_{76}S_5E_{76}$ alone; the dotted curve labelled P_{39} shows that for solutions of $E_{62}P_{39}E_{62}$ alone. The filled circles are data points obtained by the tube inversion method for the mixture; the unfilled squares are data points from rheometry (see Section 3.3).

at temperatures below the low-T boundary, whereas micellisation of copolymer $E_{62}P_{39}E_{62}$ is incomplete. As temperature is increased, the extent of micellisation of copolymer $E_{62}P_{39}E_{62}$ increases until, at a critical temperature for packing, a hard gel is formed. Thus, the lower boundary for the mixture depends critically on the extent of micellisation of $E_{62}P_{39}E_{62}$, the least micellisable of the two copolymers under the prevailing conditions.

Results for aqueous solutions of mixture 2 [copolymer $E_{62}P_{39}E_{62}$ with $E_{82}S_9E_{82}$, 50/50 wt.%] are shown in Fig. 3. The pattern of behaviour is similar to that shown in Fig. 2 for mixture 1, as would be expected considering the similar gelation behaviour of the two $E_mS_nE_m$ copolymers (see Fig. 1b). The value of c^* was lower for mixture 2 than for mixture 1, but the value of T^* was similar (see Table 3). This difference in concentration carried through to higher concentrations: e.g. a gelation temperature of 30 °C was obtained with a 34 wt.% solution of mixture 1, but a 30 wt.% solution of mixture 2.

Table 3
Concentration (c^*) and temperature (T^*) at which hard gel is first detected for aqueous solutions of copolymer $E_{62}P_{39}E_{62}$ and its 50/50 wt.% mixtures with $E_mS_nE_m$ copolymers

	c^* (wt.%)	T^* (°C)
$E_{62}P_{39}E_{62}$	25	59
Mixture 1, $E_{137}S_{18}E_{137}$	26	58
Mixture 2, $E_{82}S_9E_{82}$	24	55
Mixture 3, $E_{76}S_5E_{76}$	33	65

The gel boundary found for aqueous solutions of mixture 3 [copolymer $E_{62}P_{39}E_{62}$ with $E_{76}S_5E_{76}$, 50/50 wt.%] is shown in Fig. 4. This gelation behaviour differs considerably from that of the other two mixtures, particularly in the relatively high concentration at which gel was first detected (i.e. c^* some 8 wt.% higher than the value established for solutions of $E_{62}P_{39}E_{62}$ alone, see Table 3). Another difference is the steep slope of the low-T boundary. However, it is clear that copolymer $E_{76}S_5E_{76}$ participates in the gelation process, as packing of micelles of $E_{62}P_{39}E_{62}$ alone would result in $c^* = 50$ wt.%. Micellisation of the two copolymers to a single distribution of mixed micelles is a possibility, as values of the cmc at 30 °C are similar (see Table 2). Similarity of the cmc is known to favour this type of comicellisation even though hydrophobic-block length and composition are different (Liu et al., 1999; Ricardo et al., in preparation).

The viscosity of the fluid phase below the hard gel boundary was not systematically investigated. However, observations in the tube inversion experiments showed that solutions of all three mixtures with $c \geq 35$ wt.% at 20 °C flowed slowly in the tube, whereas solutions with $c = 30$ wt.% were very mobile, with rheometric measurements indicating dynamic viscosities $\eta' \approx 0.2$ Pa s.

3.3. *Rheometry*

Temperature and frequency scans were obtained for aqueous solutions of mixtures 1 and 3. Copolymer $E_{82}S_9E_{82}$ had been used extensively in other work (Yang et al., 2003a; Ricardo et al., in preparation), and the amount remaining after definition of the gel boundary precluded investigation by rheometry.

It is convenient to describe first the results obtained for solutions of mixture 3, as this system was the most extensively investigated by rheometry. Frequency scans (f scans) were obtained for 40 wt.% solutions at intervals of temperature (5 or 10 °C) in the range 5–80 °C. Examples are shown in Fig. 5. That for the solution at 80 °C was characteristic of a viscoelastic fluid, with $G'' > G'$ over much of the frequency range.

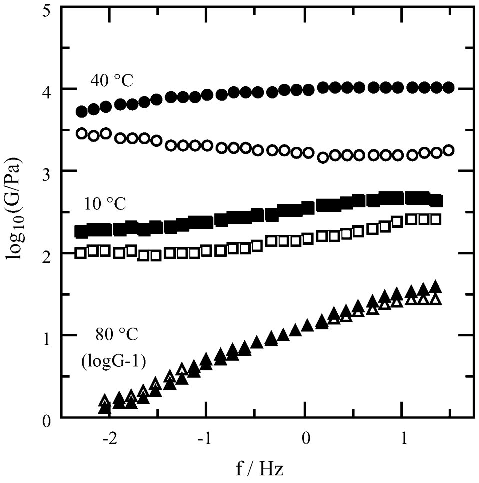

Fig. 5. Frequency dependence of the logarithm of dynamic modulus (measured at $A = 0.5\%$) for a 40 wt.% solution of mixture 3 [copolymers $E_{62}P_{39}E_{62}$ and $E_{76}S_5E_{76}$, 50/50 wt.%]. Filled symbols denote elastic modulus, G'; unfilled symbols denote viscous modulus, G''. For clarity, the data points for the solution at 80 °C have been shifted downwards by 1 unit (as indicated).

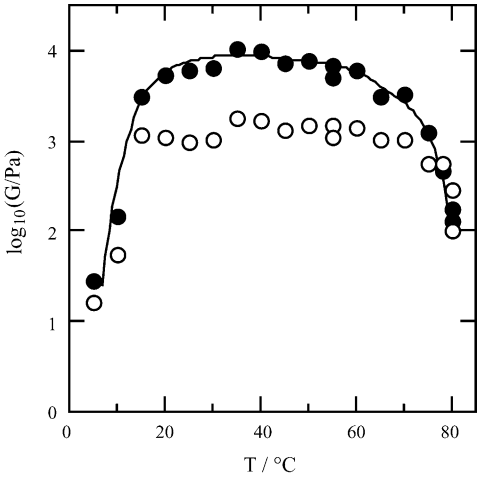

Fig. 6. Temperature dependence of the logarithm of dynamic modulus (measured at $f = 1$ Hz and $A = 0.5\%$) for a 40 wt.% solution of mixture 3 [copolymers $E_{62}P_{39}E_{62}$ and $E_{76}S_5E_{76}$, 50/50 wt.%]. Filled symbols denote elastic modulus, G'; unfilled symbols denote viscous modulus, G''.

Those for the solutions at 5, 10 (illustrated in Fig. 5) and 75 °C, were characteristic of fluids with considerable local structure, i.e. a fluid with $G' > G''$ over the whole frequency range and with higher values of G' than the solution at 80 °C. For example, at $f = 1$ Hz, $G' \approx 330$ Pa (10 °C) compared with 120 Pa (80 °C). At intermediate temperatures, specifically from 15 to 70 °C, all the f scans resembled that illustrated in Fig. 5 for the solution at 40 °C, i.e. G' insensitive to frequency and G'' passing through a minimum as frequency was increased. This pattern is characteristic of packed spherical micelles in a cubic structure (see, for example, Mason and Weitz, 1995; Zhao et al., 1996; Kelarakis et al., 2003). This structure is also reflected in the high level of the modulus throughout the intermediate temperature range, as illustrated in Fig. 6 from moduli at $f = 1$ Hz read off the f scans.

Temperature scans of G' obtained directly for 33 and 37 wt.% solutions of mixture 3, together with the temperature dependence of G' shown in Fig. 6 for the 40 wt.% solution, were used to define gelation temperatures as described previously (Hamley et al., 2001), i.e. as those temperatures at which the value of G' reached 1 kPa, equivalent to a yield stress of the gel of ca. 30 Pa for a cubic gel (Li et al., 2003). Gelation temperatures so defined for mixture 3 are plotted as unfilled squares in Fig. 4. The data from rheometry agree well with those from tube inversion at the low-T boundary, but less well at the high-T boundary.

Frequency scans were obtained for a 40 wt.% solution of mixture 1 over the range 5–40 °C. Examples are shown in Fig. 7. Solutions in the temperature interval

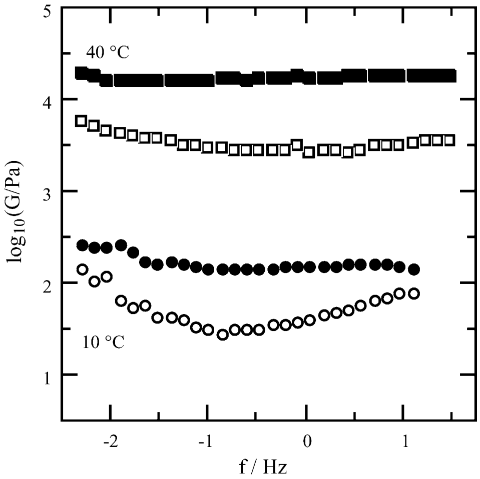

Fig. 7. Frequency dependence of the logarithm of dynamic modulus (measured at $A = 0.5\%$) for a 40 wt.% solution of mixture 1 [copolymers $E_{62}P_{39}E_{62}$ and $E_{137}S_{18}E_{137}$, 50/50 wt.%]. Filled symbols denote elastic modulus, G'; unfilled symbols denote viscous modulus, G''.

20–35 °C gave similar scans to that illustrated for the solution at 40 °C, i.e. $G' > 1$ kPa and a pattern characteristic of a cubic structure. Solutions at 15, 10 (illustrated) and 5 °C gave f scans typical of fluids with local structure.

The temperature dependence of modulus was determined for 31 and 40 wt.% solutions, and these results served to define the low-T fluid/gel boundary in the manner described for mixture 3. These gelation temperatures are plotted in Fig. 2, where they are seen to be in satisfactory agreement with the data points from tube inversion.

By the nature of the tube inversion and rheometric methods, values of G' at the fluid/gel boundary were ca. 1 kPa ($f = 1$ Hz, $A = 0.5\%$). However, gels of concentration and temperature well within the gel region had much higher values measured under the same conditions. For example, for 40 wt.% solutions at 40 °C, $G' = 17$ kPa (mixture 1) and 10 kPa (mixture 3). These values are lower than those found for solutions of copolymer $E_{62}P_{39}E_{62}$ alone, e.g. $G' \approx 25$ kPa for a 30 wt.% solution at 40 °C (Harrison et al., in press), but all are consistent with hard gels of high yield stress.

3.4. Effect of thermal history

As noted in Section 3.2, the temperatures at the upper fluid/gel boundary of the mixed systems could not be defined in a given experiment to better than ±4 °C. In replicate experiments, it became clear that the high-T boundary was sensitive to thermal history. We believe that this was a consequence of the different temperature dependences of the critical micelle concentrations of the copolymers in the mixtures. We illustrate this by the schematic (Fig. 8) which shows van't Hoff plots of log(cmc) against inverse temperature, the slope of which depends upon the standard enthalpy of micellisation through $\Delta_{\text{mic}}H^\circ = \mathrm{d}(\ln \text{cmc})/\mathrm{d}(1/T)$ (Chu and Zhou, 1996; Booth and Attwood, 2000). The lines in Fig. 8 are located by the values of the cmc at 30 °C listed in Table 2. From previous work, we estimate $\Delta_{\text{mic}}H^\circ \approx 30\ \text{kJ mol}^{-1}$ for copolymer $E_{76}S_5E_{76}$, $10\ \text{kJ mol}^{-1}$ for $E_{82}S_9E_{82}$, and zero for $E_{137}S_{18}E_{137}$. The data collected in Harrison et al., in press, lead to $\Delta_{\text{mic}}H^\circ \approx 170\ \text{kJ mol}^{-1}$ for copolymer $E_{62}P_{39}E_{62}$. The reduced slope at high concentrations of $E_{62}P_{39}E_{62}$ (corresponding to $\Delta_{\text{mic}}H^\circ \approx 30\ \text{kJ mol}^{-1}$) is consistent with reports (Yu et al., 1992; Nixon et al., 2004) for related copolymers and, as noted in Section 1, is attributed to the change in solvent conditions when copolymer concentrations exceed ca. 10 wt.%.

The importance of Fig. 8 in the present context is that the value of the cmc of copolymer $E_{62}P_{39}E_{62}$ will be significantly higher than that of a given $E_mS_nE_m$ copolymer at 5 °C, equivalent at a intermediate temperatures, and significantly lower at 85 °C. Indications from other work (Liu et al., 1999; Harrison et al., in press) are that a single distribution of micelle size will form under equilibrium conditions in a solution of a binary mixture of two copoly(oxyalkylene)s with similar values of the cmc, but that two distributions of micelle size will form when the values of the cmc are very dissimilar. Under these circumstances, and as unimers interchange between micelles and solution at all temperatures provided the micelle core is mobile, changes in the size distributions of the micelles are possible as temperature is increased. The overall volume fraction occupied by micelles will not be changed by this effect, but the detail of their packing in the gel state may be changed. As seen from Fig. 8, relative values of the cmc for our copolymers are little changed when temperatures are raised through the low-T gel boundary, i.e. from 20 to 40 °C, and gel formed in this temperature range will be stable. This is important for pharmaceutical application. Changes in the gel structure may occur as the temperature is raised beyond

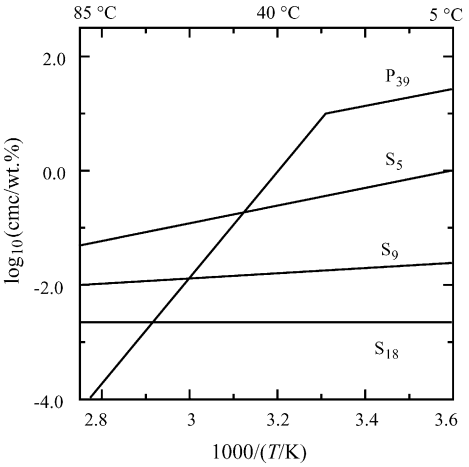

Fig. 8. Schematic showing the temperature dependence of log(cmc) for the four copolymers. The labels P_{39}, S_5, S_9 and S_{18} denote copolymers $E_{62}P_{39}E_{62}$, $E_{76}S_5E_{76}$, $E_{82}S_9E_{82}$ and $E_{137}S_{18}E_{137}$.

40 °C to the upper boundary, and may well effect the high-*T* gel/fluid transition temperature, but that temperature range would not normally be a consideration.

4. Concluding remarks

Assuming an application requiring a vehicle which is fluid at ambient and a hard gel at body temperature then, of the three systems investigated, solutions of mixture 3 (with $E_{76}S_5E_{76}$) are least useful because the steep fluid/gel boundary (see Fig. 4) severely limits the concentration range available. Solutions of concentration $c \geq 35$ wt.% have the disadvantage of poor fluidity below the low-*T* gel boundary. Consequently, we find that mixtures 1 and 2 ($E_{62}P_{39}E_{62}$ with either $E_{137}S_{18}E_{137}$ or $E_{82}S_9E_{82}$) with $c \approx 30$ wt.% have most promise. In such solutions the $E_mS_nE_m$ copolymers, by virtue of their lengthy S-blocks, form compact spherical micelles, which are stable at low temperatures. In combination with copolymer $E_{62}P_{39}E_{62}$, this leads to fluids of low viscosity below the hard gel boundary and gels of high elastic modulus above.

Note added in proof

Regarding the discussion in Section 3.1.2, a very recent SAXS investigation of a 70 wt.% gel of E76S5E76 indicates a hexagonal structure characteristic of elongated micelles (V. Castelleto and I.W. Hamley, private communication).

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