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Solubilisation of drugs in worm-like micelles of block copolymers of ethylene oxide and 1,2-butylene oxide in aqueous solution

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Abstract

Ethylene oxide and 1,2-butylene oxide were sequentially polymerised to form the diblock copolymer $E_{13}B_{10}$ (E = oxyethylene, B = oxybutylene, subscripts denote number-average block lengths in repeat units). Dynamic and static light scattering over the temperature range 10–30 °C demonstrated a transition from compact (spheroidal) micelles to larger, more elongated (worm-like) micelles with temperature increase above a critical onset temperature of about 20 °C. Determination of the solubilisation capacity for griseofulvin, carbamazepine and spironolactone of dilute micellar solutions of this copolymer, together with those of $E_{11}B_8$ and $E_{17}B_{12}$ block copolymers (which also show the sphere-to-worm transition), allowed investigation of the influence on solubilisation characteristics of hydrophobic block length and temperature. The extent of solubilisation at 25 °C of the poorly water-soluble drug spironolactone increased linearly with increase of hydrophobic block length, attributable to a concomitant increase in the proportion of worm-like micelles in solution.

Keywords: Solubilisation; Block copolymers; Worm-like micelles

1. Introduction

Following early work (Collett and Tobin, 1979), aqueous micellar solutions of the commercially available triblock copolymers of type poly(oxyethylene)–poly(oxypropylene)–poly(oxyethylene) have been extensively examined as solubilisers for poorly water-soluble drugs, as described in recent reviews (Kabanov et al., 2002; Kabanov and Alakhov, 2002; Chiappetta and Sosnik, 2007). For convenience we use the formula $E_mP_nE_m$, where E denotes an oxyethylene unit (OCH_2CH_2), P an oxypropylene unit ($OCH_2CH(CH_3)$), and *m* and *n* number-average block lengths in E or P units. Poly(oxypropylene) is not an ideal choice for a solubiliser; poly(oxyalkylene)s of greater hydrophobicity can be incorporated into the copolymers, resulting in a higher extent of micellisation at low temperatures and, with appropriate choice of hydrophobe, a micelle core which is more compatible with a given drug. Oxyanionic polymerisation provides a convenient and versatile synthetic route to copolymers with narrow block-length distributions, and we have prepared copolymers combining ethylene oxide with several alkylene oxides (Booth and Attwood, 2000). Values of the critical micelle concentration (cmc, molar units) provide a useful indicator of hydrophobicity and, for diblock copolymers, the hydrophobicity per chain unit ranks as P:B = 1:6 (Booth et al., 2006), where B denotes an oxybutylene unit, $OCH_2CH(C_2H_5)$. We have reported enhanced solubilisation of griseofulvin in 1 wt.% aqueous solutions of copolymers $E_{49}B_9$ and $E_{134}B_{19}$ at 25 °C compared with that in solutions of $E_{21}P_{47}E_{21}$ (commercially denoted P94) under the same conditions (Rekatas et al., 2001), a result which reflects, at least in part, the high critical micelle temperature (23 °C) of a 1 wt.% solution of P94 (Nixon et al., 2004). Related measurements using solutions of

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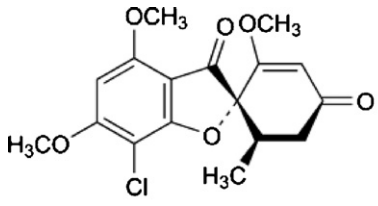
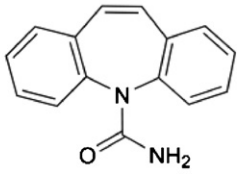
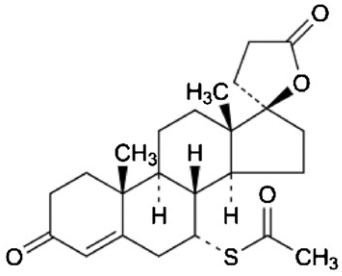


Griseofulvin



Carbamazepine



Spironolactone

Scheme 1.

copolymer $E_{11}B_8$ showed a further increase in solubilisation capacity for griseofulvin, which was related to a change from compact to worm-like micelles as temperature was increased from 25 to 40 °C (Chaibundit et al., 2002).

The effect of solubilisation on micelle geometry has been discussed from a theoretical standpoint by Nagarajan, e.g., for aqueous solutions of $E_mP_nE_m$ copolymers (Nagarajan, 1999). Eisenberg and coworkers in their interesting review point out that the differences in morphology (at the simplest level spherical and cylindrical micelles) have to be taken into account in optimising drug delivery vehicles (Allen et al., 1999). In this paper, we describe an investigation of the effect of micelle shape (spherical and worm-like) on the aqueous solubility of three drugs: griseofulvin, spironolactone and carbamazepine (see Scheme 1). Carbamazepine (pK_a of 7.0) is ionisable, and phosphate buffer was used to maintain pH. The copolymers investigated were $E_{11}B_8$, $E_{13}B_{10}$ and $E_{17}B_{12}$, with static and dynamic light scattering methods used to investigate micelle size and shape.

2. Experimental

2.1. Materials

The E_mB_n copolymers were prepared by sequential oxyanionic copolymerisation initiated by 2-(2-methoxyethoxy) ethanol partly converted to its potassium salt. Details of the preparation of copolymers $E_{11}B_8$ and $E_{17}B_{12}$ can be found elsewhere (Chaibundit et al., 2002, 2005). Copolymer $E_{13}B_{10}$ was prepared in a similar way. The copolymers were characterised by gel permeation chromatography (tetrahydrofuran eluent, refractive index detector, poly(oxyethylene) calibrants) and by ^{13}C NMR, the former to determine the ratio of weight-average to number-average molar mass (M_w/M_n), and the latter to confirm the diblock architecture and to determine the absolute value of M_n. Details of the methods have been published (Heatley et al., 1990; Bedells et al., 1993). Values of the molecular characteristics are listed in Table 1. Lutrol F127 ($E_{100}P_{67}E_{100}$) was donated by BASF. Griseofulvin (≥95% pure), carbamazepine and spironolactone (≥97 pure) were purchased from Sigma–Aldrich Co.

Table 1
Molecular characteristics of the copolymers

Copolymer	M_n (g mol^{-1})	w_B	M_w/M_n	M_w (g mol^{-1})
$E_{11}B_8$	1090	0.543	1.03	1120
$E_{13}B_{10}$	1290	0.557	1.04	1340
$E_{17}B_{12}$	1610	0.536	1.02	1640

w_B = Weight fraction of poly(oxybutylene). M_w is calculated from M_n and M_w/M_n.

2.2. Association properties in aqueous solution

Determinations of the micelle properties of copolymers $E_{11}B_8$ and $E_{17}B_{12}$ in aqueous solution have been described in detail elsewhere (Chaibundit et al., 2002, 2005). Those of copolymer $E_{13}B_{10}$ were investigated in a similar way, as described briefly below. The information available for the three copolymers from previous (Chaibundit et al., 2002, 2005) and present work, as well as the correlation of critical micelle concentrations with B-block length (Booth et al., 2006), indicates that their critical micelle concentrations are low, sufficiently so that the copolymers are essentially completely micellised in 1 wt.% aqueous solution at 25 °C and above.

Turbidity of the micellar solutions was a consideration for light scattering measurements and care was taken to work under conditions which ensured optical clarity, i.e., at temperatures several degrees below the points at which turbidity was detectable to the eye for the solutions in the concentration range used.

In an experiment, solutions were clarified by filtering through Millipore Millex filters (0.22 μm) directly into clean scattering cells. Static light scattering (SLS) intensities were measured by means of a Brookhaven BI200S instrument using vertically polarised incident light of wavelength 488 nm supplied by an argon-ion laser operated at 500 mW or less. The intensity scale was calibrated against benzene, and the scattering angle was 90° to the incident beam. Debye plots were used to obtain values of the weight-average molar mass of the micelles ($M_{w,mic}$) by extrapolation to zero concentration, and of the corresponding effective-hard-sphere (thermodynamic) radius of the micelles. Dynamic light scattering (DLS) measurements were made with the same instrument, using a Brookhaven BI9000AT digital correlator to acquire data. The data were analysed using the CONTIN program (Provencher, 1979) to obtain intensity fraction distributions of apparent hydrodynamic radius ($r_{h,app}$, radius of the hydrodynamically equivalent hard sphere) and of $r_{h,app}$ averaged over the intensity distribution, extrapolation of the latter to zero concentration giving true values of the hydrodynamic radius (r_h).

2.3. Drug solubilisation

Saturated drug-loaded solutions were prepared in glass vessels by mixing excess powdered drug (10 mg) with 2 ml of 1 wt.% copolymer solution (phosphate buffer, pH 7.4, 0.067 molar as required) and stirring at constant-temperature (25 or 37 °C) for 3 days before filtering (Millipore, 0.45 μm) to remove unsolubilised material. Alternatively, excess powdered drug was mixed with molten copolymer (2 h, 40 °C) before adding sufficient solvent at 40 °C to prepare a 1 wt.% solution. After 1 h, the mixture was cooled to 25 or 37 °C and treated as described above. Blank experiments (no copolymer) gave the solubility of drug in buffer or water.

The amount of drug solubilised was determined by HPLC, using a Spherosorb ODS2 C18 column (5 μm), a mixed mobile phase (acetonitrile/water/trifluoroacetic acid, 40/60/0.1) at 40 °C, a flow rate of 1 ml min^{-1}, and a UV detector. In an experiment, the filtrate was diluted five times with mixed solvent (50/50/0.1) before injection (5 μl). Calibration of peak area was by injection of a series of drug solutions in the same mixed solvent. In a second method for the determination of spironolactone and carbamazepine concentration, the filtrate was diluted fifty times with the (50/50/0.1) mixed solvent and the UV absorbance determined at the optimum wavelength: 285 nm for spironolactone and 292 nm for carbamazepine. Calibration with drug alone gave satisfactory Beer's Law plots. All measurements were carried out in triplicate and the results averaged. Values from the two methods were in good agreement for these two drugs. The evidence from HPLC was that spironolactone and carbamazepine were free from breakdown products after the 3 days equilibration. Our sample of griseofulvin was less pure, and degradation to soluble impurities under the conditions of the experiment was a possibility. Consequently, only the HPLC assay was used as this was not affected by the presence of such impurities.

It is known that anhydrous carbamazepine in aqueous solution transforms rapidly into a stable dihydrate (Kahela et al., 1983). In our experiments, the time allowed for equilibration was sufficient to obtain a saturated solution characteristic of the dihydrate.

3. Results and discussion

3.1. Micelle size and shape

Values obtained for the two micelle radii and for the weight-average association number of the micelles, N_w defined as $M_{w,mic}/M_w$, where M_w is the weight-average molar mass of the unassociated copolymer molecules (unimers), are listed in Table 2. The formation of elongated (worm-like) micelles on heating the solution is indicated by a sharp rise in value of all three micellar parameters. The effect in DLS is illustrated for copolymer $E_{13}B_{10}$ in Fig. 1, and elsewhere (Chaibundit et al., 2002, 2005) for copolymers $E_{11}B_8$ and $E_{17}B_{12}$.

Fig. 1 shows the change in the intensity fraction distribution of $\log(r_{h,app})$ as the temperature of a 1 wt.% solution of $E_{13}B_{10}$ is increased from 20 to 36 °C. The size distribution curves are consistent with a relatively narrow distribution of small spherical micelles at 20 °C, and a broader distribution of large elongated micelles at 32 and 36 °C with much reduced scattering intensity from small micelles. The attribution to elongated micelles is based on static light scattering through consideration of the core size of the micelles, as described previously for the other two copolymers (Chaibundit et al., 2002, 2005). The specific volume of poly(oxybutylene) at 30 °C is 1.036 $cm^3\ g^{-1}$ (Mai et al., 1997), so the average core volume of micelles with $N_w = 290$

Table 2
Micelle properties

Copolymer	T (°C)	r_h (nm)	$M_{w,mic}/10^5$ (g mol^{-1})	N_w	r_t (nm)
$E_{11}B_8$[a]	25	5.0	0.7	63	3.7
	30	7.6	0.9	80	4.0
	35	9.0	1.5	140	4.9
	40	16	3.8	340	7.2
$E_{13}B_{10}$	10	5.7	0.6	45	2.9
	20	6.0	0.9	66	3.8
	30	14	3.8	290	9.3
$E_{17}B_{12}$[b]	10	7	1.6	98	5.0
	15	6	2.0	120	6.0
	20	19	5.3	320	15

[a] Values from Chaibundit et al. (2002).
[b] Values from Chaibundit et al. (2005).

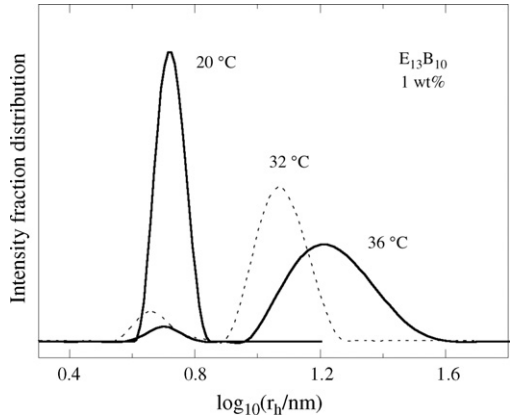


Fig. 1. Intensity fraction distributions of log(micelle hydrodynamic radius) for a 1 wt.% solution of copolymer $E_{13}B_{10}$ at the temperatures indicated.

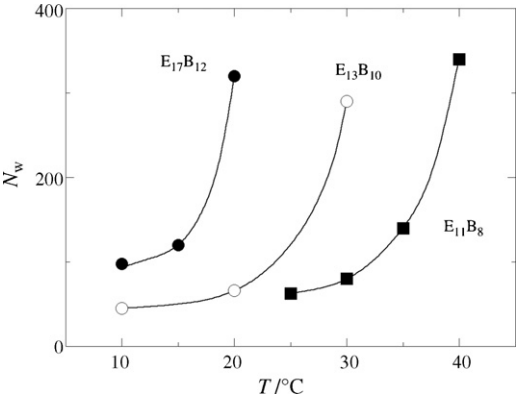


Fig. 2. Temperature dependence of micelle association number (N_w) for E_mB_n copolymers.

and B_{10} core blocks is approximately 360 nm^3 and, if spherical, the micelles would have a radius of 4.4 nm whereas, given 0.363 nm per B unit (Flory, 1969), the length of a B_{10} block is only 3.6 nm. On average, the B blocks would be over-stretched in a spherical core, and a cylindrical core would result. In support of this argument, the rheological characteristics of solutions of $E_{17}B_{12}$ indicate worm-like micelles (Chaibundit et al., 2005). Also small-angle neutron scattering from dilute aqueous solutions of copolymer $E_{18}B_{10}$ at temperatures of 45 °C and higher is also consistent with worm-like micelles (Hamley et al., 2001; Fairclough et al., 2006). The indication from Fig. 1 is a transition from compact to worm-like micelles in solutions of copolymer $E_{13}B_{10}$ at temperatures above 20 °C which is still incomplete at 36 °C, and with the elongated micelles increasing in length as the temperature is increased. The temperature effect reflects the positive enthalpy of micellisation in these systems, which is typical of many amphiphilic copolymers in water, and has its origin in the hydrophobic effect (Tanford, 1980).

Some impression of the weight percentages of copolymer forming spherical and worm-like micelles can be obtained from the DLS and SLS results, bearing in mind that the fractional scattering intensity in DLS depends on $cM_{w,mic}$ whereas SLS yields $M_{w,mic}$, where c is the mass concentration of the species. For the solution at 32 °C, the peak corresponding to spherical micelles is *ca.* 10% of the whole. Assuming that $M_{w,sph} \approx 1 \times 10^5$ g mol^{-1} (similar to the SLS value for 20 °C), and that $M_{w,worm} \approx 5 \times 10^5$ g mol^{-1} (higher than the SLS value at 30 °C) then there will be approximately 30 wt.% (compact) and 70 wt.% (worms) in the solution of $E_{13}B_{10}$ at 32 °C. The proportion of spherical micelles in solution at 36 °C will be somewhat lower, but not negligible.

The plots of association number versus scattering intensity shown in Fig. 2 illustrate the similarity in behaviour of the three copolymers as the temperature is raised. Given that a deviation from the low-T baseline indicates the onset of the sphere-to-cylinder transition, the curves in Fig. 2 indicate onset temperatures (T_{onset}) of approximately 15, 20 and 30 °C, respectively, for $E_{17}B_{12}$, $E_{13}B_{10}$ and $E_{11}B_8$ in dilute aqueous solution.

3.2. Drug solubilisation

Solutions of copolymer $E_{17}B_{12}$ were faintly turbid at temperatures above 20 °C (Chaibundit et al., 2005). The effect was ascribed to the presence of very long worm-like micelles. These solutions, which were stable over long periods of time, were avoided in the light scattering experiments but were used in the solubilisation experiments. The effect of turbidity on the UV signal during drug assay was negligible because the solutions were clear when diluted for this purpose. Solutions of copolymer $E_{11}B_8$ and $E_{13}B_{10}$ were optically clear at the temperatures used for solubilisation.

Solubilities (S) were determined as milligram drug solubilised per decilitre of solution, which is equivalent to mg/g for 1 wt.% copolymer solution. Values were determined for the three drugs in micellar solutions of the E_mB_n copolymers at 25 °C, this temperature being representative of the conditions used in formulation and storage. Additional measurements were made for spironolactone and carbamazepine in solution at 37 °C. In Table 3, we report values of the enhancement of solubility (S/S_0), where S_0 (mg dl^{-1}) is the solubility of the drug in the blank, and of the solubilisation capacity, $S_{cp} = S - S_0$ in mg g^{-1}.

Dissolving spironolactone and carbamazepine in the copolymer melt before making up the solution had only a marginal effect on the solubilisation capacity, typically <20% increase: a smaller effect than observed previously for griseofulvin in solutions of E/B copolymers (Crothers et al., 2005). This may well be an effect of increased degradation of griseofulvin at the higher temperature used in preparing the micellar solution from the melt which would not have been recognised in the previous work using a UV assay alone.

Carbamazepine is moderately soluble in the buffer solution (it is approximately 28% ionized at pH 7.4) and, as a consequence of its affinity for the aqueous phase, the enhancement of solubility by use of a micellar solution is low, $S/S_0 < 2$ for solutions at 25 °C. Comparison can be made with a value of $S/S_0 = 1.25$ obtained for the commercial copolymer Lutrol F127 under the same conditions: solubilisation by micellar solutions of the E_mB_n copolymers is better, but not remarkably so. The weight fraction of the hydrophobic block in F127 is about half that in the E_mB_n copolymers, 0.3 compared with *ca.* 0.55 (see Table 1), and a lower value might be expected on that account. More importantly, the critical micellisation temperature of a 1 wt.% solution of F127 is about 24 °C, so the copolymer is barely micellised at 25 °C. The fact that the solubilisation capacity of a poorly-micellised solution of F127 is similar to that of a

Table 3
Solubilisation of drugs in 1 wt.% block copolymer solution

	S/S_0 solution	S_{cp} solution (mg g^{-1})	S/S_0 melt	S_{cp} melt (mg g^{-1})
Griseofulvin[a]				
T = 25 °C				
$E_{11}B_8$	3.0	2.0	–	–
$E_{13}B_{10}$	4.7	3.7	–	–
$E_{17}B_{12}$	5.5	4.5	–	–
Spironolactone[b]				
T = 25 °C				
$E_{11}B_8$	2.82	3.09	3.49	4.23
$E_{13}B_{10}$	5.12	6.97	5.71	8.00
$E_{17}B_{12}$	7.18	10.5	7.76	11.5
T = 37 °C				
$E_{11}B_8$	3.28	6.62	3.52	7.31
$E_{13}B_{10}$	4.41	9.93	4.62	10.5
$E_{17}B_{12}$	4.93	11.4	5.31	12.5
Carbamazepine[c]				
T = 25 °C				
$E_{11}B_8$	1.43	5.1	1.45	5.3
$E_{13}B_{10}$	1.79	9.3	1.95	11.3
$E_{17}B_{12}$	1.91	10.7	2.07	12.6
T = 37 °C				
$E_{11}B_8$	1.57	11.5	2.10	13.0
$E_{13}B_{10}$	1.92	18.4	2.76	20.8
$E_{17}B_{12}$	1.94	18.9	2.80	21.2

[a] S_0 = 1.0 mg dl^{-1} (25 °C) (Yalkowsky and He, 2003).
[b] S_0 = 1.7 mg dl^{-1} (25 °C) and 2.9 mg dl^{-1} (37 °C).
[c] S_0 = 11.8 mg dl^{-1} (25 °C) and 20.1 mg dl^{-1} (37 °C).

well-micellised solution of $E_{11}B_8$ is a clear indication that solubilisation in the micelle core is not an over-riding factor for this drug. Since carbamazepine is poorly ionized under our experimental conditions then penetration into the hydrophobic core must be low.

Griseofulvin and spironolactone are poorly soluble in water, and values of S/S_0 are higher: in the range 3–7 for solutions at 25 °C. A low value of $S/S_0 \approx 2$ was measured for griseofulvin in 1 wt.% F127 solution at 25 °C, attributable in part to the low extent of micellisation of the copolymer at that temperature.

3.2.1. Effects of block length and temperature on solubilisation capacity

For griseofulvin and spironolactone, it is reasonable to assume that the solubilised drug is predominantly in the micelle core. Indeed, evidence that this is so for griseofulvin has been reported (Crothers et al., 2005). Here, we focus attention on the more complete results for spironolactone. Regarding the form of the micelles in solution, it is clear from the light scattering results that micelles of $E_{11}B_8$ are compact (spherical) in solution at 25 °C, but that solutions of $E_{11}B_8$ at 37 °C, and those of the other two copolymers at 25 and 37 °C, contain worm-like micelles to an extent which increases with increase in temperature over the onset temperature for formation of elongated micelles, where $T_{onset} = 15$, 20 and 30 °C for $E_{17}B_{12}$, $E_{13}B_{10}$ and $E_{11}B_8$, respectively. Thus, so far as formation of worm-like micelles is concerned, we might expect micelles of $E_{11}B_8$ in solution at 37 °C to be similar to those of $E_{13}B_{10}$ at 25 °C, and those of $E_{13}B_{10}$ in solution at 37 °C to be similar to those of $E_{17}B_{12}$ at 25 °C. Solubilisation capacity S_{cp} is plotted against B-block length in Fig. 3: the dotted lines illustrate the connections pointed out above. We note that this direct comparison of results for the three copolymers is valid since the proportion of hydrophobic block in each (w_B in Table 1) is very similar.

The solubilisation capacity at 25 °C is linearly dependent on block length, which we relate to the increase in the proportion of worm-like micelles as the value of $T–T_{onset}$ is increased. The increase in length of the worm-like micelles, indicated by the shift in peak in the DLS distribution to higher values of the apparent radius of hydration (see Fig. 1) will be of less importance, as end effects will be small once the worms reach a certain length. The solubilisation capacity of solutions of copolymer $E_{17}B_{12}$ increased very little in the temperature interval 25–37 °C, consistent with effective completion of the spheres-to-worms transition at $T–T_{onset} > 20$ °C.

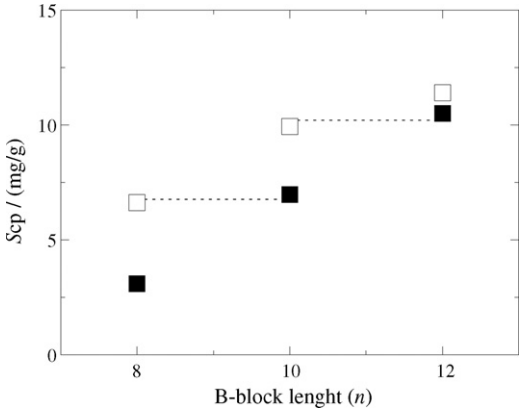


Fig. 3. The dependence of solubilisation capacity on B-block length for copolymers $E_{11}B_8$, $E_{13}B_{10}$ and $E_{17}B_{12}$ in aqueous solution at (■) 25 °C and (□) 37 °C.

Other copolymers, which form worm-like micelles in aqueous solution have been investigated as potential drug solubilisers. For example, copolymer $E_{17}S_8$ (S denotes an oxyphenylethylene unit, $OCH_2CH(C_6H_5)$, from polymerisation of styrene oxide) forms worm-like micelles in solution at 25 and 37 °C and, as a consequence, has higher solubilisation capacities for griseofulvin than those of copolymers which form spherical micelles under corresponding conditions (Crothers et al., 2005). An aqueous solution containing worm-like micelles of copolymer $E_{40}(EE)_{40}$ (EE denotes an ethylethylene unit, $CH_2CH(C_2H_5)$) has been used to solubilise triamterine, but without comparison with corresponding solutions of copolymers forming spherical micelles (Kim et al., 2005).

4. Concluding remarks

The design of block copolymers with appropriate composition and architecture to form micelles with high solubilisation capacity for poorly water-soluble drugs is an important goal. In this study, we have explored the potential use of worm-like micelles to achieve improved drug loading capacity. We have shown that the micelles of the block copolymer $E_{13}B_{10}$ undergo a transition at about 20 °C from spherical to elongated worm-like micelles in dilute aqueous solution as the number of unimers per micelle increases. A consideration of the solubilisation capacity of dilute aqueous solutions of $E_{13}B_{10}$ and that of other E_nB_m copolymers that also form worm-like micelles has shown a linear increase of the efficiency of solubilisation of the poorly water-soluble drug spironolactone as the proportion of micelles in worm-like form in solution is increased. Enhancement of the solubilising capacity of the more water-soluble drug carbamazepine was less pronounced than that of both spironolactone and griseofulvin. The micelle/water partition coefficient for this partially ionised drug is expected to be significantly lower and solubilisation in the micelle core is consequently not such a determining influence on drug solubility in the block copolymer solutions. Finally, in considering the possibility of in vivo application of these copolymers we note that the temperature of the sphere-to-cylinder transition in related copolymer systems is lowered by the presence of structure-forming salts (see, e.g., Jørgensen et al., 1997), and we take this as a strong indication that the favourable results we report will be reproduced in practice.

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