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Mini review

Block copolymers for drug solubilisation: Relative hydrophobicities of polyether and polyester micelle-core-forming blocks

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Abstract

Published values of the critical micelle concentration are tabulated for diblock copolymers E_mP_n, E_mB_n, E_mS_n, E_mL_n, E_mVL_n and E_mCL_n, where E denotes a chain unit derived from ethylene oxide, P from propylene oxide, B from 1,2-butylene oxide, S from styrene oxide, L from DL-lactide, VL from γ-valerolactone and CL from ε-caprolactone, and the subscripts denote average chain lengths. Noting that log(cmc/mol dm^{-3} is proportional to the standard Gibbs energy of micellisation, the dependence of this quantity on hydrophobic block length (n) is explored for a given E-block length. Superposition of data allows ranking of the hydrophobicities of the chain units. The ratios relative to the least hydrophobic unit are:

P : L : B : VL : S : CL = 1 : 4 : 6 : 10 : 12 : 12

Transitions in the slope of log(cmc) versus n are assigned to changes in the unimer-micelle equilibrium and related to the formation of unimolecular micelles and, at high values of n, to the completion of that process. The formation transition is seen in the plots for all the copolymers except the least hydrophobic, E_mP_n. The completion transition is seen in the plots for E_mCL_n and E_mL_n copolymers, as these alone include results for copolymers with very lengthy hydrophobic blocks.

Keywords: Solubilisation; Block copolymers; Critical micelle concentrations; Micelles

Contents

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1. Introduction

Micelles with poly(oxyethylene) blocks forming the hydrophilic corona and hydrophobic poly(ether) blocks forming the core have been investigated as vehicles for drug solubilisation in dilute aqueous solution. The commercially-available triblock copolymers of type poly(oxyethylene)–poly(oxypropylene)–poly(oxyethylene) were first investigated for this purpose (Collett and Tobin, 1977) and the considerable body of work since has been reviewed (Kabanov et al., 2002; Kabanov and Alakhov, 2002; Chiappetta and Sosnik, 2007). For convenience we denote these copolymers as $E_mP_nE_m$, 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. We have used sequential oxyanionic chemistry to prepare copolymers with different block architectures and poly(oxyalkylene) core-forming blocks (Booth and Attwood, 2000; Booth et al., 2006); e.g., diblock copolymers such as E_mP_n, E_mB_n and E_mS_n, where B denotes an oxybutylene unit, $OCH_2CH(C_2H_5)$, prepared from 1,2-butylene oxide, and S an oxyphenylethylene unit, $OCH_2CH(C_6H_5)$, prepared from styrene oxide. Values of the critical micelle concentration (cmc, molar units) provide a useful indicator of hydrophobicity, and for diblock copolymers the hydrophobicities per chain unit determined in this way rank as P:B:S = 1:6:12 (Booth et al., 2006). The longest P block available commercially is ca. P_{70} (e.g., in Pluronic F127, poloxamer 407, nominally $E_{98}P_{67}E_{98}$) which is equivalent to P_{35} in a diblock copolymer, in turn equivalent, so far as hydrophobicity is concerned, to B_6 and S_3 blocks. Accordingly, if the requirement in formulation is a high extent of micellisation in aqueous solution at room temperature, say 25 °C, then E_mP_n or $E_mP_nE_m$ copolymers are poor candidates compared with diblock or triblock copolymers with B or S blocks. Several reports confirm the superior solubilisation capacities for griseofulvin of solutions of copolymers with B or S blocks at 25 °C compared with those of P blocks caused, at least in part, by their higher extent of micelisation (see, e.g., Attwood and Booth, 2007).

Poly(oxyethylene)–polyester copolymers with hydrophobic blocks prepared by oxyanionic polymerisation of cyclic esters have proved to be an attractive alternative to $E_mP_nE_m$ copolymers. Early reports of pharmaceutical interest include the use of diblock copolymers of ethylene oxide and DL-lactide as micellar carriers for paclitaxel and testosterone in 1996 (Zhang et al., 1996; Hagan et al., 1996), of micellar solutions of diblock copolymers of ethylene oxide and ε-caprolactone for solubilisation of indomethacin (Kim et al., 1998a), and, comparatively recently, of copolymers of ethylene oxide and γ-valerolactone for solubilisation of paclitaxel (Lee et al., 2005). Statistical copolymerisation of glycolide with DL-lactide has been used to prepare copolymers with core-forming blocks of lower hydrophobicity, but aimed at thermoreversible gelation of concentrated micellar solutions rather than at drug solubilisation in dilute micellar solution (Jeong et al., 1999; Zentner et al., 2001). Several general reviews include copolymers with polyester blocks (Aliabadi and Lavasanifar, 2006; Savic et al., 2006; Gaucher et al., 2005; Attwood et al., in press) and point to high solubilisation capacities for certain drugs in these systems

Our aim in this study was to use published values of the critical micelle concentrations in aqueous solution of diblock copolymers of these two classes of copolymer to obtain a direct comparison of the hydrophobicities of their chain units. We use the notation E_mL_n, E_mCL_n and E_mVL_n to describe the diblock copolymers with hydrophobic blocks prepared from cyclic esters. Thus L denotes carbonyloxymethylmethylene, $CO{\cdot}OCH(CH_3)$, from DL-lactide, CL denotes carbonyloxypentamethylene, $CO{\cdot}O(CH_2)_5$, from ε-caprolactone, and VL denotes carbonyloxytetramethylene, $CO{\cdot}O(CH_2)_4$, from γ-valerolactone. The focus on diblocks removes certain sources of uncertainty. Triblock $E_mP_nE_m$ copolymers prepared by oxyanionic polymerisation often have broad chain-length distributions, typically with a shoulder on the high-elution-volume side of their gel permeation chromatography (GPC) curves (see, e.g., Yu et al., 1997a), the result of hydrogen abstraction from the methyl group. Slow initiation of the E blocks of B_nE_m and $E_mB_nE_m$ leads to broadened chain length distributions (Yu et al., 1997b), although this is not a problem for S_nE_m and $E_mS_nE_m$ copolymers. Interchange reactions prohibit triblock copolymers with ester central blocks being made by sequential copolymerisation, and coupling reactions introduce unwanted groups into the chain, e.g., urethane links (Hwang et al., 2005). Reverse triblock copolymers, e.g., $CL_nE_mCL_n$, can be useful if block lengths are short, but the association of these copolymers with long hydrophobic blocks is complicated by micelle bridging.

2. Critical micelle concentration: effect of hydrophobic block length

For closed association of a block copolymer (A) to micelles (A_N) with a narrow distribution and average association number *N*, the equilibrium expressed per mole of molecules is

$$A_D(1/N)A_N \tag{1}$$

and the equilibrium constant is given by

$$K_c = \frac{[A_N]^{1/N}}{[A]} \tag{2}$$

when concentrations are expressed in mol dm^{-3}. At the cmc, and for large *N*,

$$K_c = \frac{1}{\text{cmc}} \tag{3}$$

If this condition is met, and Hall in his detailed study of the thermodynamics of associating systems suggests $N > 50$ (Hall, 1987), then the standard Gibbs energy of micellisation is obtained without significant error from

$$\Delta_{\text{mic}}G^\circ = -RT\ \ln\ K_c = RT\ \ln(\text{cmc}) \tag{4}$$

We use the standard state of ideally dilute solution in which both unimers and micelles are of unit molarity. In this paper, we are concerned with the effect of the nature and length of the hydrophobic block on the extent of micellisation, and we use

log(cmc) as a convenient pointer to the position of equilibrium in the system.

Within a series of copolymers, values of the cmc are affected by variation of E-block length. It is known that the dependence of the cmc on the number of E units in a copolymer (ν) is weak unless the hydrophobic-block length is short: see, e.g., Reddy et al. (1990). Nevertheless, it is prudent to account for variation in E-block length, and in constructing plots of log(cmc) against hydrophobic block length we have followed the procedure used previously (Booth et al., 2006) and adjusted the values of the cmc to a common number of E units (E_{100}) per hydrophobic block. The largest correction made in this work, for $E_{17} \rightarrow E_{100}$, was 0.33 on the log scale −2 to −8.

Values of the cmc for the copolymers of interest, taken from the literature, are listed in Tables 1 and 2. The results for copolymers with polyether hydrophobic blocks in Table 1 are all for copolymers with narrow chain length distributions, as indicated by M_w/M_n (from GPC) in the range 1.03–1.06. Copolymers with polyester blocks have somewhat broader chain length distributions, the result of inevitable ester-interchange reactions, and values of M_w/M_n are likely to be in the range 1.1–1.2. The solvent is usually pure water: certain results (Letchford et al., 2004; Zastre et al., 2002) for copolymers dissolved in dilute buffer solution are not distinguished. A few results from studies which overlap those listed have not been included, nor has a study of diblock copolymers with L-lactide blocks for which data were presented graphically but not tabulated (Dai et al., 2004). A value of the cmc reported for $E_{45}L_5$ (Lo et al., 2007) was judged to be at the limit for micelle formation in the EL system, and so to be overly sensitive to the block length distribution. Results for triblock $CL_nE_mCL_n$, copolymers (Martini et al., 1994) were plotted and found to support the conclusions drawn from the data for the diblocks: however, for simplicity of presentation, they are not included here.

Values of the cmc in Table 1 are all for solutions at 30 °C, either measured directly at that temperature or interpolated from a range of results using van't Hoff plots. Solution temperatures for the copolymers in Table 2 are not consistently given by the authors, but those supplied lie in the range 20–37 °C, and the implication in context is that the others lie within this range. Unlike copolymers with P blocks, but like copolymers with B and S blocks (Booth et al., 2006), values of the cmc for the copolymers with polyester blocks are weakly dependent on temperature, and combining results for a range of temperature should not invalidate the present comparison, particularly so as values of the cmc are plotted on a log scale.

2.1. E_mCL_n copolymers.

The results for the E_mCL_n copolymers, converted to molar values and adjusted to constant E-block length, are plotted against hydrophobic length in Fig. 1. Comparison is made with results for diblock copolymers of ethylene oxide and styrene oxide, which are only available for copolymers with relatively

Table 1
Critical micelle concentrations for copolymers with polyether hydrophobic blocks: aqueous solution, 30 °C

Copolymer	M_n (g mol^{-1})	M_w/M_n	cmc (g dm^{-3})	Reference
Propylene oxide				
$E_{102}P_{37}$	6630	1.04	9.5	Altinok et al., 1999
$E_{104}P_{52}$	7590	1.05	1.0	
$E_{92}P_{55}$	7240	1.04	1.2	
$E_{104}P_{60}$	8060	1.06	0.5	
$E_{98}P_{73}$	8550	1.04	0.11	
1,2-Butylene oxide				
$E_{27}B_7$	1690	1.05	5.8	Tanodekaew et al., 1993
$E_{11}B_8$	1130	1.03	0.63	Chaibundit et al., 2002
$E_{41}B_8$	2380	1.04	0.35	Yu et al., 1997b
$E_{18}B_{10}$[a]	1510	1.04	0.063	Kelarakis et al., 2002
$E_{24}B_{10}$	1780	1.05	0.3	Bedells et al., 1993
$E_{50}B_{13}$	3140	1.06	0.02	
$E_{106}B_{16}$	5820	1.03	0.035[b]	Rippner et al., 2002
$E_{96}B_{18}$	5500	1.03	0.01	Mingvanish et al., 1999
Styrene oxide				
$E_{50}S_4$	2620	1.02	0.28	Mai et al., 2000
$E_{50}S_5$	2810	1.04	0.058	
$E_{51}S_7$	3020	1.03	0.044	
$E_{45}S_{10}$	3180	1.04	0.018	Crothers et al., 2002
$S_{13}E_{60}$	4290	1.03	0.0049	Kelarakis et al., 2001

[a] Commercial copolymer: the Dow Chemical Co. notation is BM45-1600.
[b] Range 0.02–0.05 g dm^{-3} (Rippner et al., 2002), mean value used.

Table 2
Critical micelle concentrations for copolymers with polyester hydrophobic blocks: aqueous solution, temperature in the range 20–37 °C

Copolymer	M_n (g mol^{-1})	cmc (g dm^{-3})	T (°C)	Reference
Lactide				
$E_{45}L_{28}$	4000	0.0038	–	Lee et al., 2007
$E_{136}L_{42}$	9000	0.0045	25	Yagusi et al., 1999
$E_{130}L_{75}$	11100	0.0035		
$E_{139}L_{108}$	13900	0.0025		
$E_{45}L_{28}$	4000	0.016	25	Burt et al., 1999
$E_{45}L_{19}$	3330	0.03		
$E_{114}L_{30}$	7140	0.03		
$E_{133}L_{74}$	11200	0.0016	–	Kim et al., 1998b
$E_{42}L_{12}$	2540	0.35	25	Tanodekaew et al., 1997a
$E_{38}L_{16}$	2820	0.04		
$E_{45}L_{20}$	3420	0.035	20	Hagan et al., 1996
$E_{114}L_{26}$	6890	0.035		
$E_{45}L_{12}$	2840	0.60	25	Zhang et al., 1996
Caprolactone				
$E_{17}CL_2$	980	0.697	37	Letchford et al., 2004
$E_{17}CL_5$	1320	0.0176		
$E_{17}CL_{10}$	1890	0.0038		
$E_{45}CL_4$	2440	0.66	37	Zastre et al., 2002
$E_{44}CL_{21}$	4330	0.0012	–	Luo et al., 2002
$E_{114}CL_{36}$	9120	0.00316	–	Shin et al., 1998
$E_{114}CL_{49}$	10600	0.00128		
$E_{114}CL_{74}$	13450	0.000847		
Valerolactone				
$E_{45}VL_6$	2580	0.176	–	Lee et al., 2005
$E_{45}VL_{10}$	2980	0.0804		
$E_{45}VL_{20}$	3980	0.0233		
$E_{114}VL_{11}$	6120	0.161		
$E_{114}VL_{26}$	7620	0.0733		
$E_{114}VL_{49}$	9920	0.0353		

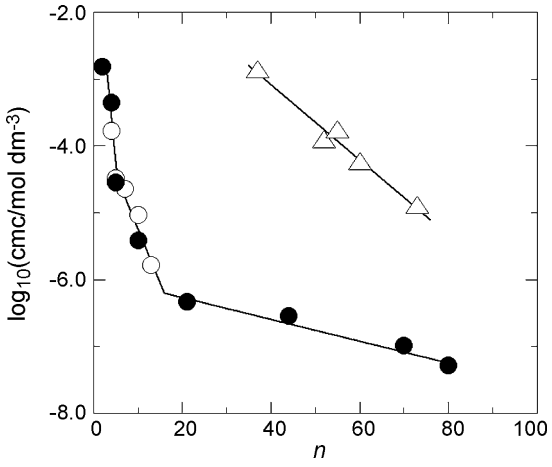

Fig. 1. Dependence of critical micelle concentration on hydrophobic block length for (●) E_mCL_n, (◯) E_mS_n and (△) E_mP_n block copolymers. Values of the cmc are adjusted to a common E-block length of E_{100}. See Tables 1 and 2 for sources of data.

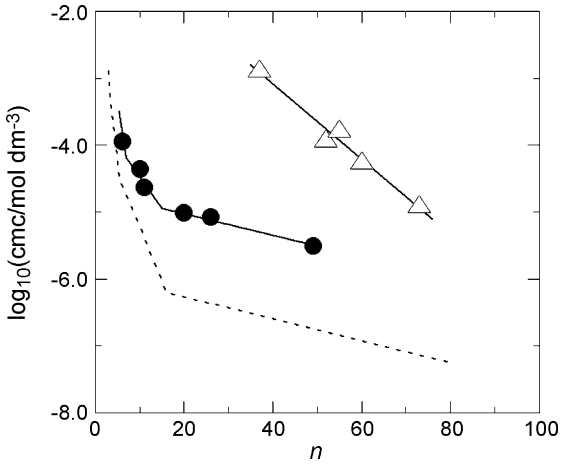

Fig. 2. Dependence of critical micelle concentration on hydrophobic block length for (●) E_mVL_n, and (△) E_mP_n block copolymers. Values of the cmc are adjusted to a common E-block length of E_{100}. The dotted lines represent the data for E_mCL_n copolymers in Fig. 1. See Tables 1 and 2 for sources of data.

short S blocks. The lines lead the eye through the data points and emphasise the similarity of the data sets over the low-n range. Values of the cmc of E_mP_n copolymers also shown in Fig. 1, illustrate the much higher hydrophobicity of CL and S chain units, quantitatively in ratio 12:1.

The transition in the data for the E_mS_n copolymers has been assigned (Booth et al., 2006) to the onset of formation of unimolecular micelles, i.e., to collapse of the longer S blocks when the average block length exceeds a critical value ($n > 5$) prior to association into multimolecular micelles. This assignment is supported by the observation of low values of the standard (van't Hoff) enthalpies of micellisation when $n > 5$, the values (and the values of the calorimetric enthalpy of micellisation) approaching zero when $n \geq 10$ (Booth et al., 2006). The inference from Fig. 1 is that E_mCL_n copolymers behave in the same way. It has long been recognised that the hydrophobic block of a copolymer will collapse to a compact conformation whilst leaving the hydrophilic block in a coiled conformation, and such unimolecular micelles have been discussed by many authors; see, for example, Brown et al. (1989), Tuzar and Kratochvil (1993), Chu (1995) and Cooke and Williams (2003). A consequence of collapse of the hydrophobic block is reduced contact with water and so a reduced hydrophobic effect, as discussed in detail elsewhere (Kelarakis et al., 2001). The absence of this effect in copolymers with poly(propylene oxide) blocks is consistent with their much lower hydrophobicity.

The results for E_mCL_n copolymers include samples with long CL blocks, and the plot reveals a second change in slope at $n \approx 16$. Discussion of this effect is reserved until Section 3. We note that copolymers with long CL blocks can be difficult to dissolve in water, and may be taken into aqueous solution using a water-compatible organic solvent followed by dialysis (Luo et al., 2002; Shin et al., 1998).

2.2. E_mVL_n copolymers

The corresponding plot for E_mVL_n copolymers, shown in Fig. 2, has a more restricted data set, but can be interpreted by reference to Fig. 1 and related text. For convenience, the results for E_mCL_n copolymers (Fig. 1) are indicated by the dotted lines. The solid lines through the data points for E_mVL_n copolymers are consistent with the onset of unimolecular micelle formation at $n = 6$, and completion of the process at $n \approx 15$. The results for E_mCL_n and E_mVL_n copolymers with short hydrophobic blocks ($n < 15$) can be brought into approximate correspondence by plotting the E_mVL_n data against $5n/6$, consistent with a ranking of hydrophobicities per chain unit of P:VL:CL = 1:10:12.

2.3. E_mL_n copolymers.

The results for the E_mL_n copolymers, converted to molar values and adjusted to constant E-block length, are plotted against hydrophobic length in Fig. 3. Comparison is made with data for diblock copolymers of ethylene oxide and 1,2-butylene oxide, which are available for copolymers with relatively, short B-

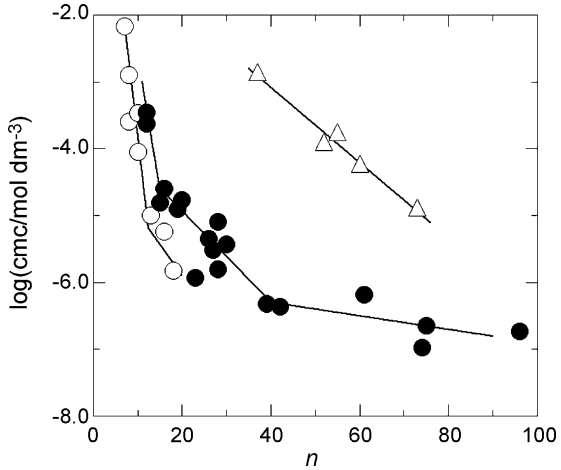

Fig. 3. Dependence of critical micelle concentration on hydrophobic block length for (●) E_mL_n, (◯) E_mB_n and (△) E_mP_n block copolymers. Values of the cmc are adjusted to a common E-block length of E_{100}. See Tables 1 and 2 for sources of data.

block lengths. The data points representing values of the cmc of E_mP_n copolymers illustrate the higher hydrophobicity of L and B blocks. The data points for the E_mL_n copolymers are more scattered than those for the E_mCL_n and E_mVL_n copolymers, possibly reflecting the larger number of laboratories involved (see Table 2), possibly a result of the greater susceptibility of the less-hydrophobic lactide block to hydrolysis. Even so, it is clearly possible to construct lines through the data points which are analogous to those drawn through the data points for E_mCL_n and E_mVL_n copolymers in Figs. 1 and 2, and which are consistent with the results for the E_mB_n copolymers in the range $n < 20$. For E_mL_n copolymers, the results are consistent with the onset of unimolecular micelle formation at $n \approx 15$. Compared with E_mB_n copolymers, the data for the E_mL_n copolymers can be brought into approximate coincidence by plotting them against $2n/3$, consistent with the ranking P:L:B = 1:4:6. Previously (Tanodekaew et al., 1997a) we reported a ranking P:L:B = 1:5:6, but that was based on a small data set, and the present result is preferred.

The availability of results for E_mL_n copolymers with long L blocks reveals a second transition at $n \approx 40$. Like the E_mCL_n copolymers with lengthy hydrophobic blocks, these copolymers are taken into aqueous solution by prior dissolution in a water-compatible organic solvent followed by dialysis to remove the organic solvent (Yagusi et al., 1999; Kim et al., 1998b).

3. Discussion

Diblock copolymers with poly(ethylene oxide) hydrophilic blocks and various hydrophobic blocks derived from cyclic ethers and cyclic esters show a consistent pattern of micellisation behaviour in dilute aqueous solution. For polyether and polyester hydrophobic blocks alike, there is evidence of a change in the dependence of the logarithm of the cmc (molar units, directly related to the standard Gibbs energy of micellisation) on block length which is consistent with the equilibrium between unimers and multimolecular micelles being replaced, in part at least, with one between unimolecular micelles and multimolecular micelles. This effect, which has been examined in detail for copolymers with polyether hydrophobic blocks (Booth et al., 2006), is now seen to extend to copolymers with polyester hydrophobic blocks. The exception is the E_mP_n series: because of the low hydrophobicity per P, unit blocks considerably longer than P_{60} would be required before the effect of unimolecular micelle formation on the cmc became apparent.

An interesting feature, which comes from considering results for E_mCL_n and E_mL_n copolymers with long blocks, 100 chain units or more, is the recognition of a second transition. Kataoka and coworkers (Yamamoto et al., 2002) have reported values of the cmc obtained for copolymer $E_{139}L_{75}$ in aqueous solution over a wide temperature range 25–55 °C. Values were constant for $T < 40$ °C, i.e., a van't Hoff enthalpy of micellisation of zero, and increased with temperature at higher temperatures. The change in behaviour correlated with a loss of mobility of the lactide block in the micelle core, as detected by broadening of the ^{1}H NMR signal from the CH proton. Similar observations were made by ^{1}H NMR for a micellar gel of copolymer $E_{77}L_{26}$ with a similar onset temperature for loss of mobility (Tanodekaew et al., 1997b). However, in each case the authors remarked that the rapid unimer-micelle equilibration demanded a thermodynamic rather than a kinetic effect. To explain the insensitivity of the cmc to temperature, Kataoka et al. deduced a change in the solubility of the unimers, for which the likely explanation was the formation of unimolecular micelles (Yamamoto et al., 2002). This background is useful, as the point to be made is that the form of the dependence of cmc on hydrophobic block length is common to both E_mL_n and E_mCL_n copolymers, i.e., to hydrophobic chains having very different mobilities as judged by values of T_g for lengthy chains, i.e., $T_g \approx 55$ °C for poly(DL-lactide) and $T_g \approx -60$ °C for poly(ε-caprolactone). Accordingly, we assign the value of n at the second transition point to the average block length above which essentially all hydrophobic blocks in the block length distribution of the unimers are collapsed, i.e., complete conversion of unimer coils to unimolecular micelles prior to formation of multimolecular micelles.

The evidence in Figs. 1–3 for copolymers with short chains is that the dependence of the value of the cmc on hydrophobic block length takes the same form for polyesters and polyethers alike, which allows the prediction that the second transition would be found for copolymers with polyether blocks if diblock copolymers with longer hydrophobic blocks were available. In the respect, we note that insensitivity of the cmc to temperature has been observed for aqueous solutions of a number of diblock copolymers with polyether hydrophobic blocks and assigned to the formation of unimolecular micelles, e.g., $E_{106}B_{18}$ (Kelarakis et al., 1998), $S_{13}E_{60}$ (Kelarakis et al., 2001), $E_{45}S_{10}$ (Crothers et al., 2002), and G_5E_{67} (Taboada et al., 2006: G denotes the $OCH_2CH(CH_2OC_6H_5)$ chain unit from phenyl glycidyl ether). The glass transition temperatures of lengthy chains range from −70 °C (B) through 18 °C (G) to 33 °C (S), confirming that the glass-to-rubber transition is not an important factor.

Coming to the main thrust of the paper, combining the present results leads to the following quantitative ranking of the hydrophobicities of the chain units of the copolymers considered, i.e.,

$$P : L : B : VL : CL : S = 1 : 4 : 6 : 10 : 12 : 12$$

Solubilisation of a drug in the micelle core of a copolymer in aqueous solution depends on the extent of micellisation, which in turn depends on the hydrophobicity per chain unit and the length of the block. Direct discussion of the effect of choice of ether or ester block on solubilisation capacity is difficult because there are no quantitative results allowing comparison of the two systems (Attwood et al., in press). However, considering copolymers with hydrophobic blocks with the same number (n) of CL or S chain units, the extent of micellisation will be governed by hydrophobicity and will be equally high, hence solubilisation capacity, whether in small or large micelles, will depend on total volume available to the drug and on compatibility of the drug with the core material. Compatibility may be judged qualitatively, perhaps by choosing an aromatic core material for solubilisation of an aromatic drug (Rekatas et al., 2001; Crothers et al., 2005) or may be judged quantitatively, based, e.g., on solubility parameter theory (Allen et al., 1999; Liu et al., 2004). Assuming good compatibility in each case,

the volume of a drug-swollen core will depend on choice of hydrophobic block. The radius of a spherical micelle core is limited by the stretched length of the hydrophobic block. For micelles of copolymers with hydrophobic blocks of the same length in terms of chain units, the blocks composed of CL units ($CO{\cdot}O(CH_2)_5$, seven backbone atoms) will be more than twice as long as those composed of S units ($OCH_2CH(C_6H_5)$, three backbone atoms), hence the CL-core volume available to a core compatible drug will be some 10 times that of an S core. Other things being equal, higher solubilisation capacities would be expected for micellar solutions of E_mCL_n copolymers compared with E_mS_n copolymers, and there is ample evidence that this is the case (Attwood et al., in press).

4. Conclusions

(i) Based on the critical micelle concentrations of diblock copolymers, the hydrophobicity per chain unit relative to that of a P unit is:

$$P : L : B : VL : CL : S = 1 : 4 : 6 : 10 : 12 : 12$$

(ii) The dependence of log(cmc) on hydrophobic block length (n) shows transitions related to the effect of unimolecular micelle formation on the micelle-unimer equilibrium. This effect should be common to all copolymers provided the hydrophobic blocks are long enough.

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