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Solubilization of a Poorly Soluble Aromatic Drug by Micellar Solutions of Amphiphilic Block Copoly(oxyalkylene)s*

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Abstract

This chapter is a summary of our work on the design of block copolymer micellar systems with improved solubilization capacity for poorly soluble aromatic drugs. The copolymers of interest are block copoly(oxyalkylene)s with linear di- or triblock architecture which combine hydrophilic poly(ethylene oxide) with hydrophobic blocks formed from poly(propylene oxide), poly(1,2-butylene oxide), poly(styrene oxide) or poly(phenyl glycidyl ether). A comparison of the solubilization capacity per gram of hydrophobic block for the model poorly soluble drug griseofulvin shows an increase in solubilization capacity with increase in the hydrophobicity of the core-forming block and the volume of the core of spherical micelles. As a consequence of their larger core diameter, diblock copolymers are more effective solubilizers than triblock copolymers of similar composition and chain length. Copolymers with short hydrophilic blocks relative to the length of the hydrophobic block may form cylindrical or worm-like micelles of high aggregation number resulting in an increased solubilizing capacity. The formulation of mixed block copolymer systems of high solubilization capacity and favorable gelation characteristics for use in controlled drug delivery is discussed.

2.1

Introduction

It is estimated that almost half of the potentially useful drug candidates identified by high-throughput methods of screening have pronounced solubility problems. Although many of these are highly potent, their very low aqueous solubility usually gives rise to poor or erratic absorption characteristics and consequently these compounds are frequently not taken forward to formulation development. A variety of colloidal delivery systems, including, for example, liposomes, nanoparticles, micro-

* An explanation of the notation used can be found at the end of this chapter.

spheres, dendrimers and cyclodextrins, have been investigated for their potential as drug carriers in attempts to overcome this problem. In this chapter, we focus on the application of block copolymer micelles as alternative carriers for poorly water-soluble drugs. In these systems, the hydrophobic micelle core is stabilized by the hydrophilic chains of the micelle corona and provides a suitable microenvironment for solubilization of the drug. A poly(oxyethylene) corona allows the micelles to evade scavenging by the mononuclear phagocyte system, resulting in lengthy circulation times in the bloodstream [1, 2]. Within limits, the composition of the core can be varied independently of the E-block corona, and copolymers with a wide range of hydrophobic blocks have been examined for their potential for solubilizing poorly soluble drugs, as described in a number of reviews (e.g. [2–5]), recently by Torchilin [6], who has reviewed the literature (including the numerous patents) relating to the use of amphiphilic block copolymers in the solubilization of poorly soluble drugs and strategies to target these micellar carriers to tumors. Allen et al. [3] have summarized the characteristics to be sought in a micellar system for drug delivery: small micelle size, narrow size distribution, a low critical micelle concentration (c.m.c.) giving a high extent of micellization and stability on injection, and high solubilization capacity. This last can be achieved by ensuring compatibility of the micelle core with the target drug, a point which is emphasized in [3] by the comparison of partition coefficients of pyrene between water and micelle, i.e. a variation in order from 10^2 for micelles with a poly(propylene oxide) core to 10^5 for micelles with a polystyrene core. We can add the requirement of mobility of the chains comprising the core, a feature which controls the rate of uptake and release of the drug. Allen et al. [3] also note that micelle morphology is an important variable, particularly when micelles are formed by predissolution in a water-compatible organic solvent followed by dialysis against water to remove the solvent.

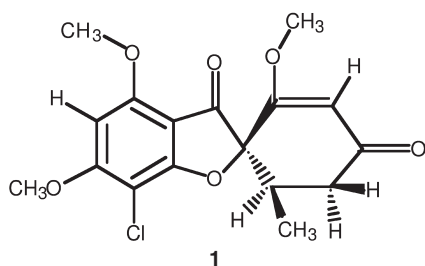
Within the family of copoly(oxyalkylene)s, many studies of the solubilization of drugs and drug models have been carried out with the commercially available linear triblock copolymers of ethylene oxide and propylene oxide, type $E_mP_nE_m$. Relevant references can be found in published reviews and it is not our intention to revisit that work. However, we mention early work in our laboratory [7] and, particularly, the extensive work of Kabanov and coworkers (e.g. [4, 8]). Useful guidelines emerge from related work. Hatton and coworkers studied, both experimentally [9] and theoretically [10], the solubilization of polycyclic aromatics in solutions of $E_mP_nE_m$ copolymers. In addition to showing the beneficial effect of a high P content, they showed that linear copolymers are preferable to branched. Theory showed an increase in micelle association number with concentration of aromatic solute [10], an effect supported by the Monte Carlo simulations of Li and Mattice [11]. This effect implies a lowering of the c.m.c. in the presence of hydrophobic solutes, as predicted theoretically by Nagarajan and Ganesh [12] for diblock P_nE_m copolymers in water. Nagarajan and coworkers had used a diblock P_nE_m copolymer in an investigation of the solubilization of aliphatic and aromatic solutes [13], and corresponding theory was developed through the years, initially for P_nE_m copolymers [12, 14] and later for $E_mP_nE_m$

copolymers [15, 16]. Detailed information was obtained on the extent of solubilization in spherical micelles and the effect of an increase in extent of solubilization in inducing sphere-to-cylinder and cylinder-to-lamella transitions [16].

In this chapter, we draw together our work over several years aimed at improving the solubilization capacity of block copoly(oxyalkylene)s for poorly soluble aromatic drugs. We have used copolymers prepared and characterized under controlled conditions to explore effects of block architecture and composition on micellization in dilute solution [17] and on the gelation of concentrated micellar solutions [18] and additionally, as discussed below, to explore pharmaceutical application in drug delivery. The emphasis has been on block copoly(oxyalkylene)s which form spherical or near spherical micelles on dissolution in water. However, spherical micelles of copolymers with short E-block lengths relative to the length of the hydrophobic (core-forming) block may undergo a sphere-to-cylinder transition on heating the solution, an effect which has been recognized for certain $E_mP_nE_m$ copolymers for many years, e.g. for copolymers $E_{27}P_{39}E_{27}$ (denoted P85) and $E_{21}P_{47}E_{21}$ (denoted P94) (see, e.g., [19–24]). As indicated by Nagarajan [16], there is an advantage so far as solubilization capacity is concerned in using copolymers which form cylindrical micelles and we have synthesized copolymers which form cylindrical, even worm-like, micelles at room temperature or just above [25–27].

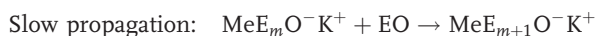
In our work, all solutions were prepared by dissolving the copolymers directly in water at room temperature and, since values of the glass transition temperature (T_g) of the hydrophobic blocks are low, it can be safely assumed that all results are for systems at equilibrium. Of the components of the copolymers considered in this chapter, only poly(styrene oxide) and poly(phenyl glycidyl ether) have values of T_g above 0°C , namely *ca.* 40 and 18°C , respectively [28–30], but these values apply to lengthy chains and T_g is much lower for the short blocks of the copolymers, as demonstrated directly for S blocks by investigation of chain dynamics in micellar cores [31].

Bearing in mind earlier studies by Elworthy and coworkers on poly(oxyethylene) alkyl ethers [32, 33], we have used griseofulvin (**1**) as the standard aromatic drug for comparing the solubilization capacity of micellar solutions of our different block copolymers. Griseofulvin 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 [34].



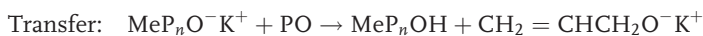
2.2 Copolymers

The preparation of the copoly(oxyalkylene)s by sequential anionic polymerization of two monomers from an appropriately chosen monofunctional or difunctional initiator is a well-established technique [35]. The underlying reaction can be illustrated by the polymerization of ethylene oxide (EO) initiated by a monofunctional diethylene glycol monomethyl ether, part of which is in the form of its alkali metal salt (e.g. $-\text{O}^-\text{K}^+$). Initiation is instantaneous and the reaction scheme is written as follows:



where E_m and E_n represent growing chains. The active center is an ion pair and the rapid equilibration ensures that all chains are equally likely to grow. This ideal reaction produces a polymer with a number-average molar mass (M_n) given by the mass of EO polymerized relative to the moles of initiator used and with a Poisson distribution of chain lengths [36]. In the absence of deliberate or accidental termination, the system is living and is ideal for preparation of block copolymers.

The same scheme applies to propylene oxide (PO), but with the addition of a hydrogen-abstraction transfer reaction [37]:



This reaction reduces M_n and broadens the chain length distribution, since the unsaturated alcohol initiates new chains. It has consequences for the compositions of E/P block copolymers, not only broadening the P-block-length distribution, but also giving rise to a proportion of diblock PE copolymers in purportedly $\text{E}_m\text{P}_n\text{E}_m$ triblocks and of homopoly(oxypropylene) if P is added in the second stage of sequential copolymerization. A similar reaction has been recognized in the polymerization of phenyl glycidyl ether [38], but it is absent in the anionic polymerization of 1,2-butylene oxide (BO) and styrene oxide (SO) under laboratory conditions [39, 40], although it may occur in polymerization under the more extreme conditions (high temperatures) used in industry [35]. Impurities arising from this effect, and from initiation by moisture accidentally introduced with the monomers, are either accounted for in interpretation of results or, preferably, are removed [41].

A second effect arises because monomers other than EO add to a growing chain to give secondary oxyanions and slow initiation of the polymerization of EO by a first-formed block terminated in this way may result, leading to a widened E-block distribution. This effect has been recognized in the copolymerization of EO on to a preformed B chain [42, 43]. If the E-block is short, uncapped

ends may be present at the completion of the reaction. In forming a triblock copolymer with E end blocks, uncapped ends imply a proportion of diblock copolymer. This problem is avoided in the preparation of diblock copolymers by polymerizing the E-block first. For triblocks and diblocks polymerized in reverse order, the effect is minimized if the E blocks are lengthy.

We stress the importance of the thorough molecular characterization of our copolymers. Complete information is obtained by monitoring the copolymerization at each stage using analytical gel permeation chromatography (GPC) (appropriately calibrated) to check the chain length distribution and ^{13}C nuclear magnetic resonance spectroscopy (carried out under conditions which give complete relaxation between pulses and with due allowance, where appropriate, for differential nuclear Overhauser enhancements) for absolute number-average chain length and confirmation of the block structure. Valuable supplementary

Table 2.1 Poly(oxyalkylene)s investigated.

Copolymer	w_E (wt%)	M_n (kg mol $^{-1}$)	M_w/M_n	Ref.
E ₁₃₀ P ₅₈	0.63	9.1	1.05	44
E ₁₀₇ P ₆₉	0.54	8.7	1.05	44
E ₆₂ P ₃₉ E ₆₂ (F87)	0.70	5.0	–	–
E ₂₁ P ₄₇ E ₂₁ (P94)	0.40	4.6	–	–
E ₂₁ P ₆₇ E ₂₁ (P123)	0.30	5.8	–	–
E ₉₈ P ₆₇ E ₉₈ (F127)	0.70	12.5	–	–
E ₁₁ B ₈	0.46	1.1	1.03	25
E ₄₉ B ₉	0.77	2.8	1.03	45
E ₉₆ B ₁₈	0.76	5.5	1.03	46
E ₁₃₄ B ₁₉	0.81	7.3	1.03	47
E ₄₃ B ₁₄ E ₄₃	0.69	4.8	1.08	48
E ₅₀ S _{3.5}	0.84	2.6	1.02	49
E ₅₀ S ₅	0.78	2.8	1.04	49
E ₅₁ S _{6.5}	0.74	3.0	1.03	49
E ₁₇ S ₈	0.44	1.7	1.05	26
E ₄₅ S ₈	0.67	2.9	1.06	50
E ₄₅ S ₁₀	0.62	3.2	1.04	51
S ₁₀ E ₁₃₅	0.83	7.1	1.04	50
S ₁₃ E ₆₀	0.63	4.2	1.03	31
S ₁₅ E ₆₃	0.61	4.6	1.04	51
S ₁₇ E ₆₅	0.58	4.9	1.04	51
S ₂₀ E ₆₇	0.55	5.3	1.05	51
E ₈₂ S ₈ E ₈₂	0.88	8.2	1.07	52
E ₂₀ S ₁₀ E ₂₀	0.59	3.0	1.03	50
E ₆₆ S ₁₃ E ₆₆	0.79	7.4	1.04	52
E ₆₇ S ₁₅ E ₆₇	0.77	7.7	1.04	52
G ₅ E ₆₇	0.79	3.7	1.03	53
E ₇₁ G ₇ E ₇₁	0.85	7.3	1.05	54
E ₆₂ G ₈ E ₆₂	0.82	6.7	1.05	54
E ₃₈ G ₁₂ E ₃₈	0.65	5.2	1.05	54

information can be obtained from matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) mass spectrometry. These procedures are possible because the chain lengths involved seldom exceed 500 chain units ($M_n \leq 20\,000 \text{ g mol}^{-1}$). Other methods of molecular characterization (e.g. static light scattering, membrane osmometry), which are indispensable at higher molar masses, may also provide useful supplementary information.

The copolymers used for solubilization in our work are listed in Table 2.1. The characteristics listed are the weight fraction of the E blocks (w_E) and the number-average molar mass (M_n) from NMR spectroscopy, and the ratio of weight- to number-average molar mass (M_w/M_n) from GPC. The references give additional information about their preparation and characterization. The $E_mP_nE_m$ copolymers were commercial samples (as indicated) and were used as received.

2.3

Micellization and Micelle Properties

Ideally copolymers for drug solubilization should be completely micellized in dilute solution in water at 25 °C. This would allow drugs to be solubilized and the solutions stored at room temperature prior to injection at body temperature. This restriction effectively rules out $E_mP_nE_m$ copolymers. For selected copolymers, Table 2.2 shows values of the critical micelle concentration at 25 °C and of the critical micelle temperature (c.m.t.) of 1 wt% solutions. These copolymers have values of the 1 wt% c.m.t. lower than those reported for other $E_mP_nE_m$ copolymers. The micellization range is *ca.* 20 °C [55–57], implying that P123, the copolymer with the lowest c.m.c. in wt% units, is completely micellized only at *ca.* 36 °C. It is interesting that much early experimental work on the solubilization of aromatics was carried out at 25 °C, i.e. under conditions where the extent of micellization could be very low [9, 13, 58].

It is characteristic of $E_mP_nE_m$ copolymers that the c.m.c. is very temperature dependent, e.g. values listed by Alexandridis et al. [59] for copolymer F127 vary

Table 2.2 Micellization of $E_mP_nE_m$ copolymers.

Copolymer	Nominal formula	c.m.c. (25 °C) (wt%)	c.m.t. (1 wt%) (°C)	Ref.
F87	$E_{62}P_{39}E_{62}$	2.6	30	61
P94	$E_{21}P_{47}E_{21}$	0.3	23	55
P103	$E_{20}P_{54}E_{20}$	0.07	20	59
P104	$E_{31}P_{54}E_{31}$	0.1, 0.3	19, 22	59, 61
P105	$E_{38}P_{54}E_{38}$	0.2	22	59
L122	$E_{13}P_{67}E_{13}$	0.01	18	62
P123	$E_{21}P_{67}E_{21}$	0.03	16	59
F127	$E_{98}P_{67}E_{98}$	0.7, 1.0	24, 25	57, 59, 63

from *ca.* 1 wt% at 25 °C to *ca.* 0.02 wt% at 37 °C. In this respect, we note that the values of the c.m.c. in Table 2.1 are considerably higher than those listed by Kabanov and coworkers in their review [4], reflecting the difference in solution temperature, 25 versus 37 °C [60].

Based on a comparison of values of c.m.c.s for diblock copolymers in molar units [17, 51], at 25 °C the relative hydrophobicities per chain unit are as follows:

$$P:C:B:S:G = 1:5:6:12:14 \quad (1)$$

with similar values for triblock copolymers [17, 52]. We include the value for the methylene unit of an alkyl ethoxylate (denoted C) to keep contact with work in that area. With the exception of copolymers with P blocks, the effect of temperature on these ratios can be ignored over the temperature range 25–37 °C. Using the standard (van't Hoff) enthalpy of micellization as a measure of the temperature dependence of the c.m.c., the values reported for copolymers with P blocks are high, 200–400 kJ (mol copolymer)⁻¹, whereas those for the other copoly(oxyalkylene)s are relatively low, even approaching zero for lengthy blocks [17, 51, 52], an effect attributed to collapse of the hydrophobic block prior to micellar association [64, 65].

In polymer solution theory (Flory–Huggins theory), the interaction parameter used to characterize the interaction between components is based on a common segment volume. Using known specific volumes of related homopolymers, the ranking of hydrophobicity for segments of equal volume becomes

$$P:B:S:G:C = 1:5:7:7:18 \quad (2)$$

The determining factor for micellization, i.e. the product of the interaction parameter and the chain length measured in chain segments, is unchanged by choice of segment volume. The ranking based on a common segment volume gives a more realistic view of the variation of hydrophobicity with chemical composition than that based on chain units, particularly so for alkyl chains, and more importantly because it relates directly to the hydrophobicity of micelle cores of equal volume. However, block lengths in chain units, which relate directly to chemical composition, are more usual and are used in this chapter.

The c.m.c.s at 25 °C and c.m.t.s of 1 wt% solutions are listed in Table 2.3. When values were not measured directly or interpolated from measurements at nearby temperatures, values of the c.m.c. were estimated making use of the plots of log(c.m.c./molar units) against hydrophobic block length, while values of the c.m.t. were estimated making use of van't Hoff plots of log *c* against reciprocal temperature: examples of these plots can be found elsewhere (e.g. [17, 51, 52]). The c.m.t.s of 1 wt% solutions are below 0 °C for all except the copolymers with P blocks. Values of the micelle hydrodynamic radius (*r_h*) determined by dynamic light scattering are listed as an indicator of micelle size, albeit one which is dominated by the width of the E-block corona. Values of the

Table 2.3 Micellization and micelle properties^{a)}.

Copolymer	c.m.c. (25 °C) (wt%)	c.m.t. (1 wt%) (°C)	r_h (25 °C) (nm)	Ref.
E ₁₃₀ P ₅₈	<i>0.1</i>	16	–	66
E ₁₀₇ P ₆₉	<i>0.02</i>	14	–	66
E ₆₂ P ₃₉ E ₆₂ (F87)	2.6	30	9 (50 °C)	61
E ₂₁ P ₄₇ E ₂₁ (P94)	0.3	23	8	23, 55
E ₂₁ P ₆₇ E ₂₁ (P123)	0.03	16	10 (30 °C)	59, 67
E ₉₈ P ₆₇ E ₉₈ (F127)	0.7	25	12 (35 °C)	57, 59, 67, 68
E ₁₁ B ₈	0.07	^{b)}	5	25
E ₄₉ B ₉	<i>0.01</i>	^{b)}	–	69
E ₉₆ B ₁₈	0.001	^{b)}	15	46
E ₁₃₄ B ₁₉	<i>0.004</i>	^{b)}	–	46
E ₄₃ B ₁₄ E ₄₃	0.04	^{b)}	6	48
E ₅₀ S _{3,5}	0.03	^{b)}	7	49
E ₅₀ S ₅	0.007	^{b)}	7	49
E ₅₁ S _{6,5}	0.005	^{b)}	7	49
E ₁₇ S ₈	<i>0.003</i>	^{b)}	8	26
E ₄₅ S ₈	<i>0.003</i>	^{b)}	–	51
E ₄₅ S ₁₀	0.002	^{b)}	10	51
S ₁₀ E ₁₃₅	<i>0.002</i>	^{b)}	–	51
S ₁₃ E ₆₀	0.0005	^{b)}	10	65, 70
S ₁₅ E ₆₃	<i>0.0004</i>	^{b)}	12	51
S ₁₇ E ₆₅	<i>0.0002</i>	^{b)}	13	51
S ₂₀ E ₆₇	<i>0.0001</i>	^{b)}	16	51
E ₈₂ S ₈ E ₈₂	0.04	^{b)}	7	52
E ₂₀ S ₁₀ E ₂₀	<i>0.01</i>	^{b)}	–	52
E ₆₆ S ₁₃ E ₆₆	0.005	^{b)}	8	52
E ₆₇ S ₁₅ E ₆₇	0.003	^{b)}	8	52
G ₅ E ₆₇	0.006	^{b)}	8	53
E ₇₁ G ₇ E ₇₁	0.01	^{b)}	6	54
E ₆₂ G ₈ E ₆₂	<0.01	^{b)}	6	54
E ₃₈ G ₁₂ E ₃₈	<0.001	^{b)}	7	54

a) Italics indicate estimated values based on results in the reference given.

b) Indicates a c.m.t. below 0 °C.

weight-average micelle association number, which relate to the size of the micelle core, can be found in Table 2.4.

2.4

Drug Solubilization

The extent of drug solubilization was determined absolutely by ¹H NMR spectroscopy [31, 50], after calibration by UV spectroscopy [25, 50, 53, 54], and by gas–liquid chromatography [71]. Copolymer concentrations were in the range

Table 2.4 Solubilization capacity (method 1).

Copolymer	T (°C)	N_w ^{a)}	s_{cp} (mg g ⁻¹) ^{b)}	s_h (mg g ⁻¹)	Ref.
E ₁₃₀ P ₅₈	25	50	1.5	4	31
E ₁₀₇ P ₆₉	25	150	3.9	8	31
E ₆₂ P ₃₉ E ₆₂ (F87)	25	^{c)}	0	0	74
	37	^{c)}	0.8	3	
E ₂₁ P ₄₇ E ₂₁ (P94)	25	^{c)}	1.2	2	31
E ₂₁ P ₆₇ E ₂₁ (P123)	25	^{c)}	3.0	4	67, 71
	37	90	3.8	5	
E ₉₈ P ₆₇ E ₉₈ (F127)	25	^{c)}	2.2	6	71
E ₁₁ B ₈	25	63	3.9	7	25
	37	200	9.0	17	
	40	339	21	38	
E ₄₉ B ₉	25	21	2.9	12	31
E ₉₆ B ₁₈	25	163	3.3	13	25
	35	170	3.1	13	
	40	174	3.9	12	
E ₁₃₄ B ₁₉	25	130	3.9	19	31
E ₄₃ B ₁₄ E ₄₃	25	9	2.3	7	31
E ₅₀ S _{3.5}	25	20	2.8	16	31
E ₅₀ S ₅	25	35	4.0	17	31
E ₅₁ S _{6.5}	25	50	4.9	18	31
E ₁₇ S ₈	15	160	—	—	26, 50
	25	250	29.5	52	
	30	420	—	—	
	37	800	35.0	62	
E ₄₅ S ₈	25	80	7.5	22	50
E ₄₅ S ₁₀	25	103	11.2	29	50
	37	108	19.1	50	
S ₁₀ E ₁₃₅	25	50	6.0	35	50
S ₁₃ E ₆₀	25	105	14.1	37	31
S ₁₅ E ₆₃	25	140	11.4	28	50
	37	145	15.0	38	
S ₁₇ E ₆₅	25	150	11.7	28	50
	37	153	17.2	41	
S ₂₀ E ₆₇	25	189	12.4	27	50
	37	191	17.5	39	
E ₈₂ S ₈ E ₈₂	25	11	2.7	21	50
E ₂₀ S ₁₀ E ₂₀	25	40	11.8	28	50, 52
E ₆₆ S ₁₃ E ₆₆	25	21	4.0	18	50
	37	24	4.3	19	
E ₆₇ S ₁₅ E ₆₇	25	25	5.6	22	50
	37	28	7.1	29	
G ₅ E ₆₇	25	50	12.4	54	53
E ₇₁ G ₇ E ₇₁	25	16	6.0	40	54
E ₆₂ G ₈ E ₆₂	25	20	8.0	44	54
E ₃₈ G ₁₂ E ₃₈	25	77	17.8	51	54

a) Italics indicate estimated values based on results in the reference given.

b) Estimated uncertainty ± 1 mg g⁻¹.

c) Partially or not micellized.

1–2.5 wt%. We were aware of the possibility of impurities in the griseofulvin and instability in aqueous solution, so background measurements were made after dissolution in pure water. Also, in order to assess the solubilization of griseofulvin in the E-block corona of the micelles, measurements were made using solutions of poly(ethylene glycol) of $M_n=6000 \text{ g mol}^{-1}$ (PEG6000, E₁₃₆, 5–30 wt% in water).

Two methods of solubilization were explored. In method 1, a portion of stock copolymer solution was added to finely ground griseofulvin powder and the mixture stirred at constant temperature for 3–5 days before being filtered at the same temperature to remove unsolubilized drug. This method is equivalent to the so-called shake-flask method (ASTM E1148-02). Because of the low water solubility of griseofulvin, we were concerned that solubilization should not be limited by slow diffusion of the drug into the micelle core. Accordingly, in certain experiments (method 2), ground griseofulvin was added to the copolymer melt at 65 °C before dissolution in water at the same temperature, cooling to 25 °C and proceeding as in method 1.

The solubilization capacity of the copolymer in solution (s_{cp}) is reported in milligrams of drug solubilized per gram of copolymer in solution after correction for the solubility of griseofulvin in water. No systematic differences in values of s_{cp} were observed for different copolymer concentrations and by the different methods of analysis and the values listed are averages of several determinations. Also calculated are values of the solubilization capacity per gram of hydrophobic block, calculated from average values of s_{cp} as $s_h=s_{cp}/w_h$, where w_h is the weight fraction of the hydrophobic block (i.e. $w_h=1-w_E$, values of w_E taken from Table 2.1) after correction for the small amount of drug solubilized in the micelle corona. This quantity gives a direct measure of the efficiency of solubilization of griseofulvin in the micelle core.

2.4.1

Method 1

Values of the solubilization capacity (s_{cp} and s_h) obtained using method 1 at temperatures in the range 25–40 °C are listed in Table 2.4. Values of the weight-average micelle association number (N_w) are also listed. These values were either determined directly by static light scattering, interpolated or extrapolated where necessary, or were estimated from related values using the scaling law established for copolymers of the type under discussion to describe the dependence of N_w for spherical micelles on hydrophobic and hydrophilic block length [72]. These estimated values are shown in italics.

2.4.1.1 Effect of Composition and Micelle Core Size: 25 °C

As would be expected from the discussion in Section 2.3, low values of the solubilization capacity were determined for solutions of copolymers with hydrophobic P blocks, reflecting high values of c.m.t., hence low extents of micellization.

Although the size of the micelles may be large (as high as $N_w=50-150$; see Table 2.4), they are few in number at 25 °C [55, 73]. The values of the solubilization capacity for griseofulvin determined for solutions at 37 °C are no higher, which indicates poor solubilization of this drug even under conditions when $E_mP_nE_m$ copolymers are relatively well micellized.

The other copolymers are essentially completely micellized in solution at 25 °C. With the exception of copolymers $E_{17}B_8$ and $E_{38}G_{12}E_{38}$, at this temperature all the micelles are spherical or near spherical. Apart from a change in core composition, the results may also be affected by changes in core size. It is convenient to use core volume as an approximate indicator of core size, calculated as

$$v_c = N_w n M_0 v_{sp} / N_A$$

where M_0 (g mol^{-1}) is the molar mass of a B, S or G chain unit, v_{sp} ($\text{cm}^3 \text{g}^{-1}$) is the specific volume of the corresponding high polymer (discussed in [25, 26, 51–54]) and N_A (mol^{-1}) is Avogadro's constant.

Plots of s_h against micelle core volume are shown in Fig. 2.1 for solutions of copolymers forming spherical micelles in solution at 25 °C. It is clear that the solubilization capacity increases with increase in core size, reaching a limiting value when v_c exceeds *ca.* 100 nm^3 , corresponding to a core radius $r_c \approx 3$ nm. The dashed lines indicate limiting values of the solubilization capacity at 25 °C of $s_h = 16, 31$ and 54 mg g^{-1} for copolymers with B, S and G cores, respectively. Thus, through Fig. 2.1, our results provide clear evidence of the benefit of a large core volume and an appropriate choice of core composition if solubilization capacity is to be maximized.

Results for solutions of copolymer $E_{38}G_{12}E_{38}$ are not included in Fig. 2.1. As seen in Table 2.4, the value of N_w determined for this copolymer is high compared with those of the other $E_mG_nE_m$ copolymers, which, together with other evidence [54], indicates the formation of nonspherical micelles. The relatively

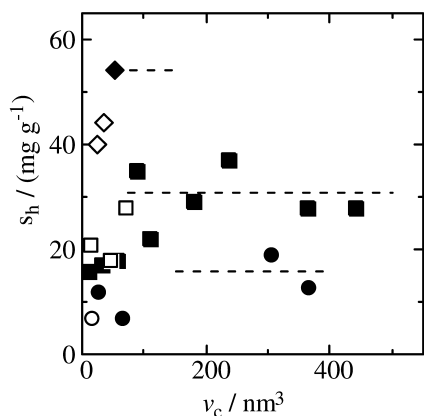


Fig. 2.1 Dependence on micelle core volume of solubilization capacity (s_h) for griseofulvin. Aqueous micellar solutions at 25 °C of (●) E_mB_n , (○) $E_mB_nE_m$, (■) E_mS_n and S_nE_m , (□) $E_mS_nE_m$, (◆) G_nE_m and (◇) $E_mG_nE_m$ copolymers. The dashed lines indicate the plateau values at high values of the core volume.

high value of s_h (see Table 2.4) is consistent with this assignment, as there is other evidence (see Section 2.4.1.2) [3, 16] that the extent of solubilization is enhanced if micelles are cylindrical rather than spherical.

2.4.1.2 Effect of Solubilization Temperature

Plots of s_h against micelle core volume are shown in Fig. 2.2 for solutions of copolymers $E_{11}B_8$ and $E_{96}B_{18}$ in the range 25–40 °C. It is well established that raising the temperature of micellar solutions of block copoly(oxyalkylene)s results in an increase in micelle association number [17, 75]. However, for spherical micelles a limit is reached when the hydrophobic blocks of the core are highly stretched and, as discussed in Section 2.1, any further increase in N_w can only be at the expense of a change from spherical to cylindrical geometry. The micelles of copolymer $E_{96}B_{18}$ are seen to approach, but not exceed, that limit over the range 25–40 °C (see Table 2.4). Consequently, the values of ν_c plotted in Fig. 2.2 are almost invariant and, for this copolymer, the solubilization capacity does not change significantly. In contrast, the micelles of copolymer $E_{11}B_8$ are spherical at 25 °C but are cylindrical, even worm-like, at 40 °C [25] and the solubilization capacity is much increased. The determining factor is the value of the association number in relation to the average length of the hydrophobic block: a copolymer with a short hydrophobic block cannot form a large spherical micelle core.

Plots of s_h against ν_c for solutions of E/S copolymers, both diblock and triblock, are shown in Fig. 2.3. Copolymer $E_{17}S_8$ has been shown to form cylindrical micelles at temperatures in the range 25–30 °C [26] and, no doubt, does so at 37 °C. In keeping with this, solubilization capacities measured for this copolymer are high compared with those found for the other copolymers, which form spherical (or near spherical) micelles. Even so, the results for the other diblock copolymers are of interest. The association numbers of their micelles are large and almost independent of temperature, characteristic of spherical micelles ap-

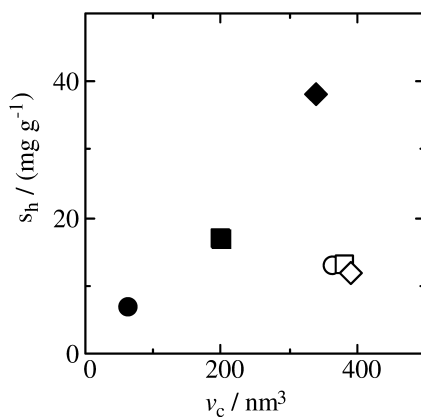


Fig. 2.2 Dependence on micelle core volume of solubilization capacity (s_h) for griseofulvin. Aqueous micellar solutions of copolymers $E_{11}B_8$ (filled symbols) and $E_{96}B_{18}$ (open symbols) at (●, ○) 25, (■, □) 37 and (◆, ◇) 40 °C.

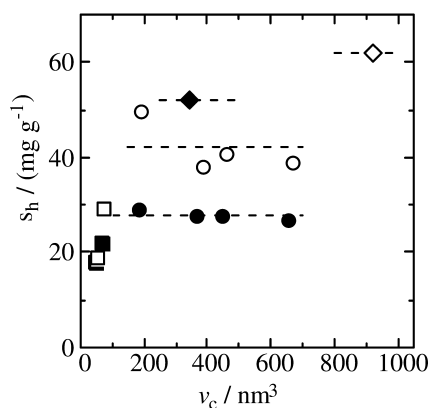


Fig. 2.3 Dependence on micelle core volume of solubilization capacity (s_h) for griseofulvin. Aqueous micellar solutions at (open symbols) 25 °C and (filled symbols) 37 °C of (●, ○) $E_m S_n$ and $S_n E_m$ and (■, □) $E_m S_n E_m$ copolymers forming spherical micelles and of (◆, ◇) $E_{17} S_8$.

proaching their upper size limit. However, unlike micellar solutions of copolymer $E_{96} B_{18}$, the solubilization capacity increases as temperature is increased: compare Figs. 2.2 and 2.3. The reason for this difference in behavior has not been established. As indicated by the difference in glass transition temperatures of lengthy S and B chains, $T_g \approx +40^\circ\text{C}$ compared with -80°C [29], S blocks in a micelle core at low temperatures will be less mobile than B blocks and it may be that a change in mobility between 25 and 37 °C affects the rate of uptake of the drug from solution.

2.5

Method 2

Values of the excess solubilization capacity of the copolymer solutions for griseofulvin obtained by method 2 are listed in Table 2.5. As for method 1, results for different copolymer concentrations (1 or 2 wt%) were averaged. For comparison, values of s_h obtained at 25 °C by method 1 are included. On average, the solubilization capacity is approximately doubled by incorporating griseofulvin into the melt before dissolving the copolymer in hot water. The effect is similar

Table 2.5 Solubilization of griseofulvin in block copolymer solutions (method 2).

Copolymer	s_{cp} (mg g ⁻¹) (method 2)	s_h (mg g ⁻¹) (method 2)	s_h (mg g ⁻¹) (method 1)
$E_{96} B_{18}$	6.9	29	13
$E_{43} B_{14} E_{43}$	6.1	19	7
$E_{45} S_8$	10.7	32	22
$S_{10} E_{135}$	9.6	56	35
$E_{82} S_8 E_{82}$	5.8	48	21
$E_{20} S_{10} E_{20}$	31.4	77	28

for both E/S and E/B copolymers, although at a lower level for the E/B copolymers.

The limiting conditions for microphase separation in E/B copolymer melts are well known and the melts of $E_{96}B_{18}$ and $E_{43}B_{14}E_{43}$ are certainly disordered [76]. Microphase separation has not been detected in the melts of E/S copolymers, no doubt because the charge-transfer interaction between ether oxygen and the phenyl ring greatly reduces the value of the Flory–Huggins χ parameter, much as observed for block copolymers of poly(ethylene oxide) and styrene [77]. We conclude that the marked effect seen in Table 2.5 is not a result of griseofulvin favoring less polar domains in an ordered melt, but rather a rapid and irreversible transfer to the micelle cores from the disordered melt at the point of micellization when the drug-loaded melt is transferred to the aqueous phase at 65 °C before equilibration at 25 °C and subsequent filtration. It is possible that method 2 is equivalent to a variant of method 1 carried out at 65 °C, albeit over a much shorter time period, 1 h rather than 3–5 days. We have not explored that possibility, being wary of the degradation of both copolymer and drug held in solution at high temperature.

A change in micelle shape from spherical to cylindrical caused by solubilization of a core-compatible substance has been predicted by Nagarajan [16]. A change in temperature from 25 to 65 °C will cause an increase in association number and favor a sphere-to-cylinder transition. Copolymer $E_{20}S_{10}E_{20}$ is an obvious case to consider. Looping of the S block in the core means that this copolymer is geometrically equivalent to an $E_{20}S_5$ diblock and might be compared with copolymer $E_{17}B_8$ (see Section 2.4.1.2) [26], in which case a substantial increase in N_w to a value approaching 100 will certainly result in formation of cylindrical micelles and so the very high value of s_h which is observed.

2.6 Gelation

A property of concentrated solutions of Pluronic F127 ($E_{106}P_{69}E_{106}$), which was recognized as early as 1972, is the formation of a hard gel on warming from ambient to body temperature, so-called ‘cold gelation’ [78]. This sol–gel transition is a consequence of a decrease in solubility of the copolymer in water on heating, which results in the formation of additional micelles and subsequent gel formation as the micelles become so tightly packed that their mobility is restricted. The potential application of this characteristic has been explored for a wide range of drug delivery systems, mainly using Pluronic F127 as the delivery vehicle, including for ophthalmic [79–82], rectal [83], nasal [84] and parenteral use [85–90]. Unfortunately, although it is possible to enhance significantly the solubilization capacity of block copolymer micelles beyond that of the $E_mP_nE_m$ copolymers by increasing the hydrophobicity of the cores as discussed in this chapter, none of these compounds in our experience exhibits cold gelation. Thus, although the $E_mS_nE_m$ and $E_mG_nE_m$ copolymers have greatly improved sol-

ubilization capability and readily form gels in concentrated solution, nevertheless they are unsuitable for use in delivery systems which depend on the cold gelation effect.

We have recently shown [91] that a solution with the desired gelation characteristics may be formed by mixing a triblock $E_mP_nE_m$ copolymer with a suitable $E_mS_nE_m$ copolymer. Our study has shown, for example, that 50:50 wt% mixtures of $E_{62}P_{39}E_{62}$ (Pluronic F87) 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. These mixed systems, which combine the desirable gelation characteristics of solutions of the $E_mP_nE_m$ copolymers with the greater solubilizing capacities of solutions of the $E_mS_nE_m$ copolymers, have potential as vehicles for the controlled delivery of solubilized drug from gels formed *in situ* following subcutaneous injection of a low-viscosity aqueous solution. Recently, it has been shown that micellar solutions of mixed copolymers $E_{137}S_{18}E_{137}$ (80 wt%) and $E_{62}P_{39}E_{62}$ (20 wt%) undergo cold gelation and have a high solubilization capacity for griseofulvin [74].

2.7

Conclusion

Our current interest is in the potential use of micellar solutions of block copolymers for the solubilization of aromatic drugs of low aqueous solubility. Comparison of the solubilization properties of a range of copoly(oxyalkylene)s shows that solubilization capacities in milligrams per gram of hydrophobe for griseofulvin rank in the order $G > S > B \gg P$, where $G = \text{OCH}_2\text{CH}(\text{CH}_2\text{OC}_6\text{H}_5)$, $S = \text{OCH}_2\text{CH}(\text{C}_6\text{H}_5)$, $B = \text{OCH}_2\text{CH}(\text{C}_2\text{H}_5)$ and $P = \text{OCH}_2\text{CH}(\text{CH}_3)$. The results also show that solubilization of griseofulvin by diblock copolymers is enhanced compared with that of comparable triblock copolymers.

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Notation

The block copoly(oxyalkylene)s of interest combine hydrophilic poly(ethylene oxide) with hydrophobic poly(propylene oxide), poly(1,2-butylene oxide), poly(styrene oxide) or poly(phenyl glycidyl ether). To describe the repeat units we

use the following notation: E = oxyethylene, OCH_2CH_2 ; P = oxypropylene, $\text{OCH}_2\text{CH}(\text{CH}_3)$; B = oxybutylene, $\text{OCH}_2\text{CH}(\text{C}_2\text{H}_5)$; S = oxyphenylethylene, $\text{OCH}_2\text{CH}(\text{C}_6\text{H}_5)$ from styrene oxide; G = oxy(phenyloxymethylene)ethylene, $\text{OCH}_2\text{CH}(\text{CH}_2\text{OC}_6\text{H}_5)$ from phenyl glycidyl ether. We use subscripts m and n to denote number-average lengths of the hydrophilic and hydrophobic blocks, respectively, in repeat units so that, for example, a triblock copolymer formed by sequential copolymerization of propylene oxide and ethylene oxide is denoted $\text{E}_m\text{P}_n\text{E}_m$.

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