Expert Opinion

Poly(ethylene oxide) based copolymers: solubilisation capacity and gelation

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It is thought that almost half of potentially useful drug candidates fail to progress to formulation development because of their low aqueous solubility and associated poor or erratic absorption characteristics. A response to this challenge has been the development of a variety of colloidal delivery systems in which the therapeutic agent is encapsulated in nanosized particles. In this review, attention is focussed on colloidal vectors based on amphiphilic block copolymers, the micelles of which can accommodate a wide range of water-insoluble guest molecules, and particularly on copolymers with poly(oxyethylene) as the hydrophilic block and with poly(oxyalkylene) or polyester hydrophobic blocks, taking advantage of the 'stealth' properties of the poly(oxyethylene) corona of their micelles. Although copolymers of this type have been commercially available for several decades in the form of the Pluronic® (BASF) polyols, which have a poly(oxypropylene) hydrophobic block, they have not found wide application for drug solubilisation, primarily because of their low solubilisation capacity. In attempts to achieve greater drug loading, recent work has concentrated on copolymers in which the core-forming blocks are designed to be more hydrophobic and more compatible with the drug to be encapsulated. Progress in this area has been reviewed and recent developments in the design of block copolymers of this type that combine high drug loading capacity with thermally reversible gelation characteristics in the temperature range suitable for potential application as *in situ* gelling vehicles following subcutaneous injection have also been discussed.

Keywords: block copolymer, polymeric micelles, solubilisation capacity, thermoreversible gelation

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1. Introduction

Many excellent reviews describe pharmaceutical applications, actual or potential, of aqueous micellar solution of block copolymers for solubilisation and release of poorly soluble drugs (e.g., [1-13]). In this article, attention is focussed on straight-chain copolymers with poly(oxyethylene) as the hydrophilic component combined with poly(oxyalkylene) or polyester as the hydrophobic component – materials that have been of considerable interest over past decades. The considerable body of work on copolymers with other types of hydrophobic blocks (e.g., poly(amino acid), poly(acrylate)) has been omitted as well as recent work on copolymers with other hydrophilic blocks formed using RAFT (reversible addition-fragmentation chain transfer) polymerisation, for example poly(2-(methacryloyloxy)ethyl phosphorylcholine) [14,15] and poly(*N*-isopropylacrylamide) below its lower critical temperature [16].

The block copoly(oxyalkylene)s and polyesters of present interest combine hydrophilic poly(ethylene oxide) with a range of hydrophobic groups, including poly(propylene oxide), poly(1,2-butylene oxide), poly(styrene oxide),

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Table 1. Notation for repeat units used in this paper.

E	OCH_2CH_2 from ethylene oxide
P	$OCH_2CH(CH_3)$ from propylene oxide
B	$OCH_2CH(C_2H_5)$ from 1,2-butylene oxide
S	$OCH_2CH(C_5H_6)$ from styrene oxide
G	$OCH_2CH(CH_2OC_5H_6)$ from phenyl glycidyl ether
L	$COOCH(CH_3)$ from DL-lactide
VL	$COO(CH_2)_4$ from γ-valerolacton
CL	$COO(CH_2)_5$ from ε-caprolactone

poly(phenyl glycidyl ether), poly(DL-lactide), poly(γ-valerolactone) and poly(ε-caprolactone). To describe the repeat units we use the notation presented in **Table 1**.

The subscripts *m* and *n* have been used to denote number-average lengths in repeat units of the hydrophilic and hydrophobic blocks respectively, so that, for example, a triblock copolymer formed by sequential copolymerisation of propylene oxide and ethylene oxide is denoted P_nE_m.

The ring-opening oxyanionic polymerisation of ethylene oxide was among the first 'living' polymerisations to be investigated and understood. The narrow Poisson distribution of chain lengths resulting under ideal conditions from this polymerisation was thoroughly described by Flory as early as 1940 [17,18]. The potential of oxyanionic polymerisation for the formation of well-defined block copoly(oxyalkylene)s with reliably reproducible properties was realised at an early stage, and the well-known triblock copolymers of oxyethylene and oxypropylene (type $E_mP_nE_{m)}$ were commercialised as Pluronic® polyols by Wyandotte Chemical Corp. (now BASF-Wyandotte) in 1951. Hydrogen abstraction from the methyl group of oxypropylene groups results in chain transfer and broadens the chain length distribution of poly(oxypropylene) compared with that of poly(oxyethylene) (e.g., [19]), but this was not a bar to the manufacture of useful products. Micellisation of certain $E_mP_nE_m$ copolymers in dilute aqueous solution, established by dye solubilisation, was reported in 1965 by Schmolka and Raymond [20], followed soon after by an account of the gelation of concentrated solutions [21]. The possibility of using Pluronic polyols for the solubilisation and delivery of drugs was raised by Schmolka in his 1977 review [22], and the solubilisation of a series of *p*-substituted acetanilides in micellar solution of these copolymers was reported in the same year by Collett and Tobin [23,24], the enhanced solubilisation of the more hydrophobic solutes being correctly assigned to uptake in the micelle core. The availability of a wide range of Pluronic polyols allowed rapid progress, particularly by Kabanov and co-workers [25-30]. The other commercially available range of copolymers of ethylene oxide and propylene oxide are the Tetronic® (BASF) poloxamines, the polymerisation of which is initiated with tetrafunctional ethylene diamine to produce a molecule with four P_nE_m arms [31]. Pluronic copolymers have also been modified for use in drug solubilisation, notably by Bromberg in grafting poly(acrylic acid) to a Pluronic backbone in order to introduce pH sensitivity and bioadhesion [32].

Flory also described the polymerisation of cyclic esters [18], indicating the potential for living polymerisation to form polyesters with narrow chain length distributions, albeit with the complication of ester interchange, which broadens the distribution over the ideal. Attention has centred on copolymers with hydrophobic blocks formed from ε-caprolactone, DL-lactide and DL-glycolide. Perrett and Skoulios [33] reported the synthesis of $CL_nE_mCL_m$ block copolymers in 1972, and the first investigations of micellisation in aqueous solution of triblock and diblock copolymers of this type came much later, motivated by the perceived advantage of biodegradable copolymer micelles for drug delivery [34-37]. Churchill and Hutchinson [201] described the synthesis of copolymers of poly(oxyethylene) and DL-lactide in 1988, and the micellar properties of diblock L_nE_m were first reported some 10 years later [38-40].

Block copolymer micelles possess many desirable features for use in pharmaceutical formulation. They have a core/shell structure; the micelle core acts as a locus for the solubilisation of poorly water-soluble drugs and the poly(oxyethylene) shell, although a potential site of solubilisation for some more hydrophilic drugs, is also important from a pharmaceutical viewpoint in conferring stealth properties to the micelle, allowing them to avoid uptake by macrophages of the reticular endothelial system so prolonging their lifetime in the blood circulation [11,12]. Moreover, a low critical micelle concentration (cmc) confers stability to the micelles on dilution, allowing them to circulate in the bloodstream for sufficient time to accumulate at tumour sites after intravenous injection by the enhanced permeability and retention effect. The permeability of blood vessels increases in tumours and in disease states involving inflammation because of a loss of junction integrity between endothelial cells. As a result, pores are formed that are sufficiently large (several hundred nanometres in diameter) to allow the internalisation of micelles, which accumulate in the interstitial fluid because of impaired lymphatic drainage. In general, after accumulation by the enhanced permeability and retention effect in this way, the drug carriers are taken up to cells by endocytosis. It is suggested that this effect has potential application in the delivery of drugs to tumour sites, as drugs solubilised in the internalised micelles will be accumulated in the tumours [2]. In addition, the molecular weight of the block copolymers used in solubilisation studies is generally sufficiently low for them to be filtered by the kidney and excreted in the urine (less than ~ 15,000 g mol^{-1} [41]).

However, despite these potential advantages, micellar solubilisation finds comparatively little commercial application as a means of enhancing uptake into solution of drug candidates, the low solubility of many of which remains a major obstacle in their formulation. One of the problems

associated with micellar solubilisation, which has contributed to its neglect in drug formulation compared with other colloidal systems for encapsulation of drugs, such as liposomes and cyclodextrins, is their perceived low solubilisation capacity. In many instances this has been the result of the choice, often dictated by commercial availability, of copolymers that are incompletely micellised at room temperature, a problem which is discussed further in this review. The design of copolymers of favourable architecture for solubilisation has been the focus of many studies, with the aim of enhancing the solubilisation capacity for poorly soluble drugs. This review summarises progress in achieving this goal. However, in many cases the choice of copolymer remains uninformed and it is hoped that this review might provide guidance in the selection of a suitable copolymer for improved solubilisation.

A characteristic property of many block copolymer systems is that of the thermally reversible gelation of their moderately concentrated micellar solutions. This is of particular pharmaceutical interest when it occurs at temperatures between ambient and body temperature, as in such cases there is potential for the development of *in situ* gelling drug-loaded micellar fluids for use for subcutaneous injection. This topic has not been reviewed in recent years and progress will be summarised.

2. Solubility enhancement by micellar solubilisation

2.1 Data selection

The specific objective in reviewing the considerable quantity of published work describing the use of poly(oxyalkylene) and polyester block copolymer micelles for the encapsulation of drugs or bioactive materials was to compare their solubilising capacities. In fact, only a minority of publications contain quantitative information, and those that do may not present their results in a readily understood form. With this in mind, several criteria have been used in the selection of material for inclusion in this article.

This review has been restricted to the solubilisation of drugs with solubilities in water of < 10 mg dl^{-1}, although a few examples of more soluble drugs have been included for completeness. Drugs of higher aqueous solubility will partition preferentially in the aqueous phase rather than into the micelle and solubility enhancement is not expected to be significant, as indeed is found in practice. In cases where results are given for a range of drug/copolymer ratios without the express purpose of determining a saturation solubility of micelles, the highest drug loading achieved for that system has been reported. Similarly, where a range of copolymer concentrations have been used, the data relating to the most dilute solution, preferably 1 wt%, have been selected. Thus, although data are sometimes available for solubilisation into the micellar gels formed at high copolymer concentration (typically > 20 wt%) these have not been included in the comparisons on the grounds that such concentrated systems are not representative of the conditions prevailing in dilute solution.

Solubilisation capacities have been presented as the ratio of the solubility of the drug in the copolymer micelles (S) expressed as milligrams per gram of copolymer to that in aqueous solution (S_o) under similar conditions. Where possible, aqueous solubilities determined by the authors rather than literature values have been used, even though in some systems this has necessitated extrapolation of solubility data to zero polymer concentration and hence the introduction of a degree of approximation into the S/S_o value. All aqueous solubilities estimated in this manner were compared to established values [42], where available, to check their reliability.

Examination of the literature shows a variety of methods of preparation of the solubilised system and this can have a significant influence on the solubilisation capacity. Aliabadi and Lavasanifar [1] have given a clear description of the main methods used and only a brief outline is given here. The simplest and most commonly used method of incorporation of the drug is the so-called 'shake flask' method, in which excess solid drug is equilibrated with the micellar solution and unsolubilised drug subsequently removed by filtration or centrifugation. Larger amounts of drug can often be solubilised by co-mixing the drug and copolymer at elevated temperature (typically ~ 60ºC) and adding the resultant intimate mixture to water or buffer to form the solubilised micellar solution. This method is referred to here as 'melt loading'. Other methods involve the use of nonaqueous solvents to dissolve the drug and copolymer. In the dialysis method, drug and copolymer are dissolved in a water-miscible organic solvent, followed by dialysis against water until the organic phase is replaced with water. In the solvent evaporation method, the drug and copolymer are dissolved in volatile organic solvents, which are allowed to evaporate at room temperature; the resultant dried drug/copolymer film is pulverised and dispersed in water. Alternatively, a micellar solution is formed by adding water slowly to a solution of drug and polymer in a water-miscible organic solvent (cosolvent) and removing the organic solvent by evaporation (cosolvent evaporation method). In a variation of this method, an oil-in-water emulsion is formed by mixing the organic solvent containing dissolved drug with an aqueous solution of the copolymer; the volatile solvent is then allowed to evaporate leaving the solubilised micellar solution. The method of preparation is indicated in the tables of solubilisation capacities so that its possible influence on the perceived solubility enhancement may be considered.

An important factor influencing water solubility, and hence micelle/water partitioning, is the ionisation state of the drug if this is a weak electrolyte, for example indometacin. In most of the solubilisation determinations reported in **Tables 2 – 4**, no information is provided on the pH of

Table 2. Solubilisation capacities of $E_mP_nE_m$ copolymers.

Drug	*T* (°C)	S_o (mg dl^{-1})	Copolymer	cmt/°C (1 wt%)	Copolymer wt%	Experimental method	*S* (mg g^{-1})	S/S_o*	Ref.
Allopurinol	25	78	F127	24	2.5	SF	92	1.2	[43]
Camptothecin	25	0.4	F127	24	1	D	1.4	6	[44]
Clonazepam	25	0.1	F68	50	10	SF	0.3	3	[45]
Diazepam	25	3	F108	30	6	SF	6	2	[46]
Estradiol	25	0.4	F127	24	1	SF	1.9	5	[47]
Griseofulvin	25	1	P94	23	1	SF	2.2	2	[48]
	25		P123	16	1	SF	4	4	‡
	25		F127	24	1	SF	3.2	3	‡
Indometacin	37	1	P85	30	5	SF	1.7	2	[49]
Ketoprofen	37	11	P85	30	5	SF	13.6	1.2	[49]
Lorezapam	25	4.8	F68	50	10	SF	16	3	[45]
Pyroxicam	30	8	F98	> 30	1§	SE	13	2	[50]
	37	3.1	P85	30	5	SF	4	1.3	[49]
Tropicamide	25	560	F127	24	5	SF	790	1.4	[51]

*Solubility enhancement expressed as the ratio of solubility per gram of copolymer (*S*; equivalent to solubility in 1 dl of 1 wt% copolymer solution) to solubility in water (S_o).

‡Unpublished data.

§Concentration of F98 was assumed to be 1 wt%.

cmt: Critical micelle temperature; D: Dialysis; EPE: F68: poloxamer 188 ($E_{80}P_{30}E_{80}$); F98: poloxamer 288 ($E_{125}P_{47}E_{125}$); F108: poloxamer 338: ($E_{148}P_{56}E_{148}$); F127: poloxamer 407 ($E_{106}P_{69}E_{106}$); P85: poloxamer 235 ($E_{27}P_{39}E_{27}$); P123: poloxamer 403 ($E_{19}P_{69}E_{19}$); SE: Solvent evaporation method; SF: Shake flask method.

measurement, and it is assumed that the solubilised systems are not buffered. Consideration must, therefore, be given to the state of ionisation of the drug in these systems when interpreting the data.

For simplicity, the solubilisation has not been reported in terms of the amount solubilised per gram of hydrophobe (S_H), although this is often useful for comparative purposes, being independent of the block copolymer composition. This parameter may readily be calculated from the relationship $S_H = (S\text{-}S_o)/w_H$, where w_H is the weight fraction of hydrophobe (for example $w_H = 0.3$ for Pluronic F127).

Where possible, data have been reported at 25ºC or room temperature, rather than 37ºC, as it is the temperature of interest when solubilisation is used in the formulation of dosage forms. Micellisation of the block copolymers is an endothermic process driven by the positive entropy change associated with the hydrophobic effect. The positive enthalpy of micellisation is large in the case of the $E_mP_nE_m$ copolymers, implying a significant decrease of the cmc with increase of temperature and a greater potential for solubilisation at higher temperatures because of the increased number of micelles in solution. This temperature effect should be borne in mind when comparing solubilisation capacities of the Pluronic polyols, many of which are incompletely micellised at room temperature. When considering solubilisation by this type of copolymer, values have been given of the critical micelle temperature (cmt), which is the temperature at which micelles are first observed at a selected concentration (chosen here to be 1 wt%).

2.2 Solubilisation capacities of poly(oxyalkylene)s

The solubilisation capacities of a selection of Pluronic polyols are presented in **Table 2**. In general, S/S_o values for solutions at 25°C are in the range 1 – 3, with a maximum value of 6. This relatively low ability of the Pluronic polyols to solubilise water-insoluble drugs is in part a consequence of their high cmt values and consequent limited micellisation at room temperature. Although any micelles formed at ambient temperature may be large, they are few in number and this is reflected in their poor solubilising capacity. This effect is clearly demonstrated in a study by Molpeceres *et al.* [52] of the solubilisation of ciclosporin A by Pluronic F68, in which solubilisation was noted only at a temperature of 50ºC, which corresponds to the cmt of this copolymer. The data for the solubilisation of indometacin, ketoprofen and pyroxicam by Pluronic P85 included in **Table 2**, and that for griseofulvin by Pluronic P123, show that even at temperatures above the cmt the solubilisation capacity is poor.

Table 3 shows solubilisation by both di- and tri-block copolymers with hydrophobic blocks formed from 1,2-butylene oxide, styrene oxide and phenyl glycidyl ether. The cmt values of 1 wt% solutions of these copolymers are well below 25ºC and micellisation is, therefore, essentially complete at room temperature. Despite this, there is only a

Table 3. Solubilisation capacities of di- and triblock copolymers with hydrophobic blocks formed from 1,2-butylene oxide, styrene oxide and phenyl glycidyl ether*.

Drug	*T* (°C)	S_o (mg dl^{-1})	Copolymer	*S* (mg g^{-1})	S/S_o	Ref.
Carbamazepine	25	12	$E_{11}B_8$	17	1.4	‡
			$E_{17}B_{12}$	23	2	
Frusemide	25	0.5	$E_{67}S_{15}E_{67}$	16	32	‡
			$S_{15}E_{63}$	21	42	
			$E_{17}S_8$	53	104	
Griseofulvin	25	1	$E_{43}B_{14}E_{43}$	4.3	4	[53]
			$E_{96}B_{18}$	4.3	4	
			$E_{20}S_{10}E_{20}$	13	13	
			$E_{45}S_8$	9	9	
			$E_{45}S_8$§	12	12	
			$E_{45}S_{10}$	12	12	
			$E_{17}S_8$	31	31	
			$E_{38}G_{12}E_{38}$	19	19	[54]
			G_5E_{67}	13	13	[55]
Halofantrine	25	7	$E_{67}S_{15}E_{67}$	27	4	‡
			$S_{15}E_{63}$	26	4	
			$E_{17}S_8$	67	10	
Nabumetone	25	0.5	$E_{67}S_{15}E_{67}$	8	16	‡
			$S_{15}E_{63}$	17	34	
			$E_{17}S_8$	82	164	
Spironolactone	25	1.7	$E_{11}B_8$	4.8	3	‡
			$E_{17}B_{12}$	12	7	

*Copolymer concentration for all solubilisation measurements was 1 wt% and all were carried out by the shake flask method except where indicated. Solubility enhancement expressed as the ratio of solubility per gram of copolymer (*S*; equivalent to solubility in 1 dl of 1 wt% copolymer solution) to solubility in water (S_o).
‡Unpublished data.
§Melt loading method.

slight improvement of the solubilisation capacity when the poly(oxypropylene) block of the Pluronic polyols is replaced by a poly(oxybutylene) block. Marked improvement of solubilisation is noted for copolymers with hydrophobic blocks of poly(styrene oxide) and poly(phenyl glycidyl ether). A comparison of the hydrophobicities per repeat unit based on the cmc values in molar units for the four types of block rank in the approximate ratio G:S:B:P ≈ 15:12:6:1 [55]. The relationship between the solubilisation capacity of block copolymer micelles and the compatibility of the solubilisate with the hydrophobic block that forms the micelle core was stressed by Nagarajan *et al.* [56]. On this basis it might be expected that block copolymer micelles with poly(styrene oxide) or poly(phenyl glycidyl ether) cores might be more efficient solubilisers of aromatic drugs, the aromatic nature of these cores being more conducive to their solubilisation than the poly(propylene oxide) cores of the Pluronic polyols.

For copolymers of similar composition and architecture, there is an improvement of solubilisation capacity associated with an increase of the length of the hydrophobic block. Some examples are shown in **Table 3**, for example $E_{45}S_{10}$ is a better solubiliser of griseofulvin than $E_{45}S_8$, and $E_{17}B_{12}$ is able to solubilise larger amounts of carbamazepine and spironolactone than $E_{11}B_8$. Other examples of this effect have been reported by Rekatas *et al.* [48] and Crothers *et al.* [53]. However, the most dramatic improvement of solubilising capacity is with $E_{17}S_8$, where an increase of the S/S_0 ratio of two- to fivefold is seen compared with other diblock copolymers of styrene oxide. Although the hydrophobic chain length of this copolymer is short, it forms micelles composed of > 240 unimers at 25°C. As a consequence, these micelles cannot form a spherical core as with the other copolymers listed in **Table 3** and must be highly elongated, probably worm like [57]. This enhances solubilisation in the core [53] and adds to the advantage of the relatively high weight fraction

Table 4. Solubilisation capacities of polyesters with caprolactone, valerolactone and DL-lactide hydrophobic blocks.

Drug	*T* (°C)	S_o (mg dl^{-1})	Copolymer	Copolymer wt%	Experimental method	*S* (mg g^{-1})	S/S_o*	Ref.
Ciclosporin A	–	2.3	$E_{114}CL_{44}$	1	CSE	104	45	[58]
17β-Estradiol	25	0.4	$E_{45}CL_{23}$	1	D	1900	4750	[59]
Ellipticine	–	0.015	$E_{114}CL_{35}$	1	D	325	22000	[60]
			$E_{114}L_{58}$			1.2	80	
Dihydrotestosterone (androstanolone)	25	0.52‡	$E_{44}CL_{20}$	1	D	1300	2500	[62]
Indometacin	25	0.094§	$E_{114}CL_{27}$	1	D	350	3700	[63]
Paclitaxel	25	0.05	$E_{86}L_{49}$-X¶	1	D	45	900	[64]
			$E_{45}VL_{20}$	10	SE	92	1800	[65]
			$E_{45}L_{18}$	0.04		20	400	[39]
Testosterone	25	2.3	$E_{50}L_{23}$	0.25	SF	7	3	[38]

*Solubility enhancement expressed as the ratio of *S* = solubility per gram of copolymer (equivalent to solubility in 1 dl of 1 wt% copolymer solution) to S_o = solubility in water.
‡From [61].
§From [42].
¶$E_{86}L_{49}$-X micelles are core polymerised.
CSE: Cosolvent evaporation method; D: Dialysis method; SE: Solvent evaporation method; SF: Shake flask method.

of S in copolymer $E_{17}S_8$. There is evidence from experimental work on other systems [8] of enhanced solubilisation when micelles are cylindrical rather than spherical.

An example of the enhanced solubilisation resulting from the use of a melt loading method compared with the more widely used shake flask technique is seen from the solubilisation of griseofulvin by $E_{45}S_8$ (**Table 3**). Other examples showing a similar increase in solubilisation efficiency compared with the shake flask method are reported by Crothers *et al.* [53] and have been attributed to a rapid and irreversible transfer to the micelle cores from the disordered melt at the point of micellisation when the drug-loaded melt is transferred to the aqueous phase at elevated temperature.

2.3 Solubilisation capacities of polyesters

This review has been restricted to polyesters composed of blocks of two monomers, one of which is the poly(ethylene oxide) hydrophilic block. Exclusions include, for example, block terpolymers with poly(ethylene oxide), poly(lactide) and poly(glycolide) blocks, block copolymers with statistical poly(lactide-co-glycolide) hydrophobic blocks, and copolymers of Pluronic polyols and poly(caprolactone), $CL_x(E_mP_nE_m)CL_x$.

The solubilisation capacities of a selection of polyesters with poly(caprolactone), poly(valerolactone) and poly(DL-lactide) hydrophobic blocks are presented in **Table 4**. Very high S/S_o ratios are noted with the caprolactone block copolymers, although it is stressed that these values are dependent on the precision of S_o values, which are usually very low for the drugs involved.

It is clear from **Table 4** that hydrophobic blocks of poly(caprolactone) confer a much higher solubilising capacity than those of poly(lactide). This observation is in agreement with predictions [60] of the degree of compatibility between the anticancer drug ellipticine and several polymers including poly(caprolactone) and poly(DL-lactide), based on estimations of their solubility parameters using the group contribution method.

A related more general conclusion may be drawn from the relative hydrophobicites of the two copolymers based on consideration of literature values of the cmcs for a wide range of samples. Comparison with results for ES, EB and EP copolymers indicates that the hydrophobicity of a CL unit is similar to that of an S unit, and that the hydrophobicity of an L unit is slightly less than that of a B unit and hence the hydrophobicities are in the approximate ratio CL:L:P = 12:4:1.

Values of the cmc for EVL copolymers indicate, as would be expected, a hydrophobicity per VL unit between those of L and CL, which is in agreement with the results shown in **Table 4**.

It is interesting to note that the radius of the ellipticine-loaded $E_{114}CL_{35}$ micelles at maximum drug-loading was reported to be 33 nm [60], which is similar to the length of the CL block, suggesting the presence of non-spherical micelles in these systems of very high solubilisation capacity. Changes in micelle geometry caused by solubilising solutes in the core have been predicted theoretically by Nagarajan [7].

The micellar systems in **Table 4** have low critical micelle concentrations and exhibit a slow rate of micelle dissociation; nevertheless their stability may be further increased by

chemical stabilisation of the hydrophobic core. For example, core stabilisation of the $E_{86}L_{49}$ copolymers described by Kim *et al.* [64] was achieved by polymerisation of a methacryloyl group attached to the poly(lactic acid) block, providing drug carrier micelles with the potential to retain their integrity under all physiological conditions. **Table 4** shows that it was possible to incorporate 30 – 60 mg of paclitaxel per gram of polymerised copolymer, which is comparable to the drug loading achieved for this drug by Zhang *et al.* [39] in a micellar solution of conventional $E_{45}L_{18}$.

3. Thermoresponsive micellar gels

As described in Section 2, many block copolymers form dilute micellar solutions that can be used to solubilise and deliver poorly soluble drugs. Here attention is focussed on concentrated micellar solutions that reversibly transform from mobile fluids to immobile gels on heating in the interval 25 – 37°C. Because of the high concentration, typically 20 – 30 wt% copolymer, values of solubilisation capacity defined for dilute micellar solutions assume less importance. Moreover, the thermodynamics of micellisation and solubilisation in concentrated solution differ from those in dilute solution: the continuous phase in the concentrated micellar solution is no longer structured water, but, effectively, a concentrated solution of poly(ethylene oxide), itself contributing to solubilisation.

The gelation of aqueous micellar solutions of $E_mP_nE_m$ copolymers was reported in the 1960s [21]. The gelation of solutions of copolymer $E_{106}P_{69}E_{106}$ (F127) on cooling from a high temperature (hot gelation) or on heating from a low temperature (cold gelation) was clearly described, with films formed on the skin by cold gelation being recommended for the treatment of burns [66]. Concentrated solutions of F68 ($E_{80}P_{30}E_{80}$) also commanded early attention [67]. Quantitative study of drug release followed [68] and pharmaceutical applications were explored (e.g., [69,70]), and the topic continues to be of interest in recent times (e.g., [71-76]).

Figure 1 shows the gel diagram for aqueous solutions of F127, which is typical of many other block copolymer systems with pharmaceutical application. For this particular sample, an 18 wt% solution forms a gel at 25°C and the dynamic elastic modulus of the gel at 37°C is 12 kPa.

The physical chemistry of aqueous micellar gels of $E_mP_nE_m$ and related copolymers has been reviewed [78-82]. The gels of pharmaceutical interest are ordered liquid crystals of spherical micelles, that is gels of high modulus with face-centred cubic structures if the micelles pack as hard spheres, or body-centred cubic structures if the micelle–micelle interaction potential is soft [81], which is the case for the F127 gel. Gelation is a property of the micelles. The importance of the underlying characteristics of the copolymer molecules (chemical composition, block length, block architecture) lies in determining the extent of micellisation and the micelle geometry, and so the conditions under which the micelles will fill the available volume. Accordingly, the chemistry of the hydrophobic block may vary considerably without changing the established pattern.

Gel formation on heating the block copolymer solution (cold gelation) is of present interest. As mentioned in Section 2.1, micellisation is entropy driven, that is the standard entropy and enthalpy of micellisation are both positive, reflecting the increased disorder of the water when the hydrophobic block is removed to the micelle core: the hydrophobic effect. The value of the standard enthalpy of micellisation is an indicator of the magnitude of the hydrophobic effect, and for $E_mP_nE_m$ copolymers in dilute solution the value is high ($\Delta_{mic}H^o$ = 150 – 350 kJ mol^{-1}) [78,83]. However, in more concentrated solution (e.g., 20 wt%) the value is much lower (e.g., 20 kJ mol^{-1}) [81,84], which is consistent with the poly(oxyethylene) blocks modifying the water structure and weakening the hydrophobic effect. The implication is that a poly(oxyethylene)-based surfactant may be incompletely micellised in a concentrated solution at 20°C, even though it is well micellised in aqueous solutions at the same temperature at lower concentrations. The broad transition from dilute- to concentrated-solution behaviour occurs at ~ 10 wt% [84]. However, given the endothermic nature of the micellisation process, the extent of micellisation in the concentrated solution increases with temperature and a packed micellar gel forms at a critical gelation temperature (e.g., at 25°C for an 18 wt% solution of F127; **Figure 1**), although the value may vary from sample to sample [85].

Although the low temperature gel boundary is attributable to the formation of additional micelles, the copolymer is completely associated at the high temperature boundary, and the mass concentration of micelles is constant. This boundary results from a reduction in micelle volume at constant concentration, which is a consequence of the negative temperature coefficient of solubility of poly(oxyethylene) and leads to contraction of the micelle corona.

Either gel boundary can be sharply defined by tube inversion or by oscillatory rheometry, in the latter case placing the boundary where the elastic modulus (G') passes through 1 kPa [86]. The agreement between the two methods is illustrated in **Figure 1**. The maximum value of G' for a cubic gel away from the boundary is much higher, typically ≥ 10 kPa.

The gelation point is often taken as the point at which G' and the viscous modulus (G'') cross over. However, micellar solutions may be classified as sol ($G'' > G'$), soft gel ($G' > G''$, but fluid) and hard gel ($G' > G''$, but immobile) [81]. The crossover condition describes the sol/soft-gel boundary, whereas the boundary of interest in drug delivery is the fluid/hard-gel boundary. The condition G' = 1 kPa holds for cubic gels, with lower values of G' for less rigid mesophases [86].

So far as gelation is concerned, diblock copolymers and triblock copolymers with oxyethylene terminal

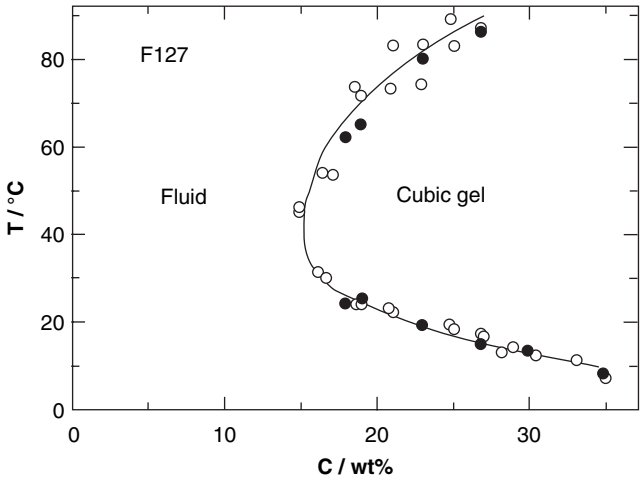

Figure 1. The gel boundary for aqueous solutions of copolymer F127. The filled circles are data points obtained by the tube inversion method for the mixture. The unfilled squares are data points from rheometry.
Adapted from [77].

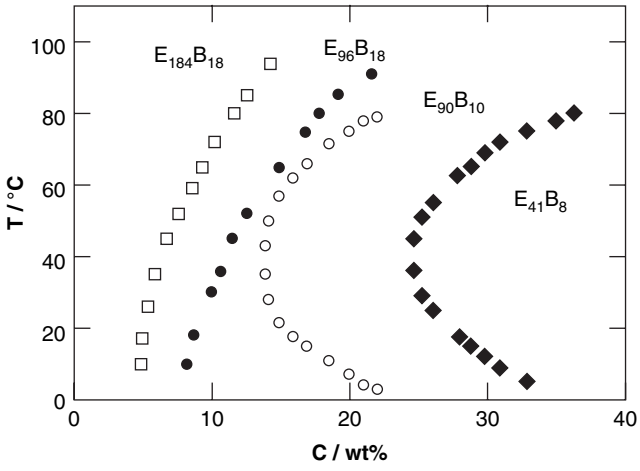

Figure 2. Gel boundaries for aqueous solutions of E_mB_n diblock copolymers, as indicated.
Smoothed data points, adapted from [93,94].

blocks of similar overall composition (E_mP_n and $E_mP_{2n}E_m$) behave in the same way, but copolymers with the reverse triblock architecture ($P_nE_{2m}P_n$) differ. As described by Mortensen *et al.* for copolymer $P_{15}E_{156}P_{15}$ [87], and well characterised for alkyl-terminated poly(oxyethylene)s, which act as associative thickeners [88], copolymer chains bridge between micelles to form transient networks in moderately concentrated solutions. At higher concentrations, the network fills the whole volume, and at high-enough concentrations an ordered gel is formed. The sharp boundary characteristic of the formation of packed micellar gels is replaced by a more gradual mobile/immobile transition, and the network gel has a lower elastic modulus (e.g., G'max < 1 kPa for copolymer concentration ≤ 45 wt%) [87].

So far in this short account examples have been taken our examples from results for triblock copolymers of ethylene oxide and propylene oxide. Gel formation, rheology and structure have been investigated for copolymers of ethylene oxide and other epoxides (i.e., 1,2-butylene oxide, styrene oxide and phenyl glycidyl ether) [54,81,89,90], with some emphasis on diblock architectures (e.g., [91,92]). Copolymers with these more hydrophobic blocks, which are known to provide satisfactory solubilisation of griseofulvin in dilute micellar solution (see Section 2.2), form packed micellar gels that are stable at low temperatures. Changing the length of the blocks may produce the required gelation behaviour: increasing the length of the hydrophobic block lowers the cold-gelation boundary and broadens the temperature range of the gel; increasing the length of the hydrophilic block reduces the minimum concentration for gel formation. The gel boundaries for copolymers $E_{41}B_8$, $E_{90}B_{10}$, $E_{96}B_{18}$ and $E_{184}B_{18}$, shown in **Figure 2**, illustrate these effects. Of note is that the hydrophilic/hydrophobic ratio itself is not an important consideration, as is evident from **Figure 2** where copolymers $E_{96}B_{18}$ and $E_{41}B_8$ have similar overall compositions (84.2 and 83.6 mol% E, respectively), but very different gelation behaviours.

Copolymers of ethylene oxide with poly(DL-lactide) and poly(caprolactone) blocks are also much more hydrophobic than those with poly(propylene oxide) blocks (see Section 2.3). As for the copolyethers, the advantage of micelle stability for drug solubilisation at low temperature may prove an obstacle to satisfactory cold-gelation behaviour (e.g., [95,96]). Block lengths required for satisfactory cold gelation of $CL_nE_mCL_n$ and $E_mCL_nE_m$ copolymers (the latter formed by linking monofunctional diblocks with hexamethylene isocyanate) have been defined [97,98]. An alternative approach has been to reduce the hydrophobicity of poly(lactide) blocks by copolymerisation with glycolide [99-102], and copolymers of this type are available under the tradename Regel® (Protherics) [101]. Others have used statistical polymerisation of glycolide and caprolactone to the same effect [103]. Copolymerisation of monomers with different reactivities carries with it the possibility of tapering of composition along the copolymer chain, introducing an unwanted variable into copolymer preparation. Forming the hydrophobic block from 3-methyglycolide provides an elegant (if invariable) solution to this problem, giving a uniform structure of alternating lactide and glycolide units along the chain [104].

A more general approach to the control of gelation, avoiding the need for synthesis, is to use a mixture of two copolymers with different attributes, that is, to combine the satisfactory gelation characteristics of a micellar solution of one copolymer with the more favourable solubilisation characteristics of micelles of another. For example, a micellar solution of $E_{137}S_{18}E_{137}$ is a good solubiliser for aromatic

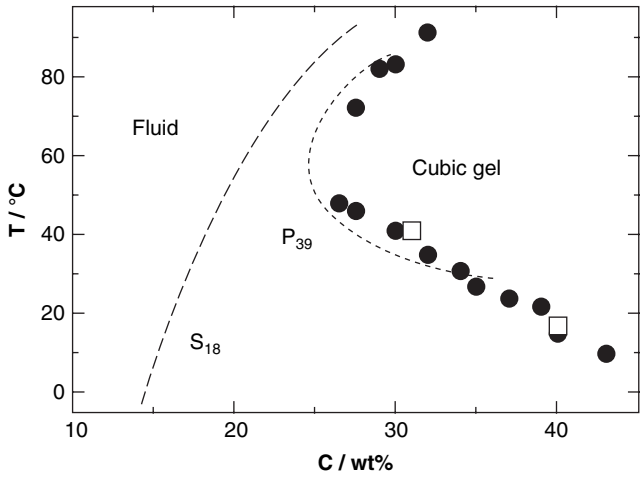

Figure 3. A gel diagram for aqueous solutions copolymers $E_{137}S_{18}E_{137}$ and $E_{62}P_{39}E_{62}$, 50/50 wt%. The dashed curve labelled S_{18} shows the gel boundary for solutions of $E_{137}S_{18}E_{137}$ alone; the dotted curve labelled P_{39} shows that for solutions of $E_{62}P_{39}E_{62}$ alone. The filled circles are data points obtained by the tube inversion method for the mixture. The unfilled squares are data points from rheometry.
Adapted from [108].

drugs [53], and a solution of $E_{62}P_{39}E_{62}$ (F87) has satisfactory gelation behaviour, similar to that of F127 [105]. **Figure 3** shows the gel diagram obtained for a 50/50 wt% mixture of the two copolymers [106]. It is seen that the gelation behaviour of the mixture is similar to that of F87 (i.e., dominated by the formation of $E_{62}P_{39}E_{62}$ micelles as the temperature is increased). Similar results have been obtained for other mixed systems [106,107] and appropriately chosen mixed gels have been shown to have body-centred cubic structures [107]. For the $E_{137}S_{18}E_{137}$/F87 mixture, it has been shown that it is possible to maintain solubilisation capacity and preserve gelation behaviour whilst reducing the proportion of F87 [108].

4. Conclusions

This review has highlighted features of the block copolymer composition and architecture that have the potential to achieve high drug loading capacity. Chief among these is the compatibility between the guest molecule and the hydrophobic environment provided for its encapsulation. An increase of the hydrophobicity of the micelle core by replacing the poly(oxypropylene) hydrophobic block of the widely used Pluronic polyols with poly(oxyalkylene) blocks formed from butylene oxide, styrene oxide or phenyl glycidyl ether has resulted in a progressive increase of efficiency of the solubilisation of highly insoluble drugs, which for the model drug griseofulvin can be of the order of 10-fold under identical experimental conditions. An obvious requirement, but one that in the case of the Pluronic polyols is often seemingly overlooked, is the extent of micellisation at the formulation temperature. The temperature at which micelles of the commonly used Pluronic polyols are first observed (the cmt) is around or above room temperature and consequently the extent of their micellisation is low – an important factor contributing to their poor solubilisation capacity. Increasing the core size by increasing the chain length of the hydrophobic block is an obvious ploy to increase the solubilisation capacity for molecules solubilised at this location, but unless the balance of hydrophobic and hydrophilic properties of the block copolymer molecule is carefully considered, there is potential for increasing the hydrophobicity of the block copolymer to such an extent that the copolymer has poor water solubility. The caprolactone block copolymers of **Table 4** are very efficient solubilisers, but because of their long caprolactone chain lengths, this high solubilisation capacity comes at the expense of a difficulty of preparation of the solubilised systems often necessitating the use of organic cosolvents and dialysis techniques. An increase of core volume and consequent increase of solubilising capacity can sometimes be achieved by inducing a transition from spherical to cylindrical or worm-like micelles. The determining factor is the ratio of hydrophilic to hydrophobic block length and its effect on the micelle association number (the number of block copolymer molecules per micelle) in relation to the average length of the hydrophobic block: a copolymer with a short hydrophobic block is unable to form a large spherical micelle because the diameter cannot exceed that of two fully extended chains.

It has been known for many years that concentrated micellar solutions of the Pluronic polyols can transform from mobile fluids to immobile gels on warming from ambient to body temperature, leading to suggestions for their use as *in situ* gelling drug delivery vehicles for administration by subcutaneous injection. A factor determining their applicability is their solubilisation capacity. Careful choice of hydrophilic and hydrophobic block lengths or change of the composition of the hydrophobic blocks by copolymerisation (e.g., with the lactide/glycolide copolymers) can provide other poly(oxyalkylene) and polyester block copolymers with the favourable gelling characteristics of the Pluronic polyols, but with higher drug-loading capacity. Recent studies have provided an alternative approach avoiding the need for synthesis, in which a copolymer with good solubilising characteristics is mixed in a suitable ratio with a second copolymer having favourable gelation properties.

5. Expert opinion

Block copolymer micelles based on poly(oxyethylene) offer many important advantages for the solubilisation and delivery of poorly water-soluble drugs over other colloidal delivery vehicles. Their core/shell structure allows for considerable flexibility in the design. The composition of the core can be tailor-made to provide suitable environments

for the solubilisation of selected guest molecules, whilst the poly(oxyethylene) shell confers stealth properties allowing the micelles to evade uptake by the reticuloendothelial system. The ability to avoid reticuloendothelial system uptake is crucial if the micelles are to remain in the bloodstream for a sufficient time for them to deliver the encapsulated therapeutic agents to the site of action. They also offer the potential for active targeting either by covalent binding of pilot molecules or by utilising polymeric micelles sensitive to external stimuli. If the cmc is low, the micelles are stable to dilution *in vivo* and consequently loss of encapsulated drug through micelle dissociation is low. However, there is potential for further improvement of stability by crosslinking the core or shell to form highly stable assemblies with good affinity towards a variety of chemical entities.

Despite this developing interest in the application of poly(oxyethylene)-based block copolymers for drug delivery, there has been relatively little advance in the rational design of the block copolymers to enhance their solubilisation capacity. Attainment of a sufficiently high solubilisation capacity is essential to avoid the necessity for an unacceptably high concentration of these surfactants in the formulation. Early work on solubilisation of drugs using poly(oxyethylene)-based copolymers has focussed on the use of the Pluronic polyols and has led to disappointingly low levels of incorporation of therapeutic agent. Nevertheless these copolymers are commercially available, and in the absence of facilities for synthesis, continue to be used. An interesting departure has been the use of mixtures of copolymers to form stable dispersions of small particle size, which show a 10-fold increase in dye solubilisation compared with F127 alone. Workers who have used more hydrophobic core-forming blocks have reported much higher levels of drug incorporation, although in the case of the poly(caprolactone)/poly(oxyethylene) block copolymers, which show the highest solubilising capacities, this has been achieved at the expense of a more complex method of formation of the solubilised systems.

Of the many factors involved in drug solubilisation in dilute micellar systems, which should be considered in the design of block copolymers with high solubilisation capacity, the most important are the hydrophobicity of the core block, as this determines the stability of the micelle under formulation conditions, and the compatibility of the drug with the core-forming block, which determines its partitioning between the aqueous phase and core. The specific nature of the compatibility requirement means that there can be no universal micellar system for drug solubilisation. Indeed Allen *et al.* [8] have pointed to the huge range in water/core partition coefficients for pyrene and various core polymers, from order 10^2 for poly(propylene oxide) to 10^5 for poly(styrene). Accordingly, progress in the field is related to progress in polymer chemistry, when new methods of polymerisation will give rise to a greater range of core-forming materials. Given favourable hydrophobicity and compatibility, the system can be optimised by increasing the length of the core-forming block, as this increases core volume and so solubilisation capacity. Within limits a long hydrophobic block (i.e., in relation to the length of the hydrophilic block) causes a change in micelle geometry from spherical to cylindrical, with possible beneficial effect.

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