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Note

Solubilisation of drugs in micellar solutions of diblock copolymers of ethylene oxide and styrene oxide

Michael Crothers[a], Nagíla M.P.S. Ricardo[b], Frank Heatley[c], S. Keith Nixon[c], David Attwood[a,*], Colin Booth[a]

[a] School of Pharmacy and Pharmaceutical Sciences, University of Manchester, Manchester M13 9PL, UK
[b] Department of Organic and Inorganic Chemistry, Federal University of Ceará, CX 12200 Fortaleza, Brazil
[c] School of Chemistry, University of Manchester, Manchester M13 9PL, UK

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ABSTRACT

The solubilisation of two poorly soluble drugs, furosemide and nabumetone, in micellar solutions of diblock copolymers of ethylene oxide and styrene oxide has been studied at 25 and 37 °C and solubilisation capacities compared with published values for griseofulvin and docetaxel. Solubilisation in the micelle core, corrected for the different proportions of poly(styrene oxide) in the copolymers, was similar for all four drugs. The highest solubilisation capacities were found for a copolymer with worm-like micelles.

1. Introduction

As described in recent reviews, aqueous solutions of poly(oxyethylene)–poly(oxypropylene)–poly(oxyethylene) triblock copolymers have been extensively examined as solubilisers for poorly water-soluble drugs (Kabanov et al., 2002; Kabanov and Alakhov, 2002; Chiappetta and Sosnik, 2007). Poly(oxypropylene) is not an ideal choice for the hydrophobic block (Attwood and Booth, 2007; Attwood et al., 2007) and poly(oxyalkylene) chains of greater hydrophobicity have been incorporated into related copolymers, resulting in a higher extent of micellisation at low temperatures. Sequential oxyanionic polymerisation of cyclic ethers provides a convenient and versatile route to copolymers with narrow block-length distributions, and aqueous micellar solutions of block copolymers of poly(ethylene oxide) combined with poly(1,2-butylene oxide), poly(styrene oxide) or poly(phenyl glycidyl ether) have been investigated as drug solubilisers (see, for example, Rekatas et al., 2001; Crothers et al., 2005; Taboada et al., 2006; Elsabahy et al., 2007). Values of the critical micelle concentration (cmc, molar units) provide a useful indicator of hydrophobicity and, for diblock copolymers, the hydrophobicity per chain unit ranks as P:B:S:G = 1:6:12:15 (Taboada et al., 2006). Here P denotes an oxypropylene unit, $OCH_2CH(CH_3)$, B an oxybutylene unit, $OCH_2CH(C_2H_5)$, S an oxyphenylethylene unit, $OCH_2CH(C_6H_5)$, and G an oxy(phenyloxymethylene)ethylene unit $OCH_2CH(CH_2OC_6H_5)$. As reviewed recently (Attwood and Booth, 2007), compared with $E_mP_nE_m$ copolymers (n and m denote number-average block lengths in chain units) copolymers with B, S or G blocks show enhanced solubilisation capacities for griseofulvin in 1 wt% aqueous solutions at 25 °C, results which reflect, at least in part, the low extent of micellisation of the $E_mP_nE_m$ copolymers.

Previously we have used griseofulvin as a standard drug in order to compare the solubilisation capacities of micellar solutions of a range of copolymer compositions in a uniform way. In this article we present new results for two other poorly soluble drugs, furosemide and nabumetone, solubilised in aqueous solutions of diblock copolymers of ethylene oxide and styrene oxide. pH was not controlled in our experiments. The values obtained are compared with published results for the solubilisation of griseofulvin (Crothers et al., 2005) and docetaxel (Elsabahy et al., 2007), which are the only other results available for the solubilisation of drugs in closely related copolymers.

* Corresponding author. Tel.: +44 161 2752328; fax: +44 161 2752396.
E-mail addresses: david.attwood@manchester.ac.uk, mbpssda2@man.ac.uk (D. Attwood).

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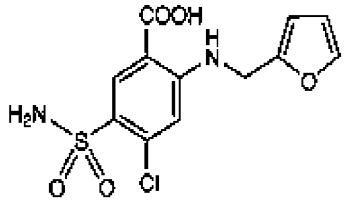

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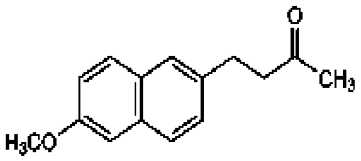

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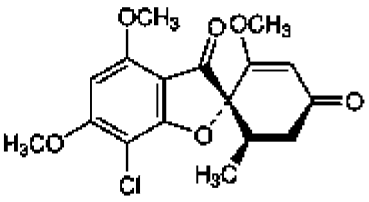

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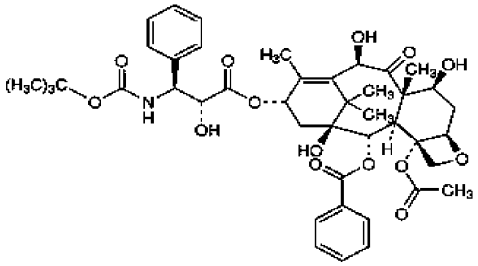

Docetaxel

2. Experimental

2.1.Materials

The molecular characteristics and micellar properties of the block copolymers used in the study are listed in Table 1: the notation E_nS_m and S_nE_m indicates the order of sequential polymerisation of the diblock copolymers. The copolymers were characterised by gel permeation chromatography (tetrahydrofuran eluent, poly(ethylene oxide) calibrants) and by ^{13}C NMR, the former to determine the ratio of weight-average to number-average molar mass (M_w/M_n), and the latter to confirm the diblock architecture and to determine the absolute value of M_n. Details of the methods of preparation and characterisation can be found elsewhere (Crothers et al., 2002; Yang et al., 2003). Furosemide and nabumetone were purchased from Sigma–Aldrich Co., UK.

2.2. Drug solubilisation

Saturated drug-loaded solutions were prepared in glass vessels by mixing excess powdered drug with 1 wt% copolymer solution and stirring at constant temperature (25 or 37 °C) for 3–5 days before filtering (Millipore, 0.45 μm) to remove unsolubilised material. Blank experiments (no copolymer) gave the solubility of the drug in water.

The amount of furosemide and nabumetone solubilised was determined by NMR spectroscopy. The method provides an absolute measurement of the ratio of drug to polymer. A filtered solution was freeze dried, the entire sample dissolved in CD_3OD (furosemide) or $CDCl_3$ (nabumetone) and the ^1H NMR spectrum recorded under the conditions reported previously (Rekatas et al., 2001). As described for the solubilisation of griseofulvin (Rekatas et al., 2001), for each system weak resonances at 6.3–6.4 ppm (furosemide) and 7.7 ppm (nabumetone) attributable to drug could be distinguished from those of the copolymer. The integrated intensities were used to determine the molar ratio of drug to copolymer, and hence, given their respective molar masses, the mass ratio of drug to copolymer.

Alternatively, the amount of drug solubilised was determined by UV spectroscopy. Maximum absorbance was at wavelength 272 nm (furosemide) or 270 nm (nabumetone). Calibration with dilute solutions of the drugs dissolved in methanol gave satisfactory Beer–Lambert plots. In a solubilisation experiment the filtered solution was diluted 50-times or so with methanol, the amount of water after dilution being low enough to allow direct use of the calibration plot. The absorbance deriving from copolymer in the diluted solution (some 10–20 wt% of the total) was measured using a blank and used to correct the total.

In order to check that solubilisation was predominantly in the core rather than in the E-block corona the extent of solubilisation in the corona was estimated from experiments performed using 5–30 wt% aqueous solutions of polyethylene glycol $M_n = 6000\ g\ mol^{-1}$ (see Crothers et al., 2005). Only minimal solubilisation in the corona was indicated for the present drugs in 1 wt% solutions of the copolymers; values were in the range 0.4–1.2 mg (g copolymer)$^{-1}$, the highest values being for furosemide.

Table 1
Molecular and micellar characteristics[a] of the copolymers

Copolymer	M_n (g mol^{-1})	w_S	M_w/M_n	cmc (wt%)	N_W	r_h (nm)
$E_{17}S_8$	1700	0.562	1.05	0.003	250	8
$S_{15}E_{63}$	4570	0.394	1.04	0.0004	140	12
$S_{17}E_{65}$	4940	0.416	1.04	0.0002	150	13
$S_{20}E_{67}$	5300	0.449	1.05	0.0001	189	16

[a] Micellar characteristics at 25 °C from Attwood and Booth (2007), w_S = weight fraction of poly(styrene oxide), N_w = aggregation number, r_h = hydrodynamic radius.

3. Results

Solubilisation capacities are listed in Table 2. They are denoted S_{cp} (mg g^{-1}) (mg drug per gram of copolymer in solution), equivalent to S_{cp} (mg dl^{-1}) for a 1 wt% solution of copolymer. Values are averages of at least three determinations. Agreement between the results from NMR and UV is good. For ease of comparison, values of the saturation solubilities of the drugs in pure water (S_o) are given in units of mg dl^{-1}. The values obtained for the solubility in water are in satisfactory agreement with values from other laboratories:

Table 2
Drug solubilisation capacity of 1 wt% aqueous copolymer solution compared with the solubility in water

Copolymer	Furosemide		Nabumetone	
	NMR	UV	NMR	UV
25 °C				
Water	–	0.6	–	0.6
$E_{17}S_8$	–	52	–	52
$S_{15}E_{63}$	21	20	16	17
$S_{17}E_{65}$	22	–	16	–
$S_{20}E_{67}$	20	–	16	–
37 °C				
Water	–	0.8	–	1.0
$E_{17}S_8$	–	58	–	59
$S_{15}E_{63}$	32	–	31	–
$S_{17}E_{65}$	32	–	34	–
$S_{20}E_{67}$	31	–	35	–

Units: mg dl^{-1}, equivalent to mg (g copolymer)$^{-1}$.

furosemide, S_o = 0.5–0.8 mg dl^{-1} (Fioritto et al., 2007; Wishart et al., 2007; Yalkowsky and He, 2003; Avdeef et al., 2000); nabumetone, S_o = 0.6–0.7 mg dl^{-1} (Roberts and Sloan, 2001; Martini, 2002). We estimate an experimental error of ±2 mg g^{-1} in S_{cp}.

Solubilisation is mainly in the micelle core (see previous section), and it is useful to obtain values of the solubilisation capacity corrected for the different proportions of poly(styrene oxide) in the copolymers. This was done by calculating the solubilisation capacity of the micelle core, $S_H = S_{cp}/w_H$, where weight fraction $w_H = w_S$ taken from Table 1. The values of S_H listed in Table 3 were also corrected for the small amounts of drug solubilised in the micelle corona (as discussed above) and for the solubility of the drug in water. Average values of S_{cp} were used when measurements were made using NMR and UV methods.

4. Discussion

Values of the solubilisation capacity are available for solutions of docetaxel in aqueous solutions of copolymer $E_{45}S_{15}$ (Elsabahy et al., 2007), and of griseofulvin in solutions of copolymer $S_{15}E_{63}$ (Crothers et al., 2005). The micelles of these two copolymers are spherical and have similar properties ($E_{45}S_{15}$ at 20 °C: cmc = 4.5 × 10^{-3} g dm^{-3}, N_w = 307 and r_h = 10 nm (Elsabahy et al., 2007); $S_{15}E_{63}$ at 25 °C: cmc = 4.0 × 10^{-3} g dm^{-3}, N_w = 140 and r_h = 12 nm (Attwood and Booth, 2007)). Combining these results with present results for solutions of copolymer $S_{15}E_{63}$ allows direct comparison for copolymers with the same S-block length (see Table 4). The value of S_o = 0.6 mg dl^{-1} for the solubility of docetaxel in water at 25 °C is from the literature (Ali et al., 1995), and that of S_o = 1.0 mg dl^{-1} for griseofulvin is an average value from Yalkowsky's tables (Yalkowsky and He, 2003). The results for docetaxel are for solutions at 20 °C. The values of S_H are corrected for water solubility and solubility of the drug in the micelle corona, with docetaxel being assumed to behave like nabumetone. We have previously estimated a maximum uncertainty of ±4 mg g^{-1} in values of S_H and it is expected that the present results will have a similar uncertainty.

Table 3
Drug solubilisation in the micelle core: S_H (mg g^{-1})

Copolymer	Furosemide	Nabumetone
25 °C		
$E_{17}S_8$	90	91
$S_{15}E_{63}$	47	39
$S_{17}E_{65}$	48	36
$S_{20}E_{67}$	42	33
37 °C		
$E_{17}S_8$	100	102
$S_{15}E_{63}$	75	73
$S_{17}E_{65}$	72	77
$S_{20}E_{67}$	64	74

Table 4
Drug solubilisation in aqueous solutions of E/S block copolymers: 20–25 °C

	$S_{15}E_{63}$			$E_{45}S_{15}$
	Furosemide	Nabumetone	Griseofulvin	Docetaxel
S_o (mg dl^{-1})	0.6	0.6	1	0.6
S_{cp} (mg g^{-1})	21	17	11	35
S_{cp}/S_o	35	28	11	58
S_H (mg g^{-1})	47	39	28	71

$E_{45}S_{15}$: w_S = 0.476.

The direct solubilisation of a drug in a micellar solution is a complex equilibration which involves the saturation solubility of the crystalline drug and the interaction of the drug with the material of the micelle core. The effect of saturation solubility is emphasized in the ratio S_{cp}/S_o, while the value of S_H reflects the overall equilibrium and is a better comparator of systems. It is clear that solubilisation in the micelle core is similar for all four drugs, with values of S_H differing by no more than a factor of two. The high value of S_H for docetaxel may well reflect the different method used for loading the micelles, i.e. dissolution of drug and copolymer in ethanol, evaporation of the solvent, and equilibration of the drug/copolymer solution in water (Elsabahy et al., 2007). Previously, we have shown that dissolving griseofulvin in copolymer prior to equilibration in water can increase the solubilisation capacity compared with that achieved by direct equilibration of the crystalline drug with the micellar copolymer solution, as discussed in Crothers et al., 2005.

It remains to comment on the details of Table 3. The high values of S_H found for both drugs in micellar solutions of copolymer $E_{17}S_8$ can be related to the worm-like geometry of the micelles, as discussed elsewhere in connection with the solubilisation of griseofulvin (Crothers et al., 2005; Chaibundit et al., 2002) and other drugs (Zhou et al., 2008). The increase in the values of S_H with increase in temperature implies a change in the balance between the drug–water and the drug–core interactions.

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