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Note

Solubilisation of griseofulvin in aqueous micellar solutions of diblock copolymers of ethylene oxide and 1,2-butylene oxide with lengthy B-blocks

Maria Elenir N.P. Ribeiro[a], Igor Marques Cavalcante[a], Nágila M.P.S. Ricardo[a], Shao-Min Mai[b], David Attwood[c,*], Stephen G. Yeates[d], Colin Booth[d]

[a] Department of Organic and Inorganic Chemistry, Polymer Laboratory, Federal University of Ceará, CX 12.200, CEP 60455-760, Fortaleza, Ceará, Brazil
[b] Department of Chemistry, University of Sheffield, S3 7HF Sheffield, UK
[c] School of Pharmacy and University of Manchester, Manchester M13 9PL, UK
[d] School of Chemistry, University of Manchester, Manchester M13 9PL, UK

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ABSTRACT

The influence of hydrophobic-block length on solubilisation capacity was examined for micelles of E_mB_n copolymers (E = oxyethylene, B = oxybutylene, subscripts denote number-average block lengths in repeat units) with B-block lengths in the range of 30–76 and with E-blocks of sufficient length to ensure the formation of spherical micelles. Griseofulvin was used as a model poorly-water-soluble drug known to be almost exclusively solubilised in the micellar core. Combination of solubilisation data with those of a previous study has shown that the amount of drug solubilised per gram of hydrophobe is essentially independent of B-block length when this exceeds about 15 B units, suggesting that core size is not a major influence on solubilisation.

1. Introduction

As described in recent reviews (Attwood and Booth, 2007; Chiappetta and Sosnik, 2007; Savic et al., 2006; Gaucher et al., 2005; Adams et al., 2003), aqueous micellar solutions of block copolymers based on poly(ethylene oxide) as the hydrophilic component combined with a wide range of hydrophobic blocks have been investigated as vehicles for drug solubilisation. A particular advantage of this family of copolymers is the so-called 'stealth' property of the poly(oxyethylene) corona of their micelles which allows the drug-loaded micelles to evade scavenging by the mononuclear phagocyte system, so resulting in increased circulation times in the blood. This note concerns diblock copolymers of ethylene oxide and 1,2-butylene oxide. To describe the repeat units of the blocks we use the notation: E = OCH_2CH_2 (from ethylene oxide) and B = $OCH_2CH(C_2H_5)$ (from 1,2-butylene oxide), while subscripts are used to denote number-average block lengths in repeat units. Thus a diblock copolymer formed by sequential copolymerisation of ethylene oxide followed by 1,2-butylene oxide is denoted E_mB_n.

Drug solubilisation in aqueous micellar solutions of E_mB_n copolymers has been investigated previously (Rekatas et al., 2001; Chaibundit et al., 2002; Crothers et al., 2005; Elsabahy et al., 2007; Zhou et al., 2008). One of these investigations (Zhou et al., 2008) focused on the extent to which drug solubilisation in the E_mB_n system could be enhanced by using copolymers tailored to form worm-like micelles, i.e. by preparing copolymers with short E-block lengths relative to their B-block lengths (m = 11–17, n = 8–12). The solubilisation capacity for solutions at 25 °C increased linearly as the B-block length was increased, an effect attributed to an increase in the proportion of worm-like micelles. However, it is well established for poly(oxyethylene)-based copolymers that, at a given temperature, the micelle association number (and so the micelle-core volume) is increased as the hydrophobic-block length is increased or as the hydrophilic-block length is decreased (see, e.g., Booth et al., 2006), and it might be argued that an increase in core volume of spherical micelles might lead to a similar enhancement of solubilisation capacity. In the work described in this note we have investigated this possibility. Specifically, we have taken advantage of the availability of a series of E_mB_n copolymers prepared for study of microphase separation in block-copolymer melts (Ryan et al., 2001) to investigate the solubilisation of griseofulvin in micellar solutions at 25 °C of block copolymers with lengthy B-blocks and with E-blocks sufficiently long to ensure formation of compact (spherical) micelles.

* Corresponding author. Tel.: +55 85 40089977; fax: +55 85 40089978.
E-mail addresses: naricard@ufc.br (N.M.P.S. Ricardo), david.attwood@manchester.ac.uk (D. Attwood).

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Table 1
Number-average molar mass, weight fraction poly(oxybutylene), and critical micelle concentration.

Copolymer	M_n/kg mol^{-1}	w_B	cmc/mg dm^{-3}
$E_{110}B_{30}$	7.00	0.309	0.50
$E_{209}B_{45}$	12.4	0.261	1.70
$E_{100}B_{51}$	8.07	0.455	0.30
$E_{114}B_{56}$	9.05	0.446	0.37
$E_{155}B_{76}$	12.3	0.445	0.40

Table 2
Solubilisation capacities at 25 °C for 1 wt% copolymer solutions with griseofulvin incorporated by solution, melt and film methods.

Copolymer	Solution		Melt		Film	
	S_{cp}	S_h	S_{cp}	S_h	S_{cp}	S_h
$E_{110}B_{30}$	3.9	13	8.7	28	5.0	16
$E_{209}B_{45}$	2.9	11	7.1	27	4.5	17
$E_{100}B_{51}$	4.9	10	9.4	21	7.8	17
$E_{114}B_{56}$	4.7	11	9.2	21	6.4	14
$E_{155}B_{76}$	5.1	11	–	–	–	–

S_{cp} in mg drug per gram of copolymer; S_h in mg drug per gram of hydrophobe.

2. Experimental

Five E_mB_n copolymers with narrow chain-length distributions ($M_w/M_n \approx 1.05$) and long B-block lengths ($E_{110}B_{30}$, $E_{209}B_{45}$, $E_{100}B_{51}$, $E_{114}B_{56}$, $E_{155}B_{76}$) were available from a previous study: see Ryan et al. (2001) for details. Values of the number-average molar masses (M_n) of the copolymers, and of the weight fractions of poly(oxybutylene) (w_B) in the copolymers, are listed in Table 1, together with values of the critical micelle concentration (cmc) in aqueous solution at 25 °C taken from Ribeiro et al. (2008). It is seen that the values of cmc are very low, <0.0002 wt%, ensuring effectively complete micellisation in 1 wt% solution.

Griseofulvin (Sigma–Aldrich, Poole, Dorset, UK) was loaded into solutions (1 wt% copolymer) in three ways, as described below. Excess drug was removed by filtration using 0.45 μm Millipore filters and/or by centrifugation (Hettich Zentrifugem EBA 12, 6000 rpm, 30 min). In each case the extent of drug solubilisation was determined by UV spectroscopy using a U-2000 Hitachi Spectrophotometer. As described by Crothers et al. (2005), a drug-loaded solution was diluted quantitatively with sufficient methanol to enable determination of its absorbance at the optimum wavelength of 292 nm, which was then compared with a Beers Law plot for griseofulvin in methanol. The water content after dilution was low enough to allow the calibration for methanol solutions to be used without correction. Blank experiments (no copolymer) gave the solubility of the drug in water.

Method 1, Solution. 10 g of stock copolymer solution (1 wt%) prepared with Milli-Q water was added to finely ground (1 mm^2 mesh) griseofulvin powder (0.1 g). The mixture was stirred at 25 °C for 4 days before being filtered to remove unsolubilised drug. This method is equivalent to the so-called Shake-Flask method (Crothers et al., 2005).

Method 2, Melt. Griseofulvin powder (0.1 g) was added to copolymer melt (1 wt%) at 65 °C, allowing 3 h for dissolution, followed by addition of the required amount of Milli-Q water at 65 °C. This temperature was maintained for 1 h before cooling to 25 °C, and stirring for 4 days before filtering to remove unsolubilised drug.

Method 3, Film. Copolymer (0.1 g) and griseofulvin powder (0.1 g) were dissolved in ethanol (10 ml). The solvent was evaporated under vacuum at room temperature to form a thin film. Sufficient Milli-Q water was added (10 ml) to form a 1 wt% copolymer solution which was stirred at 25 °C for 24 h before centrifuging and filtering to remove unsolubilised drug.

3. Results and discussion

Solubilisation capacities (S_{cp}), defined as milligram drug solubilised per gram of copolymer in given volume of solution in excess of that dissolved in an equivalent volume of water, are listed in Table 2. Solubilisation of griseofulvin is known to be almost exclusively in the hydrophobic micelle core (Crothers et al., 2005) so we also list values of the solubilisation capacity per gram of hydrophobe, defined as $S_h = S_{cp}/w_B$, where w_B is the weight fraction of poly(oxybutylene) in the copolymer, as listed in Table 1. Shortage of material meant that solubilisation in solutions of copolymer $E_{155}B_{76}$ was investigated only by the solution method.

As seen in Table 2, variation of copolymer composition leads to variation in S_{cp} which largely disappears if the solubilisation capacity per gram of hydrophobe, S_h, is considered. This quantity is plotted against B-block length in Fig. 1, where we include solubilisation capacities for copolymer $E_{96}B_{18}$ obtained by identical solution and melt methods (Crothers et al., 2005). In the figure, the dotted lines indicate average values for the three methods, i.e. 12, 16 and 25 mg/g for the solution, film and melt methods, respectively, with a standard error less that 2 mg/g.

The evidence is that the solubilisation of griseofulvin in the cores of E_mB_n copolymer micelles, as measured by S_h, is essentially independent of B-block length in the range of concentrations investigated. As B-block length is the major determinant of core size for compact micelles (see, e.g., Booth et al., 2006) it can be concluded that core size is not a major consideration when n exceeds about 15 B units. Of course, in pharmaceutical practice S_{cp} is the important quantity, and the value of S_{cp} will be high if the weight fraction B in the copolymer is high. The copolymers featuring in Fig. 1 have values of w_B in the range of 0.26–0.45.

As noted in the introduction, E_mB_n copolymers with relatively short E-blocks (e.g., $E_{17}B_{12}$, $w_B \approx 0.54$) may form worm-like micelles in solution, an effect which enhances solubilisation. Copolymers with relatively short B-blocks may have significantly higher values of the cmc and may be incompletely micellised in 1 wt% solution at 25 °C (e.g., $E_{41}B_8$, $w_B \approx 0.24$, cmc ≈ 0.1 wt%, Yu et al., 1997), an effect which reduces the extent of solubilisation. Given that copolymers with short blocks are more easily prepared, our study suggests $E_{30}B_{15}$ ($w_B = 0.45$) as a satisfactory target composition for a copolymer for solubilisation of aromatic drugs in compact micelles in dilute solution. The general considerations arising from this study should extend to other poly(oxyethylene)-based copolymers, including those with polyester hydrophobic blocks.

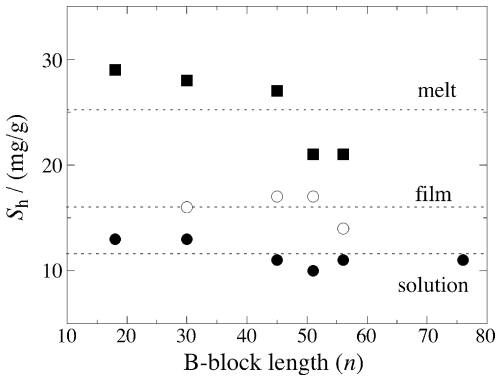

Fig. 1. The effect of B-block length on the solubilisation of griseofulvin in micellar solutions of E_mB_n copolymers at 25 °C.

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