



Note

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

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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.

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1. Introduction

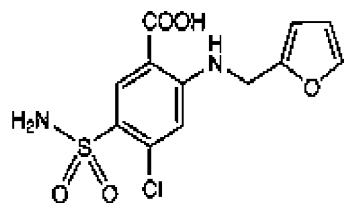
As described in recent reviews, aqueous solutions of poly(oxyethylene)–poly(oxypropylene)–poly(oxyethylene) triblock copolymers have been extensively examined as solubilisers for poorly water-soluble drugs (Kabanov et al., 2002; Kabanov and Alakhov, 2002; Chiappetta and Sosnik, 2007). Poly(oxypropylene) 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, Rekatat 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, OCH₂CH(CH₃), B an oxybutylene unit, OCH₂CH(C₂H₅), S an oxyphenylethylene unit, OCH₂CH(C₆H₅), and G an oxy(phenyloxymethylene)ethylene unit OCH₂CH(CH₂OC₆H₅). 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.

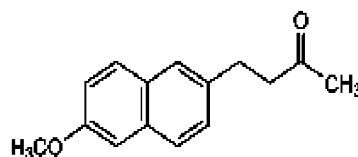
Previously we have used griseofulvin as a standard drug in order to compare the solubilisation capacities of micellar solutions of a range of copolymer compositions in a uniform way. In this article we present new results for two other poorly soluble drugs, furosemide and nabumetone, solubilised in aqueous 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.

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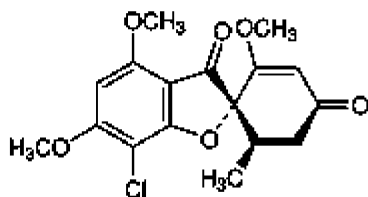
E-mail addresses: david.attwood@manchester.ac.uk, mbspssa2@man.ac.uk (D. Attwood).



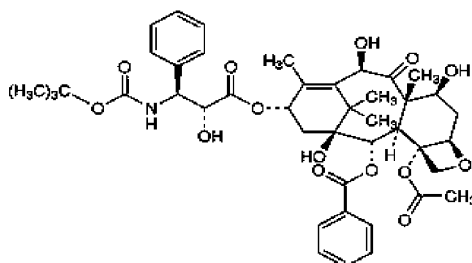
Furosemide



Nabumetone



Griseofulvin



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 $M_n = 6000 \text{ g mol}^{-1}$ (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.

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_0) 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 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.

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