Worm-like micelles of triblock copolymer of ethylene oxide and styrene oxide characterised using light scattering and Taylor dispersion analysis

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Abstract

A triblock ESE copolymer ($E_{16}S_8E_{16}$, S = styrene oxide and E = ethylene oxide) was synthesised by sequential oxyanionic copolymerisation of styrene oxide followed by ethylene oxide. Light scattering studies demonstrated a shape transition from spherical micelles to worm-like micelles above a critical temperature of approximately 18^{o}C. Taylor dispersion analysis (TDA) also indicated a size growth when the temperature increased from 25 to 40 ^{o}C due to the formation of worm-like micelles. The hydrodynamic radii and diffusion coefficients obtained by these two techniques were in good agreement. The solubility of a hydrophobic drug, terfenadine, in dilute micellar solutions of the copolymer was increased at least 20-fold under the conditions. The transition to worm-like micelles at raised temperatures led to enhanced solubilisation capacities due to a larger hydrophobic core volume.

The behaviour of the novel ESE copolymer shows the utility of TDA to follow conformational changes using nanolitre quantities and explore critical quality attributes for this type of drug delivery system.

Key words:

Poly(oxyalkylenes), Worm-like micelles, Dynamic light scattering, Taylor dispersion analysis, Drug solubilisation.

Introduction

The use of amphiphilic block copolymers for drug solubilisation and delivery has been extensively investigated, as reviewed in a number of publications over the last decade (Torchilin, 2001; Adams et al., 2003; Chiappetta and Sosnik, 2007). Nonionic amphiphilic block copolymers are considered to be more suitable for use in drug solubilisation and drug delivery systems since they have lower toxicity and greater biological compatibility than cationic and anionic surfactants (Grindel et al., 2002). Their low critical micelle concentration results in a high degree of micellization, and highly stable micelles can be formed at comparatively low concentrations. The micelle core, which is composed of hydrophobic components, provides a suitable microenvironment for the incorporation of lipophilic drugs, while the hydrophilic micelle corona serves as a stabilising interface between the hydrophobic core and the external medium.

Block copoly(oxyalkylene)s, consisting of a hydrophilic poly(ethylene oxide) (E) block and a hydrophobic block, e.g. poly(propylene oxide) (P), poly(1, 2-butylene oxide) (B) or poly(styrene oxide) (S), can micellise in dilute aqueous solution (Booth and Attwood, 2000). The synthesis and

micellisation of block copoly(oxyalkylene)s with various architectures have been widely investigated (Booth et al., 2006). Significant solubility enhancement for poorly water-soluble drugs can be achieved in dilute micellar solutions of block copoly(oxyalkylene)s at ambient temperatures. (Crothers et al., 2005; Attwood et al., 2007; Zhou et al., 2008). It is understood that solubilisation capacity is dependent on the hydrophobicity of core-forming blocks and the volume of the hydrophobic cores. For block copoly(alkylene)s with long block lengths, which normally form spherical micelles, the volume of micellar cores is limited by the stretched length of hydrophobic blocks. However, Booth and Attwood have indicated that copolymers with short E blocks, (which leads to high association numbers), and with short hydrophobic blocks, (which places a low ceiling on the radius of a spherical micelle), are more likely to form elongated micelles (Booth and Attwood, 2000). A range of diblock copoly(oxyalkylene)s, e.g. $E_{17}B_{12}$ (Chaibundit et al., 2005), $E_{13}B_{10}$ (Zhou et al., 2008), $E_{11}B_{8}$ (Chaibundit et al., 2002) and $E_{17}S_{8}$ (Yang et al., 2003), have been synthesised and investigated for their micelle properties using light scattering. An abrupt increase of hydrodynamic radii and aggregation number with temperature was observed for these copolymers, which indicates the formation of worm-like micelles. Solubilisation studies show that these worm-like copolymer solutions have much greater solubilisation capacities than those of conventional spherical micelles under similar conditions. Triblock copolymers, e.g. $E_{20}S_{10}E_{20}$, with relatively short block length, are also assumed to be able to form elongated micelles, and as previously reported that their solubilisation capacity for griseofulvin is much higher than small spherical micelles (Crothers et al., 2005). However, a full characterisation of micelle properties has never been performed for such triblock ESE copolymers in order to understand their micellisation behaviour. For triblock copolymers to be useful for drug delivery applications such characterisations are essential to evaluate critical quality attributes.

In this work, we aim to prepare a triblock ESE copolymer with well-chosen block lengths that can form worm-like micelles under ambient temperature. Micellar properties of the copolymer will be

determined using light scattering and Taylor dispersion analysis (TDA) techniques. TDA is a technique for the determination of diffusion coefficients and hydrodynamic radii, presented by Geoffrey Taylor in 1953 (Taylor, 1953) and further developed by Aris in 1956 (Aris, 1956). The principal of this technique is based on band broadening of a solute plug in a straight capillary under laminar flow conditions. TDA has been explored for the size measurement of many substances, e.g. protein aggregates (Hawe et al., 2011), cyclodextrin-drug aggregates (Zaman et al., 2017), super-paramagnetic nanoparticles (Lemal et al., 2018), poly-L-lysine dendrigrafts (Cottet et al., 2007), and micelles and microemulsions (Chamieh et al., 2015). Here TDA is first employed to investigate the shape transition of micelles of block copolymers upon changes in temperature. The specific objectives of this work are to synthesise and characterise a triblock ESE copolymer, investigate the micellisation behaviour of the copolymer using light scattering and Taylor dispersion analysis techniques, and evaluate the solubilisation capacities of the copolymer for a poorly water-soluble model drug utilising a UV assay.

Experimental

Materials

Ethylene oxide, styrene oxide, terfenadine, Pluronic F127 were purchased from Sigma-Aldrich (UK). HPLC grade THF and methanol were obtained from Fisher Scientific Ltd. UK. NMR grade chloroform-d and methanol-d were from Cambridge Isotope Laboratories (USA).

ESE block copolymers

The copolymer was prepared by sequential oxyanionic copolymerisation of styrene oxide followed by ethylene oxide (Fig. S1). The general method has been described in detail previously (Yang et al., 2003b). Briefly, the difunctional initiator was potassium hydroxide and water. Freshly dried styrene

oxide was transferred into the ampoule and heated at 85°C for 8 weeks. Then ethylene oxide was distilled into the ampoule and kept at 65°C for about 3 weeks until polymerisation was completed. The copolymer was characterised by gel permeation chromatography (GPC, Agilent 1260 Infinity with triple detectors and two Agilent PLgel Mixed-D columns, tetrahydrofuran eluent, calibrated with poly(styrene) standards for measurement of molecular weight and polydispersity. ^{1}H and ^{13}C NMR spectroscopies (Bruker Avance 400, Bruker, Coventry, UK) were used to determine the composition of the copolymer (Figs. S2 and S3). The assignment for the peaks of ESE copolymers was made according to relevant references (Heatley et al., 1991).

Critical micelle concentration

The critical micelle concentration (CMC) of the ESE copolymer at 20 °C was determined by surface tension measurement using the pendant drop method. An FTA1000 video system (First Ten Ångstroms Inc) was used to visualise liquid drops formed on the tip of a stainless-steel needle (20 gauge). The image was taken using aperture 22 with 50% brightness and contrast. Surface tension of aqueous polymer solutions with a range of concentration from 0.001 to 2 % w/v was calculated via drop-shape analysis. Ten measurements were recorded for each sample and the results averaged. The standard deviation of the drop-shape analysis was approximately ± 0.5 mN m^{-1} and the measurement error was less than 5%.

Light scattering

The micelle properties of the copolymer were measured by static and dynamic light-scattering techniques. Solutions were filtered through Millipore Millex filters (0.22 μm porosity) into glass scattering cuvettes. Static light scattering (SLS) intensities were measured at temperatures in the range

of 15-40°C using Malvern Zetasizer Nano ZS. The intensity scale was calibrated against scattering from toluene. Analysis of the SLS results was based on the Debye equation,

$$K^* c/R_\theta = 1/M_w + 2A_2 c \ \ldots \quad (1)$$

where R_θ is the ratio of scattered light to incident light of the sample, c is the concentration (in g dm^{-3}), M_w is the weight-average molar mass of the solute, A_2 is the second virial coefficient (higher coefficients being neglected), and K^* is the appropriate optical constant, including the specific refractive index increment, dn/dc. Values of dn/dc were measured using a refractometer (RM50, Mettler Toledo). The data were in good agreement with the equation established previously for a range of block copolymers of ethylene oxide and styrene oxide (Yang et al., 2003b). Values of the weight-average molar mass of the micelles ($M_{w,mic}$) were obtained from Debye plots by extrapolation to zero concentration.

Dynamic light scattering (DLS) were measured with the same instrument at a range of temperatures. The correlation functions were analysed to determine intensity fraction distributions of the apparent diffusion coefficient (D_{app}) and the apparent hydrodynamic radius ($r_{h,app}$) via the Stokes-Einstein equation.

$$r_{h,app} = kT/(6\pi\eta D_{app}) \quad (2)$$

where k is the Boltzmann constant and η is the viscosity of water at temperature T.

Taylor Dispersion Analysis

Malvern Viscosizer 200 (VS 200) equipped with TDA and UV imaging was employed to measure hydrodynamic radii and diffusion coefficients of ESE copolymer in solution. A sample solution is injected into the running buffer solution driven by a pressure pump into the fused silica capillary. The solute plug is imaged at two windows by a UV detector. The instrument calculates band broadening from the absorbance recorded at a given wavelength versus time.

The Viscosizer 200 was used with a fused silica capillary of 75 μm internal diameter and a total length of 130 cm. The length to window 1 is 45 cm and to window 2 is 85 cm, respectively. Measurement were carried out using an optical filter at 214 nm. The instrument was calibrated by stray light corrections using an appropriate stray light test solution of 10 mg/ml L-tryptophan in water that shows strong UV absorption. This minimises the effect of stray light (originated from the spectral components of the instrument) on the image element of the system and allows accurate cross talk between two measuring windows. The hydrodynamic radius of 1% w/v ESE solution was measured at various temperatures. A dilute ESE solution above CMC (0.1% w/v) was used as the running buffer to avoid possible morphology change during diffusion. The sample solutions were incubated for an hour at the experimental temperatures (25°C and 40°C) prior to loading. The samples were run in triplicate as the sequence followed: rinse and refill running buffer at 2000 mbar for 2 mins, reset baseline for 1min and load sample for 20 sec at 140 mbar, and run the test at 140 mbar. The software automatically processed absorbance versus time data to obtain r_h based on the equation shown below (Hawe et al., 2011):

$$r_h = 4k_bT(\tau_2^2-\tau_1^2)/(\pi\eta r^2(t_2-t_1)) \quad (3)$$

Where k_b is the Boltzman constant; η is the viscosity; r is the radius of the capillary; T is the temperature; t_1 and t_2 correspond to peak centre times at the first and second windows; τ_1 and τ_2 are the corresponding standard deviations of band broadening.

Drug solubilisation

The solubilisation capacities of micellar solutions of the ESE copolymer for the model drug terfenadine were measured. The solubilisation in EPE copolymer F127 were also measured under the same conditions to compare the solubility enhancement.

The method has been described before (Zhou et al, 2008, 2009). Briefly, saturated drug-loaded solutions were prepared by adding excess drug (10 mg) in 2 ml of 1 and 2 wt% micellar solutions. The samples were incubated at 25 or 37°C for 2 days and then filtered (0.45 μm Millipore) to remove any unsolubilised drug. The drug solubility was determined by UV assay. The filtrate was diluted with methanol and the UV absorbance measured at 230 nm. Calibration with drug alone yielded satisfactory Beer's Law plots (Fig. S4). All measurements were carried out in triplicate and the results averaged.

Results and discussion

ESE copolymer

The block length and composition of ESE copolymer was determined by NMR with reference to the peak assignments described by Heatley et al. 1991. For ^{13}C NMR, the integrals of the peaks from polymer backbone and end groups were used to determine the block lengths. In ^{1}H NMR, the peaks of aromatic protons were between 7.0-7.6 ppm while all the aliphatic protons peaks were between 3.3 to 4.7 ppm, which provides the information on the relative ratio of E and S block lengths. The molecular formula calculated in combination of both spectra was $E_{16}S_8E_{16}$ (MW 2368 g mol^{-1}). The GPC measurements revealed the molecular weight of the copolymer to be 2433 g mol^{-1} with a polydispersity of 1.13, which is in good agreement with findings from NMR.

Critical micelle concentration.

The critical micelle concentration of copolymer $E_{16}S_8E_{16}$ was measured at room temperature (approx. 20 °C). Fig. 1 shows the plot of surface tension versus logarithm concentration for the ESE copolymer. The commencement of curvature is an indication of the start of the micellisation process. The CMC determined from the inflection point was 0.73 g dm^{-3}. The CMCs for a range of ESE copolymers with various block lengths have been reported previously (Yang et al., 2003b). The values of CMC are mainly related to the length of hydrophobic S blocks. Compared to diblock copolymers, the S block of triblock ESE copolymers are more extended due to the two E blocks and thus show higher CMCs. Copolymer $E_{82}S_8E_{82}$, with a comparable S block length, has a CMC of 0.51 g dm^{-3} at 20 °C, which is within the same range as $E_{16}S_8E_{16}$. At higher temperatures, the CMC values decrease due to a less favourable interaction between water and hydrophilic E blocks. In the micellisation and solubilisation study of this work, the micellar solutions of copolymer $E_{16}S_8E_{16}$ were investigated at 1% w/v or above (10 g dm^{-3}), which is much higher than its CMC. Hence it was assumed that micellisation is complete at the concentration and temperature.

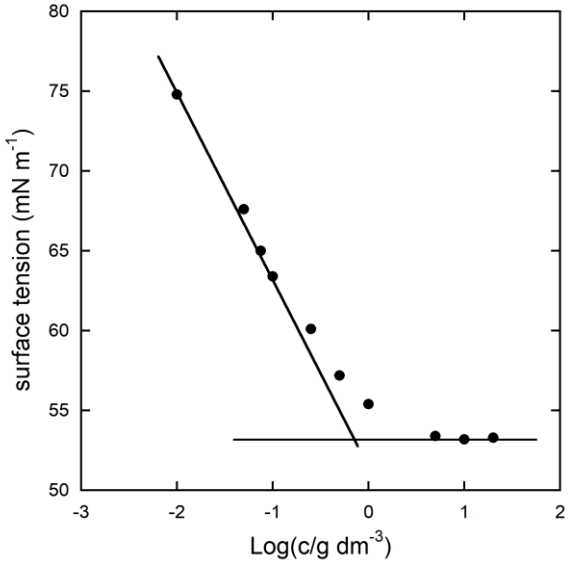

Figure 1. Surface tension versus logarithm concentration (g dm^{-3}) for $E_{16}S_8E_{16}$ copolymer at 20°C.

DLS

Micellisation behaviour of poly(oxyalkylene)s is mainly determined by the hydrophobicity and length of their hydrophobic blocks. Our previous work indicates that the temperature of worm-like micelles formation decreases with an increase of hydrophobic block length (Zhou et al., 2008). In this work we prepared the copolymer $E_{16}S_8E_{16}$ with an E:S ratio of 4:1 that is anticipated to form worm-like micelles at ambient temperature while possessing good solubility in water. The micelle properties of the ESE copolymer in aqueous solution at different temperatures (< 40 °C) were determined using static and dynamic light scattering. Care was taken to work under conditions which ensured optical clarity for the solutions. Dynamic light scattering was performed at different temperatures to obtain intensity fraction distributions of hydrodynamic radii for the ESE copolymer. Figure 2 shows the change in the intensity fraction distribution of log(r_h) as the temperature of a 1 %w/v solution of $E_{16}S_8E_{16}$ is increased from 5 to 40 °C. The size distribution curves indicate a relatively narrow distribution of small spherical micelles at 5 °C, and a broader distribution of large elongated micelles at 40 °C. The shift in peak position to higher values of r_h indicates a transition from compact to worm-like micelles in solutions of copolymer $E_{16}S_8E_{16}$.

The temperature dependence of r_h of a 1 %w/v solution of $E_{16}S_8E_{16}$ is shown in Fig. 3. The r_h almost remains constant at low temperatures. When the temperature increases above a certain value, the curve rises from the baseline and increases gradually, followed by an abrupt increase at high temperatures. Such behaviour indicates that the size of the micelles exceeds the limit for spherical micelles. The commencement of curvature is used as an indication of the transition from spherical to elongated micelles. The transition temperature (ca. 18°C) is determined more reasonably by the intersection point of the tangent line of the curvature and the baseline. The same phenomenon was also observed for diblock EB ($E_{17}B_{12}$, $E_{13}B_{10}$ and $E_{11}B_8$) (Zhou et al., 2008) and ES ($E_{17}S_8$) (Yang et al., 2003) copolymers that have been proven to form worm-like micelles at raised temperature. The increase in

hydrodynamic radius above the transition temperature is consistent with a gradual increase in the size of elongated micelles. The transition temperature is dependent on the hydrophobicity of core-forming blocks and shows a decreasing tendency with increasing hydrophobic block lengths. However, such temperature effect was absent for the copolymers with long E block lengths. For a range of triblock ESE copolymers, e.g. $E_{82}S_8E_{82}$, the weight-average micelle molar mass and the aggregation number remain consistent with increasing temperature (Yang et al., 2003b). Such a finding indicates that the micelle size has almost reached the limit for spherical micelle in this system.

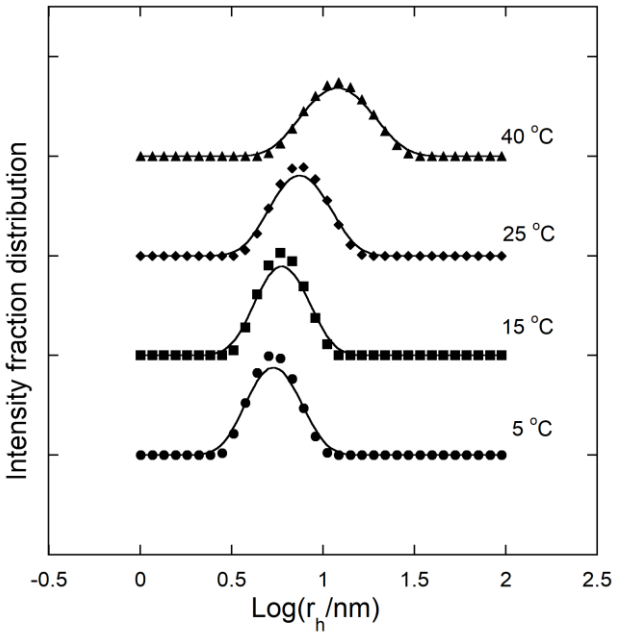

Figure 2. Comparison of micelle size distributions of a 10 g dm^{-3} solution of copolymer $E_{16}S_8E_{16}$ at the temperatures indicated measured by DLS.

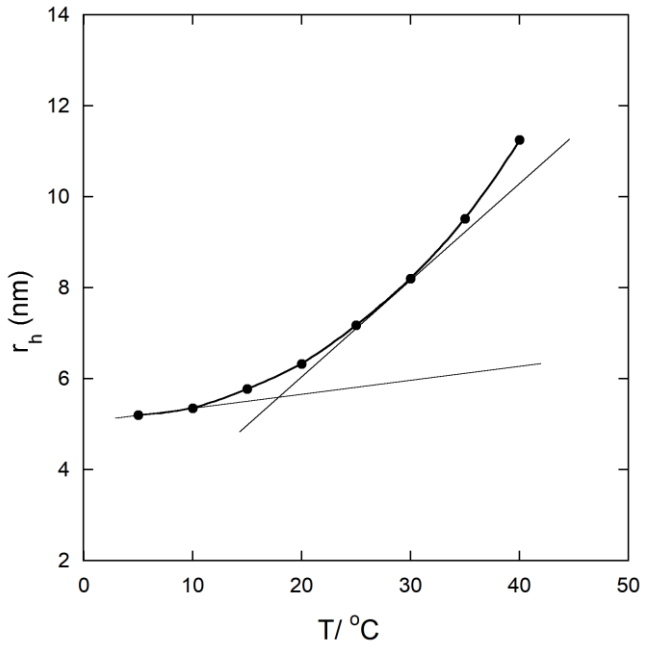

Figure 3. Temperature dependence of hydrodynamic radius of a 10 g dm^{-3} solution of copolymer $E_{16}S_8E_{16}$ measured by DLS.

SLS

Debye plots were used to obtain the average molar masses, association numbers and thermodynamic radii of the micelles (Fig. 4). Each data set was fitted with a curve, based on scattering theory for hard spheres using the Carnahan-Starling analysis (Carnaham and Starling, 1969). However, at higher temperatures, more than one species of micelle exists in the micellar solutions due to the transition of spherical micelles to elongated micelles. Hence, the results obtained from the Debye plot were the average values for all the micelles in the solution. The intercept of each Debye plot yields the reciprocal weight-average micelle molar mass ($M_{w,mic}$) and the curvature gives values for the thermodynamic expansion factor (δt). The weight-average association number (N_w) was subsequently calculated from $M_{w,mic}/M_w$, where Mw is the weight-average molar mass of the copolymer.

Values obtained for the $M_{w,mic}$ and M_w, hydrodynamic radius from dynamic light scattering are listed in Table 1. Calculation of the thermodynamic radius (effective hard-sphere radius) from the thermodynamic volume of the micelles and aggregation number is not strictly applicable for this polymer forming non-spherical micelles. The increase in hydrodynamic radius is consistent with micelle shape change, as the hydrodynamic radii of spherical micelles of block copoly(oxyalkylene)s are almost independent of temperature (Booth and Attwood, 2000; Booth et al., 2006). The association numbers of the ESE copolymer increase dramatically with increasing temperature, which corresponds to the transition of spherical micelles to elongated micelles at higher temperatures. At 25 °C, the value of N_w is 146 and, given that the specific volume of poly(oxystyrene) at 25 °C is 0.87 cm^3g^{-1}, the average core volume of a micelle is approximately 200 nm^3 and, if the micelles were spherical, the core radius would be 3.64 nm. Taking the length of an S unit to be 0.363 nm (Flory, 1969), the extended length of an S_8 block is approximately 3 nm. Hence the S_8 blocks would be over stretched in a spherical core, and an elongated core would result. Considering the transition temperature is ca. 18 °C, the solution at 25 °C is a mixture of spherical (compact) micelles and wormlike (elongated) micelles, which is already confirmed by the evidence from DLS.

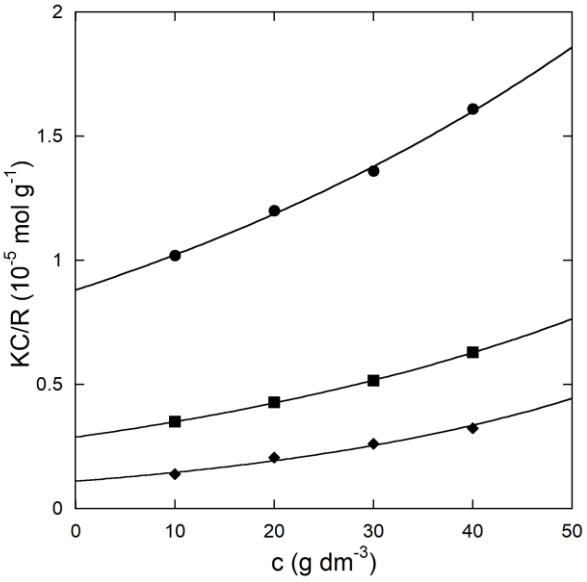

Figure 4. Debye plots for aqueous solutions of copolymer $E_{16}S_8E_{16}$ at (●) 15, (■) 25 and (♦) 40°C.

Table 1. Micelle properties of copolymer $E_{16}S_8E_{16}$ in aqueous solution [a]

T /°C	$M_{w,mic}$/ 10^5 gmol^{-1}	N_w	r_h [b] /nm	D_{app} [b] / μm^2 s^{-1}	r_h [c] /nm	D_{app} [c] / μm^2 s^{-1}
15	1.14	48	5.8			
25	3.45	146	7.2	34.3	7.2	33.9
40	9.09	384	11.2	31.4	12.6	27.6

a Estimated uncertainties: ±1 in r_h; ±10 % in $M_{w,mic}$ and N_w.
b Measured by DLS
c Measured by TDA

TDA

This work is the first attempt to employ Taylor dispersion analysis to investigate the effect of temperature on the micellisation of polymeric surfactants. Compared to light scattering, TDA is less sensitive to dust particles and does not require strict sample preparation/filtration. A dilute copolymer solution above CMC was used as running buffer to prevent micellar dissociation during diffusion. Compared to DLS that required a few millilitres of sample solution for filtration and measurement, TDA technique only utilised several hundred nanolitres for the measurement at two temperatures. Fig. 5(a) shows a standard TDA profile of a 1%w/v copolymer $E_{16}S_8E_{16}$ solution at 25 °C. The sample was run in triplicates. For convenience, the hydrodynamic radii and diffusion coefficients measured by TDA are also included in Table 1. The Skewed taylorgram in Fig. 5 is due to the minor interaction of micelles with the walls of the uncoated capillary. Nonetheless this deviation had no effect on the hydrodynamic radii, as the Viscosizer 200 fitting algorithm demonstrated that the data obtained had a 98% fit to that of the sample. This indicates an appropriate Taylor dispersion profile. As discussed above, the micellar solution of ESE copolymer has a spherical-to-elongated transition temperature at ca.

18 °C. It is assumed that a mixture of spherical and elongated micelles co-exists in the solution at 25 °C. With a further increase of temperature to 40 °C, the shape transition is considered to complete, and the worm-like micelles are dominant. Hence, like SLS, the size measured by TDA is an apparent value for all the micelle species in the solution. As seen in Table 1, the hydrodynamic radius at 40 °C is approximately double than that at 25 °C due to shape transition and size growth of worm-like micelles. Fig. 5(b) shows the TDA profiles of 1%w/v copolymer solution at 25 and 40 °C under the same measurement conditions. The shorter elution time at 40°C is attributed to lower viscosity of running buffer and relatively larger micelle particles that are expected to show less radial diffusion within the capillary compared to small micelles. Hence the TDA data also demonstrate the formation of elongated micelles at higher temperatures. It is clearly seen in Table 1 that the results from TDA and DLS are in good agreement. The values of hydrodynamic radii and diffusion coefficients obtained by these two techniques are very close, which suggest that TDA is reliable alternative to DLS for size measurement. However, it should be noted that TDA measures the weight- average hydrodynamic radius and diffusion coefficient with a mass concentration-sensitive detector whilst DLS leads to z-average values of hydrodynamic radius and diffusion coefficient. These two techniques should only report the same hydrodynamic radius for monodisperse samples (Chamieh et al., 2015).

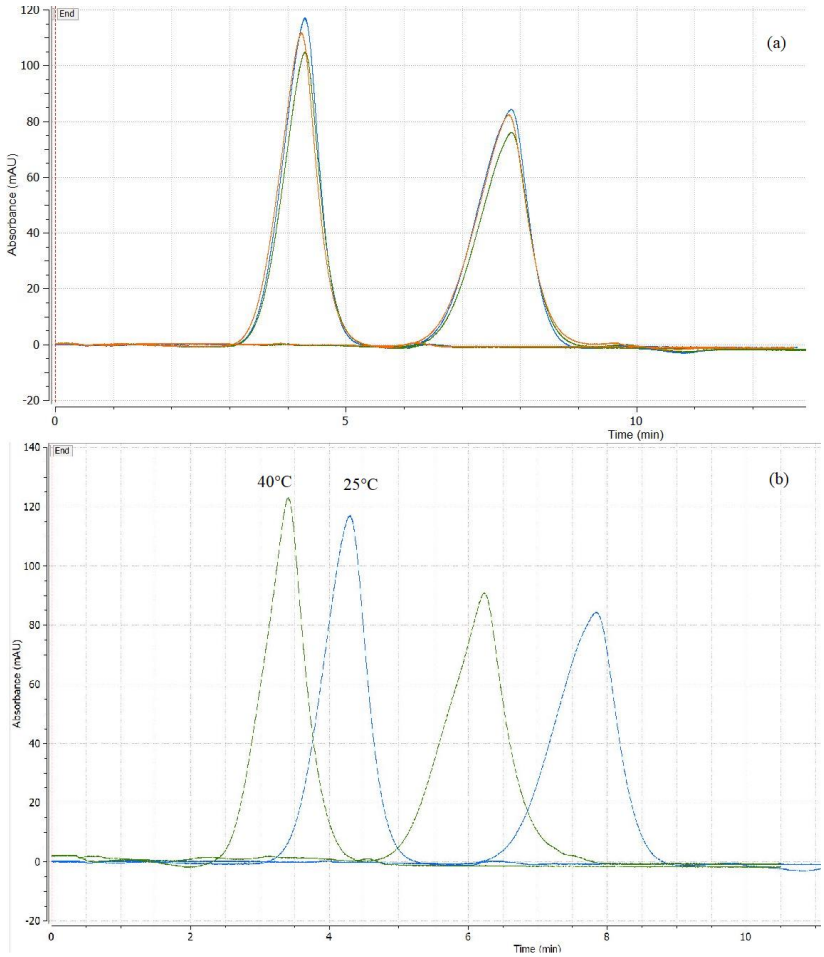

Figure 5. (a) TDA profile showing an overlay of three runs for a 1%w/v copolymer $E_{16}S_8E_{16}$ solution at 25°C; (b) Comparison of TDA profiles of the copolymer solution at 25 and 40°C.

Drug solubilisation.

The solubilisation of model drug, terfenadine (Fig. 6), in dilute micellar solutions of the ESE copolymer was investigated with comparison to Pluronic F127 (EPE triblock copolymer). The solubilisation capacity (S_{cp}) was expressed as milligram drug per gram of copolymer (mg g^{-1}). The solubility of terfenadine in the water (0.01 mg ml^{-1} at 30 °C) was subtracted from the solubility of terfenadine (*S*) in micellar solutions to determine the amount of drug solubilised in the micelles. The solubilisation capacities for terfenadine in 1 and 2 %w/v micellar solutions of the copolymers at 25 and 37 °C are listed in Table 2.

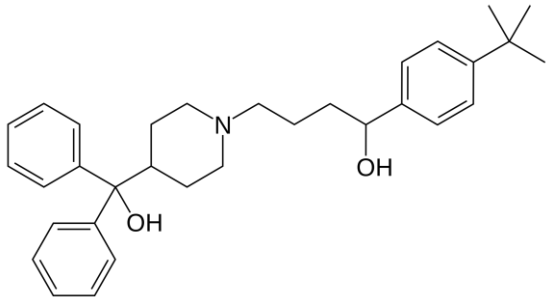

Figure 6. Molecular structure of terfenadine.

As seen in Table 2, the solubilities of terfenadine in the micellar solutions are much higher than that in water, e.g. nearly 20-fold increase in 1% w/v ESE solution at 25 °C. The ESE copolymer shows enhanced solubilisation capacities (3-fold) than F127 under the same conditions due to the higher hydrophobicity of the core-forming S blocks compared to P blocks. It was known from our previous work that the hydrophobic core is the domain for drug solubilisation. Furthermore, elongated micelles were formed in the micellar solutions of ESE copolymer, which have larger hydrophobic core volume than spherical micelles and thus show higher solubilisation efficiency. Increasing the temperature from 25 to 37 °C leads to an enhancement of the solubilisation capacities of ESE copolymer. This is probably attributed to the complete transition to elongated micelles at 37 °C and size growth of worm-like micelles. An increase of concentration of micellar solutions shows no significant influence on the solubilisation capacities of ESE copolymer. The number of micelles increase with concentration, which leads to a higher drug solubility. However, micellar interaction at higher concentration could hinder the growth of micelles. Hence the solubilisation capacities remain the same or even a bit lower at higher concentrations. A similar tendency is also demonstrated for F127.

Table 2. Solubilisation of terfenadine in micellar solutions of copolymer $E_{16}S_8E_{16}$ and F127[a]

	T /°C	Conc. /%w/v	S /mg ml^{-1}	S_{cp} /mg g^{-1}
ESE	25	1.0	0.188	18.8
		2.0	0.337	16.9
	37	1.0	0.286	28.6
		2.0	0.508	25.4
F127	25	1.0	0.059	5.9
		2.0	0.116	5.8

a. Estimated error ±10%.

Conclusions

The synthesis and characterisation of triblock copolymer $E_{16}S_8E_{16}$ are reported. Light scattering studies indicated that, with carefully-chosen block lengths and composition, the triblock copolymer is able to self-associate in aqueous solution and form worm-like micelles at ambient temperatures. Like other diblock copo(oxyalkylene)s of this kind, a transition temperature from spherical to elongated micelles was observed for $E_{16}S_8E_{16}$ at ca. 18 °C. The shape transition was also demonstrated by TDA measurement, which shows a near doubling of micellar size at 40 °C. The results from light scattering and TDA are in good agreement on hydrodynamic radii and diffusion coefficients at the temperatures investigated. The sample sparing capability of TDA provides for its more extensive use in this field. The ESE copolymer shows much greater solubilisation capacities for a poorly water-soluble model drug than a Pluronic comparator because of the hydrophobic nature of S blocks and formation of worm-like micelles for the ESE copolymer.

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References

Adams M. L., Lavasanifar A., Kwon G. S., 2003. Amphiphilic block copolymers for drug delivery. J. Pharm. Sci., 92, 1343–1355.

Aris R., 1956. On the dispersion of a solute in a fluid flowing through a tube. Proc. R. Soc. A, 235, 67–77.

Attwood D., Zhou Z., Booth C., 2007. Poly(ethylene oxide) based copolymers: solubilisation capacity and gelation. Expert Opin. Drug Deliv., 4, 533–546.

Booth C., Attwood D., 2000. Effects of block architecture and composition on the association properties of poly(oxyalkylene) copolymers in aqueous solution. Macromol. Rapid Commun., 21, 501–527.

Booth C., Attwood D., Price C., 2006. Self-association of block copoly(oxyalkylene)s in aqueous solution. Effects of composition, block length and block architecture. Phys. Chem. Chem. Phys., 8, 3612–3622.

Carnahan N. F., Starling K. E., 1969. Equation of State for Nonattracting Rigid Spheres. J. Chem. Phys., 51, 635–636.

Chaibundit C., Ricardo N. M. P. S., Crothers M., Booth C., 2002. Micellization of diblock(oxyethylene/oxybutylene) copolymer $E_{11}B_8$ in aqueous solution. Micelle size and shape. Drug solubilization. Langmuir, 18, 4277–4283.

Chaibundit C., Sumanatrakool P., Chinchew S., Kanatharana P., Tattershall C. E., Booth C., Yuan X. F., 2005. Association properties of diblock copolymer of ethylene oxide and 1,2-butylene oxide: $E_{17}B_{12}$ in aqueous solution. J. Colloid Interface Sci., 283, 544–554.

Chamieh J., Davanier F., Jannin V., Demarne F., Cottet H., 2015. Size characterization of commercial micelles and microemulsions by Taylor dispersion analysis. Int. J. Pharm., 492, 46–54.

Chiappetta D. A., Sosnik A., 2007. Poly(ethylene oxide)-poly(propylene oxide)-poly(ethylene oxide) block copolymer micelles as drug delivery agents. Improved hydrosolubility, stability and bioavailability of drugs. Eur. J. Pharm. Biopharm., 66, 303–317.

Cottet H., Martin M., Papillaud A., Souaïd E., Collet H., Commeyras A., 2007. Determination of dendrigraft poly-L-lysine diffusion coefficients by Taylor dispersion analysis. Biomacromolecules, 8, 3235–3243.

Crothers M., Zhou Z., Ricardo N. M. P. S., Yang Z., Taboada P., Chaibundit C., Attwood D., Booth C., Solubilisation in aqueous micellar solutions of block copoly(oxyalkylene)s. Int. J. Pharm., 293, 91–100.

Flory P. J., 1969. Statistical mechanics of chain molecules. Interscience, New York, p. 165.

Grindel J. M., Jaworski T., Piraner O., Emanuele R. M., Balasubramanian M., 2002. Distribution, metabolism, and excretion of a novel surface-active agent, purified poloxamer 188, in rats, dogs, and humans. J. Pharm. Sci., 91, 1936–1947.

Hawe A., Hulse W. L., Jiskoot W., Forbes R. T., 2011. Taylor dispersion analysis compared to dynamic light scattering for the size analysis of therapeutic peptides and proteins and their aggregates. Pharm. Res., 28, 2302–2310.

Heatley F., Yu G. E., Draper M. D., Booth C., 1991. Analysis of the ^{13}C-NMR spectra of poly(styrene oxide) and of block and statistical copolymers of styrene oxide and ethylene oxide. Eur. Polym. J., 27, 471–478.

Lemal P., Balog S., Geers C., Taladriz-Blanco P., Palumbo A., Hirt A. M., Rothen-Rutishauser B., Petri-Fink A., 2019. Heating behavior of magnetic iron oxide nanoparticles at clinically relevant concentration. J. Magn. Magn. Mater., 474, 637–642.

Taylor G., 1953. Dispersion of soluble matter in solvent flowing slowly through a tube. Proc. R. Soc. A, 219, 186–203.

Torchilin V. P., 2001. Structure and design of polymeric surfactant-based drug delivery systems. J. Control. Rel., 73, 137–172.

Yang Z., Booth C., Crothers M., Attwood D., Collett J. H., Ricardo N. M. P. S., 2003. Association properties of ethylene oxide/styrene oxide diblock copolymer $E_{17}S_8$ in aqueous solution. J. Colloid Interface Sci., 263, 312–317.

Yang Z., Crothers M., Ricardo N. M. P. S., Chaibundit C., Taboada P., Mosquera V., Kelarakis A., Havredaki V., L. Martini G. A., Valder C., Collett J. H., Attwood D., Heatley F., Booth C., 2003b. Micellization and gelation of triblock copolymers of ethylene oxide and styrene oxide in aqueous solution. Langmuir, 19, 943–950.

Zaman H., Bright A. G., Adams K., Goodall D. M., Forbes R. T., 2017. Characterisation of aggregates of cyclodextrin-drug complexes using Taylor Dispersion Analysis. Int. J. Pharm., 522, 98–109.

Zhou Z., Chaibundit C., D'Emanuele A., Lennon K., Attwood D., Booth C., 2008. Solubilisation of drugs in worm-like micelles of block copolymers of ethylene oxide and 1,2-butylene oxide in aqueous solution. Int. J. Pharm., 354, 82–87.

Zhou, Z., D'Emanuele, A., Lennon, K., Attwood, D., 2009. Synthesis and micellization of linear–dendritic copolymers and their solubilization ability for poorly water-soluble drugs. Macromolecules 42, 7936–7944