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ARTICLE *in* THE JOURNAL OF PHYSICAL CHEMISTRY B · AUGUST 2012

Impact Factor: 3.3 · DOI: 10.1021/jp303185m · Source: PubMed

THE JOURNAL OF PHYSICAL CHEMISTRY B

Article

pubs.acs.org/JPCB

Effect of Temperature, Cosolvent, and Added Drug on Pluronic–Flurbiprofen Micellization

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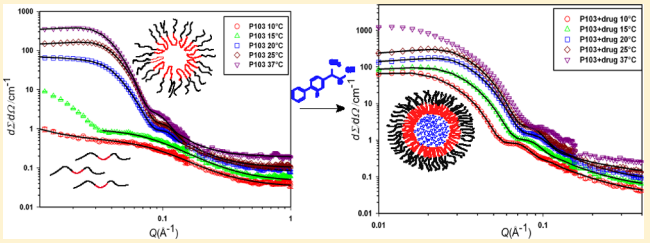
ABSTRACT: Structural changes in the micellization of Pluronics P103 and P123, as a function of temperature, cosolvent (ethanol, 10 v/v %), and the addition of the hydrophobic drug flurbiprofen, were investigated by SANS and tensiometry. Addition of ethanol increases the critical micellization concentration of the Pluronics (making the polymer more soluble), while increasing the repulsive interactions between the flurbiprofen–Pluronic spherical complexes. However, increasing temperature and addition of drug increases both the aggregation number and core radius and leads to a more dehydrated core. The addition of flurbiprofen to Pluronic P103 was also found to reduce the critical micellization temperature from between 15 and 20 °C to below 10 °C and at higher drug concentrations leads to an attractive interaction between micelles and eventually phase separation.



1. INTRODUCTION

Over the past few years, the associative interactions between the Pluronic triblock copolymers and drugs have been intensively studied using small-angle neutron scattering (SANS).[1−4] Poly(ethylene oxide)−poly(propylene oxide)−poly(ethylene oxide) (PEO−PPO−PEO) triblock copolymers (known as Pluronics) are one of the best candidates to be used as vehicles for controlled drug release and, above all, for the encapsulation of hydrophobic drugs due to their high biocompatibility and low toxicity.[5−10]

Foster et al.,[3] Valero et al.,[4] and Chi et al.[11] have studied the effects of some of the nonsteroidal anti-inflammatory drugs (NSAIDs) on Pluronic copolymer solutions. It has been found that the addition of drug to the aqueous solutions of the Pluronic copolymers altered their aggregation properties such as the CMC and CMT, aggregation number, and the structure of the micelles. SANS is an excellent technique to provide information on the structure and size of the micelles as well as the interaction and localization of the drug within the aggregates.[12−16]

NSAIDs are a series of drugs having analgesic, antipyretic, and, in higher doses, anti-inflammatory effects.[17] Among those, flurbiprofen is used to treat pain, tenderness, and swelling, caused by osteoarthritis and rheumatoid arthritis. Flurbiprofen can be superior to other NSAIDs due to less symptomatic side effects (pain, cramping, and swelling), as well as having a high efficacy/tolerance ratio.[18,19]

Cosolvents (such as ethanol and glycols such as polyethylene glycol) are often present in drug delivery formulations in order to improve the solubility of the drug.[20,21] The solvent quality is an important factor in the self-assembly of block copolymers; in a solvent that is selective for one block and poor for another, amphiphilic copolymers form micelles with a poorly soluble core and a soluble corona.[22,23]

In the case of Pluronic triblock copolymers where water is a selective solvent for the PEO block, the addition of cosolvent can influence micellization properties such as their CMT, CMC, and sol–gel boundaries.[24−26]

The temperature sensitivity of polymer solutions and polymer aggregation has also been widely studied, with properties such as the lower critical solution temperature and the CMT being of particular interest.[27−31]

We have previously used PFGSE-NMR and surface tension measurements to study the effect of concentration of drug and polymer on the aggregation behavior of Pluronic micelles (P103, P123, and L43),[32] as well as SANS to study the effect of pH on drug release.[33]

This paper is a continuation of the previous studies, however, in this case, we describe a structural study using SANS from Pluronics P103 and P123 (molar mass, volume, and scattering length densities are given in Table 1) upon addition of the hydrophobic drug, flurbiprofen.

We also consider factors influencing micelle formation such as addition of a cosolvent (ethanol), variation in temperature, and presence of drug on the CMT of the micelles. Complementary data on the CMC of these polymers have also been obtained. Previously, we concluded that the formation of L43–drug complexes is unfavorable, and consequently, we confine the study of the cosolvent and temperature effects on the polymer–drug complexes to P123–

Received: April 3, 2012
Revised: August 21, 2012

   dx.doi.org/10.1021/jp303185m | J. Phys. Chem. B XXXX, XXX, XXX–XXX

Table 1. Values of Molar Masses, Molecular Volumes, Density, and Scattering Length Density of Polymers and Solvents

	molar mass (g mol^{-1})	molecular vol (Å^3)	density (g cm^{-3})	SLD^c (10^{-6} Å^{-2})
EO	44	62	1.14	0.67
PO	58	96	1.01	0.34
D_2O	20	30	1.11	6.38
D_2O/ethanol-d_6 (90:10)	20/52	35	1.08	6.28
P123 ($PEO_{20}PPO_{70}PEO_{20}$)^a	7100^b	11350	1.04^a	0.42
P103 ($PEO_{17}PPO_{60}PEO_{17}$)^a	5600^b	8944	1.04^a	0.42

^{a}Values supplied by BASF.[34] ^{b}Determined using MALDI-TOF MS. ^{c}Calculated from the density values using literature data.[29,35] SLD values of the solvent mixture and the Pluronics are an average using the SLD and volume fraction of each component.

and P103−flurbiprofen systems. Each of these polymers has the same PEO/PPO ratio (30% PEO), but they have different chain lengths, and therefore, different aggregation behavior such as different CMC, CMT, and phase behavior.

2. MATERIALS AND METHODS

All compounds were used as received. Both Pluronics were provided by BASF and used as supplied. Flurbiprofen was supplied by Sigma Aldrich. D_2O (99.94 atom % D) and ethanol-d_6 (99 atom % D) were purchased from Goss Scientific Instruments Ltd.

2.1. Sample Preparation. The Pluronic and the solvent (10% v/v ethanol-d_6 in D_2O) were weighed into vials and placed on a roller mixer for two hours. The drug was then added to the solution, and samples were sonicated for 2 h. They were left on a roller mixer for a further 24 h before measurements. The drug was not soluble in the ethanol−water mixture, but after the addition to Pluronic solutions well above the critical micelle concentration, the mixture became clear, indicating solubilization. All the samples were made with 5 w/v % polymers and 0.05 wt % drug in a range of 10 to 37 °C.

2.2. Small-Angle Neutron Scattering. The SANS measurements were carried out on the D11 instrument at the Institute Laue-Langevin (ILL), Grenoble, France. Neutrons with a wavelength of 8 Å and two sample-detector positions (1.2 and 8 m) were used, to provide a Q-range of 0.002−0.4 Å^{-1}. All the samples were measured in 1 mm path length rectangular quartz cells and D_2O/ethanol-d_6 mixture (90:10 v/v) was run as a background sample. The measurements were carried out at 298 K unless otherwise mentioned. The data reduction was carried out using the LAMP program,[36] and micellar data were fitted using the Pedersen model.[3,13] This model uses a form factor for a spherical core surrounded by non-interacting Gaussian chains. This model allows the coexistence of both unimers and micelles at the same time and therefore parameters such as the following: aggregation number (N_{agg}), volume fraction of solvent in the core (ϕ_{sol}), the equivalent hard sphere volume fraction (ϕ_{HS}), fraction of micellization (f_{mic}), the relative (Gaussian) polydispersity[37] of the aggregation number (σ), the interaction radius (R_{int}/Å) which is taken as $R_c + 2R_{g(PEO)}$, and the core radius (R_c/Å) can be obtained.

Parameters such as the Q resolution, the number of ethylene oxide units (N_{EO}), and propylene oxide units (N_{PO}), concentration (c/w/v), and scattering length density of the solvent (ρ_{sol}/Å^{-2}) were fixed as they are determined by the experimental conditions. Uncertainties quoted here are the results of a least-squares residual fitting algorithm.

ϕ_{sol} was obtained using the scattering length density of the solvent (SLD_{sol}) and polymer (SLD_{ppo}), which are given in Table 1:

$$SLD_{core} = \phi_{sol}SLD_{sol} + \phi_{ppo}SLD_{ppo} + \phi_{drug}SLD_{drug} \quad (1)$$

where $\phi_{sol} + \phi_{ppo} + \phi_{drug} = 1$. The relatively small amount of drug that is located in the Pluronic micelle core means that ϕ_{drug} is negligible. Moreover, since drug and polymer have very similar SLDs we neglect this term in treating the scattering data as drug and polymer are indistinguishable in the scattering experiment in any case. We must accept that this approximation necessarily entails that the values for N_{agg} reported here will be systematically too high, but since perdeuterated flurbiprofen is not available, there is little prospect of correcting for this effect through experiments with further SLD contrasts. As has previously been shown by Foster et al.[3] and Alexander et al.,[33] the correction to N_{agg} is much smaller than the size of the changes in N_{agg} observed through the solubilization of drug into the micelles allowing analysis of the trends in micellization as will be presented below.

The nonaggregated data (unimers) were fitted to the Guinier−Debye model which describes the scattering from polymers in good solvent.[38] The scattering intensity given by:

$$I(Q) = NV^2(\Delta\rho)^2 \frac{2(\exp[-(QR_g)^2] + (QR_g)^2 - 1)}{(QR_g)^4} + B \quad (2)$$

where

$$NV^2 = \frac{c\overline{M_n}}{N_A(\delta)^2} \quad (3)$$

The parameters used for fitting data to the Guinier−Debye model are the scattering length density difference between the polymer and solvent, $(\Delta\rho)^2$, concentration of polymer present in the sample, c, number-average molar mass of the polymer used, $\overline{M_n}$, radius of gyration of the polymer in solution, R_g, incoherent background scattering, B, and density of the bulk polymer, δ.

In this model, the concentration, molar mass, and scattering length density difference have the same effect on the data fit; therefore two of these parameters were fixed throughout the fitting.

2.3. Surface Tension. The surface tensions of the two Pluronic solutions (10 wt %) in 10/90 vol % ethanol/H_2O mixture, and in pure water, were determined using a K100 Wilhelmy Plate surface tensiometer at the Krüss Surface Science Centre at the University of Bristol. All the samples were filtered through a 0.45 μm Millipore filter to remove any impurities before the measurements. The measurements were carried out at 298 K.

3. RESULTS AND DISCUSSION

3.1. Effects of Cosolvent and Drug Concentration on the Pluronic Micelle Structure. Solutions of the Pluronic P103 and P123 (5 w/v %) with and without drug (0.5 w/v %)

dx.doi.org/10.1021/jp303185m | J. Phys. Chem. B XXXX, XXX, XXX−XXX

were studied using SANS at 298 K, at two different solvent compositions: 10/90 vol % ethanol-d_6/D_2O mixture and pure D_2O, as shown in Figure 1.

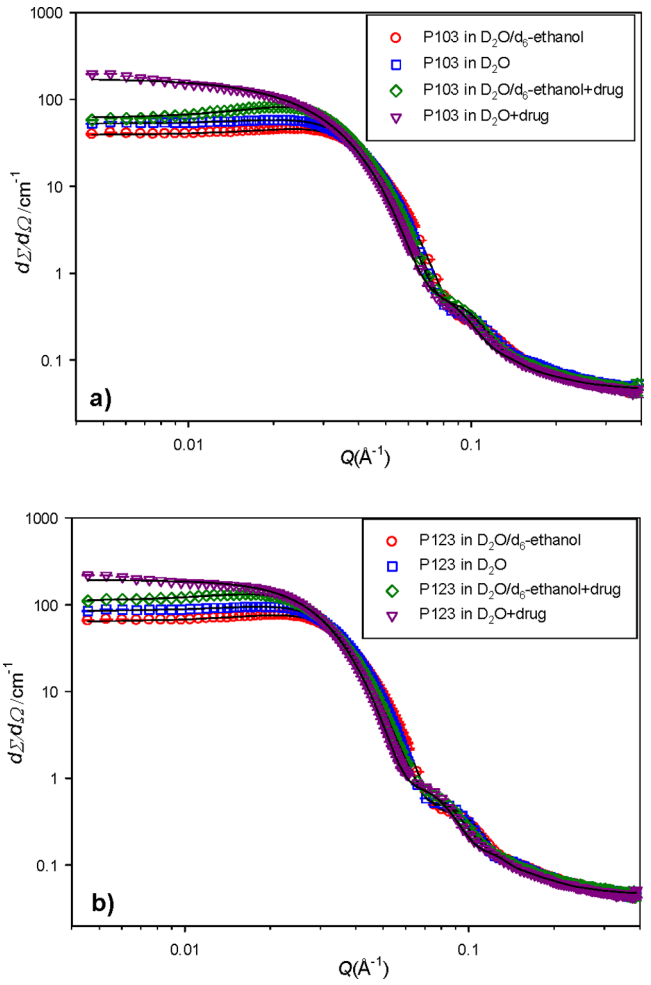


Figure 1. SANS from (a) Pluronic P103 and (b) Pluronic P123, 5 w/v %, with 0.5 w/v % flurbiprofen, at two solvent compositions: D_2O and 10/90 vol % ethanol-d_6/D_2O. The data were fitted to the Pedersen model.

The data were fitted using the Pedersen model; the details regarding the form factors and structure factor of the spheres and unimers for this model are discussed fully by Pedersen et al.[13,14,37,39] As can be seen from Figure 1, both P103 and P123 have typical scattering patterns expected from a core shell micelle. P123 shows slightly higher aggregation numbers than P103, which is due to the longer length of the PPO blocks (N_{po}) and the larger core radius. The aggregation number (N_{agg}) is directly related to the core radius (R_c) according to[37]

$$N_{agg} = \frac{4\pi R_c^3(1 - \phi_{sol})}{3N_{PO}V_{PO}} \quad (4)$$

where V_{PO} = 96.3 Å^3 is the propylene oxide volume and is calculated from its mass density (ρ_{PO} = 1.01 g/cm^3).

Addition of ethanol has a pronounced impact on the micelle structure. It can be seen from the fitting parameters in Table 2 that the aggregation number of P123 is reduced by around 17% from 85 to 71, whereas for P103 it is reduced by 26% from 56 to 41. These results are in good agreement with results obtained for 5 wt % Pluronic P123 in D_2O and D_2O/ethanol-d_6 mixtures by Jangher et al.[40] The core radius and the fraction of micellization of both P123 and P103 were lowered, while the fraction of solvent in the core of the micelles increased upon addition of ethanol to the system.

The decrease in the fraction of polymer micellized and the increase in the amount of solvent in the core, observed in the ethanol−water solvent mixture, corresponds to the fact that ethanol is a better solvent for both PEO and PPO blocks. The addition of ethanol, therefore, increases the solubility of the PPO blocks, which leads to an increase in the solvent fraction in the core and, consequently, affects the structure of the micelles.

The same behavior was observed by Alexandridis,[41] who studied Pluronic P105 in various ratio of cosolvents/water and observed a decrease in core radius and aggregation number as well as a more solvated PPO core. The CMC of P123 and P103 for the two solvent compositions was obtained using surface tension measurements, which are presented in Table 3. The

Table 3. Surface Tension Data for the Pluronics in Pure Water and (10/90 vol %) Ethanol/Water

	CMC (wt %)		% micellized (f_M) ± 1.1 at C_{tot} = 5 wt %	
copolymer	D_2O	D_2O/ethanol-d_6	D_2O	D_2O/ethanol-d_6
P103	0.07 ± 0.01	0.16 ± 0.01	98.6	96.8
P123	0.008 ± 0.003	0.029 ± 0.003	99.8	99.4

Table 2. SANS Parameters for 5 w/v % Pluronics P103 and P123, with 0.5 w/v % Flurbiprofen in (10:90) D_2O/Ethanol-d_6 and pure D_2O at 298 K[a]

	P103		P123		P103 + drug		P123 + drug	
sample	D_2O	D_2O/ethanol-d_6	D_2O	D_2O/ethanol-d_6	D_2O	D_2O/ethanol-d_6	D_2O	D_2O/ethanol-d_6
N_{agg} ± 1.5	56	41	85	71	71	68	138	120
ϕ_{sol} ± 0.03	0.34	0.37	0.22	0.35	0.25	0.29	0.12	0.18
ϕ_{HS} ± 0.003	0.11	0.11	0.11	0.12	0.002	0.11	0.05	0.12
f_{mic} ± 0.03	0.97	0.91	0.99	0.93	0.98	0.93	0.995	0.98
R_c/Å ± 1.5	49	45	56	55	51	50	64	62
R_{int}/Å ± 1.5	76	71	85	89	79	88	86	96
σ ± 0.03	0.59	0.78	0.59	0.51	0.61	0.83	0.64	0.68

[a]Data fitted to the Pedersen model. The $R_{g(PEG)}$ values for P103 and P123 were 13.5 and 17.5 Å ± 0.54, in both solvent conditions, respectively. The $R_{g(PEG)}$, for the P103 and P123 in the presence of the drug, were fixed at the above values. The $R_{g(unimer)}$ were obtained as 14.9 ± 0.5 Å and 18.7 ± 0.5 Å for P103 and P123 respectively.

dx.doi.org/10.1021/jp303185m | J. Phys. Chem. B XXXX, XXX, XXX−XXX

results show that addition of ethanol also increases the CMC and decreases the fraction of micellization.[42,43] The fraction of micellization (f_M) was obtained using surface tension data, which is given by $f_M = (C_{tot} - CMC)/C_{tot}$.

Upon addition of drug, both Pluronics showed significant changes in their aggregation behavior (Table 2). There is an increase in the aggregation number (N_{agg}), the fraction of polymer micellized (f_{mic}), and the core radius (R_c) for both solvents. The volume faction of solvent in the core (ϕ_{sol}) decreases on addition of the drug, indicating the uptake of the drug mainly by the hydrophobic PPO core, which gives rise to the larger core radius. These results show that flurbiprofen increases the driving force for aggregation of the Pluronic micelles.

The main difference between the Pluronic−drug complexes in D_2O and D_2O/ethanol-d_6 is the gradient of the scattering in the low Q region (Figure 1). For complexes in pure D_2O systems, the negative gradient could be due to either an increase in attractive interactions between the micelles, which might lead to phase separation, or a change in the shape of the micelles. As reported in Table 2, these D_2O data were also analyzed using the Pedersen model; however, this model is unable to take account of changes in shape or the presence of an attractive structure factor, giving an unrealistically small ϕ_{HS} for the structure factor. At this composition micelles might be approaching their solubility limits and/or onset of structural change from spherical to cylindrical or rodlike; future cryo-TEM experiments may help understand this apparent structural change.

For the D_2O/ethanol-d_6 samples, the gradient at low Q is positive (Figure 1) and the hard-sphere volume fraction that provides the repulsive structure factor in the Pedersen model has more physically realistic values for these samples. The polymer−drug solutions in water were clear but slightly bluish compared to the solutions in ethanol/water, which were completely colorless. This could also indicate the presence of larger aggregates as reported by Foster et al.[3] for solutions of 5 wt % P103 solutions with 0.5 wt % ibufropen in pure water. In our previous studies, we also observed similar behavior for 5 wt % P103 solutions with 0.75 wt % flurbiprofen in ethanol/water and 5 wt % P123 solutions with 1 wt % flurbiprofen in ethanol/water.[32] It was concluded that these large aggregates with R_h of ~410 Å suggest the onset of attractive interaction between the micelles or phase separation in the system, which could be due to the loading capacity of the polymers being exceeded. Flurbiprofen solubility in water, at pH 7, is about 0.04 wt %.[44] In 10 v/v % ethanol/water mixture the solubility increases approximately by another factor of 2.[33]

SANS from P123 with varying amount of drug (Figure 2) shows that the higher percentage of drug, the larger the aggregation numbers (Table 4), until the drug concentration exceeds the micelle saturation point (Figure 2, P123 + 1% drug). At high additive loadings, formation of cylindrical or lamellar structures has previously been reported[45] along with attractive interaction between the aggregates[32] and eventually phase separation.

3.2. Effect of Temperature on the Pluronic Micelles and Addition of Drug on CMT of the Micelles. As the micellization of Pluronics depends on temperature as well as concentration, both polymers (5 w/v %) were investigated as a function of temperature (10 to 37 °C), with and without drug, in (10/90 vol %) ethanol-d_6/D_2O. The scattering patterns are shown in Figure 3. At low temperature (below the CMT),

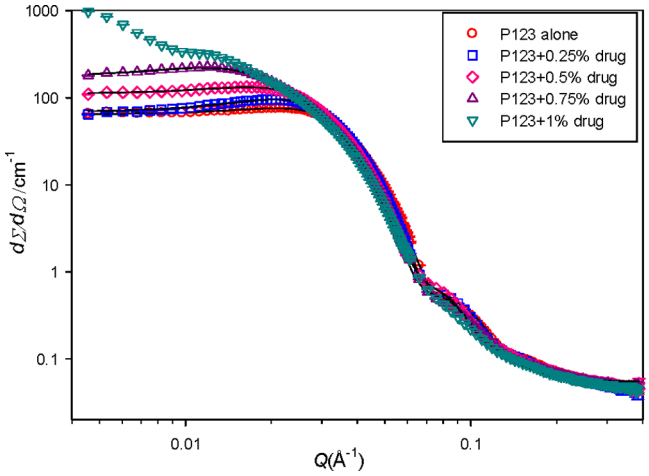


Figure 2. SANS from Pluronic P123, 5 w/v %, with increasing flurbiprofen concentration, in 10/90 vol % ethanol-d_6/D_2O. Solid lines are fits to the Pedersen model.

Table 4. Pedersen Model Analysis of 5 w/v % P123 with Increasing Drug Concentration, at 298 K

flurbiprofen concn (w/v %):	0	0.25	0.5	0.75
N_{agg} ± 1.2	71	93	120	128
ϕ_{sol} ± 0.03	0.35	0.21	0.18	0.02
ϕ_{HS} ± 0.003	0.12	0.12	0.12	0.07
f_{mic} ± 0.03	0.93	0.97	0.98	0.99
σ ± 0.09	0.51	0.52	0.68	0.71
R_c/Å ± 1.2	55	57	62	62

water is a good solvent for both the PPO and PEO blocks and therefore the block copolymers are in the form of unimers, which gives a low scattering intensity as shown in Figure 3 for P103 at 10 and 15 °C. The scattering data for these samples were fitted to the Guinier−Debye function; the scattering length density difference, between the polymer and solvent mixture, was fixed at 5.86×10^{-6} Å^{-2}, and the concentration was fixed at 0.05. Values of $R_g = 17.5 \pm 0.34$ Å and 19.2 ± 0.29 Å were obtained for the Pluronic P103 at 10 and 15 °C respectively. As can be seen from Figure 3a, at low temperature (particularly close to the CMT of 17 °C in pure water[46]), the SANS scattering at low Q increases, which implies the presence of aggregates.[33] Alvarez-Ramirez et al.[46] observed an increase in both R_h and scattering intensity around the CMT of P103 using scattering light scattering. Kositza et al.[47] also observed an increase in light scattering intensity near the CMT of the Pluronic L64 that disappeared after the industrial sample was purified. Consequently it is believed that the increase in scattering intensity near the CMT is due to the existence of diblock impurities in the unpurified industrial samples, and these impurities disappear once the micelles are formed. The data for P103 at 15 °C can also be fitted by the Pedersen model showing the formation of a small population of micelles with $N_{agg} \sim 14$. Therefore, the increase in intensity at 15 °C could also indicate the onset of micelle formation.

As the temperature rises (above the CMT), the PPO blocks become water insoluble and, therefore, formation of micelles with a core of PPO and corona of PEO blocks[41,48] then gives rise to an increase in scattering intensity due to the difference between the scattering length density of the core, corona, and solvent. For the Pluronic P103, the scattering pattern indicates the presence of micelles for temperatures above 15 °C. This is

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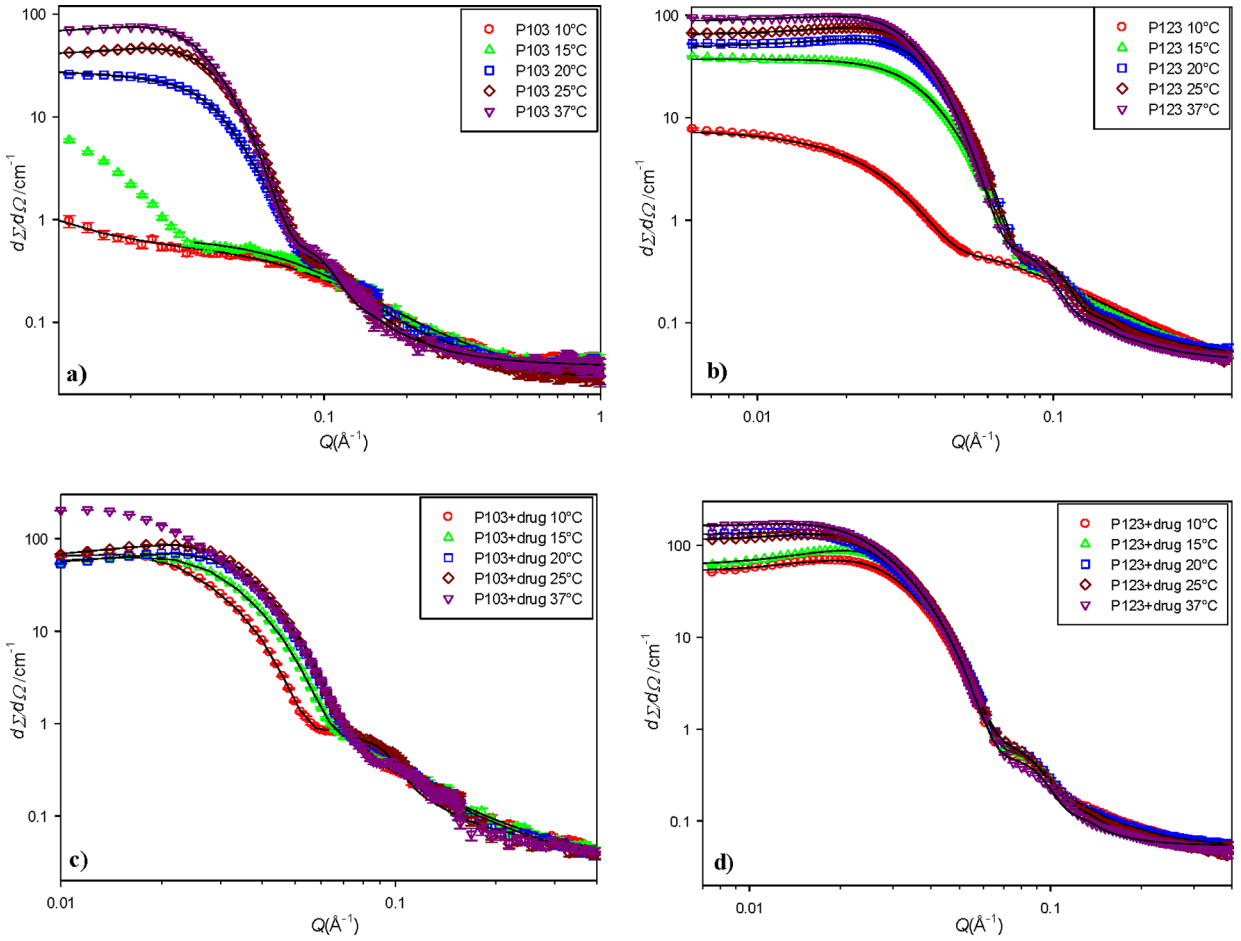

Figure 3. SANS from (a) P103, (b) P123, (c) P103 + 0.5 wt % flurbiprofen and, (d) P123 + 0.5 wt % flurbiprofen. Each sample is in ethanol-d_6/D_2O and measured at the temperatures indicated. Solid lines are fits to the Guinier–Debye function for free polymer and the Pedersen model for micelles.

Table 5. Pedersen Model Analysis of 5 w/v % Pluronic P103 and P123, at a Range of Temperatures, in D_2O/Ethanol-d_6

	P103			P123				
temp (°C):	20	25	37	10	15	20	25	37
N_{agg} ± 2.3	29	41	56	31	44	55	71	88
ϕ_{sol} ± 0.03	0.59	0.37	0.33	0.47	0.44	0.32	0.35	0.19
ϕ_{HS} ± 0.001	0.12	0.11	0.10	0.004	0.06	0.11	0.12	0.10
R_{int}/Å ± 1.1	64	71	77	75	81	85	89	88
f_{mic} ± 0.03	0.89	0.91	0.94	0.67	0.71	0.90	0.93	1.0
R_c/Å ± 2.3	46	45	48	46	51	51	55	56
σ ± 0.05	0.70	0.78	0.86	0.82	0.45	0.51	0.51	0.59

very close to the previously reported CMT of 17 °C in pure water.[46] The scattering data in Figure 3a (without flurbiprofen at 37 °C) is characteristic of spherical micelles in an ethanol/water mixture. However, Alvarez-Ramirez et al.[46] studied the phase behavior of the Pluronic P103 in water and reported cylindrical micelles, for 5 wt % polymers at 37 °C, which differs from our data presented here. This is due to the presence of the cosolvent, ethanol, which affects the micellar structure as well as the micelle aggregation parameters.

The CMT of the Pluronic P123 (5 wt %) was reported previously to be 12.5 °C by Alexandridis et al.[49] However, as can be seen in Figure 3b even at 10 °C, micelles are observed but the intensity of the scattering is low, which corresponds to a small N_{agg} and f_{mic} (Table 5). It is believed that the presence of impurities and molecular mass dispersity of the commercial Pluronics could affect the micellization behavior and broaden the CMC and CMT.[3,46,50,51]

On raising the temperature, increases in the core radius, the aggregation number, and the fraction of polymer micellized and a decrease in the volume fraction of solvent in the core were observed (Table 5). The core of the Pluronic P123 micelles is more hydrated around the CMT (10 and 15 °C) with ϕ_{sol} of 47% and 44% respectively; however, at higher temperatures, ϕ_{sol} decreases to around 19%, because of the dehydration of the PPO blocks in the core. These results are in good agreement with those reported by Manet et al.,[29] who found a decrease in the volume fraction of pure water in the core of P123 from around 40% at 20 °C to ~20% at 40 °C. These are all clear signs that the driving force for micellization increases with temperature, as PPO is less soluble at higher temperatures.

dx.doi.org/10.1021/jp303185m | J. Phys. Chem. B XXXX, XXX, XXX–XXX

Table 6. Pedersen Model Analysis of 5 w/v % Pluronic P103 and P123, with 0.5 wt % Drug at a Range of Temperatures, in D_2O/Ethanol-d_6

	P103				P123				
temp (°C):	10	15	20	25	10	15	20	25	37
$N_{agg} \pm 1.3$	42	45	48	68	63	68	83	120	122
$\phi_{sol} \pm 0.05$	0.84	0.7	0.58	0.29	0.45	0.41	0.20	0.18	0.07
$\phi_{HS} \pm 0.008$	0.076	0.084	0.11	0.11	0.1	0.13	0.06	0.12	0.07
R_{int}/Å ± 1.1	144	107	92	88	104	103	124	96	120
$f_{mic} \pm 0.05$	0.26	0.4	0.56	0.93	0.86	0.91	0.94	0.98	1.0
R_c/Å ± 1.3	73	60	55	51	57	58	56	62	60
$\sigma \pm 0.05$	0.43	0.54	0.59	0.8	0.48	0.55	0.83	0.60	0.62

As can be seen in Figure 3c,d, upon addition of drug to the micelles, both Pluronic copolymers respond differently to temperature, as the presence of the drug alters the CMT of the Pluronic micelles so that even at 10 and 15 °C micelles exist.

An unexpected result for P103 is that, in the presence of drug but below the CMT, the micellar core radius decreases with increasing temperature. This is surprising as with the lower PPO solubility at higher temperature an increase in size was expected. The key to understanding this is the high volume fraction of solvent found in the micelles at low temperatures (84% at 10 °C and 70% at 15 °C). The higher micellization driving force leads to a large amount of solvent being expelled from the core, which explains the observed decrease in R_c, and higher aggregation number.

Foster et al observed the same behavior for 5 w/v % Pluronic P104 with 0.5 wt % ibuprofen. It was observed that the core radius increased with the temperature above 20 °C, although it decreased in size from 13 to 20 °C.[3] These results were also confirmed by dynamic light scattering with R_H of 160, 90, and 80 Å at 20, 25, and 30 °C respectively.

The results analysis of the SANS data with the Pedersen model, upon addition of the drug, are shown in Table 6, and it can be seen that as the temperature increases, the fraction of micellized polymer, the aggregation number, and the core radius increase.

As can be seen in Figure 3c (P103 with flurbiprofen at 37 °C), the scattering at low Q increases and the shape of the scattering pattern changes. One possibility is that the Pluronic micelles in this condition are in transition from a sphere to a cylinder.[46] This change in structure at the given temperature was not observed for the Pluronic P103 without drug and P123 micelles with drug. This indicates that the presence of flurbiprofen and also the hydrophobicity of the polymers influence the micelle structure as well as the temperature at which the structural changes occur.

4. CONCLUSIONS

SANS was used to investigate the structural aggregation behavior of Pluronics P123 and P103 under various conditions of cosolvent, temperature, and drug concentration. The data showed that the CMC of the micelles and the fraction of polymer micellized are affected by the presence of ethanol: the CMC increases and fewer micelles are formed. In the presence of 0.5 wt % flurbiprofen, the ethanol/water mixture offered better conditions as the micelle−flurbiprofen complexes in pure water are close to phase separation.

The effect of drug addition to the micelles as a function of concentration was also studied. The scattering pattern obtained using SANS showed that higher drug concentrations (1 wt % flurbiprofen) can lead to micelles' attractive interactions and/or the change in the micelles' structure.

The scattering pattern showed an increase in scattering intensity with increasing temperature, resulting from a higher aggregation number, fraction of micellization, and core radius and a lower degree of solvent in the micelle core. The presence of drug altered the CMT of the micelles, as polymers without any drug existed mainly as unimers at 10 and 15 °C. However the fraction of micellization increased with 0.5 wt % of drug to 25% and 40% at 10 and 15 °C respectively for Pluronic P103.

These results illustrate the sensitivity of the micellization of Pluronics to various environmental conditions including the temperature, presence of cosolvent, hydrophobic species such as drug molecules, impurities, and hydrophobicity of the Pluronics, factors which will need to be considered carefully in any clinical or industrial applications.

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We thank Dr. Wiebe de Vos for useful discussions and support and Miss Beatrice Cattoz for assistance with SANS measurements. We are also grateful to the EPSRC and Revolymer Ltd for funding and the Institut Laue-Langevin (ILL) for awarding us with neutron beam time. Dr. Peter Lindner is thanked for his support during these experiments.

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