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Effect of anti-inflammatories on Pluronic® F127: micellar assembly, gelation and partitioning

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Abstract

We present results on the effect of two anti-inflammatory agents, naproxen and indomethacin, on the structure, assembly and gelation transitions of Pluronic® F127 micelles. Small-angle neutron scattering experiments on micellar solutions indicate that the micelle aggregation number decreases significantly in the presence of drug solutes, causing the number density of micelles to increase. However, only slight changes were observed in the critical micelle concentration of F127 in the presence of these drugs. Both anti-inflammatory agents were found to shift the liquid-to-gel and gel-to-liquid transitions of the copolymer to lower temperatures. This may be the result of an increase in the micellar volume fraction, caused by the presence of the hydrophobic drugs. Using an ultraviolet spectroscopy technique, we have also measured the solubilities and micelle–water partition coefficients (K_{mw}) of naproxen and indomethacin in water and F127 solutions. The values of K_{mw} for naproxen and indomethacin are 355 ± 64 and 474 ± 33, respectively. They are larger than previously reported lipid–water partition coefficients, indicating that F127 micelles may be a better choice for drug loading than lipid vesicles. The slightly greater effects of indomethacin on the gelation boundary as compared with naproxen may be attributable to a higher value of K_{mw}.

Keywords: PEO–PPO–PEO; SANS; TIM; Liquid–gel transition; Partition coefficient; DLS

1. Introduction

Pluronic® F127 is one member of a family of triblock copolymers of poly(ethylene oxide)–poly(propylene oxide) (PPO)–poly(ethylene oxide) (PEO), generically called poloxamers (Schmolka, 1972). It exhibits thermoreversible gelation and has therefore generated considerable interest as a novel method for the delivery of drugs through controlled release (Bromberg and Ron, 1998). The PPO segment of one of these polymer chains is relatively hydrophobic compared to either of the PEO segments surrounding it. Therefore, when several chains are placed into an aqueous solvent such as water, they aggregate to form self-assembled micellar structures above the critical micelle concentration (Lange, 1999). The liquid-phase micelles formed by F127 undergo transitions into liquid crystal gel phases in response to changes in temperature (Wanka et al., 1994). At moderate concentrations, F127 solutions are liquid at ambient temperature and elastic gels at body temperature. Drugs delivered with F127 are generally administered using the cold liquid phase and then released from the warm gel phase.

It is important to be able to predict the gelation behavior of drug-loaded copolymer formulations.

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Pluronic® drug delivery applications often rely on a transition from liquid to gel occurring at a specific temperature. Aqueous F127 solutions display a liquid-to-gel transition at physiological temperatures; this is referred to as the gelation transition or the lower gel phase boundary. At higher temperatures the systems liquefy again; referred to as the gel-to-liquid transition, degelation, or the upper gel phase boundary. Both transitions can be influenced by the presence of hydrophobic drug solutes in the formulation. The hydrophobicities of various solutes have been shown to affect the copolymer phase behavior (Ivanova et al., 2002) and liquid-to-gel transition (Gilbert et al., 1987; Malmsten and Lindman, 1992; Kwon et al., 2001) in F127 systems, as has the presence of cosolvents (Pandit and Mcintyre, 1997) and cell media components (Matthew et al., 2002). Kwon et al. (2001) studied the effects of alcohols and found that the alkyl chain length of added alcohols influenced the gelation temperature. In agreement with the findings of Malmsten and Lindman (1992) (who had previously studied the effects of salts on the gelation temperature), they proposed that this was due to disruption of the water structure around micelles and changes in polymer solubility. Furthermore, increasing the length of the alkyl chain decreases the hydrophilic nature of an alcohol molecule. *Para*-xylene is a moderately hydrophobic solute that has been found to decrease the gelation temperature of a Pluronic® F127 solution (Malmsten and Lindman, 1992). Other solutes that are hydrophobic and have been investigated include the drugs lidocaine and prilocaine in mixtures of Pluronic® F127 and F68 (Scherlund et al., 2000), and a series of *para*-hydroxybenzoate esters (Gilbert et al., 1987). The latter study also indicated that the solutes decreased the temperature at which the systems changed from liquid to gel according to the length of the alkyl chain, once again suggesting a correlation with solute hydrophobicity (Gilbert et al., 1987).

Other than the work of Malmsten and Lindman (1992), there have been few studies concerning the effects of higher molecular weight solutes and pharmaceuticals (MW > 200) on the internal structure of Pluronic® F127 aggregates. Once it is known that a drug–polymer system is stable, it is of primary importance to know the particle size and aggregation number in a micellar drug delivery system (Malmsten, 2002). Therefore, in order to better understand the effects that solubilized drugs may have on the micellar structure and gelation mechanism, we have carried out small-angle neutron scattering (SANS) experiments on F127 solutions and gels in the presence and absence of naproxen and indomethacin (anti-inflammatory drugs that are candidates for controlled delivery with Pluronic® gels). From these experiments, the spherical nature of the micelles (Wanka et al., 1994) can be confirmed and both the size and aggregation number of the micelles can be determined. In addition, we used dynamic light scattering (DLS) to measure the critical micelle concentration of F127 in water, in the absence and presence of naproxen and indomethacin. We have also investigated the effects of both drugs on the liquid-to-gel and gel-to-liquid transitions of Pluronic® F127 solutions using the tube inversion method (TIM).

Design of F127-based formulations requires knowledge of the solubility and partitioning behavior of drug molecules into copolymer micelles. This has traditionally been estimated using the partition coefficient (K) of the drug molecules, which is the ratio of the concentration of drug in a hydrophobic phase (such as octanol or lipids) to the concentration in a hydrophilic phase (such as water). Hydrophobicity is one of the most studied physicochemical properties of a drug, along with its electronic and steric properties (Patrick, 1995). It can be quantified by the partition coefficient and is a crucial indicator of the ease with which a drug will cross cell membranes and possibly how it will interact with receptors (Patrick, 1995). Furthermore, the partition coefficient is also used to give an indication of biological activity (Patrick, 1995). While octanol–water and lipid–water partition coefficients can provide good estimates of in vivo absorption, they do not provide accurate representations of how drug molecules disperse themselves over copolymer micelles, since the PPO cores of the micelles are somewhat hydrated and thus not strongly hydrophobic (Wanka et al., 1994). If a drug is to be delivered using F127, it is important to know the distribution of the drug in the system in order to predict several important parameters of performance, including release rate and estimated bioavailability. We have used an ultraviolet spectroscopy (UV) technique described by Lin and Kawashima (1985a) to measure both the solubilities and micelle–water partition coefficients (K_{mw}) of drugs in copolymer mi-

celles, and applied it to naproxen and indomethacin in F127 solutions. These experiments may help provide some insight into the strength of the hydrophobic interactions between the drug molecules and water, in these systems, as well as providing information useful for performance characterization. By understanding how the gelation properties of F127 micellar systems change in the presence of drugs, it may be possible to make better formulations of existing drugs. With information on the internal structure and properties of the micelles, such as size, aggregation number and critical micelle concentration, predictions of in vitro release profiles can be estimated for new potential candidate drugs that are in low supply.

2. Materials and methods

2.1. Materials

Pluronic® F127 was obtained from Sigma-Aldrich Co. and used without further purification. All solutions of F127 were made using the cold method described by Schmolka, whereby prescribed amounts of copolymer were added to water at ambient temperature, prior to dissolution at refrigerator temperature (∼4 °C) (Schmolka, 1972). Naproxen and indomethacin were also obtained from Sigma-Aldrich Co. and used without further purification. All solutions were made on a mass basis using nanopure water obtained from a Barnstead NANOpure® Infinity UF filtration unit. For the SANS experiments, deuterium oxide (99.9% D) from Cambridge Isotope Laboratories, Inc. was used in place of water. The solubility experiments utilized ethanol (from Pharmaco products, Inc.) that was 200 proof, absolute (dehydrated).

2.2. Determination of critical micelle concentration: dynamic light scattering

The critical micelle concentration was determined using dynamic light scattering. Eight samples of F127 in water at concentrations of between 0.1 wt.% (0.0778 mmol/dm^3) and 1 wt.% (0.778 mmol/dm^3) were made. To remove any dust that may have been present, the samples were filtered slowly through 0.45 μm Millex®-HV syringe driven filters (Millipore Corp.) into clean light scattering tubes. These tubes had been thoroughly washed with nanopure water, dried and cleaned with a Kensington Dust Blaster™ compressed gas duster before use. Light scattering experiments were carried out using a 514.5 nm Lexel 958 W Argon Ion Laser working at a constant power output of 200 mW. The light scattering tubes containing the filtered samples were placed into a decahydronaphthalene vat jacketed by a temperature-controlled water bath with a set point of 25 °C. All samples were allowed to equilibrate to the water bath temperature for at least 30 min in the BI 200SM Goniometer set up (Brookhaven Instruments Corp.) before any data collection was started. The Brookhaven Instruments photo multiplier detector tube (in photon counting mode) was kept at a fixed angle of 90° to the incident beam path, with a pinhole aperture size of 200 mm. Time-dependent intensity fluctuation data was collected from the instrument and correlated with a BI 9000AT digital correlator (Brookhaven Instruments Corp.) over a delay range of 25 ns to 100 ms (using 342 channels plus 4 extended channels). Analysis of the autocorrelation function obtained from the correlator in terms of particle size distribution was done numerically using a Non-Negatively Constrained Least Squares (Regularized CONTIN) method over a particle size range of 1.00–100 nm. All samples showed a small diameter population corresponding to unimers, and samples at higher concentrations also showed a micellar population of greater diameter. The lowest concentration at which this micellar population was observed was taken to be the critical micelle concentration. The experiments were repeated for solutions of F127 containing drug solutes at either 0.07 wt.% naproxen or 0.10 wt.% indomethacin in order to see if the drugs affected the critical micelle concentration. These concentrations both correspond to an equal molality of 3.215×10^{-6} mol drug/g water, which is the approximate solubility limit of indomethacin in the 13 wt.% copolymer (10.1 mmol/dm^3) stock solution used to make the samples.

2.3. Determination of micelle structure: small-angle neutron scattering

Samples of 2 wt.% (1.56 mmol/dm^3) and 16 wt.% (12.4 mmol/dm^3) Pluronic® F127 in D_2O were made with either no drug, 0.07 wt.% naproxen, or 0.10 wt.% indomethacin. Neutron scattering experiments on these samples were performed on the small-angle

diffractometer (SAD) at the Intense Pulsed Neutron Source at Argonne National Laboratory at 25 °C in quartz sample cells. Spectra were collected for up to 8.5 h each on the 2 wt.% samples in cells with a path length of 2.0 mm, and 1 h each on the 16 wt.% samples in cells with a path length of 1.0 mm. D_2O was used to quantify the solvent scattering, which was subsequently subtracted off. The incoherent scattering from each sample was estimated from the signal at high q and was also subtracted from the data. Data was obtained for $0.006\,Å^{-1} > q > 0.8\,Å^{-1}$, however, due to the large uncertainty at low and high values of q, SANS data is shown over a slightly smaller range (i.e. $0.007\,Å^{-1} > q > 0.3\,Å^{-1}$ for 2 wt.% solutions, and $0.01\,Å^{-1} > q > 0.6\,Å^{-1}$ for 16 wt.% solutions).

2.4. Determination of gel boundary: tube inversion

Tube inversion has been used previously by several groups (Li et al., 1997; Bentley et al., 1999; Kwon et al., 2001) to determine the gel boundary of copolymer solutions, and similar results for the gel boundary have been obtained using both TIM and rheology (Li et al., 1997). Sealed sample tubes containing F127 in water at concentrations of between 14 wt.% (10.9 mmol/dm^3) and 30 wt.% (23.3 mmol/dm^3) were placed into a controlled thermal environment (Fisher Scientific Isotemp 1016 Circulating Water bath). Using a temperature step of 1 °C, the samples were allowed to reach thermal equilibrium at each temperature between 5 and 100 °C. Other researchers have used equilibration periods of more than 10 min (Kwon et al., 2001). However, by measuring the temperature inside and outside for select sample tubes, it was found that samples could equilibrate thermally with the water bath in about 5–10 min. Thus, the water bath temperature was observed for all subsequent experiments. After achieving thermal equilibration at each temperature, the samples were tested by quick inversion of the sample tubes and visual observation for changes in flow behavior. The time that each sample spent outside the water bath during the testing period was kept at a minimum to prevent the ambient temperature from affecting it, and the testing method was kept consistent from sample to sample. Initially, at the lowest temperature, all samples behaved as liquids. The temperature at which all flow ceased to occur and the sample had set as a hard gel in the sample tube was taken to be the liquid-to-gel transition point. These points for all the samples were used to form the liquid-to-gel boundary. The temperature at which the gel in a sample tube then began to flow again as a freely flowing liquid was taken to be the gel-to-liquid transition point. These points for all the samples were used to form the gel-to-liquid boundary.

This method was repeated using samples that contained the same polymer concentrations but with either naproxen or indomethacin additionally present at concentrations of 0.07 and 0.10 wt.%, respectively. In addition, tube inversion was carried out on samples of 0.23 wt.% naproxen, which corresponds to its approximate solubility limit in the 13 wt.% copolymer (10.1 mmol/dm^3) stock solution used to make the samples. All gel boundary TIM experiments were repeated three times.

2.5. Determination of partition coefficients: UV spectroscopy

Micelle–water partition coefficients for naproxen and indomethacin in F127 solutions were calculated from UV measurements using an expression and procedure adapted from previous studies (Herries et al., 1964; Lin and Kawashima, 1985a). Since it is the micelle core that promotes solubilization of a hydrophobic solute, we assume that this region is a relatively hydrophobic phase. Note that the core will contain both PPO and water; however, this does not affect our analysis. The micelle PEO corona and aqueous solvent together comprise a relatively hydrophilic phase. When the activity coefficients of the solute in both phases are assumed to be 1 (as in the case of a dilute system), the partition coefficient, K, is given by the ratio of the concentration of solute in each phase (Harris, 1991):

$$K = \frac{[X]_{\text{core}}}{[X]_{\text{aq}}} \tag{1}$$

where $[X]_{\text{core}}$ (the concentration of solute in the hydrophobic phase or micellar cores) can be written as $n_{\text{core}}/\beta V$ and $[X]_{\text{aq}}$ (the concentration of solute in the hydrophilic phase, i.e. the aqueous solvent and micellar coronas) can be written as $n_{\text{aq}}/(1-\beta)V$; with n_{core} and n_{aq} being the number of moles of solute in the hydrophobic micelle cores and hydrophilic aqueous regions, respectively; β being the volume fraction occupied by micelle cores in the system; and V being

the overall volume of the system. Substituting and rearranging, we obtain an expression for n_{core}:

$$n_{core} = \frac{n_{aq} K\beta}{1-\beta} \quad (2)$$

We can express the fraction of solute present in the hydrophilic phase, α, as

$$\alpha = \frac{n_{aq}}{n_{aq} + n_{core}} = \frac{1}{1 + K\beta/(1-\beta)} \quad (3)$$

which can be rearranged to give the following:

$$\frac{n_{aq}}{1-\beta} = \frac{n_{aq} + n_{core}}{K\beta + 1 - \beta} \quad (4)$$

If the total number of moles of solute present is increased until the system is saturated, then Eq. (4) would still apply, and the saturation concentration of the solute in the absence of micelle cores (C^0_{sat}) and the saturation concentration of solute in the presence of micelle cores (C_{sat}) could be written as

$$C^0_{sat} = \frac{n_{aq}}{(1-\beta)V} \quad (5)$$

$$C_{sat} = \frac{n_{aq} + n_{core}}{V} \quad (6)$$

The volume fraction of the system occupied by micelle cores (β) can be written using R_1 (the radius of a micelle core), C_{surf} (the concentration of surfactant molecules), C_{cmc} (the critical micelle concentration), N_{agg} (the aggregation number of a micelle), and N_{AV} (Avogadro's number):

$$\beta = \frac{4}{3}\pi R_1^3 (C_{surf} - C_{cmc}) \frac{N_{AV}}{N_{agg}} \quad (7)$$

Substituting Eqs. (5)–(7) into Eq. (4) and rearranging, the following expression, an expansion of that derived by Herries et al. (1964), is obtained:

$$\frac{C_{sat}}{C^0_{sat}} = 1 + (K-1)\left(\frac{4}{3}\pi R_1^3 (C_{surf} - C_{cmc}) \frac{N_{AV}}{N_{agg}}\right) \quad (8)$$

If it is assumed that the solubility in a system without micellar PPO cores (i.e. solvent and PEO coronas present) is the same as the solubility in just the solvent, then C^0_{sat} can be measured from the saturation concentration (solubility) in the absence of surfactant micelles; and C_{sat} can be obtained by measuring the saturation concentration in the presence of micelles at various surfactant concentrations above the critical micelle concentration. We measured the solubility of naproxen and indomethacin in PEO-13K and water, and found that the concentration did not increase; in fact it decreased slightly. However, due to the difficulty of accurately representing the PEO corona regions of a Pluronic F127 micelle with another PEO polymer, and the extra uncertainties introduced by using such a measurement for C^0_{sat}, we believe it is more accurate to use the solubility in water as an approximation. Eq. (8) then yields a linear relationship between C_{sat}/C^0_{sat} and $(C_{surf} - C_{cmc})$ from which the approximate partition coefficient, K can be extracted from the slope. With water as the aqueous solvent, this becomes K_{mw}, the "apparent" micelle–water partition coefficient.

Our solubility measurements were carried out using ultraviolet spectroscopy on a μQuant Universal Microplate Spectrophotometer (Bio-Tek Instruments®, Inc.). For both solutes, the wavelength of maximum absorption, λ_{max}, was found to be 229 nm, and hence all quantitative readings were carried out at this value. Standard solutions of naproxen (up to 0.001 wt.%) and indomethacin (up to 0.01 wt.%) in 3:2 ethanol/water with appropriate amounts of Pluronic® F127 were prepared to obtain linear calibration lines. A solvent containing ethanol was used in order to access concentrations higher than the solubility point of the drug in water alone. Saturation concentration (solubility) measurements were then made by dissolving an excess amount of solute in either water or F127 solutions (between 1 wt.% (0.778 mmol/dm^3) and 8 wt.% (6.22 mmol/dm^3)). These solutions were allowed to equilibrate at 25 °C before being filtered very slowly using a 0.45 μm Millex®-HV syringe driven filter (Millipore Corp.). The filtrate obtained was weighed and an appropriate amount of ethanol was added to obtain a 3:2 ethanol/water ratio in all samples. Note that the addition of ethanol did not change the measured value of C^0_{sat} (or C_{sat} for an F127 solution), since the amount of drug present in the solution remained the same. The solutions were diluted by known factors to give quantitative UV responses within the linear region of the appropriate calibration lines. The mass of solute in each sample was determined and C^0_{sat} (or C_{sat}) was calculated. The densities of all solutions for these calculations were assumed to be equal to the density of water, and solute masses were assumed to be negligible in calculating

the amount of ethanol to be added to the filtrates. The results were plotted to obtain the partition coefficients for naproxen and indomethacin from the slopes. Note that since the path lengths for the raw data obtained from the UV spectrometer varied from well to well, the data was corrected by a calculated path length for each well (obtained by measuring the absorbance at 900 and 977 nm). All experimentation and sample preparation was carried out at 25 °C, and each UV measurement was repeated four times.

3. Results

From our dynamic light scattering studies, the critical micelle concentration of each of the three systems was estimated. All samples showed a population with an average hydrodynamic radius of between 0.50 and 0.69 nm, corresponding to single chains of F127. Samples at higher concentrations also showed a population with an average hydrodynamic radius of between 3.9 and 13 nm, corresponding to micelles of F127. The values of the critical micelle concentration obtained from the dynamic light scattering measurements are given in Table 1.

Table 1
Critical micelle concentration from DLS data, and core-corona form factor model fit parameters from SANS data of Pluronic® F127 micelles with no drug present and either naproxen (0.07 wt.%) or indomethacin (0.10 wt.%) present (i.e. at a molality of 3.215×10^{-6} mol/g water)

System	No drug	Naproxen	Indomethacin
C_{cmc} (wt.%)	0.26 ± 0.03	0.33 ± 0.04	0.24 ± 0.02
C_{cmc} (mmol/dm^3)	0.20 ± 0.02	0.26 ± 0.03	0.19 ± 0.02
N_{agg}	88.6 ± 1.5	51.9 ± 0.8	50.6 ± 0.6
R_1 (nm)	4.60 ± 0.22	3.93 ± 0.19	3.92 ± 0.14
R_2 (nm)	7.09 ± 0.38	6.04 ± 0.29	6.01 ± 0.21
σ (%)	10.4 ± 0.1	9.8 ± 0.1	9.0 ± 0.1
$N \times 10^{16}$ (cm^{-3})	1.02 ± 0.02	1.66 ± 0.03	1.80 ± 0.02

Errors in C_{cmc} are based on the increments in concentration for the samples; errors in N_{agg}, R_1, R_2, σ, and N are based on the uncertainty in the parameters, as obtained from the residuals of the fits.

The results from the small-angle neutron scattering experiments on 2 wt.% F127 (1.56 mmol/dm^3) solutions are shown in Fig. 1. The data from these solutions

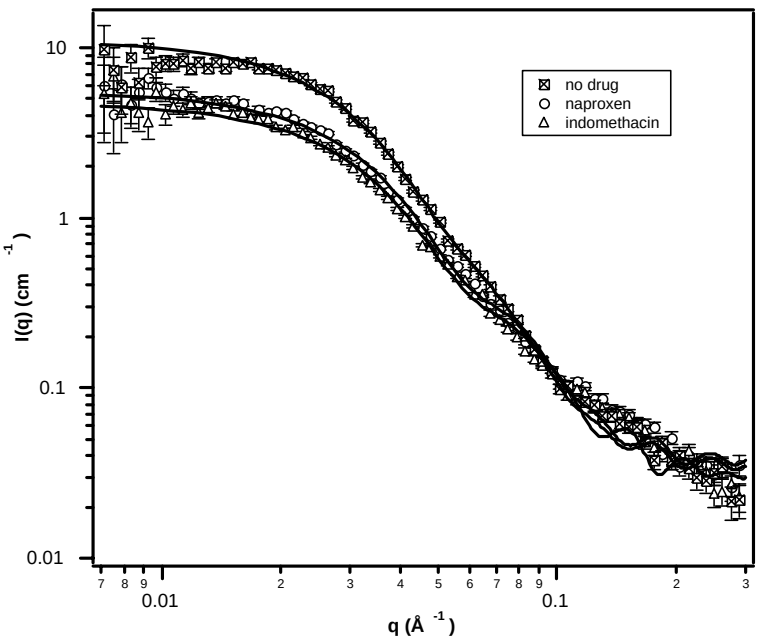

Fig. 1. SANS results from 2 wt.% Pluronic® F127 (1.56 mmol/dm^3) micelles with no drug present and either naproxen (0.07 wt.%) or indomethacin (0.10 wt.%) present at a molality of 3.215×10^{-6} mol/g water (same molality as gel boundary experiments). The data with no drug present have been plotted with crossed open squares for clarity. Solid lines indicate fits to the data using the core-corona form factor model with polydisperse corona radius (Eqs. (10)–(13)).

were fitted to the spherical core-corona model proposed by Goldmints et al. (1999) which assumes that the intensity will comprise scattering from a spherical core and scattering from a surrounding spherical corona. This model has essentially three parameters: the radius of the micelle core, R_1; the radius of the micelle corona, R_2; and the micelle aggregation number, N_{agg}. The equations for the entire model are:

$$I(q) = N\,(\Delta\rho)^2\,P(q)S(q) \tag{9}$$

$$(\Delta\rho)^2 P(q) = \left[\frac{4\pi}{3}R_1^3(\rho_1-\rho_2)\frac{3j_1(qR_1)}{qR_1} + \frac{4\pi}{3}R_2^3(\rho_2-\rho_S)\frac{3j_1(qR_2)}{qR_2}\right]^2 \tag{10}$$

$$j_1(x) = \frac{\sin x - x\cos x}{x^2} \tag{11}$$

where $I(q)$ is the measured scattering intensity, N is the number density of scattering centers (micelles and monomers), $(\Delta\rho)^2P(q)$ is the combined contrast and intraparticle form factor (Goldmints et al., 1999), $S(q)$ is the interparticle structure factor, and ρ_1, ρ_2, and ρ_S are the scattering length densities of the core, corona and solvent, respectively. N can be calculated from N_{agg} and the concentration of copolymer (C_{surf}) using (Goldmints et al., 1999):

$$N = \frac{(C_{surf} - C_{cmc})N_{AV}}{N_{agg}} \tag{12}$$

Since polydispersity tends to "smear" features in the SANS pattern, we can also add polydispersity in the core and corona size in our model. However, we do not have enough resolution in our spectra to distinguish between polydispersity in the core size or the corona size. Thus, to keep the number of fitted parameters reasonable, we only use a single polydispersity, σ, which is the half-width of a gaussian distribution about R_2. The scattered intensity is then obtained by integrating this distribution over all positive values:

$$I(q) = N\left(\int_0^\infty \frac{1}{\sigma\sqrt{2\pi}}e^{-(r-R_2)^2/2\sigma^2}(\Delta\rho)^2P(q)\,dr\right) \times S(q) \tag{13}$$

In order to fit our data to the model, we have assumed that the micellar cores are comprised of only PPO and D_2O, and the coronas are comprised of only PEO and D_2O, with ρ_1 and ρ_2 weighted by the amount of solvent in the core and corona, respectively. We have also used the values for C_{cmc} determined from dynamic light scattering. The model fits are shown as solid lines on Fig. 1, and the resulting values of N_{agg}, R_1, R_2, σ, and N for the three systems are given in Table 1. In fitting our data at 2 wt.% copolymer, $S(q)$ has been assumed to be unity due to the low polymer concentration, and the integration was carried out numerically using the trapezoidal rule. The results from the SANS experiments on 16 wt.% F127 (12.4 mmol/dm^3) solutions are shown in Fig. 2. These data were not fitted to a model owing to the fact that at this high concentration, such a model would require the assumption of interparticle interactions. Instead, we choose to qualitatively discuss the effects seen in the scattering spectra.

Through tube inversion experiments, the liquid-to-gel and gel-to-liquid boundaries of F127 in water with and without naproxen and indomethacin were completely characterized. The effect of the addition of naproxen at two different concentrations is shown in Fig. 3, and a comparison of the effect of naproxen and indomethacin at the same molality (i.e. equal solute/solvent ratio) is shown in Fig. 4. Thermodynamic quantities associated with gel formation were calculated from the liquid-to-gel boundary data shown in Fig. 4. The standard Gibbs free energy change of gelation (ΔG°_{gel}), standard enthalpy change of gelation (ΔH°_{gel}), and standard entropy change of gelation (ΔS°_{gel}) were calculated using (Yu et al., 1992):

$$\Delta G^\circ_{gel} = RT_{gel}\ln\left(\frac{C_{gel}}{N_{agg}}\right) \tag{14}$$

$$\Delta H^\circ_{gel} = R\left[\frac{d\left(\ln[C_{gel}/N_{agg}]\right)}{d(1/T_{gel})}\right] \tag{15}$$

$$\Delta S^\circ_{gel} = \frac{\Delta H^\circ_{gel} - \Delta G^\circ_{gel}}{T_{gel}} \tag{16}$$

where R is the molar gas constant, T_{gel} is the temperature at which the liquid-to-gel transition occurs (set at 298 K to obtain the thermodynamic quantities at the standard state), and C_{gel} is the concentration of surfactant molecules (in molar units) that produces a liquid-to-gel transition at this temperature. The value of C_{gel} is estimated from the liquid-to-gel boundary data of Fig. 4, and ΔH°_{gel} is obtained from the slope

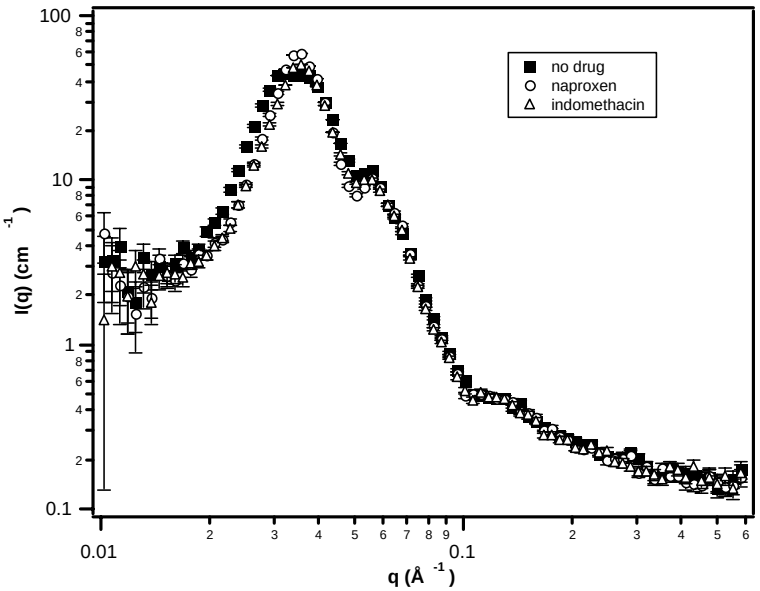

Fig. 2. SANS results from 16 wt.% Pluronic® F127 (12.4 mmol/dm^3) micelles with no drug present and either naproxen (0.07 wt.%) or indomethacin (0.10 wt.%) present at a molality of 3.215×10^{-6} mol/g water (i.e. same molality as gel boundary experiments).

of a van't Hoff plot (the derivative shown in Eq. (15)). The values of N_{agg} used in these calculations were taken from the SANS data fits. The calculated thermodynamic quantities are given in Table 2.

From our ultraviolet spectroscopy experiments, the solubilities of naproxen and indomethacin in water were calculated to be 0.0287 ± 0.0005 wt.% and 0.0146 ± 0.0004 wt.%, respectively. The solubilities of each drug in the presence of various concentrations of F127 are listed in Table 3. Increasing the copolymer concentration caused the solubility of naproxen to increase almost linearly up to 8 wt.% copolymer (6.22 mmol/dm^3), where the solubility was approximately 6.1 times greater than in water alone. Indomethacin solubility increased almost linearly by approximately 8.3 times with the addition of copolymer up to 8 wt.%. The solubility data were normalized and plotted against the departure of the copolymer concentration from the critical micelle concentration, according to Eq. (8). The results are shown in Fig. 5. The partition coefficients for naproxen and indomethacin were calculated from the slopes of this plot. In generating the plot, C_{cmc} was taken to be the value measured from the DLS experiments for each system; in calculating the partition coefficients, the micelle cores were assumed to be monodisperse spheres with R_1 and N_{agg} equal to values obtained from the SANS data fits (Table 1). The partition coefficient of naproxen was found to be 355 ± 64, and for indomethacin, 474 ± 33. The values of K_{mw} and $\log(K_{mw})$ for the two drugs are shown in Table 3.

Table 2
Standard Gibbs free energy, enthalpy and entropy changes of Pluronic® F127 gel formation from TIM data with no drug present and either naproxen (0.07 wt.%) or indomethacin (0.10 wt.%) present (i.e. at a molality of 3.215×10^{-6} mol/g water)

System	No drug	Naproxen	Indomethacin
ΔG°_{gel} (J/mol)	−21785 ± 37	−20577 ± 17	−20701 ± 30
ΔH°_{gel} (J/mol)	29703 ± 3001	30659 ± 2517	27992 ± 2172
ΔS°_{gel} (J/mol K)	173 ± 10	172 ± 8	163 ± 7

The errors on ΔG°_{gel} and ΔS°_{gel} are based on the uncertainty in the gelation temperature readings, and the error on ΔH°_{gel} is based on the error of the slope from the van't Hoff plot.

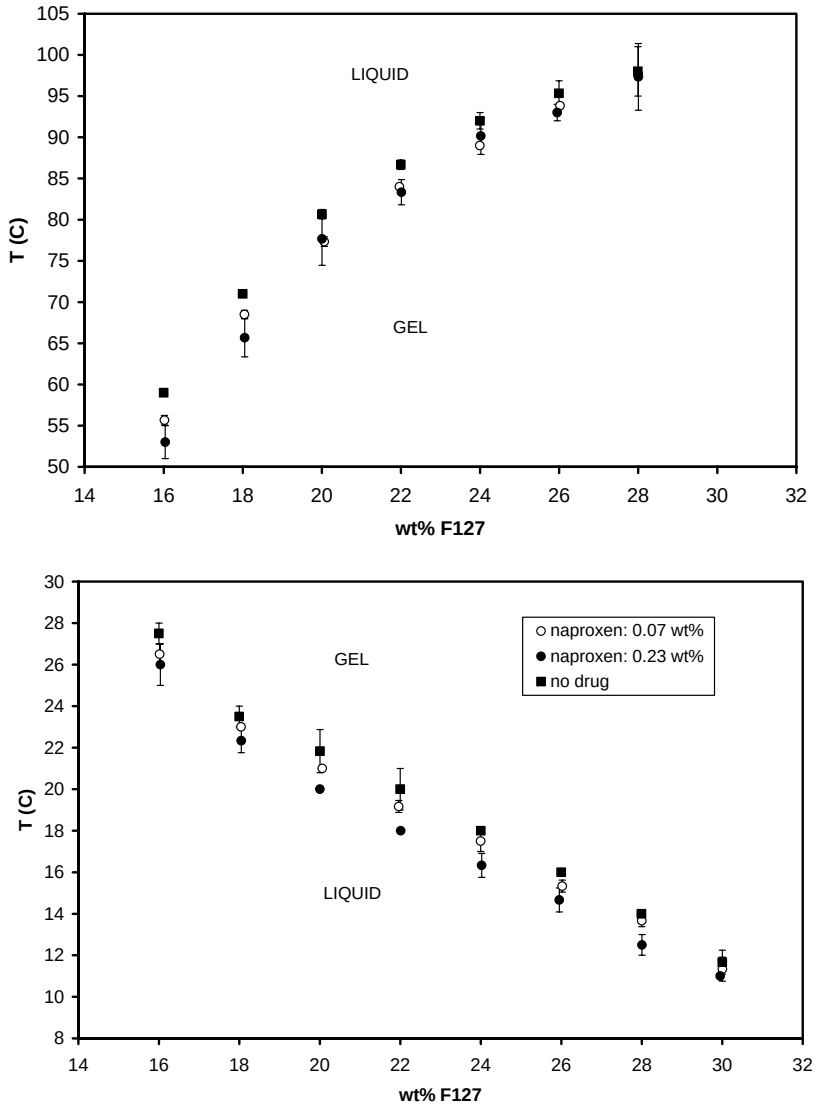

Fig. 3. Liquid-to-gel (bottom) and gel-to-liquid (top) boundaries of Pluronic® F127 in water with no drug present and naproxen present at 0.07 and 0.23 wt.%. Error bars represent standard deviations from three repeat experiments.

4. Discussion

4.1. Critical micelle concentration and drug ionization

The observations from dynamic light scattering studies show a value for F127 in water to be about 0.26 ± 0.03 wt.% (0.20 ± 0.02 mmol/dm^3), which is of the same order as previously reported values by others. Our value is somewhat close to the value of 0.12% (w/v) reported by Wanka et al. (1994), but is considerably lower than 0.7% (w/v) as reported by Alexandridis et al. (1994), and 2 wt.% as reported by Desai et al. (2001). The critical micelle concentration appears to increase slightly to 0.33 ± 0.04 wt.% (0.26 ± 0.03 mmol/dm^3) in the presence of naproxen and essentially remains the same at 0.24 ± 0.02 wt.% (0.19 ± 0.02 mmol/dm^3) in the presence of indomethacin.

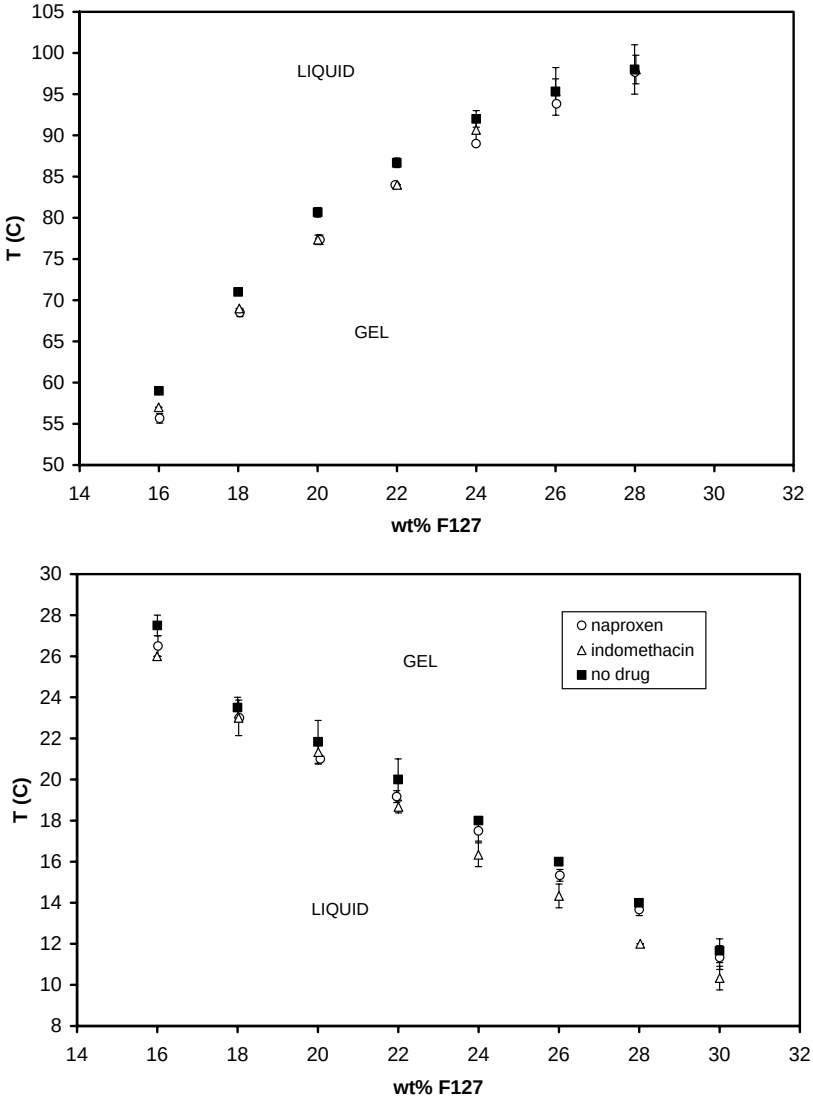

Fig. 4. Liquid-to-gel (bottom) and gel-to-liquid (top) boundaries of Pluronic® F127 with no drug present and either naproxen (0.07 wt.%) or indomethacin (0.10 wt.%) present (i.e. at a molality of 3.215×10^{-6} mol/g water). Error bars represent standard deviations from three repeat experiments.

With such a large variation in reported findings and considering the size of the relative errors on our measurements, these small changes are likely not significant.

It is interesting to note that both naproxen and indomethacin have an acidic character with p*K*a values of 4.2 (Suh and Jun, 1996) and 4.5 (Budavari, 1996), respectively. Therefore, when placed in water, some degree of ionization may be expected, depending on the concentration. Such ionization effects could have potentially affected C_{cmc} and the micelle structure. To test for this, we tested the pH of our solutions and found them to be neutral, including the samples that were used for SANS, DLS, and solubility measurements. This indicates that the effect of ionization is probably not a signif-

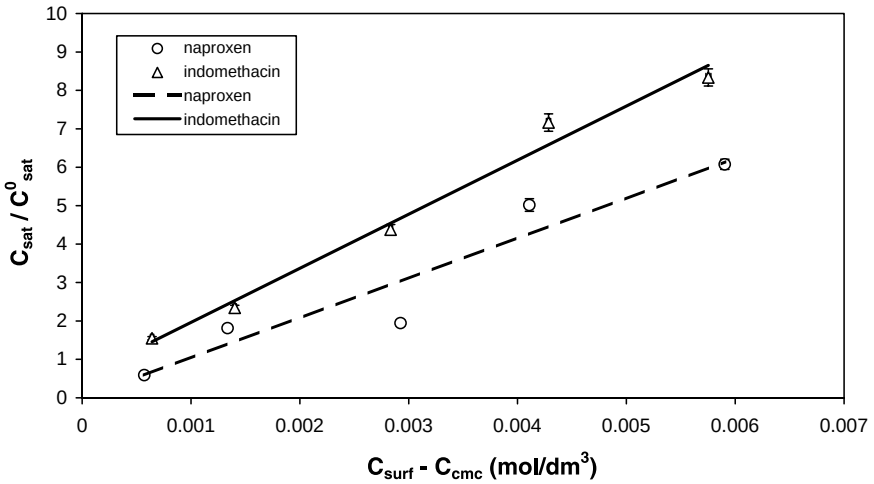

Fig. 5. Plot of C_{sat}/C^0_{sat} against $(C_{surf} - C_{cmc})$ for anti-inflammatory agents naproxen and indomethacin. Dashed and solid lines are linear fits with R^2 values of 0.911 and 0.986, respectively. Error bars represent standard deviations from four repeated runs.

icant problem at the low concentrations used in our studies.

4.2. SANS studies

The scattering data from 2 wt.% F127 (1.56 mmol/dm^3) solutions (Fig. 1) show features that are characteristic of a spherical object. Micelles of F127 have been found to be spherical up to 20 wt.% (Mortensen and Talmon, 1995; Lam et al., 1999). Evidence for non-spherical micelles have only been shown at temperatures greater than about 65 °C (Mortensen and Talmon, 1995; Lam et al., 1999), so our analysis is not affected. From our results the scattering features do not seem to change in the presence of either naproxen or indomethacin. However, there is a decrease in the scattering intensity at low values of q, as compared to data from samples with no drug molecules present. These observations suggest that the drug molecules do not affect the shape of F127 micelles, instead affecting either the size or aggregation number. From Table 1, we see that the core-corona form factor model with a polydisperse corona radius yields a micelle core radius of 4.60 nm for F127 in water, which agrees well with a previously reported core size of 4.4 nm (Prudhomme et al., 1996). The corresponding corona radius obtained from the data is 7.09 nm with a polydispersity of 10.4%. This micelle size is a little larger than 5.7 nm, which is the F127 micelle size reported previously (Wanka et al., 1994). However, our findings are reasonable, considering the magnitude of the polydispersity, and the fact that the corona radius we observe from SANS is generally smaller than the hydrodynamic radii observed from this and other dynamic light scattering studies, 11–15 nm (Yu et al., 1992; Prudhomme et al., 1996; Desai et al., 2001). The aggregation number we obtain for F127 in water is approximately 89, which is higher than expected. Previous studies have reported aggregation numbers

Table 3
Solubilities of the anti-inflammatory agents naproxen and indomethacin in various concentrations of Pluronic® F127 (as measured by UV spectroscopy), and the calculated micelle–water partition coefficients and their logarithms for each drug

F127 concentration		Solubility of naproxen (wt.%)	Solubility of indomethacin (wt.%)
wt.%	mmol/dm^3		
0	0	0.0287 ± 0.0005	0.0146 ± 0.0004
1	0.778	0.0169 ± 0.0003	0.0226 ± 0.0003
2	1.56	0.0521 ± 0.0008	0.0342 ± 0.0004
4	3.11	0.0559 ± 0.0019	0.0640 ± 0.0012
6	4.67	0.1441 ± 0.0039	0.1048 ± 0.0020
8	6.22	0.1746 ± 0.0022	0.1219 ± 0.0010
K_{mw}		355 ± 64	474 ± 33
log(K_{mw})		2.55 ± 0.08	2.68 ± 0.03

from 37 (Wanka et al., 1994) to 72 (Desai et al., 2001), with the variability in findings to be most likely due to the differences in experimental methods (Yu et al., 1992). With the addition of the anti-inflammatory drugs, the cores decrease in size by about 0.7 nm and the coronas of the micelles decrease in size by about 1.1 nm. More significantly, the aggregation number of the system decreases by almost a factor of 2, to 52 in the case of naproxen, and 51 in the case of indomethacin. This indicates that with the drug solutes present, fewer surfactant molecules are involved in the formation of a single micelle. Since the concentration of Pluronic® F127 is above the critical micelle concentration, the remaining surfactant molecules are likely involved in the formation of additional micelles. This is confirmed by the corresponding increase in N that is observed in the presence of both drugs. We note that the largest change brought about by the presence of either drug is in the aggregation number.

It is important to know the size and aggregation numbers of F127 micelles, since larger micelles have been found to be more efficient at solubilizing drugs (Malmsten, 2002). The capacity of micelles to solubilize a drug molecule is dependent upon several factors, including molecular weight, composition and micellar structure (Malmsten, 2002). For efficient solubilization, the aggregation number should be high and the micellar core needs to be sufficiently large and hydrophobic (Malmsten, 2002).

The data obtained from the experiments on 16 wt.% (12.4 mmol/dm^3) samples (Fig. 2) show a very distinct peak, with smaller peaks at higher values of q. At this concentration, the primary peak corresponds to the intermicellar spacing, analogous to the Bragg spacing of a lattice. Scattering data from all samples are essentially the same and consistent with cubic packing of micelles in the gel state (Prudhomme et al., 1996). This suggests that gelation may proceed by the same mechanism with and without drugs present, and the final structure is essentially the same. An additional feature of our results is the subtle difference in the peak heights and widths when the anti-inflammatory drugs are present. The primary peak is more distinct and narrower for the samples containing naproxen and indomethacin, indicating that the drug-loaded systems are slightly more structured or ordered. The increased order may be due to a higher number density of micelles in drug-loaded samples, as indicated by our dilute data. This greater degree of order may also allow for gelation at lower temperatures or concentrations in formulations containing naproxen and indomethacin.

4.3. Gelation transitions

None of the systems formed gels below 16 wt.% copolymer (12.4 mmol/dm^3) over the entire range of temperatures. This result is in agreement with previous findings that F127 solutions will only show gel phases above a certain copolymer concentration (Gilbert et al., 1987; Malmsten and Lindman, 1992; Kwon et al., 2001). These copolymer concentrations have generally been found to be about 15 wt.% (11.7 mmol/dm^3), which is close to our result. Above 16 wt.%, increasing the concentration decreases the temperature of the liquid-to-gel transition and increases the temperature of the gel-to-liquid transition, as can be seen from the shape of the measured boundaries.

The effects of the drug molecules on the gelation boundaries are small but significant, as can be seen from Figs. 3 and 4. Both naproxen and indomethacin shift the liquid-to-gel and gel-to-liquid boundaries to lower temperatures. In general, the phase boundaries seem to shift by approximately 1.5 °C, with differences as large as 5 °C for some points at the higher concentration of naproxen. The somewhat small magnitudes for all the differences seen may be a result of the low concentrations of drugs used. Due to the poor solubility of indomethacin in the 13 wt.% F127 (10.1 mmol/dm^3) stock solution used to make the samples, the drug concentrations used in these experiments were severely limited. Additionally, there seems to be a slightly greater effect from indomethacin when compared at the same molality (Fig. 4). This small difference may be due to the larger partition coefficient for indomethacin in F127. However, for certain F127 concentrations, the difference between the gel boundary for naproxen and indomethacin-loaded systems is not significant, which again may be due to the low drug concentrations used. Finally, the effect of increasing drug concentration is to shift the liquid-to-gel boundary to lower temperatures, as can be seen on Fig. 3. At a higher molality, there are more drug molecules present per water molecule, so the total hydrophobic interactions could be greater, causing larger changes in the micellar structure.

The thermodynamic quantities associated with gel formation, given in Table 2, support the observation that there may indeed be a subtle difference in the liquid-to-gel boundaries when drug molecules are present in the system. In both the absence and presence of anti-inflammatory drugs, the standard Gibbs free energy change of gelation is negative. This indicates that at the liquid-to-gel transition temperature, all the systems favor the gel state as opposed to the liquid state. From the calculation, the presence of drug solutes results in a significant difference in the standard Gibbs free energy change of gelation. The calculated standard enthalpy changes of gelation are of the same order as those reported by other groups (Yu et al., 1992), and are much smaller than the enthalpy change of micellization (∼2,350,000 J/mol) (Cabana et al., 1997). Note that the values are similar (within the calculated uncertainty) in all three systems. The standard entropy changes of gelation are positive and do not seem to differ significantly with the drugs present when compared to the sizes of their calculated uncertainties.

4.4. Solubility and partitioning

Our solubility results correspond with the findings of Suh and Jun (1996) who showed a linear increase in the solubility of naproxen up to 8 wt.% F127 (6.22 mmol/dm^3) in water/HCl mixtures. The solubility of indomethacin has also been shown to increase in a linear fashion in other Pluronics® (Lin and Kawashima, 1985a). Our findings confirm that hydrophobic drugs that are difficult to dissolve in aqueous solvents can be solubilized to a much greater extent through the addition of PEO–PPO–PEO copolymers. Also, the dosage of a drug loaded into a Pluronic® system could be tuned to a specific concentration by simply adjusting the copolymer concentration and then filtering.

The partition coefficients of naproxen and indomethacin that we have calculated are quite different to those measured using other techniques and surfactant systems. The partition coefficient of naproxen in F127 has been estimated previously as 1814 at 25 °C (Suh and Jun, 1996), which is higher than our measured value. However, this previous estimate was based on extrapolation of data taken at low F127 concentrations to 100% F127, in order to estimate the concentration of drug in the micelle core. The method we have used here is a more direct measurement, which we believe to be more accurate. Lasonder and Weringa (1990) reported partition coefficients in egg phosphotidyl choline (EPC) vesicles of 14.1 for naproxen and 251 for indomethacin, in comparison to our values of 355 ± 64 and 474 ± 33, respectively. The contrasting difference in absolute values can be attributed to the different surfactants used. In EPC vesicles, the hydrophobic phase provided by the lipid surfactant molecules is a very different hydrophobic environment to that provided by the PPO segments of F127. This results in a different affinity for hydrophobic drugs. The relatively high K_{mw} values that we report show that the drugs favor the micellar cores of F127, and indicate that F127 may be a better choice for drug-loading than other lipid delivery systems. In addition, an accurate partition coefficient in F127 is much more useful for the development of a pharmaceutical anti-inflammatory F127 formulation. We also observe a difference between the partition coefficients of the two anti-inflammatory agents, with indomethacin slightly more hydrophobic (i.e. slightly higher calculated value of K_{mw}), which is consistent with its lower solubility in water. This may be the reason for the slightly greater effects that are apparent for indomethacin from both the TIM and SANS observations. Furthermore, note that we have normalized the solubility measurements against the solubility in water, rather than the solubility in an aqueous phase corresponding to the micellar PEO coronas and water; thus, an intercept of less than unity on Fig. 5 is not surprising.

Knowledge of the partition coefficient of a drug in F127 is important for characterizing the performance of a potential formulation. The partition coefficient indicates the equilibrium loading of the drug and sets up the initial concentration gradient that will drive drug release. The release of drugs from micellar liquid crystalline systems has been reported to depend on the hydrophobicity (Malmsten, 2002). The drug release rate can decrease with an increasing hydrophobicity, or the relationship between drug partitioning and drug release can be more complex, making it important to know the partition coefficient (Malmsten, 2002). When new drugs are discovered, they are often available only in very small quantities making it difficult to carry out extensive

investigations into the properties of the compound. Often, important parameters can be estimated using known properties. For example, biological activity is often found to increase with increasing hydrophobicity, due to hydrophobic barriers (e.g. cell membranes) and hydrophobic receptor and enzyme binding sites (Patrick, 1995). Biological activity can increase parabolically up to a maximum at an optimal partition coefficient (Patrick, 1995). Provided it is the only influencing factor, it may be possible to predict properties such as biological activity for structurally similar compounds from accurate measurements of the partition coefficient of an existing compound. Furthermore, accurate measurement of the partition coefficient of drugs in F127 solutions may allow the calculation of substituent hydrophobicity constants (Patrick, 1995) that can be used to estimate the performance and properties of newly discovered analogue drugs that are in low supply.

4.5. Mechanism of gel formation

The mechanism of gel formation in F127 has been discussed by others and is still a topic under debate in the literature. Physically, gel formation must be related to micellar packing and volume fraction. As the temperature is increased above the critical micelle temperature, micelles are formed, inevitably increasing the volume fraction occupied by the aggregates. A further increase in the temperature has been shown to increase the micellar volume fraction until it reaches a critical value for cubic close packing (Song et al., 2000). Researchers have attributed gelation to the dehydration of PPO groups in the micelle core (Wanka et al., 1994), a change in the micellar volume (Song et al., 2000), or a decrease in the critical micelle concentration and increase in the aggregation number (Bohorquez et al., 1999). At higher temperatures, a gel-to-liquid transition is observed. The reason for the presence of this transition has been proposed to be due to the unfavorable water–PEO interaction at higher temperatures, resulting in the dehydration and shrinkage of micelle coronas (Song et al., 2000). This would effectively decrease the micellar volume and reduce the total volume fraction to below the critical value. Song et al. (2000) observed this drop in the micelle volume fraction below the critical value at higher temperatures corresponding to the gel-to-liquid boundary.

From our TIM results, we have seen that the addition of hydrophobic drug molecules to a solution of F127 micelles shifts the liquid-to-gel boundary to lower temperatures. The DLS measurements of the critical micelle concentration did not show large changes due to the presence of the drugs. However, our SANS studies showed that the drug solutes caused a more significant decrease in the aggregation number and an increase in the number density of micelles. As a result, the total micellar volume fraction is higher in a drug-loaded system than a neat F127 system at the same temperature and F127 concentration. The mechanism for gelation is the same in the presence of naproxen and indomethacin (i.e. by cubic micellar packing at a critical volume fraction); however, it can occur at a lower temperature. This accounts for the lower liquid-to-gel boundary that we have observed from TIM measurements, and the increased order that can be seen from the 16 wt.% F127 (12.4 mmol/dm^3) SANS data.

4.6. Impact on anti-inflammatory formulations

Indomethacin is a non-steroidal anti-inflammatory and anti-pyretic drug that has been used extensively for various inflammatory diseases (Miyazaki et al., 1995). However, its clinical usefulness as an orally administered drug is restricted severely by serious systemic side effects and gastric irritation, e.g. disturbance, ulceration and bleeding (Lin and Kawashima, 1985b; Miyazaki et al., 1995). Administration directly onto the inflamed site offers the advantage of delivering the drug directly, bypassing these side effects and increasing local drug concentrations (Miyazaki et al., 1995). Furthermore, sustained release would allow desirable plasma concentrations to be achieved (Miyazaki et al., 1986).

Naproxen is a non-steroidal anti-inflammatory drug used for the treatment of both rheumatic and non-rheumatic inflammatory conditions (Panderi and Parissi-Poulou, 1994). The anti-inflammatory effects are thought to be due to cyclo-oxygenase inhibition and consequent decrease in prostaglandin concentration (Panderi and Parissi-Poulou, 1994). Naproxen is generally administered orally or rectally, upon which it is completely absorbed. Administration of naproxen generally suffers from the problem of high renal clearance (95% recovery in urine) and hydrolysis;

70% of the drug is excreted as unchanged naproxen and the remainder is metabolized by hepatic microsomal oxidation into an inactive metabolite (Panderi and Parissi-Poulou, 1994). Therefore, the protection of naproxen from this clearance effect by Pluronic® micelles could make it a more effective treatment without the need for higher doses.

Pluronics® are suitable for the delivery of drugs due to their relatively low toxicity (F127 was reported to be the least toxic of commercially available copolymers) and ability to form clear gels in aqueous solvents at body temperature (Miyazaki et al., 1986). Pluronic® gels find applications for drug delivery in the skin, nose, eye, rectum and gastrointestinal tract (including esophagus) (Miyazaki et al., 1986). As rectal enemas, they find no practical difficulty in administration, and as topical agents they provide several advantages over traditional ointments, including ease of application, cosmetic acceptability (e.g. water-washability) and good drug release characteristics (Miyazaki et al., 1986). The suitability of Pluronic® gels as a vehicle for indomethacin administration has already been previously investigated (Miyazaki et al., 1986). In fact, indomethacin topical solutions were found to be superior to ointments for treating rheumatism (Miyazaki et al., 1986). The apparent extent of bioavailability was found to be the same in Pluronic® gels and commercial suppositories of indomethacin, however, Pluronic® F127 was shown to be superior by eliminating the high initial peak plasma level associated with suppositories (Miyazaki et al., 1986). This peak has been correlated with the frequency and severity of nervous system side effects (Alvan et al., 1975; Bechgaard et al., 1982). The release characteristics of Pluronic formulations have been found to change with temperature within the body temperature range (Miyazaki et al., 1986). Also, variation of the initial drug concentration has been found to affect the drug release rate. As the drug concentration increases, the release rate has been found to increase (Miyazaki et al., 1986). In a Pluronic® formulation, the extramicellar concentration of the drug cannot be controlled, however, the initial intramicellar drug concentration is dependent upon partitioning of the drugs into the micellar cores. From our results, it is clear that both naproxen and indomethacin partition strongly into the micellar cores. Using Eq. (3), the mole fraction of drug present in the micellar cores can be calculated for a typical formulation of F127, using the data that we have obtained from our SANS, UV and DLS experiments. For a 20 wt.% F127 (15.6 mmol/dm^3) formulation, greater than 94 mol% of both the drugs would be present in the micellar cores and potentially protected from external clearance mechanisms. This type of calculation also provides a starting basis for estimating the release profiles that could be achieved by various transport models. In addition, subsequent administration schedules can be determined once theoretical release profiles have been obtained.

As mentioned, protection from biological clearance is an important advantage that F127 formulations can provide for drugs, especially those that are very hydrophobic. In the case of naproxen and indomethacin, our results show that F127 is a good candidate for this function. Very hydrophobic/lipophilic drugs can be swiftly extracted from an aqueous bloodstream and stored in the fatty tissues of the body before they reach their intended target (Patrick, 1995). Good partitioning into F127 micelles may protect such hydrophobic drugs from becoming preferentially absorbed into fat tissue. Furthermore, storage of drugs in fat tissue, in this manner can also cause problems for obese patients, as dosage levels may need to be increased in order to increase the amount of available drug (Patrick, 1995). However, this can be dangerous in terms of toxicity, therefore, using a drug that partitions well into F127 micelles may allow the use of more normal dosage levels for these types of patients. This type of “F127 shielding” can also be useful in reducing the uptake of parenterally administered drugs by the reticuloendothelial system. Particles that are more hydrophobic undergo more pronounced uptake in the gastrointestinal tract by Peyer’s patches (one of its main immune systems) (Malmsten, 2002). Drugs may also be less vulnerable to mechanisms such as this if they are hidden in the cores of F127 micelles.

A major problem with drugs in the body is their degradation and subsequent clearance through the metabolic removal process (Patrick, 1995). A molecule with a high drug polarity has a greater chance of and is more efficiently removed through excretion (Patrick, 1995). Hydrophobic drugs are also susceptible to this because they can undergo Phase I reactions (oxidation/reduction/hydrolysis) by oxidases, reductases and esterases, or Phase II reactions

(conjugation), resulting in highly polar metabolite molecules (Patrick, 1995). Good partitioning into F127 micelles may protect them from these and other degradation processes. The stability of indomethacin in various Pluronic® solutions has been investigated previously (Lin and Kawashima, 1985b). Rate constants pertaining to the degradation of the drug were found to decrease in the presence of Pluronics®. Furthermore, these rate constants were found to decrease with increasing Pluronic® concentrations (Lin and Kawashima, 1985b). The mechanism of stabilization was proposed to be due to the protection from hydrolysis provided by the interior of the Pluronic® micelles (Lin and Kawashima, 1985b). In addition, Pluronics® were also found to protect indomethacin solutions from degradation by photolysis (Lin and Kawashima, 1985b). The reader is reminded that solubilization and good partitioning into copolymer micelles is dependent upon the structural properties of the micelles. Larger micelle aggregation numbers and core sizes result in better solubilization and hence partitioning.

It is clear that there are many advantages to using Pluronic® formulations for therapeutic use, especially in the case of the anti-inflammatory agents naproxen and indomethacin. An estimate of the partition coefficient and information about the micellar structure can be a powerful tool for both understanding drug behavior in these systems and predicting performance characteristics.

5. Conclusion

The structures of Pluronic F127 micelles in the presence of the hydrophobic drug molecules, naproxen and indomethacin, were investigated. It was found that these two anti-inflammatory drugs caused a slight decrease in the size of the micelles. More significantly, the drugs caused a large decrease in the observed aggregation numbers, and thus a corresponding increase in the number density of micelles. The drugs seemed to reduce both the liquid-to-gel and gel-to-liquid boundaries to slightly lower temperatures. It may be that the presence of the drug molecules promotes self-assembly of F127, causing an increase in the total micellar volume fraction and allowing the liquid-to-gel transition to occur at lower temperatures. Apparent micelle–water partition coefficients were measured for the two drugs; indomethacin was found to have a slightly greater value than naproxen. This was proposed to be a reason for the slightly greater effects observed with indomethacin, since partitioning indicates overall drug–water hydrophobic interactions. In addition, the presence of the drugs did not seem to significantly change the critical micelle concentration of the system. These parameters are important for assessing the suitability and potential performance of possible formulations.

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