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Solubilisation of model adjuvants by Pluronic block copolymers

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ABSTRACT

The effect of two model adjuvants (benzyl benzoate and benzyl alcohol) on the structure and dynamics of three Pluronic triblock copolymers (P85, P105 and F127) was studied using small-angle neutron scattering and pulsed-field gradient NMR. The two adjuvants studied have different aqueous solubilities. It was found that both adjuvants promoted the micellisation of the Pluronic block copolymers. In addition they lead to a swelling of the micelles, as shown by small-angle neutron scattering. From the pulsed-field gradient NMR results it was possible to determine the amount of adjuvant bound to the micelles.

1. Introduction

Pluronic block copolymers are amphiphilic triblock copolymers consisting of ethylene oxide (EO) and propylene oxide (PO) in the form $(EO)_n(PO)_m(EO)_n$. The polymers are water soluble and show a rich phase behaviour, which has been widely studied [1–9]. The polymers are available in a variety of EO:PO ratios and molecular weights, which govern their behaviour in aqueous solution. By varying these factors one can therefore optimise the polymers for use in a wide range of applications, and Pluronics have thus found use in a number of industrial applications, such as cleaning products, detergents, emulsification and fermentation [1,10–12].

It has been found that the phase behaviour of the Pluronics in aqueous solutions is very sensitive to both the polymer concentration and temperature [1,3–5]. Typically the Pluronics will be present as unimolecular "unimers" at low concentrations and temperatures. As the polymer concentration and/or temperature is increased the polymers begin to form spherical micelles, although there will still be a significant concentration of unimer present. Eventually, if the concentration and temperature are increased further, a "micellar liquid" phase will be formed, which consists of spherical micelles and a small number of unimers, and finally a gel phase will be reached [4,1,6]. At still higher temperatures rod-like phases and lamellar phases may be observed [4,6,7,13].

In recent years there has also been an interest in studying the ability of polymeric micelles to solubilise organic compounds [1,14,15]. The focus of these studies has mainly been the solubilising capacity of the polymer and the partitioning of the organic compound between the polymer and the solvent [16–18]. Small-angle scattering techniques have, also been used to characterise these systems. Lettow et al. [19] have for example used small-angle neutron scattering to study two aromatic compounds added to Pluronic P123, while Arleth et al. [20] have studied the reverse micelle formation of Pluronic L64 with xylene. Alexandridis and coworkers [21–23] have used small-angle X-ray scattering to study the liquid crystalline phases that may be formed by Pluronic–water–xylene mixtures.

The interest in this type of system arises from their potential use as drug delivery agents [24–27]. In this context it is important to gain a better understanding of the structural changes that occur upon the addition of organic compounds, that may be used in drug delivery systems, to the micellar solutions of the Pluronics. In addition it is important to understand the dynamics in this type of system. This paper describes structural investigations that were carried out using small-angle neutron scattering (SANS) as well as an investigation of the dynamics of the system using pulsed-field gradient nuclear magnetic resonance (PFG-NMR). The effect of adding benzyl benzoate and benzyl alcohol, two model adju-

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vants, to aqueous solutions of three Pluronic block copolymers (Pluronics P85, P105 and F127) was studied. Combining these techniques provides new and unique insight into this type of system. The choice of compounds was governed by their use in the pharmaceutical industry as adjuvants. From a physico-chemical perspective it was thought to be interesting to compare these two compounds, due to their different aqeuous solubilities. Compared to several studies reported in the literature on ternary Pluronic systems [17,28–30], the compounds studied here have such low aqeueous solubilities that they cannot be considered "cosolvents". The article will discuss the results obtained for Pluronic P85 in detail. This will be followed by a briefer discussion of the results obtained for Pluronics P105 and F127, together with a comparison of the results obtained from the different Pluronics.

2. Experimental

2.1. Materials

Pluronic P85, P105 and F127 were kindly supplied by BASF. Fully hydrogenated benzyl benzoate (99.9+%) was obtained from Fisher (Acros Organics), while partly deuterated benzyl benzoate (d_5-benzyl benzoate, 98%) was obtained from CDN Isotopes Inc. Fully hydrogenated benzyl alcohol (99+%) was obtained from Aldrich, as was the partly deuterated benzyl alcohol (d_5-benzyl alcohol, 98%). Deuterium oxide (D_2O, 99.9%) was obtained from Goss. All materials were used as received.

The samples were prepared by weighing out the polymer, adjuvant and solvent into vials. The vials were placed on a roller mixer for at least 24 h in order to allow the polymer to dissolve and for the samples to equilibrate. The sample preparation was carried out at room temperature.

2.2. Measurements

2.2.1. Small-angle neutron scattering

The SANS measurements were carried out on the LOQ instrument at ISIS, Didcot, UK and the SANS-1 instrument at GKSS, Hamburg, Germany. The instrument at ISIS is a fixed-geometry instrument, using a spread of wavelengths between 2.2 and 10 Å. The Q-range obtained was 0.009–0.29 $Å^{-1}$. The instrument at GKSS is a fixed-wavelength instrument. A wavelength of 8 Å was used, combined with four sample-detector distances: 0.7 m, 1.8 m, 4.5 m and 9.7 m. This gave a Q-range of approximately 0.005–0.25 $Å^{-1}$.

Before the measurements of the samples began, background measurements were carried out. The calibration sample used at ISIS was a partially deuterated homopolymer blend. Deuterated water was run as a background sample. In addition an empty cell was run. At GKSS water was used as the calibration sample. The solvent mixtures used to prepare the samples were measured as the background samples.

All samples were measured in pure D_2O. The samples where the adjuvants were solubilised have also been measured at two contrast match points: firstly the solvent was contrast matched to the adjuvant, leaving only the scattering from the polymer, secondly the solvent was contrast matched to the polymer, leaving only the scattering from the adjuvant.

The samples prepared in pure D_2O were measured in 2 mm pathlength Hellma quartz rectangular cells, while the samples with contrast matching were measured in 1 mm pathlength cells, due to the higher hydrogen content.

2.2.2. Pulsed-field gradient NMR

The PFG-NMR measurements were carried out using a Bruker 300 MHz spectrometer, with a ^1H diffusion probe. The pulse sequence used in the experiments was the stimulated echo sequence [31–33]. This pulse sequence employs three 90° radiofrequency pulses and two magnetic field gradient pulses, of strength g and length δ. The first and second radiofrequency pulses are separated by time τ while the second and third pulse are separated by time T. The two gradient pulses are separated by the diffusion time, Δ. Depending on the sample, the value of the gradient duration, δ, varied between 1 and 3 ms, while the diffusion time, Δ, was varied between 30 and 1000 ms. The maximum gradient strength used was 10 T/m.

2.3. Analysis

Pluronic micelles are thought to consist of a spherical core containing the hydrophobic part of the copolymer (poly(propylene oxide)). This core is surrounded by a shell of dissolved polymer chains consisting of the hydrophilic part of the copolymer (poly(ethylene oxide)) [6,7,34–37]. Pedersen et al. [35,38] have proposed an analytical expression for the form factor of a spherical micelle consisting of a dense spherical core and polymer chains attached to the surface. The form factor for the micelle is composed of four different terms: the normalised self-correlation of the sphere ($P_s(Q, R)$), the self-correlation of the chains ($P_c(Q, L, b)$), the cross term between the sphere and the chains ($P_{cc}(Q)$) and the cross term between the different chains (the poly(ethylene oxide)):

$$P_{mic}(Q) = N_{agg}^2\rho_s^2 P_s(Q, R_{core}) + N_{agg}\rho_c^2 P_c(Q, L, b) + N_{agg}(N_{agg} - 1)\rho_c^2 P_{cc}(Q) + 2N_{agg}^2\rho_s\rho_c P_{sc}(Q) \tag{1}$$

where N_{agg} is the aggregation number of the micelle, ρ_s and ρ_c are the scattering length densities of the spherical core and the chain, respectively, R_{core} is the radius of the core, and L and b are the contour length and Kuhn segment length of the chain (PEO).

Further details of these form factors can be found in the papers by Pedersen et al. [35,38].

The model uses a Schultz distribution of the aggregation number to take into account the polydispersity of the micelles, and takes into account the presence of both unimers and micelles and also introduces a structure factor to account for the intermicellar interactions. The structure factor used is based on the hard sphere structure factor derived by Lekner [39]. The overall expression for the scattering cross section is given by:

$$\frac{\partial\Sigma}{\partial\Omega}(Q) = \Phi_{mic}P_{mic}(Q)S(Q) + (1 - \Phi_{mic})P_{uni}(Q) + bg \tag{2}$$

where Φ_{mic} is the fraction of polymer micellised, $P_{mic}(Q)$ is the form factor of the micelle, $P_{uni}(Q)$ is the form factor of the unimer, $S(Q)$ is the structure factor and bg is the incoherent background.

The Pedersen model was used to fit the SANS data obtained for the pure Pluronics, as well as the data where the adjuvants were contrast matched to the solvent.

Due to the large number of variables in the model some constraints were initially used in the fitting procedure. These constraints were relaxed during the latter part of the fitting as the fits began to converge. Known parameters, such as molecular volumes and concentrations, were, however, kept fixed throughout the fitting procedure.

A model with a spherical form factor and hard sphere structure factor was used to fit the data obtained where the Pluronics were contrast matched to the solvent. The form factor is in this case given by:

$$P(Q) = \left[\frac{3(\sin(QR) - QR\cos(QR))}{(QR)^3}\right]^2 \tag{3}$$