Colloids and Surfaces B: Biointerfaces 83 (2011) 69–77

Contents lists available at ScienceDirect

Colloids and Surfaces B: Biointerfaces

journal homepage: www.elsevier.com/locate/colsurfb

# Micellization and solubilization of a model hydrophobic drug nimesulide in aqueous salt solutions of Tetronic® T904

P. Parekh[a,*], K. Singh[b], D.G. Marangoni[b], P. Bahadur[a]

[a] Department of Chemistry, Veer Narmad South Gujarat University, Surat 395 007, India
[b] Department of Chemistry, StFX University, Antigonish, Nova Scotia, Canada

ARTICLE INFO

*Article history:*
Received 10 September 2010
Received in revised form 26 October 2010
Accepted 28 October 2010
Available online 5 November 2010

*Keywords:*
Tetronics®
CMT
Nimesulide
Solublization
Dynamic light scattering (DLS)

ABSTRACT

The micellar and phase behavior of an ethylene oxide-propylene oxide branched octablock copolymer Tetronic® T 904 (hereafter written as T904) in water and NaCl solutions was examined. The copolymer shows a cloud point (CP) ranging from 74–65 °C in the concentration range of 1–10% and forms aggregates (micelles) with a hydrodynamic diameter around 10–12 nm in the temperature range 30–40 °C. Stable, bluish solutions containing aggregates of variable size (several hundred nm in some cases) were observed even at temperatures much less than the critical micellization temperature (CMT = 30 °C for a 2% solution in water). The CP and the CMT markedly decrease in the presence of NaCl due to the dehydration of the polyethylene oxide shell. The size of the micelles in water or salt solutions increases at temperatures close to the CP as inferred from viscosity measurments. A model drug compound (nimesulide, NIM) was solubilized in T904 micelles which showed a remarkable increase in solubilization at higher temperature; however, a decrease in solubilization was observed in salt solutions. The thermodynamic parameters for solubilization were obtained, and the location of NIM in the copolymer micelles was investigated by UV–Visible spectroscopy.



## 1. Introduction

Block copolymers made of polyethylene oxide (PEO) and polypropylene oxide (PPO) are commercially available as linear triblocks of the type ABA and BAB (Pluronics®) and star-blocks (Tetronic®) with varying hydrophilic-lipophilic balance (HLB). These polymeric amphiphiles self-assemble to form nanosize aggregates (micelles) in aqueous solutions and display a unique core-shell structure with spherical/rod-like morphology and a fairly low polydispersity that is strongly dependent on temperature/concentration [1,2]. Pluronic® aggregates have a micelle core consisting of a hydrophobic poly(propylene oxide) or PPO block surrounded by a heavily hydrated, hydrophilic poly(ethylene oxide) or PEO block. These polymeric surfactants are used in a variety of applications ranging from cleaning to personal care products (e.g., hard-surface cleaners, dishwashing liquids, rinse aids, and laundry detergents) and industrial processing fluids (e.g., metal working fluids, lubricants, emulsion polymerization, and water treatment) [2]. Pluronics® have also found significant applications in drug delivery systems as mainly because their micelles have a slower rate of dissociation and allow retention of loaded drugs for a longer period than other conventional surfactant based drug delivery systems; hence, these surfactants may allow a higher accumulation of the active species at the target site [3,4]. The solubilizing power of micelles depends on numerous factors, such as chemical structure of the amphiphile and the drug molecule, temperature, pH, and the ionic strength. Polymeric surfactants are generally considered to be better solubilizing agents than conventional surfactants due to their low critical micelle concentrations (CMCs) and the thermal stability of the micelles. The solubilization power and location of the solubilizate are important considerations in the utilization of surfactants, not only in drug delivery systems, but in many of the practical applications listed above.

Tetronics® are commercial star block 4-armed PEO–PPO block copolymers from BASF, with an ethylenediamine core as diagrammed in Fig. 1. These are not as heavily utilized in applications as their Pluronic® counterparts, but they find applications in the petroleum industry in corrosion prevention and as emulsion breakers [5]. Recently, Tetronic® surfactants have been studied as possible vehicles for drug delivery [6]; hence, studies on their micellar and solution behavior under a variety of conditions will be an important part of the formulation in delivery agents. Kadam et al. [7,8] have examined the formation and characterization of micelles from Tetronic® T904 in water and in salt solutions and found that a 5% T904 solution had a critical micellization temperature (CMT) of about 28 °C with the hydrodynamic diameter of micelle measuring approximately 12 nm at 30 °C. The micellar

* Corresponding author. Tel.: +91 9979200970; fax: +91 261 2256012.
*E-mail addresses:* paresh7884@gmail.com (P. Parekh), ksingh@stfx.ca (K. Singh), gmarango@stfx.ca (D.G. Marangoni), pbahadur2002@yahoo.com (P. Bahadur).

0927-7765/$ – see front matter © 2010 Elsevier B.V. All rights reserved.
doi:10.1016/j.colsurfb.2010.10.046

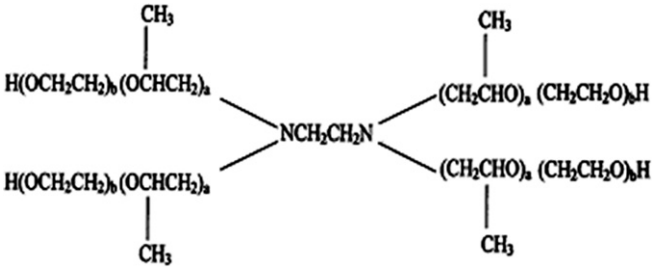


**Fig. 1.** Tetronic® T904.

and surface properties of these materials above their CMC/CMT values [9,10] indicate that Tetronics® like T904 are excellent candidates for the solubilization of hydrophobic organic compounds while interacting favourably with phospholipid bilayers [11,12]. Hence, these amphiphilic star-shaped copolymers are suitable for novel drug delivery system development [13,14]. The presence of the amine group in the Tetronics® provides some acid–base basic character and thermal stability to the amphiphiles [15,16]. Solubilization of poorly soluble drugs in amphiphilic polymeric micelles and their subsequent release studies have gained much interest in recent years [17]. As solubilization is also affected by temperature and presence of additives like salts and various nonelectrolytes, these studies are of tremendous importance in understanding the appropriate conditions for effective drug-delivery design.

NIM is a non-steroidal anti-inflammatory drug (NSAID) that is often chosen as a model hydrophobic compound for drug solubilization studies. In this paper, the aggregation of a star-shaped block copolymer surfactant (Tetronic® T904) has been studied as a function of temperature and T904 concentration in the presence of electrolyte (NaCl). Finally, the locus of solubilization of NIM has been determined in the T904 aggregates. These measurements provide significant information on the subtle balance of interactions that affect the aggregation behavior of the copolymer and, hence, provide fundamentally important information that will enable the use of T904 as drug carrier or in drug releasing systems.

## 2. Experimental

### 2.1. Materials

Tetronic® T904 copolymer (Fig. 1) was used as received from BASF Corp. Parsippany, NJ, USA. NIM (Fig. 2) was a gift sample from Arti Ltd. (India). All other reagents were of analytical grade.

## 3. Methods

### 3.1. Cloud point (CP)

Cloud points were determined at fixed concentration of the copolymer (0–10%) in the presence and absence of varying amounts of added sodium chloride by gradually heating the solution in thin 20 mL glass tubes immersed in a temperature controlled water bath. The solutions were stirred with a magnetic stirring bar while being heated. The heating rate of the samples was adjusted to 1 °C/min. The first appearance of turbidity was taken as the cloud point and the CP values were found to be reproducible within 0.5 °C.

### 3.2. Nuclear magnetic resonance (NMR) experiments

NMR measurements were made using either a Bruker AC 250 spectrometer operating at a frequency of 250.13 MHz, or a Bruker AVANCE-II nmr spectrometer operatng at 400.13 MHz, the sweep width used was 2500 Hz with a pulse width of 4.2 μs, whereas on

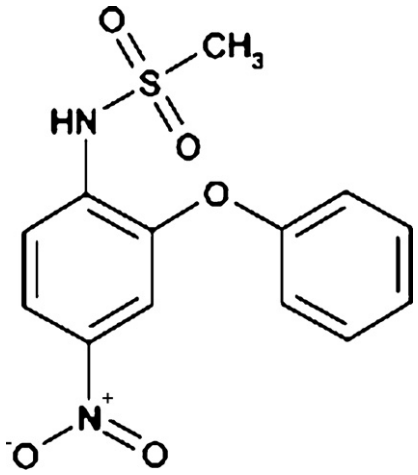


**Fig. 2.** Nimesulide.

the AVANCE-II, the sweep width was 4500 Hz and the pulse width was 6.8 μs. Solvent suppression techniques were used to partially eliminate the HDO peak due to residual water. Before being suppressed, the HDO peak was used to calibrate the chemical shift of the spectrum by setting it to 4.65 ppm at 298 K. For all $^1$H NMR experiments, the samples were measured in the temperature range 14–40 °C. $D_2O$ was used with the sample solutions as an external reference to eliminate temperature-induced shifts.

### 3.3. Viscosity

The viscosity measurements were carried out using an Ubbelohde suspended level capillary viscometer. The viscometer was suspended vertically in a thermostat with a temperature stability of ±0.1 °C in the investigated region. The viscometer was thoroughly cleaned and dried before each measurement. The flow time for constant volume of solution through the capillary was measured with a calibrated stopwatch.

### 3.4. Ultraviolet spectroscopy

In order to determine the solubility of the drug, a calibration plot was prepared in methanol. The absorbance of the standard solutions in the concentration range of 0–0.1 mg/ml was measured at 299 nm ($\lambda_{max}$) using a Shimadzu UV-2450) UV–Vis spectrophotometer. A linear calibration plot [$R^2 > 0.999$ (not shown)] for the absorbance versus concentration of the drug in a water–methanol solvent (1:2) was used to obtain the solubility of the drug in the copolymer solution. Samples at all concentrations were continuously scanned to detect any shift in $\lambda_{max}$ (in methanol). Solubility was determined in triplicate and the results reported are the averages of three trials. For the drug solubility measurements, saturated drug-loaded solutions were prepared in glass vessels by mixing excess powdered drug with T904 solution and stirring at constant temperature (30, 37, 40, 45 °C) at 200 rpm for a period of 2 days. The solutions were filtered (Millipore, 0.45 μm) to remove unsolubilized drug; the filtered solution was diluted 10 times with methanol. Blank experiments, without T904, were done to determine the solubility of the drug in water.

For the determination of the location of the NIM in Tetronic® solutions, an excess of NIM was added, and the solution was stirred at 30 °C for 2 h. The solution was filtered (Millipore, 0.45 μm) to remove any unsolubilized drug. The appropriate dilution was done by the addition of a T904 solution having the same concentration. The copolymer concentration was identical in both the reference and sample cells to eliminate the effect of surfactant on UV-absorbance.