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Tensiometric, fluorescence and ^{1}H NMR study of mixed micellization of non-steroidal anti-inflammatory drug sodium salt of ibuprofen in the presence of non-ionic surfactant in aqueous/urea solutions

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ABSTRACT

The desirable surface/bulk properties for specific applications of drug sodium salt of ibuprofen (IBF) and Triton X-100 (TX-100) can be achieved by adjusting mainly the composition of these systems. The interactions of anionic drug IBF with non-ionic surfactant TX-100 micelles have been investigated using tensiometry, fluorometry and ^{1}H NMR in aqueous as well in 250 mmol·kg^{-1} urea solutions. Different theoretical models like Clint, Rubingh, and Rosen, etc. were utilized to get information about the nature of interaction between these two in bulk and at the interface. These models disclose that the non-ideal *behavior* with attractive interaction in bulk and at the interface exists. The steady-state fluorescence quenching study was employed to evaluate micelle aggregation numbers (N_{agg}), which signify the involvement of surfactant was forever higher compared to IBF. Stern–Volmer binding constants (K_{sv}), micropolarity (I_1/I_3) and dielectric constant (D_{exp}) of the mixtures are also obtained using fluorescence method. By the addition of urea raise in the surface charge of the micelles was observed followed by halt of the micellization of drug and surfactant as well as their mixture, therefore *cmc* values increases followed by decrease in aggregation number. The ^{1}H NMR resonance intensity variations were paralleled by upfield shifts in the resonance frequencies, due to an increased shielding of IBF happening from closeness of the non-ionic TX-100 surfactant.

1. Introduction

Colloidal sized aggregates known as micelles formed by amphiphiles in aqueous/nonaqueous solutions due to the delicate balance between polar and nonpolar interactions. Owing to a unique property of the amphiphiles beyond an assured concentration identified as critical micelle concentration (*cmc*) [1–3]. Besides a vast range of applications in food, detergency, cosmetic industries and enhanced oil recovery these micelles are of prolific use in pharmaceutical applications [1]. In many pharmaceutical formulations amphiphilic substances are often used together as active compounds or excipients as interactions can influence the physicochemical property of dosage form which in turn may change the stability of the formulation and the discharge of active compound at target site. Various drug delivery and drug targeting systems have been examined in order to diminish drug deterioration and loss, to avoid risky unwanted effects as well as enhance drug bioavailability [4,5]. In contrast to other alternatives for example water soluble polymers and liposomes; micellar utilization as drug carriers/vectors are advantageous in that these have ability to solubilize the poorly soluble drugs, growing bioavailability by expansion the retention in the body to supply gradual accumulation in the mandatory area [1,6]. The tiny size of the micelles allows them to accumulate in the leaky vasculature [7]. The incorporation of additive into an aggregate of an amphiphilic drug will affect its physicochemical properties such as the degree of ionization, reaction rates and clouding or phase separation [8–11].

Ibuprofen (IBF) is a nonsteroidal anti-inflammatory drug (NSAID) that is available in a variety of prescription and nonprescription drug products [12]. IBF has symmetrically substituted chiral carbon atom with desired pharmacological effects reside exclusively in the S-enantiomer (scheme 1). The main disadvantage of this category of drugs comprise short plasma half-life, considerable gut and nephrotoxicity [12,13]. Hence, the improvement

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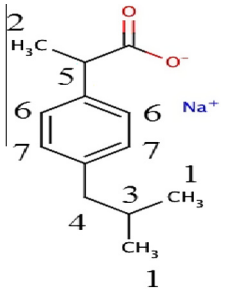
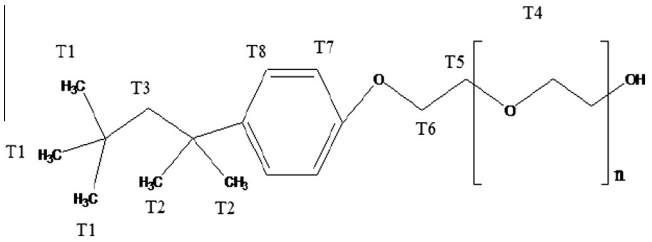


SCHEME 1. Molecular structure of sodium salt of ibuprofen (IBF).

of drug delivery system (DDS) that allows the controlled discharge of IBF would be vastly helpful chiefly in immense dose reliant managements such as chronic rheumatoid arthritis. The function of surfactant micelles in the pharmacology is of vital significance particularly owing to their capability to increase the permeability of medicines through the biological membranes. Exploitation of micelles as drug carriers is beneficial over other harsh drug carriers because of their small size (~8 to 35) nm allocation and the enhanced bioavailability and the steadiness of the drug during micelle assimilation [14]. As micelles are used as drug carriers, it brings down the drug interaction with the calm species like enzymes that was found in biological fluids and hence reduce its adverse side effects [15]. Besides, the low comparative toxicity of non-ionic surfactants makes them mainly valuable for solubilization and drug delivery purposes. Micelles formed by amphiphile (surfactant) have also been extensively utilized as a basic form for really complex biomembranes, because surfactant compose the key constituent of the membranes and the occurrence of hydrophilic (polar) and nonpolar (hydrophobic) sections in the same compounds permits studying the resemblance of small molecules for these vital essence of membrane organizations [16].

The solubilizing influence of micelles depends on several issues, for example chemical structure of the amphiphile/drug molecule, temperature, ionic strength and pH. Several techniques like surface tension, fluorescence quenching, electrical conductivity, etc. can offer simply the usual outcomes for the entire amphiphiles, however cannot differentiate the activities of every amphiphiles. Luckily, ^{1}H NMR technique have a capability to explain the performance of all kind of amphiphile in a mixture [17], as every amphiphile has possess own distinguishing proton peaks that changes in shift, or peak width according to the environment changes. Exactly for this reason, this technique also suggests the opportunity to examine the mixed micellization mechanism of the amphiphiles. In the present study, the tensiometric study has been engaged to examine the effect of TX-100 on the *cmc* and various adsorption characteristic of TX-100 (scheme 2).

Moreover, ^{1}H NMR experiments give the changes in chemical shift (δ) of IBF in the attendance of TX-100 in aqueous and non-



SCHEME 2. Molecular structure of TX-100.

aqueous (urea solution) media, which shows direct interaction between the components.

2. Experimental

2.1. Materials

All preliminary materials were of analytical grade and were used as received. Significant instruction on the source and purity of the utilized materials are shown in table 1. IBF is produced industrially as a racemate. It is an optically active compound with both S and R-isomers (racemic mixture). IBF (drug) and TX-100 (surfactant) solutions were ready by mixing perfectly measured quantities of amphiphiles in required volumes of double distilled water (DDW) in absence and presence of urea. DDW with conductivity (1 to 2)·10^{-6} S·cm^{-1} was used for all purposes.

2.2. Methods

2.2.1. Surface tension (γ) measurements

The surface tension (γ) is measured by the ring detachment technique (Attension Tensiometer, model Sigma 701, Germany). The detailed process has been described earlier [18,19]. The relative uncertainty limits on *cmc* are found to be about 3%. Figure 1 shows *cmc* of pure IBF and TX-100 as well as their mixtures at T = 298.15 K in the absence and presence of urea. Accuracy on the individual surface tension reading is approximately ±1.0 mN·m^{-1}. The experimental error in temperature was minimized to 0.2 K. All the values gathered by the tensiometry technique are given in tables S1–S2 (supporting information).

2.2.2. Spectrofluorometric measurements

The steady-state fluorescence quenching technique was utilized for determining the aggregation number (N_{agg}) of the pure amphiphiles as well as their mixture at T = 298.15 K in the absence and presence of urea. Herein pyrene was used as a probe while cetylpyridinium chloride (CPC) was utilized as a quencher. Cetylpyridinium chloride (CPC) concentration ranged from (0 to 5)·10^{-2} (mmol·kg^{-1}) (the N_{agg} of the IBF as well as their mixture with TX-100 in the absence and presence of urea was determined by assuming the Poisson distribution to be applicable for the equilibrium of solubilization between the aqueous and micellar phases). The concentration of IBF and TX-100 were kept (225 and 1) mmol·kg^{-1} respectively for N_{agg} determination in te absence and presence of 250 mmol·kg^{-1} urea. A Hitachi F-7500 fluorescence spectrometer was used for fluorescence reading. Excitation and emission were recorded at 335 nm and within the range of 350 nm to 400 nm respectively. A quartz cell of 10-mm path length was employed for all fluorescence experiments. CPC has been employed for the quenching of fluorescence of pyrene to detect N_{agg} of the solutions. All spectra contain five vibronic peaks whose intensities decrease with the increase in CPC concentration (figure 2). The experimental error in temperature was minimized to 0.2 K. The relative uncertainties on N_{agg} are estimated to be 4%.

2.2.3. ^{1}H NMR measurements

The ^{1}H NMR spectra were recorded with a Bruker ultrasheild plus 600 spectrometer at a proton resonance frequency of 600 MHz. D_2O was employed to prepare the solutions of IBF and TX-100 as well as their mixture in the absence/presence of urea. Tetramethylsilane (TMS) was used as internal standard. Nearly 1 mL of the solution was filled to a 5 mm NMR tube for experiments. Chemical shifts were reported on the δ (ppm = 10^{-6}) scale. The relative uncertainties on chemical shifts (δ, ppm) are estimated to be 4%.