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Micellization and microstructural studies between amphiphilic drug ibuprofen with non-ionic surfactant in aqueous urea solution

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ABSTRACT

Herein, we have accounted for the interaction between a non-steroidal anti-inflammatory drug ibuprofen (IBF) and non-ionic surfactant polyethoxyglycol *t*-octylphenyl ether (TX-100 (4-(1,1,3,3-tetramethylbutyl)phenyl-polyethylene glycol) and TX-114 ((1,1,3,3-tetramethylbutyl)phenyl-polyethylene glycol)), in aqueous urea solutions using tensiometric and fluorimetric techniques at $T = 298.15$ K. Surface tension measurements were carried out to evaluate the critical micelle concentrations (*cmc*) of the drug and surfactant as well as their mixtures of varying compositions. An increase in the surface charge of the micelles was observed with the addition of urea followed by halt of micelles formation. Various physicochemical parameters, such as, *cmc* values of the mixture, micellar mass fraction (X_1^{Rub}) of surfactants (TX-100/TX-114), interaction parameters (β) at the monolayer air–water interface and in bulk solutions, different thermodynamic parameters and activity coefficients (f_1^m, f_2^m) for the non-ionic surfactant and drug in the mixed micelles, were determined by using the approach of Clint, of Rubingh, and of Rosen. All results identified synergism and attractive interactions in the mixed systems of (drug–surfactant) mixtures and showed effective involvement of the non-ionic surfactant (TX-100/TX-114) component in the mixture. Micelle aggregation numbers (N_{agg}), evaluated by using steady-state fluorescence quenching studies, suggest that the contribution of non-ionic surfactant was always more than that of the drug. Micropolarity (I_1/I_3), Stern–Volmer binding constants (K_{sv}) and the dielectric constant (D_{exp}) of mixed systems have also supported the synergistic behavior of the mixed amphiphilic systems.

1. Introduction

Amphiphilic compounds consist of an ionic or non-ionic polar head group and a non-polar hydrophobic portion in the single molecule. As most of the drugs, particularly those with the local anesthetic, tranquillizing, antidepressant and antibiotic actions, are amphiphilic in nature that we have so far considered form micelles at concentrations at which they do not attain *in vivo*. It is more likely that it is their surface-active characteristics which are more imperative biologically, although the tendency of the molecules to form associations by hydrophobic bonding will manifest itself [1].

Micelle formation can be visualized as a stepwise process, characterized by a series of equilibria and equilibrium constants or as a phase separation (all or none) process such that, once a critical concentration (the critical micellar concentration (*cmc*)) is reached, further addition of the amphiphile will outcome in aggregation [2]. Numerous authors have discussed the energetics of micelle formation [3–5]. Micelles are characterized by physicochemical parameters such as the *cmc*, aggregation number (N_{agg}) and particle size. Moreover, micelles are polydispersed and the aggregation number represents the most probable individual micelle within a distribution [2].

The mixing of amphiphiles has long been the subject of intense research since solution properties of mixed amphiphiles are more interesting than those of pure amphiphiles, from both physicochemical and application points of view. By virtue of the better performances in solubilization, transportation, *etc.*, mixed amphiphiles have gained significance in industrial, pharmaceutical, and biological fields [6,7]. The study of the properties of mixtures of surface active drugs in solution provides an opening to investigate the influence of the molecular structure of the hydrophobe on the non-ideality of the mixing because of wide dissimilarity in the structure of this moiety. The knowledge of the aggregation behavior of amphiphilic drugs in aqueous medium is vital for

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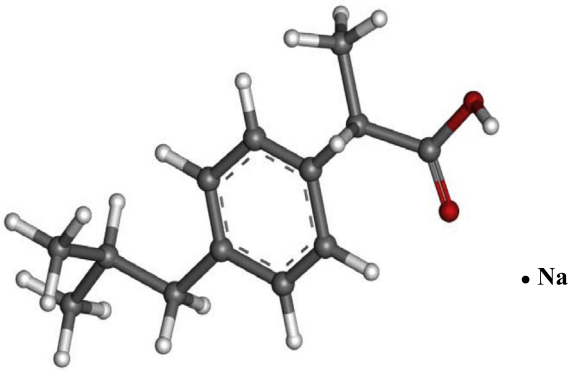
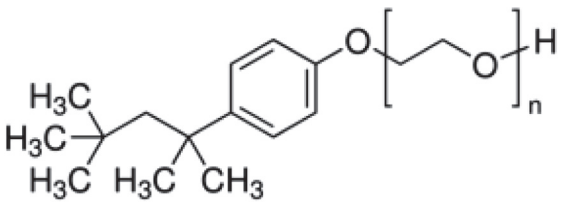
understanding how these molecules participate as components in practical applications.

Furthermore, the incorporation of multiple amphiphiles into a single system allows fabrication of mixed micelles with easily tuneable properties and functionalities by composition variation, without the need for complicated and expensive synthetic procedures. Therefore, association of mixtures of biologically relevant amphiphiles and different biocompatible surfactants has become increasingly popular and extensively studied to elucidate self-assembly behavior of these mixtures and make them attractive candidates for potential applications in biomedicine [8–10].

Herein, we have studied the interaction of the sodium salt of ibuprofen (IBF) with non-ionic surfactants (TX-100/TX-114) in 100 mM urea solution by employing surface tension and fluorescence techniques. The results may be cooperative in designing the drug delivery formulations of similar systems. IBF belongs to family of non-steroidal anti-inflammatory drugs and is commonly used for relief of symptoms of arthritis, fever, primary dysmenorrheal (menstrual pains) *etc.* (scheme 1). IBF self-associates in aqueous solution to form small aggregates in surfactant like manner. These compounds aggregate in water with 40 to 50 monomers [11]. All medicines may cause side effects, but many people have no, or minor, side effects. IBF also suffers from several drawbacks such as nausea, dyspepsia, gastrointestinal ulceration/bleeding, raised liver enzymes, diarrhea, constipation, epistaxis, dizziness, and hypertension side effects. These undesirable side effects may be reduced if the drug is appropriately targeted to the organism. The main shortcoming of this class of drugs is to encourage phospholipidosis, *i.e.*, the unnecessary intracellular accumulation of phospholipids [12]. The interaction between drug and phosphate oxygen of the lipids consequences in diminishing the amphiphilic character of lipids and therefore, it is probable that the interaction can change the physicochemical properties of the lipids found in the body. Custody the above facts in mind, for formulation of the IBF drug, it is necessary to minimize the binding tendency with phospholipids without affecting its activity. In this high opinion, we have studied the aggregation behavior of IBF in the presence of non-ionic surfactants (TX-100/TX-114) (scheme 2) in the presence 100 mM urea solutions. The analysis of data has been made in the light of various theoretical models, including those of Rubingh, Rosen, Clint, and Maeda to disclose the comparative performance of these models. Urea is found in the body and their effect on micellization will allow better designing of effective therapeutic agents. The other main important aspect of taking non-ionic surfactants are physiologically more tolerable than ionic ones and, due to their low *cmc* values; they are represented as best candidates for drug delivery, regardless of large dilution in blood. To date, to the best of our knowledge, there has been no report in the literature on such types of study of micellization of IBF with non-ionic surfactants in aqueous urea solutions such as those used in the present study.



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



(n = 9-10 (TX-100), 7 or 8 (TX-114)

SCHEME 2. Molecular structure of polyethylene glycol *tert*-octylphenyl ether.

2. Experimental

2.1. Materials

All the materials were used as received without further purification. Relevant information on the provenance and mass fraction purity of the used materials are given in table 1. Demineralized double-distilled water (DDW) with specific conductivity less than 3 $\mu S \cdot cm^{-1}$ was used to prepare the stock solutions of the drug and surfactants.

2.2. Methods

2.2.1. Surface tension measurements

The tensiometric measurements were carried out using a platinum ring by the ring detachment method with an Attension tensiometer, model Sigma 701, Germany. The ring used in the measurement was cleaned by washing with doubly distilled water (DDW) followed by heating through alcohol flame. The temperature was maintained by circulating water from an ORBIT RS10S thermostat. The experimental error in temperature was minimized to 0.2 K. A mixed micellization study of different mass fractions was prepared from stock solutions of drug and surfactant. The surface tension (γ) at each mass fraction was measured by successive addition of concentrated solution of the mixture in pure water at T = 298.15 K. The γ value decreased on each addition of solution of particular molarity in water up to a certain value and then it became constant. This break point corresponds to the *cmc* value. Each experiment was repeated to achieve good reproducibility. The accuracy of the surface tension measurements was within ±0.1 mN m^{-1}. Figure 1 shows the *cmc* of pure amphiphile in aqueous solution.

2.2.2. Spectrofluorometric measurements

The aggregation number (N_{agg}) of pure and mixed surfactant systems were determined using fluorescence measurements at T = 298.15 K. Pyrene and cetylpyridinium chloride (CPC) were used as probe and quencher, respectively. Fluorescence measurements were taken in a Hitachi F-7000 fluorescence spectrometer with excitation and emission slit widths 2.5 nm. Excitation was done at 335 nm, and emission was recorded within the range (350 to

TABLE 1
Provenance and purity of the compounds employed in this work.

Chemical name	Provenance	Mass fraction purity
Ibuprofen sodium salt (IBF)	Sigma (USA)	⩾0.99
TX-100	Fluka (Switzerland)	
TX-114	Fluka (Switzerland)	
Urea	Sigma (Germany)	0.99