Colloids and Surfaces B: Biointerfaces 121 (2014) 158–164

Contents lists available at ScienceDirect

Colloids and Surfaces B: Biointerfaces

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

Analysis of surface and bulk properties of amphiphilic drug ibuprofen and surfactant mixture in the absence and presence of electrolyte

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ARTICLE INFO

Article history:
Received 21 May 2014
Received in revised form 2 June 2014
Accepted 3 June 2014
Available online 10 June 2014

Keywords:
Mixed micelle
Ibuprofen
Interaction parameters
Aggregation number
Micropolarity

ABSTRACT

In the present work, the micellization, adsorption and aggregation behavior of mixed drug-surfactant systems, in the absence and presence of electrolyte (100 mM NaCl) were investigated by surface tension and fluorescence measurements. The critical micelle concentrations (*cmc*) of the mixtures fall between the values of the individual components, which indicate nonideal behavior of mixing of the components. On the basis of regular solution theory (RST), the micellar mole fractions of surfactant (X_1) and interaction parameter in solution (β) were evaluated, while their interfacial mole fractions (X_1^{σ}) and interaction parameters at the interface (β^{σ}) were calculated using Rosen's model. The results indicate that the surfactant's contribution is greater than that of the drug both at the interface and in micelles. The short and rigid hydrophobic structure of the drug resists its participation in micelle formation more than in the monolayer, leading to $X_1 < X_1^{\sigma}$. Values of the surface excess (Γ_{max}) and minimum area per head group (A_{min}) indicate attractive interactions. Γ_{max} increases and A_{min} decreases as the surfactant mole fraction increases. The results have applicability in model drug delivery.

1. Introduction

The amphiphilic molecules (1–5) containing both hydrophobic and hydrophilic regions are known to play a vital role in many processes of interest in both fundamental as well as applied sciences. One important property of amphiphilic molecule is the formation of colloidal sized aggregate in solution, known as micelles [1–5], which have particular significance in pharmacy. The amphiphilic mixtures are mostly applied in cosmetics, detergency, enhanced oil recovery and drug delivery, since they have improved characteristics compared to the single amphiphilic solutions [6,7]. In practical applications, reduction of the interfacial tension ensuring amphiphile usefulness in a given process is very often demanded. In many cases it is impossible to achieve proper reduction of the water surface tension by a single surfactant, therefore, different king of amphiphilic mixtures are used.

In recent years, much research has been directed toward the study of mixed amphiphilic systems (e.g., surfactant–surfactant, surfactant–cosurfactant, surfactant–polymer, surfactant–copolymer, surfactant–drug, drug–drug etc.) [8–15]. A mixed amphiphilic system can exhibit surface and colloidal properties different from those of the pure individual components. Nonideal mixing of amphiphilic components often causes synergism in the properties of the mixtures that may be exploited in their applications. When a mixed amphiphile system shows lower critical micelle concentration (*cmc*) values than that of pure components, the system is said to be synergistic. As a result, mixed micelles are commonly used in pharmaceutical formulations, in industries, and in enhanced oil recovery processes [16–18]. Conventional surfactants have *cmc* values in milli moles and may disintegrate upon being diluted. In vivo, this may result in precipitation of encapsulated drug causing a decrease in bioavailability and ability to penetrate biological barriers [19]. This problem can be overpowered by the use of mixed micelles of drug with different additives i.e., surfactants, biocompatible polymers, electrolytes etc.

Ibuprofen (IBF), 2-(4-isobutylphenyl) propionic acid, is a well-known non-steroidal ant-inflammatory drug (Scheme 1(a)) commonly used to treat chronic pain and inflammation. Unfortunately, oral consumption results in severe side effects, including gastrointestinal, ulceration and some time bleeding. Moreover, IBF is a poorly water-soluble drug. However, the sodium salt of ibuprofen used in the present study is easily soluble in aqueous solution. Therefore, the development of a drug delivery system allowing the controlled release of IBF would be useful, especially in

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http://dx.doi.org/10.1016/j.colsurfb.2014.06.009
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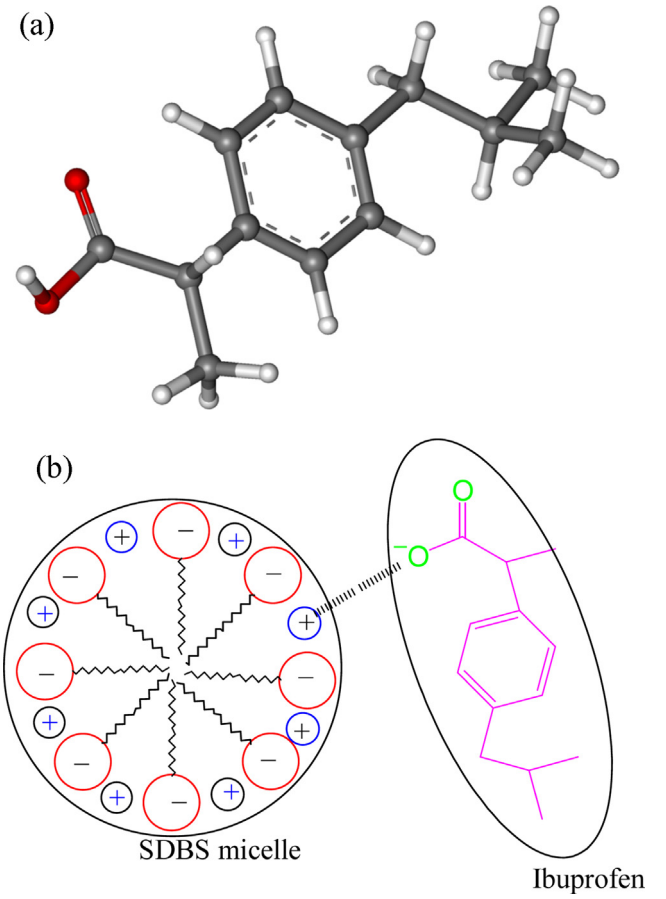

Scheme 1. Schematic diagram showing (a) chemical structure of Ibuprofen (IBF), (b) ion pair interaction between SDBS micelle and IBF.

high dose-dependent treatment, including chronic disease such as rheumatoid arthritis. Oral route is the most convenient, economical, and frequently used route of drug administration, but it suffers from a major drawback of poor gastrointestinal membrane permeability. Penetration enhancers may be incorporated into various formulations in order to overcome the problem of low permeability and bioavailability of drugs across the biological membranes. They include surfactants, fatty acids, bile salts, medium chain glycerides, calcium chelators such as ethylenediaminetetraacetic acid (EDTA), acyl carnitine and alkanoylchlolines etc. Since surfactants are often used as penetration enhancers, so their mixture with amphiphilic drug may improve their bioavailability.

Keeping the above in view and the fact that surfactant micelles, like many other amphiphilic substances, are potentially important encapsulating/solubilizing agents, we have performed tensiometric and spectrometric measurements on IBF-SDBS (Sodium dodecylbenzenesulfonate) surfactant mixed systems in absence and presence of 100 mM NaCl. As the electrolytes are found in the body and their concentration in the membranes may vary, their presence and concentration may affect the micellization tendency of the drug and surfactant as well as their mixed micelles. Therefore, it is important to have knowledge of drugs' association behavior in presence of electrolytes. Clint, Rubingh, Motomura's and Rosen's approaches have been utilized to obtain various parameters related to mixed micelles.

2. Materials and experimental

The anionic surfactant, SDBS and amphiphilic drug, IBF were the products of Sigma with purity >98%. Pyrene, used as micellar probe in the fluorescence measurements, was a Sigma product with purity >98%. A stock solution of pyrene was prepared in absolute methanol. All solutions were prepared in double-distilled water of specific conductivity: (10–50) μS cm^{-1} and experiments were done under thermostatic conditions at 298.15 K with accuracy of ±0.1 K.

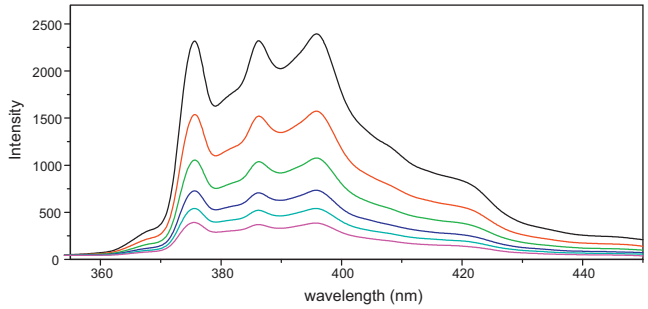

Fig. 1. Representative fluorescence (emission) spectra of 10^{-6} M pyrene in 100 mM NaCl solution of SDBS + IBF (4:6) at different quencher concentrations (maximum intensity indicates no quencher and minimum intensity indicates maximum amount of quencher).

2.1. Surface tension measurements

The *cmc* was determined by the surface tension (γ) measurement. Sigma 700 (Attention) performed the experiments using a platinum ring, the ring detachment method in a calibrated tension at a constant temperature of 298.15 K. Detailed procedure has been reported earlier [20]. Each experiment was repeated at least three times.

2.2. Electronic absorption measurements

UV–visible spectroscopy investigations have been carried out to understand the IBF-SDBS interactions. The absorbance spectra were recorded on an Evolution 300 UV–vis spectrometer with a quartz cuvette.

2.3. Fluorescence measurements

The micellar aggregation number (N_{agg}) of single and mixed amphiphilic solutions was determined by steady-state fluorescence quenching measurements. Pyrene was used as a probe and cetylpyridinium chloride (CPC) as quencher throughout the study. The steady-state fluorescence experiments were performed with a Hitachi F-7000 spectrofluorometer, connected to a PC. A 3 cm^3 silica cell was used for the spectral measurements at a constant temperature. By selecting 335 nm as the excitation wavelength of the fluorescence probe (pyrene), the emission spectra of solution components prepare in pyrene were recorded from 350 to 450 nm. The first and third vibronic peaks of pyrene appear at 373 and 384 nm respectively (Fig. 1). At a constant probe concentration of 1×10^{-6} M, the quencher concentration was varied from 0 to 1×10^{-5} M to ensure a Poisson distribution for equilibration of solubilizates between micelles.

3. Results and discussion

The aqueous solubility of IBF more than 1500 mM was checked and is found to be freely soluble in water. Fig. 2 shows plots of surface tension versus [total amphiphile] in the absence and presence of 100 mM NaCl. The *cmc* value of the pure IBF was found to be 180 mM in water at 298.15 K, which agrees well with the previously reported value in the literature (179 mM) [21]. The *cmc* values of pure SDBS also agree well with the literature (Table 1) [22]. As the