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Interaction of tetracaine hydrochloride with sodium deoxycholate in aqueous micellar phase and at the surface

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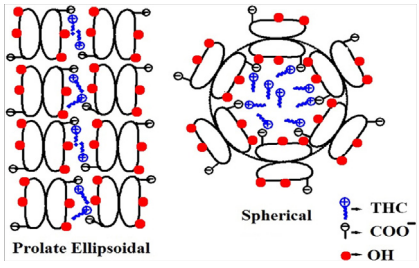
HIGHLIGHTS

- Sodium deoxycholate (SDC) and tetracaine hydrochloride (TCH) mixed system studied.
- Composition of the mixed micelle and adsorption layer evaluated.
- Interaction between TCH and SDC assessed in terms of interaction parameter.
- Hydrodynamic diameters of micelles and vesicles determined.
- The SDC micelles and vesicles are able to entrap water-soluble TCH.

GRAPHICAL ABSTRACT



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ABSTRACT

Assessing drug–surfactant interactions is important in pharmacology and for developing better pharmaceutical formulations. In this paper, we have investigated the interaction between tetracaine hydrochloride (THC) with sodium deoxycholate (SDC). The characteristics of this drug–surfactant system in solution, micellar phase, and at the surface were assessed using the mixing protocol and thermodynamic approach employed in the study of mixed surfactant systems. From the surface tension data, critical micelle concentration of the mixed system was determined and it showed synergism in the region where the solution is clear. The mole fractions of the drug and surfactant, and the interaction parameter were evaluated in the micellar phase and at the solution surface. The hydrodynamic diameters of the drug–surfactant aggregates were determined using dynamic light scattering measurements and the aggregates formed in the middle composition region are very large in size. The SDC aggregates are able to entrap water-soluble THC. From the transmission electron microscopy images, the mixed micelles appear to have spherical and prolate ellipsoidal shapes. It has been shown that activity coefficients and interaction parameter corresponding to equimolar mixed micelle can be calculated directly without resorting to iteration and these values can serve as reference values for verifying the correctness of the iterated values of mole fractions, activity coefficients and interaction parameter in the mixed micelle.

1. Introduction

Most of the drugs are organic molecules of specific molecular structures with hydrophobicity as their general feature. Many of these hydrophobic drugs have amphiphilic character and hence undergo adsorption and aggregation in aqueous medium similar to surfactants. Many of the tranquilizers, analgesics, antibiotics, antidepressants, antihistamines and local anesthetics belong to the amphiphilic type of drugs [1].

Drug–surfactant interaction studies can provide clues regarding drug–protein interactions and also about the drug solubilizing ability of micelles/vesicles/microemulsions. Analytical method for the

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quantitative determination of drug based on the formation of mixed aggregates with surfactants has been demonstrated [2]. Assessing drug–surfactant interactions is therefore pharmacologically and pharmaceutically very important, which has led to the investigation of various types of drug + surfactant combinations in recent years [3–42].

Tetracaine hydrochloride (THC) is a local anesthetic drug with amphiphilic character. Anesthesia is caused by the interaction between anesthetic molecules and lipid molecules constituting a biological membrane at the membrane interface. Surface and other physicochemical properties of anesthetics are supposed to play vital role in the mechanism of anesthesia and hence different physicochemical properties of THC have been studied [43–52]. Sodium deoxycholate (SDC) is a bile salt which performs important physiological functions [53,54]. Bile salts are structurally different from the conventional surfactants and the morphology of their aggregates is also different [53–55]. Besides studying the interaction of bile salts with other types of surfactants [56–64], a few studies on drug + SDC mixed systems have also been reported [23,29,31,32,42] and the drugs studied are promethazine hydrochloride [29,31,32], promazine hydrochloride [29], amitriptyline hydrochloride [23] and imipramine hydrochloride [42]. Interaction studies of THC with decylammonium chloride [51,52] and sodium dioctylsulfosuccinate (AOT) [46] surfactants have been reported.

In view of the importance of fundamental knowledge about the interaction of a drug with bile salt, we have investigated in this paper the behavior of the THC + SDC mixed system, a drug–surfactant system of opposite charges, in aqueous medium by measuring its surface tension. The experimental data have been analyzed to obtain the values of interaction parameter in the mixed micellar phase and at the air–solution interface. The size of the mixed aggregates was estimated from dynamic light scattering (DLS) measurement and transmission electron microscopy (TEM).

2. Materials and methods

Sodium deoxycholate (SDC, 98%) and tetracaine hydrochloride (THC, 99%) were purchased from Sigma. Millipore grade water was used for preparing the solutions. Aqueous solutions of SDC ($\alpha_1 \equiv \alpha_{SDC} = 1$, solution A) and THC ($\alpha_2 \equiv \alpha_{THC} = 1$, solution B) of known concentrations were prepared first by weighing. α denotes the mole fraction in the bulk solution. Stock solutions of THC + SDC mixtures (solution C) of different molar ratios covering the entire composition region ($0 < \alpha_{THC} < 1$) were then prepared by mixing required amounts of solutions A and B. Density of all the stock solutions were determined using Anton Paar DMA 5000 densitymeter.

Surface tension measurments were made by the Wilhelmy plate method using a K11 Krüss tensiometer. The required amount of water was taken in the sample vessel of the tensiometer and its surface tension was recorded. To this water in the sample vessel, known volume of solution A or solution B or solution C of a fixed composition was added by using micropipette and after each addition surface tension value was measured. Before every measurement, the solution was kept for sufficient time to attain thermal equilibrium. In the case of the turbid mixtures ($\alpha_{THC} = 0.4$, 0.5, 0.6, 0.7 and 0.8), they were heated in a thermostat before making surface tension measurements. At around 60 °C these mixtures were found to be homogeneous, although not clear, and the mixtures were kept in the thermostat maintained at this temperature throughout the surface tension measurement. For measuring surface tension, known volumes of the mixture kept in the thermostat were transferred quickly to the sample vessel of the tensiometer by using micropipette. After each addition the solution was left to attain thermal equilibrium and then surface tension was recorded. While making surface tension measurements of $\alpha_{THC} = 0.4$, 0.5, 0.6, 0.7 and 0.8 mixtures in this manner, it was noted that the solution in the sample vessel was clear below critical micelle concentration (cmc), but became again turbid near the cmc. All experimental measurments were made at 25 °C using Julabo F12 circulation bath.

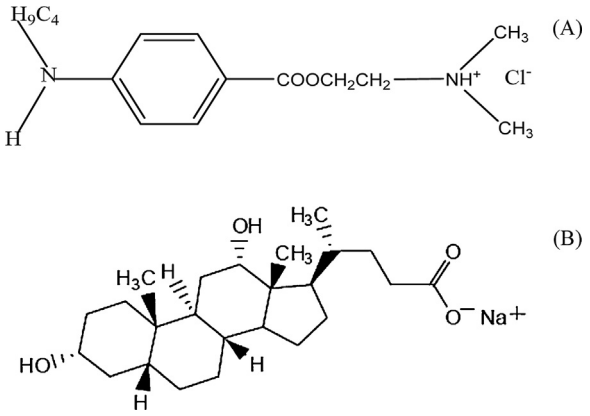

Fig. 1. Structures of (A) THC and (B) SDC.

The particle size (hydrodynamic diameter) of the single and mixed micelles was determined by making DLS measurement by using Malvern Zetasizer Nano ZS90 instrument. This instrument operates at 633 nm (4 mW HeNe laser is used) and fixed 90° scattering angle. The temperature was maintained by the built-in Pelteir temperature control unit of the instrument.

TEM images of THC + SDC solution were recorded by using a JEOL-2100 electron microscope which operates at 120 kV. A drop of the sample was first spread on a 200-mesh copper grid coated with a carbon film, another drop of the staining solution (1% of phosphotungstic acid solution) was then added, and the excess solution was sucked away by a filter paper. The sample was then air-dried and thereafter its electron micrograph was recorded.

3. Results and discussion

The structures of THC and SDC are shown in Fig. 1. The physical appearance of the THC + SDC mixtures is shown in Fig. 2. The mixtures of $\alpha_{THC} = 0.4$, 0.5, 0.6, 0.7 and 0.8 were turbid and sticky, which after about 24 h separated into two phases with clear phase at the top and the sticky phase settling at the bottom. Formation of turbid solutions is common in mixtures of cationic + anionic surfactants [59–66] and is also reported [46] in THC + AOT (sodium dioctylsulfosuccinate) system.

The surface tension (γ) values of the aqueous solutions of the THC + SDC mixtures are presented in Fig. 3 as γ versus $\ln c_s$ plots, where c_s is the concentration of the mixture. In the case of SDC and THC solutions, their surface tension plots exhibit minima near the cmc and the concentrations corresponding to these minima are taken as the cmc values. Surface tension minimum indicates presence of some impurity in the commercial (Sigma) samples of SDC and THC. Problem of impurities in bile salts has been reported earlier [59,67]. However, the present cmc values of SDC and THC equal to 4.1 and 120.0 mM (M = mol dm^{-3}), respectively, are in good agreement with the literature values [1,48,49]. The measured cmc values are shown in Fig. 4.