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Aqueous amphiphilic drug (amitriptyline hydrochloride)–bile salt mixtures at different temperatures

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ABSTRACT

The mixing behavior of amphiphilic drug amitriptyline hydrochloride (AMT) with bile salts (NaC, NaDC, NaTC) was studied at different compositions and temperatures by conductometry. Rubingh's, Motomura's and Clint's approaches were used to analyse the behavior. The obtained results indicate attractive interactions among the two components upon mixing. The experimentally obtained critical micelle concentration (*cmc*) values are always lower than ideal *cmc* values. Increase in temperature gives a peaked behavior to *cmc*. Micellar mole fraction (X_1 and X_1^m) values show that the contribution of bile salts in mixed micelles increases with the increase in concentration of these salts.

1. Introduction

Bile salts are steroidal surfactants which, in aqueous medium, form micelles [1]. Their physicochemical properties have been studied extensively and are still of importance in biology and medicine [2–5]. Bile salts behave like anionic surfactants [1]; however, the formation of bile salt micelles differs from that of the surfactants. Unlike surfactants, bile salts have a rigid steroid backbone with polar hydroxyl groups on the concave α-face and methyl groups on convex face (Scheme 1). The arrangement gives a unique facial amphiphilicity to these compounds. This causes an aggregation behavior different from that of conventional surfactants.

Bile salts have lower aggregation numbers compared with those of conventional aliphatic surfactants; for the sodium cholate micelle, lower values of 4 and higher values of 16 are reported [6]. The aggregation model suggested by Small was the primary–secondary micellar model [1]. Many papers have appeared on solution properties of bile salts [7–9]. However, the mechanism for aggregation process in bile salts is still unresolved.

The bile salts are synthesized in the liver, concentrated in gall bladder, and then discharged into a duodenum through a final biliary duct. Mixed micelles of bile salts and phospholipids solubilize cholesterol and lipids to assist favorable absorption of fats taken as food [10]. As is well known, the solubility of cholesterol, bilirubin, and lecithin in water is very small (the order being 10^{-8}, 10^{-9} and 10^{-10} M, respectively). However, their concentration in bile is more than mM. This increased solubility is due to their solubilization into bile. Under abnormal conditions the sterol gets precipitated, forming gallstones in the bladder [11,12].

Also, mixed micelles of bile salts are promising systems for drug delivery [13]. It has been observed that the bile salts form mixed micelles with the drugs [14] and that the high specificity and capacity of bile acid transport systems during their enterohepatic circulation might form the basis of research on drug–bile acid conjugates for specific drug targeting to the liver and on improving the intestinal absorption of poorly absorbed or nonabsorbed drugs, such as peptides [15,16].

The solution chemistry of micellization of bile salts is an active area of research. A variety of techniques have been used to study the micellization process of bile salts in pure and mixed states [17,18]. We have studied the micelle formation of an amphiphilic drug, amitriptyline hydrochloride (AMT), in presence of bile salts, sodium cholate (NaC), sodium deoxycholate (NaDC) and sodium taurocholate (NaTC). AMT is a drug that belongs to the family of tricyclic antidepressants (Scheme 2). It possesses a rigid, almost planar tricyclic ring system and a short hydrocarbon chain carrying a terminal nitrogen atom. AMT is a surface active drug and forms aggregates in solution, of approximately 6–12 monomers [19] by a closed association process.

AMT suffers from several drawbacks such as anticholinergic, cardiovascular and antiarrhythmic side effects. These undesirable side effects may be reduced if the drug is properly targeted to the organism. Bile salts form mixed micelles with AMT; hence they

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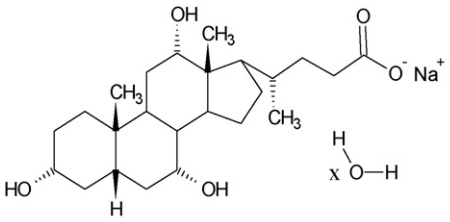
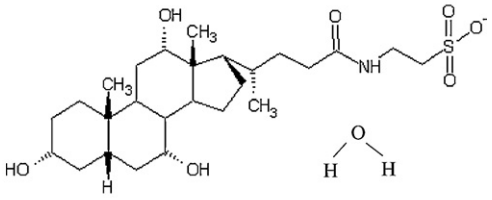
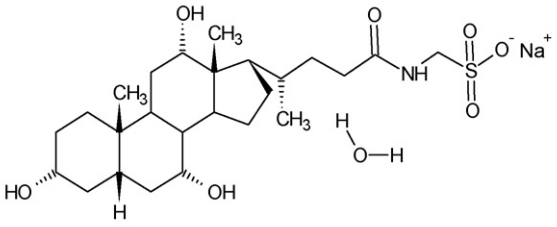


Sodium cholate (NaC)

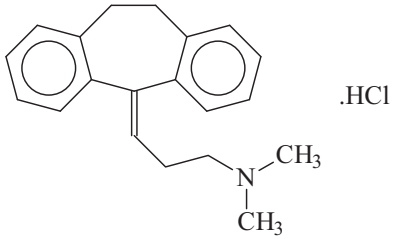


Sodium deoxycholate (NaDC)



Sodium taurocholate (NaTC)

Scheme 1. Molecular structure of bile salts.



Scheme 2. Molecular structure of amitriptyline hydrochloride (AMT).

reduce the amount of AMT to be used. This, in turn, reduces side effects and toxicity of the AMT.

Effect of bile salts' concentration and temperature was also seen. The aim of this work was to provide better knowledge about the formation of bile salt mixed micelles and to understand the behavior of such systems in biological environment and to optimize the application of these mixed systems.

2. Experimental

2.1. Materials

Amitriptyline hydrochloride (AMT, CAS Registry No. 549-18-8, 98%, Sigma, USA) and the bile salts – sodium cholate (NaC, 99%, Sigma, USA), sodium deoxycholate (NaDC, 97%, Sigma, Germany), and sodium taurocholate (NaTC, 97%, Sigma, USA) – were used as received.

Double-distilled water with conductivity lower than 3 $\mu S\,cm^{-1}$ was used to prepare the solutions. Stock solutions of bile salts were prepared by dissolving requisite amount of the compound in a known amount of water. These stock solutions were then used as solvents.

2.2. Conductometry

An ELICO conductivity meter (model CM 180) was used to perform the experiments. 12 ml water (double-distilled) was taken in a cell dipped in a thermostatic water bath. A dip-type conductivity cell of cell constant 1.026 cm^{-1} was inserted into water. A known volume of concentrated solution of drug was then added to water with a pipette and thoroughly mixed, followed by measurement of the conductance. Similar process was repeated each time addition of the drug solution was made. For drug–bile salt mixtures, the bile salt solutions of fixed concentration were used as solvent. The specific conductance (K) was then plotted against drug concentration. The plots showed change in slope above a certain concentration. Break in plot, i.e., the point at which slope changes, is considered as the *cmc* of the solution. Values of the ratio of slopes were used to obtain the degree of counterion dissociation (g), which is the ratio of post-micellar slope to pre-micellar slope. The experimental error in temperature was minimized to 0.2 K.

3. Results and discussion

Bile salts interact with the drug in solution and may form coacervates. Barry and Gray [20,21] have reported 1:1 compositions for the resulting products in solution and coacervates for dihydroxy bile salts.

The variation of *cmc* values of pure components as well as mixtures is shown in Fig. 1 and given in Table 1 . Both AMT and bile salts have rigid hydrophobic structures and their *cmc* values are higher than those of normal surfactants. Although the structure of bile salts is more rigid than that of drug, their *cmc* values are lower than the latter. The difference is due to the mode of association of these two components. AMT forms micelles in a conventional way. However, for bile salts the model suggested by Small [1] is a two step process. In this model, first, primary micelles are formed where the hydrocarbon backs of the steroid nucleus associate. After that, primary micelles associate to form secondary micelles. This model suggests