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Effect Of Bile Salt In Pharmacokinetic, Micellization And Drug Dissolution

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Key word- Sodium cholate, Sodium deoxycholate, Drugs, Critical micelle concentration, Surface tension.

Abstract- Bile is a compound made in the liver and is stored in the gall bladder, which is a small pouch connected to the liver. Bile acid synthesis is the predominant metabolic pathway for catabolism of cholesterol in humans. Modification of cholesterol to bile acids converts a hydrophobic membrane constituent to amphipathic molecules that can serve as powerful physiological detergents for absorption and transport of nutrients, fats, and drugs but also as the versatile signaling molecules that are specific ligands for activation of nuclear and membrane receptors. Bile salts are present in the intestines of humans as well as the animals used during the development of pharmaceutical products. This review provides a short introduction into the physical chemical properties of bile salts, a description of the bile concentration and composition of bile in different concentration of drugs.

Introduction-

In this review, bile salt, bile salt surfactant, and bile salt–drug interactions and their solubilization studies are mainly focused. Usefulness of bile salts in digestion, absorption, and excretion of various compounds and their rare properties in ordering the shape and size of the micelles owing to the presence of hydrophobic and hydrophilic faces are taken into consideration while compiling this review. Bile acids are derivatives of cholesterol synthesized in the hepatocyte. Cholesterol, ingested as part of the diet or derived from hepatic synthesis is converted into the bile acids cholic and chenodeoxycholic acids, which are then conjugated to an amino acid (glycine or taurine) to yield the conjugated form that is actively secreted into cannaliculi. Bile acids are facial amphipathic, that is, they contain both hydrophobic (lipid soluble) and polar (hydrophilic) faces. The cholesterol-derived portion of a bile acid has one face that is hydrophobic (that with methyl groups) and one that is hydrophilic (that with the hydroxyl groups); the amino acid conjugate is polar and hydrophilic.

Major determinants of the bioavailability of drugs are the degree of intestinal absorption and the hepatic first-pass effect. Drugs need to overcome several membrane barriers before reaching the systemic

circulation, each of which expresses an array of specialized transport proteins for drug uptake or efflux. This article aims to provide an overview of the current knowledge related to use of bile acids, their salts and various derivatives as drug penetration modifiers and consequently their potential applications in pharmaceutical dosage forms. Bile salts, which are soluble amphiphiles, possess a unique molecular structure when compared with typical detergent molecules. Greenish yellow secretion, bile or gall, is secreted by the liver and stored in the gallbladder where it is concentrated or passed to duodenum part of small intestine. Its main purpose is to emulsify fats and help their absorption in the small intestine. Its main constituents are bile acids and bile salts, cholesterol, phospholipids, water, and pigments. One of the constituents of bile that is bile salts are formed of four different bile acids, namely, cholic, deoxycholic, chenodeoxycholic, and lithocholic. These acids in turn have the capacity to interact and combine with glycine or taurine forming complex acids and salts. In water, bile salts form small aggregates called micelles. The behavior of bile salt micelles is quite different from micelles formed by detergents. Bile salt micelles are smaller, more highly charged and of different structure than detergent micelles. Bile salts form mixed micelles with a variety of other soluble and insoluble lipidic substances. While bile salts increase slightly the solubility of relatively nonpolar molecules (such as cholesterol or fatty acids), they have a striking capacity to render soluble certain important insoluble molecules of biological importance such as phospholipids and monoglycerides. In fact as little as 1 mole of bile salt can solubilize 2 moles of lecithin. Solubilization takes place in mixed bile salt micelles of unique structure and properties. These mixed micelles incorporate very appreciable amounts of insoluble molecules, such as fat-soluble vitamins. Bile salts present a class of potential bio-surfactants with biological importance [6, 7], for instance as solubilizers to cholesterol and lipids [8], emulsifiers and dispersion agents in cosmetics [9], medicines [10], and chemicals [11]. Mixed micelles are formed when bile salts are added with other amphiphiles [12–16] and also result in the formation of liquid crystalline phases [17–19]. The aggregates of bile acid salts are important owing to their physicochemical properties which are different than conventional amphiphiles. For example, their critical micelle concentration (CMC) is lower than simple ordinary surfactants, and this CMC is characterized by a range rather than an exact value with smaller aggregation number, higher charge density, and higher polydispersity [20–35]. Lecithin is the major phospholipid found in human bile. It plays an essential role in the solubilization of dietary fats in the gastrointestinal tract, and may also facilitate the dissolution of drugs from oral dosage forms. In these studies, lecithin was found to influence the dissolution of steroids in bile salt solutions by influencing both the mechanism and the extent to which dissolution rate is enhanced.

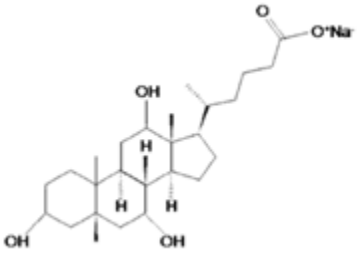

Fig1 Sodium cholate

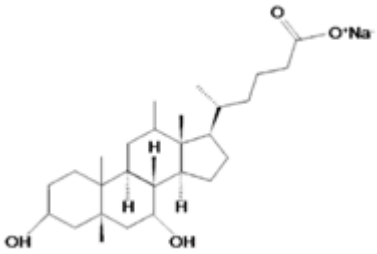

Fig2 Sodium deoxycholate

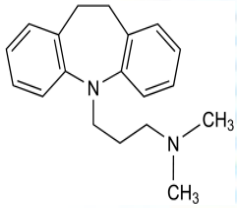

Fig 3 Ametreptylene

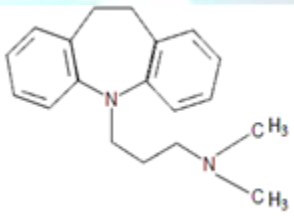

Fig 4 Imipramine

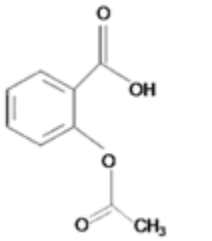

Fig 5 Disprine

Bile Salt–Surfactant Interactions

The interaction of bile salts with lipids, biocompatible polymers, surfactants, and other bioactive molecules has been extensively studied. By reason of the small aggregation number which results in small size of aggregates, hydrophobic guest molecules such as cholesterol are poorly solubilized by the micelles of bile salts. Bile salts inside human beings have the special capacity to dissolve cholesterol due to the formation of mixed micelles between bile salt and phospholipid that is lecithin. Due to this capability, they solubilize hydrophobic guest molecules in micelles. Different types of interactions occur in bile salts

with phospholipid bilayers. The bile salt monomers without disrupting the membranes are inserted into the phospholipid vesicles when their concentration is lower than CMC. Mixed micelle systems are formed as the concentration of bile salts reaches above their CMC, and solubilized with more increase in the concentration of bile salts. Surface tension and conductivity techniques were performed at 298 K in aqueous solutions of the mixed micelles of Sodium cholates and sodium deoxycholate to find the critical micelle concentrations, conductivities, and aggregation numbers. n pure and at different compositions were studied using the techniques: Conductivity and surface tension measurements were employed to study the mixed micellization behavior of bile salts (sodium cholate and sodium deoxycholate) with various d rugs like (Imipramine, Ametreptylene, Disprine etc).

Bile and Bile Salt Micelles

An average composition of human gall bladder bile is ~84% water, 11.5% bile salts, 3% lecithin, 0.5% cholesterol, and 1% other components, such as bile pigments, inorganic ions, and protein.52 In response to the intestinal presence of digestion products (especially lipid digestion products), cholecystokinin-mediated contraction of the gall bladder and relaxation of the sphincter of Oddi leads to expulsion of bile, with peak flow occurring ~30 min after meal ingestion. Although variable, typical bile salt concentrations in the fasted intestine are 4-6 mM compared with postprandial levels of 10-20 mM. In water, bile salts form small aggregates called micelles. The behavior of bile salt micelles is quite different from micelles formed by detergents. Bile salt micelles are smaller, more highly charged and of different structure than detergent micelles. Bile salts form mixed micelles with a variety of other soluble and insoluble lipidic substances. While bile salts increase slightly the solubility of relatively nonpolar molecules (such as cholesterol or fatty acids), they have a striking capacity to render soluble certain important insoluble molecules of biological importance such as phospholipids and monoglycerides. In fact as little as 1 mole of bile salt can solubilize 2 moles of lecithin. Solubilization takes place in mixed bile salt micelles of unique structure and properties. These mixed micelles incorporate very appreciable amounts of insoluble molecules, such as fat-soluble vitamins etc.

The Role of Bile in Drug Dissolution and Solubilization

The presence of bile may improve the bioavailability of poorly water soluble drugs by enhancing the rate of dissolution and/or solubility. An increase in the rate of dissolution can occur via (i) a decrease in the interfacial energy barrier between solid drug and the dissolution medium (via enhanced wetting), leading

to an effective increase in surface area, or (ii) an increase in solubility via micellar solubilization. However, a consequence of drug solubilization within the bile salt micelle is a decrease in the apparent diffusion coefficient of the drug. In general, enhanced wetting predominates at bile salt concentrations below the cmc, whereas enhanced solubility is dominant at concentrations above the cmc. It is important to note that changes in the dissolution rate of poorly water-soluble drugs due to wetting or solubilization is compound dependent due to the specificity of the interactions associated with these processes.

Drug Solubility and Dissolutions

The pH differences in the contents of the upper GI tract between fed and fasted states can influence the dissolution and absorption of weakly acidic and basic drugs. The dissolution rate of weak bases is typically greater in gastric fluids than in the intestine in the fasted state, whereas that of weak acids is at a minimum in the stomach and increases as undissolved drug is transported to the less acidic regions of the intestine. Therefore, elevation of gastric pH following a meal may enhance the dissolution of a weak acid in the stomach but inhibit that of a weak base. Furthermore, because food inhibits the rate of gastric emptying,159 prolonged retention in the stomach may increase the proportion of drug that dissolves prior to passage into the small intestine. The primary site of drug absorption is usually the small intestine because of its greater mucosal surface area and range of transport mechanisms, so the classes of drugs most vulnerable to pH-related changes in postprandial absorption are poorly water-soluble weak bases.

Bile acids as drug carrier systems

Recently, bile acids have drawn much attention in the field of drug delivery due to their ability to act as a drug carrier system in the form of mixed micelles, bilosomes and chemical conjugates with drug molecules (Figure 1).

Mixed micellar systems

As mentioned above, drugs that are slightly soluble in water may be solubilized within bile salt micelles, in order to improve their absorption. In aqueous solution, bile acid anions self-associate to form simple micelles. In the gastrointestinal tract, during the lipid digestion, salts are found to be associated with phospholipids, fatty acids and monoglycerides, forming mixed micelles. Some studies reported that the combined use of bile salts with compounds such as phospholipids, fatty acids and polyamines may

improve their effectiveness as absorption enhancers and allow a decrease in their concentration, thus lowering the risks of membranolytic effect.

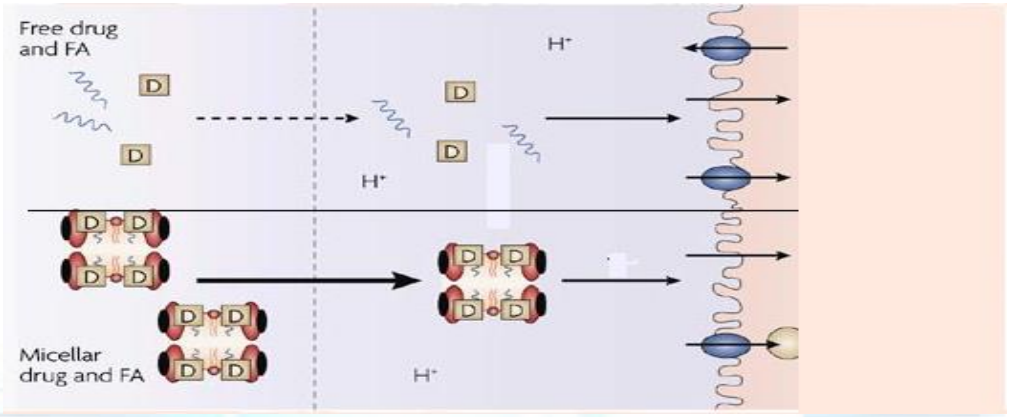

Fig 6 Drug delivery by making mixed micelle with bile salt

Determination of effect of drugs on the micellization processs of bile salts

The mixed micellization behavior and surface properties of the various antidepressant drugs-bile salt systems have been analyzed by conductivity and surface tension measurements.

Thermodynamics of micellization

Surfactant concentration is increases gradually after some time it reaches at particular concentration which shows deviation between pree miceller region and post miceller region known as cmc, from where micelle form is spontaneous. This means the free energy of surfactants molecule of micelle is always be less than the monomeric surfactants molecule when dissolving in distilled water. All the thermodynamics parameters are temperature dependent. [39].

The Gibbs free energy of micellization ΔG^{o}_{m} was calculated by using following equation [46].

$$\Delta G^{o}_{m} = (2-\alpha)\ RT\ \ln X_{cmc} \qquad (1)$$

The Calculated value of parameter is shown in Table 3 and 4 at various temperature range. The ΔG^{o}_{m} is decrease with increasing temperature, this value show that the micellization process is spontaneous in

aqueous mixtures and magnitude of hydrophobic effect is increases with increasing temperature. [39, 46] (Table 7-12). The ΔH^o_m can be derived by the Von't Hoff equation.

$$-\Delta H^o_m = (2-\alpha)RT^2 \left(\frac{d\ lnX_{cmc}}{dT}\right) \quad (2)$$

The result of the calculation shows that standard enthalpy of micellization (ΔH^o_m) is negative which indicates that the micelle formation process is exothermic which show strong interaction between drug and bile salts[39, 46].

The ΔS^o_m was determined from the calculated values of ΔG^o_m and ΔH^o_m by the help of following relationship

$$-T\Delta S^o_m = (\Delta G^o_m - \Delta H^o_m) \quad (3)$$

The ΔS^o_m is always being positive which indicate that the process of micellization is entropy dominated over the micelle formation process. The positive value of ΔS^o_m is due to the hydrophobic interaction between the surfactants and water molecule. [46, 39, 3].

Surface tension method

The surface tension of the individual unknown solution has been calculated from the known values of surface tension of water (72 dyne/cmc^{-1}) densities and weight of solution and water. Surface tension plot did not show the occurrence of a minimum, showing that no impurities are presents. The study allowed us to conclude that the ability of polar-organic solvent to act as a structure breaker and its interaction with the surfactants hydrophilic group are the controlling factors of the micellization process. From the evaluation of the thermodynamics of adsorption at the solution-air interface, it was determined that the surface activity of the surfactants decreases slightly with increasing concentration of aquo-organic solvent at given temperature [22, 46].

The plot between surface tension and concentration of surfactants show that the surface tension of surfactant solution decreases linearly with increasing concentration. The intersection between preemicellar and postmicellar reagion are called cmc are shown in Tables 1-6.

The air solvent interface data are given in Table 19 and 20. The surface excess quantities at the cmc (ζmax) was obtained from the Gibbs equation (4).

$$\zeta_{max} = -\frac{1}{2.303nRT}\left(\frac{d\gamma}{d\log C}\right)_{T,P} \quad (4)$$

where γ is the surface tension at the cmc, R is the gas constant, C is the concentration of the surfactants in solution and n is the constants which depends upon the number of the species constituting the surfactants and are absorbed at the interface. In this paper we considered a value of 1 for the 'n' parameters [51].

The minimum area per surfactant (A_{min}) at the air/solvents interface was obtained from the relation equation (5) and its value given in Table 7 and 8 [23, 51].

$$A_{min} = \left[\frac{10^{14}}{N\,\zeta_{max}}\right] \quad (5)$$

Where N is the Avogadro's number. The value of the surface pressure at the cmc (π_{cmc}) was obtained from the equation (6), where γ^0 is the surface tension of the solvents and γ_{cmc} is the surface tension of the cmc. (Table 7 and 8)

$$\pi_{cmc} = [\gamma^0 - \gamma_{cmc}] \quad (6)$$

The standards Gibbs free energy of the adsorption was obtained from the relation at equation (7). (Table 7 and 8)

$$\Delta G^{\circ}_{ad} = \left[\frac{\Delta G^{\circ}_{m} - \pi_{cmc}}{\zeta_{max}}\right] \quad (7)$$

In which ΔG°_{m} is the standards Gibbs energy of micellization and its value given in Table19 and 20 [24, 25]. The internal properties of the surfactants in solution can provide information about solute-solute and solute-solvent interaction and the effectiveness of the surface active molecule. The surface excess concentration(ζ_{max}), the minimum area per molecule(A_{min}), the surface pressure at the cmc (π_{cmc}) are listed in Tables

Development of model

The present study gives focus into the mechanism of interaction of some bile salts (like sodium cholate and sodium deoxycholate) with various drugs like Imipramine. Experimental observation explain that there is any changes in concentration ranges involved in the changes of the solubilisation of drugs by bile salts (Sodium cholate and sodium deoxycholate). Experimental observation shows that the drug concentration is dependent on the concentration of a bile salt because certain changes in the concentration of bile salt bring changes on drugs. Thus it is strongly dependent on the absolute concentrations of bile salt and not on their molar ratio. The bioavailability of orally administered drugs can be influenced by interacting with food constituent and by physico-chemical conditions in the upper gastrointestinal tract. Normally, bile salt increases the transport of lipophilic drugs across mucosal membranes. Bile salts are able to form stable mixed micelles consisting of fatty acids and phospholipids. Conventional micellar systems are known to solubilize lipophilic drugs having a low bioavailability [42].

Surfactant (bile salt) added in the drug and distilled water solution, then the dissolution rate of the Imipramine tablets increases. It concludes that even presence of small concentration of bile salts is very helpful for the dissolution of various drugs [41].

In method to observing the influence of the structure of drug on formation of mixed micelles [4] with SDC and SC, physico chemical values of micelles and mixed micelle were calculated by using experimental cmc values which.

cmc^{id}, x^{id}, X_1 and the β parameter all were calculated by using following equation [3, 38].

The cmc^{id} parameter indicates non ideal behaviour if it differs from cmc^{ex}. The values of x^{id} and the x_1 are used to calculate the β parameter. Critical micelle concentrations according to Clint's theory of ideal mixtures (cmc^{id})

$$\frac{1}{cmc^{id}} = \frac{\propto_i}{cmc_1} + \frac{1 - \propto_i}{cmc_2} \qquad (8)$$

The cmc^{id} values are shows and compared to the experimental obtained cmc (cmc^{ex}) in Table 13-18 [3]. Deviation of the experimentaly obtained cmc values from those calculated according to Clint's theory indicates nonideal behavior of examined surfactant mixtures and mutual interactions of the surfactants in the micelles.according to this experimental cmc are always be smaller than those predicted using models. The mole fraction of the more hydrophobic surfactant in the ideal mixed micelle (x^{id}), according to Motomura [2, 3 and 16], was calculated using the following relationship:

$$X^{id} = \frac{cmc_2 \propto}{cmc_2 \propto + cmc_1(1-\propto)} \quad (9)$$

The x_1 value was calculate by using following relation:

$$1 = \frac{(X_1^{Rub})^2 \ln\left(cmc^{ex} \propto / cmc_1 X_1^{Rub}\right)}{(1 - X_1^{Rub})^2 \ln\left[cmc^{ex}(1-\propto)/cmc_2(1 - X_1^{Rub})\right]} \quad (10)$$

The x^{id} and the x_1 values for the mixed micelles are presented in Table 13-18. Further according to Rubingh [3, 15], x_1 value was used to calculate the β interaction parameter, through the following equation:

$$\beta = \frac{\ln(cmc^{ex} \propto / cmc_1 X_1^{Rub})}{(1 - X_1^{Rub})^2} \quad (11)$$

β values explain the synergism or antagonism between two surfactants in mixed micelles. Its negative value indicate attractive interactions (synergism) between components of mixed micelles of drug and bile salt, The less negative value means the weaker synergistic interaction while positive values shows antagonistic interactions between surfactants in a mixture. Its value also shows the deviation between experimentally obtained (cmc^{ex}) and calculated (cmc^{id}) cmc values [3].

Solubilization Effects of Bile Salts on Drugs

To understand the absorption of various poorly soluble drug molecules, the investigation of solubility and the extent of dissolution is the primary step. It has become a well-established research area to increase the productivity and efficiency of the

Conclusions and Future Perspectives

Micelles of bile salts are more highly charged with different structure and smaller, as compared to conventional ones. Bile salts solubilize many soluble and lipidic substances owing to formation of mixed micelles. To solubilize nonpolar substances particularly cholesterol and fatty acids, their importance in solubilizing many biologically important insoluble substances such as phospholipids and monoglycerides is a new area of interest. In biotechnology and in pharmaceutical industry, cholanology (bile acid science)

plays an important role. The uniqueness of bile salts in having two binding sites makes them capable of delivering hydrophilic and hydrophobic drug molecules. Bile salts inside human beings have the special capacity to dissolve cholesterol due to the formation of mixed micelles between bile salts and phospholipids. Drug-induced liver injury (DILI) is a major and still unresolved scientific problem; thus, these types of interactions can be utilized to overcome this problem. Bile salt–drug interaction studies are not extensively studied; therefore, absorption of various poorly soluble drug molecules with the bile salts can be helpful in further investigation. Thus, being bio-surfactants, their impact on the well-being of humans will be a boon.

Bile salts (sodium cholate and sodium deoxycholate) and drug like Ametreptylene, are observed by conductometric and surface tension method. The results of the study have been analyzed by applying various theories like Clint's, Rubingh's, and Motomura's theories for mixed binary systems. The critical micelle concentration of the ideal mixed micelle (cmc^{id}), the mole fraction of the more hydrophobic surfactant in the ideal mixed micelle (x^{id}), the mole fraction of the more hydrophobic surfactant in the real mixed micelle (x_1) and the β interaction parameter of the mixed micelles were calculated by using experimental values obtained by both methods. Larger numbers of hydrophilic groups present in the bile salts give results of increased synergistic interactions. bile salt/ dietary lipid mixed micelles can initiate and increase the wetting of poor soluble drugs and increase their effective solubility and transport towards affected are [44].

The CMC and α value of sodium cholate (SC) and sodium deoxycholate (SDC) and drug (Ametreptylene) mixtures were determined in aqueous solvent mixture. It was observed that both values were depending on concentration of mixed surfactants, solvent and temperature. It was observed that micellization tendency of SC and SDC decrease in the presence of mixed micelle. The thermodynamic parameters of the process of micellization have been calculated for each system. ΔG^o_m is negative and becomes less negative with increase in concentration of mixed surfactants and solvent mixture. This suggest the micellization formation is becomes less spontaneous with increasing amount of surfactants and solvents.

The positive values of entropy of micellization indicated that the micellization process is somewhat entropy dominated. The interfacial property of the surfactants in solution can provide the information that the influence of drugs addition on the micellization process, of surfactats remaining mainly on the bulk phase of micellar solution can be approximately accounted for by considering changes in the bulk phase interface. Final observation shows that the value of ζ_{max} is generly decreases and then of A_{min} increases with increasing in amount of mixed surfactants in aqueous solvents. The value of ζmax

and A_{min} show that in general the more the amount of the solvents, the stronger the tendency of the surfactants molecule to run away from the air/solvent interface resulting in less packed surface charges in the water structure. The surface pressure at the cmc, π_{cmc} governs the surface activity of the surfactants. An increased in the amount of mixed surfactants and aqua solvents in the mixture result in a reduction of the π_{cmc} and consequently reduces the extents of the adsorption of surfactant molecules at air/ solvent interface. Thus the value of π_{cmc} is increases and ΔG°_{ad} is decreases with decreasing concentration of mixed solution.

Table 1 Critical micelle concentration and α value of various concentrations of Sodium Cholate (SC) and Ametereptylene at different temperatures.

SC+ Ametereptylene concentration		Temperature (Kelvin)					
SC (mM)	Ametereptylene (mM)	300		310		320	
		CMC (mM)	α	CMC (mM)	α	CMC (mM)	α
0.1	0.1	0.017	$8.38X10^{-3}$	0.023	0.083	0.033	0.0133
0.09	0.1	0.019	0.011	0.0211	0.0246	0.0253	0.0238
0.08	0.1	0.0163	0.0178	0.018	0.075	0.0211	0.0368
0.07	0.1	0.0154	0.0102	0.0178	0.0181	0.0212	0.04
0.06	0.1	0.0145	0.044	0.0177	0.0545	0.0228	0.075
0.05	0.1	0.0136	0.0163	0.0125	0.0272	0.015	0.052
0.04	0.1	0.0133	0.03	0.0147	0.05	0.0164	0.048
0.03	0.1	0.0123	0.749	0.013	0.07	0.0136	0.063
0.02	0.1	0.012	0.0139	0.0126	0.025	0.0141	0.071
0.01	0.1	0.01	0.0181	0.011	$7.66X10^{-3}$	0.0122	0.056

Table 2 Critical micelle concentration and α value of various concentrations of Sodium deoxyc holate (SDC) and Ametereptylene at different temperatures.

SDC+ Ametereptylene concentration		Temperature (Kelvin)					
SDC (mM)	Ametereptylene (mM)	300		310		320	
		CMC (mM)	α	CMC (mM)	α	CMC (mM)	α
0.1	0.1	0.0142	0.033	0.016	0.071	0.0166	0.0193
0.09	0.1	0.0158	0.0526	0.0165	0.032	0.018	0.119
0.08	0.1	0.015	0.142	0.0156	0.12	0.0171	0.27
0.07	0.1	0.0121	0.0126	0.0141	0.0125	0.0178	0.066
0.06	0.1	0.0123	0.0312	0.016	0.0433	0.0177	0.033
0.05	0.1	0.0115	0.025	0.0142	0.0283	0.0166	0.0167
0.04	0.1	0.0093	0.033	0.0107	0.106	0.0121	0.0121
0.03	0.1	0.0104	0.0312	0.013	0.0272	0.0162	0.0162
0.02	0.1	0.0096	0.019	0.012	0.0916	0.0133	0.0133
0.01	0.1	0.00916	0.0227	0.011	0.0267	0.0137	0.024

Table 3 Critical micelle concentration and α value of various concentrations of Sodium Deoxycholate (SDC) and Imipramine at different temperatures.

SDC+ Imipramine concentration		Temperature (Kelvin)					
SDC (mM)	Imipramine (mM)	300		310		320	
		cmc (mM)	α	CMC	α	CMC	α
0.1	0.1	0.0166	0.0181	0.0181	0.27	0.02	0.266
0.09	0.1	0.019	4.28×10^{-3}	0.023	0.03	0.0316	3.17×10^{-3}
0.08	0.1	0.0225	0.166	0.018	0.028	0.03	0.032
0.07	0.1	0.017	0.08	0.021	0.028	0.024	2.9×10^{-3}
0.06	0.1	0.01	0.772	0.0114	9.01×10^{-3}	0.016	0.14
0.05	0.1	0.0375	3.95×10^{-3}	0.0093	4×10^{-3}	0.0125	0.016
0.04	0.1	-	-	-	-	-	-
0.03	0.1	0.0216	0.077	0.0081	0.025	0.0108	0.225
0.02	0.1	0.0075	0.148	0.015	0.074	0.02	0.0238
0.01	0.1	0.0042	0.116	0.0045	6.81×10^{-3}	0.0061	0.01

Table 4 Critical micelle concentration and α value of various concentrations of Sodium Cholate (SC) and Imipramine at different temperatures.

SC+ Imipramine concentration		Temperature (Kelvin)					
SC (mM)	Imipramine (mM)	300		310		320	
		CMC	α	CMC	α	CMC	α
0.1	0.1	0.0166	0.0266	0.022	0.16	0.04	0.011
0.09	0.1	0.019	0.136	0.0316	0.05	0.047	0.082
0.08	0.1	0.0225	0.031	0.03	0.041	0.045	0.133
0.07	0.1	0.0283	0.09	0.0425	0.081	0.056	0.265
0.06	0.1	0.0133	0.225	0.02	0.437	0.04	0.015
0.05	0.1	0.0107	0.088	0.015	0.047	0.025	0.015
0.04	0.1	-	-	0.0125	0.148	-	-
0.03	0.1	0.0092	0.109	0.0108	0.06	0.0162	0.153
0.02	0.1	0.01	0.148	0.01	0.176	0.015	0.173
0.01	0.1	0.00916	0.116	0.0078	0.227	0.011	0.028

Table 5 Critical micelle concentration and α value of various concentrations of Sodium Deoxycholate (SDC) and Disprine at different temperatures.

SDC+ Disprine concentration		Temperature (Kelvin)					
SDC (mM)	Disprine (mM)	300		310		320	
		CMC	α	CMC	α	CMC	α

0.1	0.1	0.05	0.192	0.066	0.75	0.066	
0.09	0.1	0.03	0.448	0.0475	0.392	0.0633	0.137
0.08	0.1	0.0325	0.438	0.0433	0.0908	0.052	0.137
0.07	0.1	0.04	0.6	0.0566	1.25	0.071	0.013
0.06	0.1	0.0266	1.28	0.032	0.919	0.04	0.281
0.05	0.1	0.0187	0.2933	0.025	0.272	0.0375	$3.5X10^{-3}$
0.04	0.1	0.0327	0.0225	0.0054	0.357	0.0064	0.66
0.03	0.1	0.0216	0.0617	0.0433	0.111	0.065	$9.5X10^{-3}$
0.02	0.1	0.0171	0.076	0.024	0.07	0.03	0.0825
0.01	0.1	0.016	0.053	0.0183	0.24	0.0171	$1.16x10^{-7}$

Table 6 Critical micelle concentration and α value of various concentrations of Sodium Cholate (SC) and Disprine at different temperatures.

SC+ Disprine concentration		**Temperature (Kelvin)**					
SC (mM)	**Disprine (mM)**	**300**		**310**		**320**	
		CMC	**A**	**CMC**	**α**	**CMC**	**α**
0.1	0.1	0.06	0.443	0.1	0.577	0.075	0.0634
0.09	0.1	0.056	0.77	0.07	0.214	0.07	0.162
0.08	0.1	0.045	0.0204	0.06	0.206	0.09	0.0325
0.07	0.1	0.04	0.0326	0.048	0.133	0.06	0.0803
0.06	0.1	0.0314	0.0416	0.0366	0.333	0.044	0.187
0.05	0.1	0.036	0.135	0.045	0.0789	0.053	0.06
0.04	0.1	0.035	0.16	0.035	0.292	0.035	0.0175
0.03	0.1	0.0325	0.892	0.0216	0.192	0.0325	0.0416
0.02	0.1	0.0266	0.235	0.0342	0.133	0.048	0.0625
0.01	0.1	0.0244	0.124	0.0314	0.204	0.0366	0.187

Table 7 Thermodynamic parameters for the micellization of various concentration of sodium deoxycholate (SDC) with Ametereptylene [39]

SDC+ Ametereptylene (300K)				SDC+ Ametereptylene (310K)				SDC+ Ametereptylene (320K)			
CMC	ΔG°_{m} (kJ/mole)	ΔH°_{m} (kJ/mole)	ΔS°_{m} (kJ/mole)	CMC	ΔG°_{m} (kJ/mole)	ΔH°_{m} (kJ/mole)	ΔS°_{m} (kJ/mole)	CMC	ΔG°_{m} (kJ/mole)	ΔH°_{m} (kJ/mole)	ΔS°_{m} (kJ/mole)
0.0142	-74.47	-11.49	209.9	0.016	-74.87	-12.03	202.7	0.0166	-79.7	-13.16	206.2
0.0158	-73.22	-9.49	212..4	0.0165	-76.23	-10.24	278.9	0.018	-74.78	-10.43	201.0
0.015	-70.09	-9.10	203.2	0.00156	-73.09	-9.84	204.0	0.0171	-69.01	-9.64	185.5
0.0121	-76.04	-28.7	157.7	0.0141	-77.79	-30.64	152.0	0.0178	-76.94	-31..77	141.1
0.0123	-75.25	-26.8	161.4	0.016	-75.95	-28.44	153.2	0.0177	-78.28	-3.04	235.1
0.0115	-75.81	-27.12	162.3	0.0142	-77.14	-28.91	155.5	0.0166	-77.47	-30.28	147.4
0.0093	-76.55	-19.36	190.6	0.0107	-75.48	-19.91	179.2	0.0121	-79.93	-21.94	181.2
0.0104	-76.07	-35.53	135.13	0.013	-77.63	-38.01	127.8	0.0162	-79.4	-40.73	120.8
0.0096	-76.94	-24.16	175.9	0.012	-75.49	-24.85	163.35	0.0133	-80.2	-79.9	-33.85
0.00916	-77.02	-29.77	157.5	0.011	-78.5	-31.73	150.87	0.0137	-79.9	-33.85	143.9

Table 8 Thermodynamic parameters for the micellization of various concentration of sodium cholate (SC) with Ametereptylene [39]

SC+ Ametereptylene (300K)				SC+ Ametereptylene (310K)				SC+ Ametereptylene (320K)			
CMC	ΔG°_m (kJ/mole)	ΔH°_m (kJ/mole)	ΔS°_m (kJ/mole)	CMC	ΔG°_m (kJ/mole)	ΔH°_m (kJ/mole)	ΔS°_m (kJ/mole)	CMC	ΔG°_m (kJ/mole)	ΔH°_m (kJ/mole)	ΔS°_m (kJ/mole)
0.017	-74.51	-49.42	83.63	0.023	-72.6	-50.78	70.38	0.033	-75.79	-56.	61.53
0.019	-73.86	-21.3	175.26	0.0211	-75.27	-22.59	169.9	0.0253	-76.77	-24.08	164.65
0.0163	-74.37	19.14	184.1	0.018	-74.13	-19.84	175.12	0.0211	-77.21	-21.56	173.9
0.0154	-74.93	-23.79	170.46	0.0178	-76.38	-25.3	164.7	0.0212	-77.06	-26.66	157.5
0.0145	-75.24	-33.12	140.4	0.0177	-75.01	-35.17	128.51	0.0228	-75.32	-37.08	119.5
0.0136	-75.32	-7.27	226.83	0.0125	-77.83	-7.72	226.16	0.015	-78.39	-8.12	219.5
0.0133	-74.91	-15.44	198.23	0.0147	-76.12	-16.32	192.9	0.0164	-78.08	-17.40	189.6
0.0123	-47.81-	-4.702	143.7	0.013	-75.95	-7.74	220	0.0136	-78.45	-10.31	212.9
0.012	76.03	-11.98	213.5	0.0126	-77.88	-12.72	210.19	0.0141	-77.94	-13.24	202.1
0.01	-76.77	-14.74	206.7	0.011	-79.26	-15.82	204.6	0.0122	-79.29	-16.45	196.3

Table 9 Thermodynamic parameters for the micellization of various concentration of sodium deoxycholate (SDC) with Imipramine [31]

SDC+ Imipramine (300K)				SDC+ Imipramine (310K)				SDC+ Imipramine (320K)			
CMC	ΔG°_m (kJ/mole)	ΔH°_m (kJ/mole)	ΔS°_m (kJ/mole)	CMC	ΔG°_m (kJ/mole)	ΔH°_m (kJ/mole)	ΔS°_m (kJ/mole)	CMC	ΔG°_m (kJ/mole)	ΔH°_m (kJ/mole)	ΔS°_m (kJ/mole)
0.0166	-74.26	-13.81	201	0.018	-66.33	-12.82	255	0.02	-68.45	-13.75	170
0.019	-74.11	-37.98	120	0.023	-75.5	-40.03	114	0.031	-76.39	-43.24	103
0.0225	-67.33	-19.73	158	0.018	-75.94	-22.66	171	0.03	-75.56	-24.09	160
0.017	-71.83	-25.36	131	0.021	-75.11	-27.81	152	0.024	-77.82	-30.02	149.3
0.01	-47.64	-21.59	86.83	0.011	-79.02	-37.38	134	0.016	-74.52	-37.21	116
0.0375	-70.74	82	509	0.009	-80.23	87.59	541	0.012	-80.7	92.75	542
-	-	-	-	-	-	-	-	-	-	-	-
0.0216	-70.79	49.87	402	0.008	-80.08	53.25	430	0.010	-72.97	52.37	391
0.0075	-11.83	-11	2.76	0.015	-75.08	-75.46	-1.2	0.02	-78.01	-82.5	-14.03
0.0042	-80.65	-2.71	259	0.004	-83.79	-2.92	260	0.006	-84.83	-3.11	255

Table 10 Thermodynamic parameters for the micellization of various concentration of sodium cholate (SC) with Imipramine [31]

SC+ Imipramine (300K)				SC+ Imipramine (310K)				SC+ Imipramine (320K)			
CMC	ΔG°_m (kJ/mole)	ΔH°_m (kJ/mole)	ΔS°_m (kJ/mole)	CMC	ΔG°_m (kJ/mole)	ΔH°_m (kJ/mole)	ΔS°_m (kJ/mole)	CMC	ΔG°_m (kJ/mole)	ΔH°_m (kJ/mole)	ΔS°_m (kJ/mole)
0.0166	-73.94	-64.93	30.03	0.022	-69.91	-64.64	17	0.04	-74.85	-74.46	1.21
0.019	-69.22	-63.9	17.73	0.0316	-72.27	-71.37	2.9	0.047	-71.29	-74.81	-11
0.0225	-72.29	-51.06	70.76	0.03	-71.94	-54.24	57.09	0.045	-69.67	-55.08	45.5
0.0283	-69.03	-49.53	65	0.0425	-69.65	-53.13	396	0.056	-53.06	-51.19	5.84
0.0133	-67.49	-73.12	-18.76	0.02	-59.77	-68.75	-28.96	0.04	-74.68	-93.03	-57.31
0.0107	-73.74	-60.7	43.46	0.015	-78.57	-66.20	39.9	0.025	-77.16	-71.68	17.12
-	-	-	-	0.0125	-73.06	-	-	-	-	-	-
0.00928	-73.60	-39.41	113	0.0108	-77.27	-43.17	388	0.0162	-73.94	-43.8	-94.1
0.01	-71.74	-28.09	145	0.01	-73.01	-29.54	330	0.015	-73.52	-31.53	131

0.00916	-73.39	-12.9	201	0.0078	-72.01	150	716	0.011	-80.97	-15.36	205

Table 11 Thermodynamic parameters for the micellization of various concentration of sodium Deoxycholate (SDC) with Disprine [30]

SDC+ Disprine (300K)				SDC+ Disprine (310K)				SDC+ Disprine (320K)			
CMC	ΔG°_m (kJ/mole)	ΔH°_m (kJ/mole)	ΔS°_m (kJ/mole)	CMC	ΔG°_m (kJ/mole)	ΔH°_m (kJ/mole)	ΔS°_m (kJ/mole)	CMC	ΔG°_m (kJ/mole)	ΔH°_m (kJ/mole)	ΔS°_m (kJ/mole)
0.05	-62.76			0.066				0.066			
0.03	-55.86	-29.63	87.43	0.0475	-48.36	-32.78	50.2	0.0633	-67.83	-40.46	85.5
0.0325	-55.91	-27.46	94.81	0.0433	-57.88	-35.84	71.07	0.052	-68.80	-37.27	98.52
0.0425	-49.18	-26.87	74.36	0.0566	-64.68	-29.64	113.0	0.071	-71.74	-43.40	88.54
0.0266	-26.13	-10.98	50.46	0.032	-40.01	-17.61	72.25	0.04	-64.68	-29.85	108.8
0.0187	-63.4	-44.43	63.36	0.025	-65.08	-48.03	54.98	0.0375	-75.47	-59.13	51.06
0.0327	-71.5	-18.46	17.6	0.0054	-68.37	-16.20	168.2	0.0064	-42.50	-14.08	88.8
0.0216	-73.0	-79.89	22.93	0.0433	-68.45	-83.1	47.26	0.065	-72.33	-93.34	65.67

0.076	-71.9	-40.46	104.9	0.024	-72.9	-43.34	95.3	0.03	-73.62	-45.88	86.68
0.016	-65.4	-60.7	15.6	0.0183	-70.4	-51.2	61.93	0.0171	-67.9	-52.2	49.06

Table 12 Thermodynamic parameters for the micellization of various concentration of sodium cholate (SC) with Disprine [30]

SC+ Disprine (300K)				**SC+ Disprine (310K)**				**SC+ Disprine (320K)**			
CMC	**ΔG°_m (kJ/mole)**	**ΔH°_m (kJ/mole)**	**ΔS°_m (kJ/mole)**	**CMC**	**ΔG°_m (kJ/mole)**	**ΔH°_m (kJ/mole)**	**ΔS°_m (kJ/mole)**	**CMC**	**ΔG°_m (kJ/mole)**	**ΔH°_m (kJ/mole)**	**ΔS°_m (kJ/mole)**
0.06	-53.35	-13	134.5	0.1	-48.51	-12.68	115.56	0.075	-69.63	-18.28	160.45
0.056	-42.12	-10.21	106.36	0.07	-62.53	-15.92	150.35	0.07	-66.43	-17.45	153.0
0.045	-62.83	-49.57	54.18	0.06	-63.52	-49.67	365.1	0.09	-69.79	-58.05	36.68
0.04	-69.40	-29.84	131.8	0.048	-67.18	-30.24	119.1	0.06	-70.17	-33.13	115.74
0.0314	-70.27	-24.71	151.83	0.0366	-61.15	-22.46	124.8	0.044	-67.76	-26.03	130.38
0.036	-66.28	-29.98	130.9	0.045	-69.45	-29.68	128.27	0.053	-71.55	-31.94	123.7

0.035	-65.52	-19.70	152.71	0.035	-62.85	-19.53	139.73	0.035	-75.30	-24.15	159.81
0.0325	-39.66	0	132.2	0.0216	-68.78	0	221.8	0.0325	-74.78	0	233.68
0.0266	-55.43	-21.5	113	0.0342	-68.81	-44.02	79.94	0.048	-71.97	-48.68	72.78

Table13 Value of cmc^{id}/mM, Cmc^{ex}/mM, X^{id} & X_1 and the β of the mixed micelles of Ametreptylene and anionic surfactants (SC) at different mole fractions in aqueous solution [2].

Ametreptylene +SC							
α	**Cmc^{id}/mM**	**Cmc^{ex}/mM**	**X^{id}**	**X_1 Rub**	**β**	***f*1**	***f*2**
$8.38X10^{-3}$	0.0075	0.017	$2.53 X 10^{-5}$	0.283	-19.64	$4.12 X 10^{-5}$	0.207
0.011	0.0075	0.019	$3.36 X 10^{-5}$	0.068	-9.513	$2.57 X 10^{-4}$	0.956
0.0178	0.0076	0.0163	$5.43 X 10^{-5}$	0.286	-18.407	$8.43 X 10^{-5}$	0.222
0.0102	0.0075	0.0154	$3.09 X 10^{-5}$	0.270	-18.68	$4.75 X 10^{-5}$	0.256
0.044	0.0078	0.0145	$1.38 X 10^{-4}$	0.041	-7.240	$1.28 X 10^{-3}$	0.987
0.0163	0.0076	0.0136	$4.97 X 10^{-5}$	0.377	-23.059	$1.30 X 10^{-4}$	0.037

0.03	0.0077	0.0133	7.96×10^{-6}	0.029	-7.212	1.114×10^{-3}	2.32×10^{-3}
0.749	0.029	0.0123	8.87×10^{-3}	0.323	-13.219	2.33×10^{-3}	0.2517
0.0139	0.0076	0.012	4.22×10^{-5}	0.0155	-7.2426	8.94×10^{-4}	4.18×10^{-3}
0.0181	0.00763	0.01	5.52×10^{-5}	-0.182	-	-	-

Table 14 Value of cmc^{id}/mM, Cmc^{ex}/mM, X^{id} & X_1 and the β of the mixed micelles of Ametreptylene and anionic surfactants (SDC) at different mole fractions in aqueous solution [2].

Ametreptylene +SDC							
α	**Cmc^{id}/mM**	**Cmc^{ex}/mM**	**X^{id}**	**X_1 Rub**	**β**	***f*1**	***f*2**
0.033	0.00775	0.0142	4.26×10^{-5}	0.0426	-6.874	$2.58X\ 10^{-3}$	1.012
0.0526	0.00791	0.0158	6.85×10^{-5}	0.3039	-15.83	$4.57X10^{-3}$	0.233
0.142	0.00873	0.015	$2.06X\ 10^{-4}$	0.0449	-5.305	$7.91X10^{-3}$,	0.989
0.0126	0.00759	0.0121	4.02×10^{-5}	0.0185	-6.841	$1.37X10^{-3}$	0.997

0.0312	0.00774	0.0123	3.20×10^{-5}	0.0217	-6.088	2.94×10^{-3}	0.997
0.025	0.00769	0.0115	4.26×10^{-5}	0.231	-14.34	2.07×10^{-4}	0.465
0.033	0.00775	0.0093	4.02×10^{-5}	0.165	-11.58	3.11×10^{-4}	0.729
0.0312	0.00774	0.0104	4.02×10^{-5}	0.205	-13.03	2.63×10^{-4}	0.578
0.019	0.00764	0.0096	2.42×10^{-5}	-0.176	-	-	-
0.022	0.0062	0.0091	2.15×10^{-5}	0.192	-12.5	2.15×10^{-4}	0.457

Table 15 Value of cmc^{id}/mM, Cmc^{ex}/mM, X^{id} & X_1 and the β of the mixed micelles of Imipramine and anionic surfactants (SDC) at different mole fractions in aqueous solution [2].

Imipramine +SDC					
α	**Cmc^{id}/mM**	**Cmc^{ex}/mM**	**X^{id}**	**X_1**	**β**
0.0181	9.25×10^{-3}	0.0166	2.79×10^{-5}	0.036	-7.07
4.28×10^{-3}	9.13×10^{-3}	0.019	6.51×10^{-6}	0.274	-18.8
0.166	0.01	0.0225	3.01×10^{-4}	0.081	-5.764

0.08	9.87×10^{-3}	0.017	1.31×10^{-4}	0.041	-5.65
0.772	0.039	0.01	5.1×10^{-3}	-0.543	-28.94
3.95×10^{-3}	9.09×10^{-3}	0.0375	6×10^{-6}	0.356	-23.09
-	-	-	-	-	-
0.077	9.84×10^{-3}	0.0216	1.26×10^{-4}	0.0796	-6.68
1.7	-0.013	0.0075	-3.69×10^{-3}	0.409	-15.05
0.0272	9.35×10^{-3}	0.00423	41.23×10^{-5}	-0.129	-11.61

Table 16 Value of cmc^{id}/mM, Cmc^{ex}/mM, X^{id} & X_1 and the β of the mixed micelles of Imipramine and anionic surfactants (SC) at different mole fractions in aqueous solution [2].

Imipramine +SC					
α	**Cmc^{id}/mM**	**Cmc^{ex}/mM**	**X^{id}**	**X_1**	**β**
0.0266	9.33×10^{-5}	0.0166	2.06×10^{-5}	0.034	-7.32
0.136	0.0105	0.019	1.19×10^{-4}	0.048	-5.98
0.031	9.38×10^{-5}	0.0225	2.42×10^{-5}	0.073	-8.32
0.09	9.98×10^{-5}	0.0283	7.49×10^{-5}	0.109	-7.86
0.225	0.0117	0.0133	2.19×10^{-4}	0.159	-9.13
0.088	9.96×10^{-5}	0.0107	7.30×10^{-5}	0.106	-9.01
-	-	-	-	-	-
0.109	0.01	0.0092	9.26×10^{-5}	0.077	-8.01
0.148	0.0106	0.01	1.31×10^{-4}	0.078	-7.60
0.116	0.0102	0.00916	9.93×10^{-5}	0.437	-26.8

Table 17 Value of cmc^{id}/mM, Cmc^{ex}/mM, X^{id} & X_1 and the β of the mixed micelles of Disprine and anionic surfactants (SDC) at different mole fractions in aqueous solution [2].

Disprine +SDC					
α	**Cmc^{id}/mM**	**Cmc^{ex}/mM**	**X^{id}**	**X_1**	**β**
0.192	1.18	0.05	0.037	1.712	-7.52
0.448	1.66	0.03	0.116	2.975	-9.20
0.438	1.63	0.0325	0.112	2.887	-9.00
0.6	0.045	0.04	0.196	3.483	-10.47
1.28	-5.5	0.0266	-2.912	0.51	-0.29
0.293	1.33	0.0187	0.063	2.522	-9.02
0.0225	0.997	0.0327	$3.7X10^{-3}$	0.873	-8.93
0.0617	1.035	0.0216	0.01	1.30	-8.85
0.076	1.05	0.0171	0.013	1.457	-9.04
0.058	1.026	0.016	$9.03X10^{-3}$	1.343	-9.23

Table 18 Value of cmc^{id}/mM, Cmc^{ex}/mM, X^{id} & X_1 and the β of the mixed micelles of Disprine and anionic surfactants (SC) at different mole fractions in aqueous solution [2].

Disprine +SC					
α	**Cmc^{id}/mM**	**Cmc^{ex}/mM**	**X^{id}**	**X_1**	**β**
0.443	1.55	0.06	0.114	2.10	-8.73
0.77	2.74	0.056	0.352	3.698	-16.51
0.0204	0.993	0.045	$3.37X10^{-3}$	0.657	-9.11
0.0326	1	0.04	$5.45X10^{-3}$	0.769	-8.96
0.0416	1.01	0.0314	$7.01X10^{-3}$	0.869	-9.11
0.135	1.01	0.036	0.024	1.263	-8.44
0.16	1.12	0.035	0.03	1.359	-8.47
0.892	3.8	0.0325	0.573	0.535	-29.6
0.235	1.15	0.0266	0.456	0.758	-24.6
0.124	1.05	0.0244	0.352	0.885	-19.44

Table 19 Surface excess concentration, ζmax, minimum area per surfactant molecule ,A min surface press at the cmc & for sodium cholate and Ametreptylene in different solvents at 300K

Ametreptylene +SC			
10^{-3} ζ max/mol cm^{-2}	10^{-8} A_{min} nm^2 mol^{-1}	Π_{cmc} / (mNm^{-1})	G_{ad}/kj/mol^{-1}
5.6	2.96	39.83	-20.35
4.7	3.53	30.13	-20.28
5.57	2.98	42.13	-20.57
4.99	3.32	33.13	-20.85
10.4	1.58	11.04	-41.13
10.2	1.62	38.13	-10.87
8.01	2.07	38.13	-5.24
12.75	1.30	29.63	-8.06
7.34	2.26	32.3	-14.06
7.34	2.26	24.5	-11.3

Table 20 Surface excess concentration, ζmax , minimum area per surfactant molecule ,A min surface press at the cmc & for sodium deoxycholate and Ametreptylene in different solvents at 300K

Ametreptylene +SDC			
10^{-3} ζ max/mol cm^{-2}	10^{-8} A_{min} nm^2 mol^{-1}	Π_{cmc} / (mNm^{-1})	G_{ad}/kj/mol^{-1}
13.3	1.24	51.13	-9.29
3.68	4.5	44.13	-31.66
9.98	1.66	44.73	-11.78
8.62	1.92	37.12	-12.96
10.7	1.54	33.13	-9.76
12.3	1.34	32.13	-7.93
9.81	1.69	35.13	-10.74
9.62	1.72	32.13	-10.69
8.53	1.94	45.12	-13.99
13.08	1.26	30.12	-7.67

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