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Research Article

MICELLIZATION BEHAVIOUR OF BILE SALTS WITH DISPRINE

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Abstract

Solubility is an important parameter to achieve desired concentration of drug in systemic circulation for pharmacological response to be shown. Among all newly discovered chemical entities most of the drugs are lipophillic and fail to reach market due to their poor water solubility. The solubility behavior remains one of the most challenging aspect informational developments. In order to develop colloidal drug carriers with desired properties, it is important to determine physico-chemical characteristics of these systems. Bile salt mixed micelles is extensively studied as novel drug delivery systems. The objective of the present investigation is to develop and characterize mixed micelles of anionic bile salts Sodium cholate (SC) and Sodium deoxycholate (SDC) and drugs (Disprine) in various temperatures. Critical micelle concentration (cmc), extent of counter ion binding (α), thermodynamic parameters (ΔG^o_m, ΔH^o_m, ΔS^o_m) for micellization process have been reported and discussed.

Keywords: Bile salts- Sodium cholate, Sodium deoxycholate, Conductometer, Disprine, cmc, counter ion dissociation.

Introduction

Mixed surfactant systems are used in many applications due to their better performance and less consumption than the pure surfactants [1–4]. The mixed surfactant systems always show synergistic behavior, resulting reduces the total amount of surfactant used in a particular application, which in turn thus reduces both cost and environmental impact. The role of micellar catalysis in recent years has been no need to say its importance in different area such as pharmaceuticals, oil recovery industry, environmental as well as Nano technological system (Proceedings ICCE Indore 2005). The role of micellar catalysis may not be understood without its critical micelle concentration. This is the concentration where surfactant will work as micelle. Therefore, it is very interested as well as important to know this factor very correctly and accurately. To begin with, it is useful to know the critical micelle concentration (cmc) of the surfactant used [4]. Calculations based on the cmc are useful to indicate that a micellar component is likely to be present to solubilise the drug substance. Given the presence of any micellar system, it is useful to know its 'capacity' to solubilise the active substance. The Maximum Additive Concentration (MAC) or other similar attribute provides this assurance with regard to the active substance as the additive in question [7]. The micellar formulations show a remarkable sensitivity to temperature. If the cmc is an important property of surfactants, as commented before, another relevant characteristic is the Krafft temperature. This can be defined as the minimum temperature at which surfactants form micelles. Reflection paper on the pharmaceutical development of intravenous medicinal products containing active substances solubilised in micellar systems. Below that temperature the formulation will fail because the surfactant remains in crystalline form, even in aqueous solution. On the other hand, as highlighted above, temperature can have a relevant effect on MAC. Normally, micellar parenteral drug products are administered by intravenous infusion, and are therefore subject to dilution effects, which may promote the breakdown of the micellar component, with the rate of infusion sufficiently low to minimize the risk of precipitation of the active substance in vivo. The method and rate of administration may affect the disposition of

the drug substance and drug product excipients. (Note that this may not necessarily be the case with a rapid or bolus intravenous injection, where rapid breakdown of the micellar component may not occur to the same extent). The clinical dossier should justify the time and conditions of the infusion process, taking into account such issues as potential haemolysis, CNS effects, etc. As an extended aspect of the pharmaceutical development of these complex systems, it is essential to gather as much information as possible concerning what is likely to happen to the drug and the micelle component in vivo. In general, the 'persistence' and extent of the micelle component are probably of more interest than the size or electrostatic properties for small molecule surfactants. It is possible that micelles will disappear during a slow infusion, simply due to dilution and metabolism of the surfactant, but applicants should consider the number of competing equilibria to arrive at a better understanding of what is happening.

In the present work, micellization of bile salt (Sodium cholate and Sodiumdeoxy cholate) and Disprine mixture has been measured by conductometric methods.

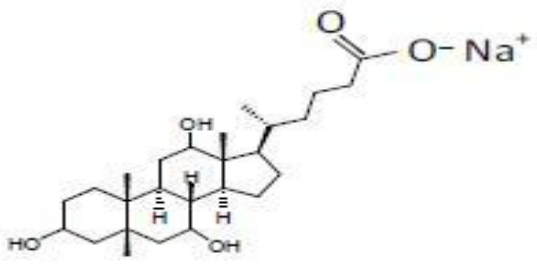


Fig.1 Sodium cholate

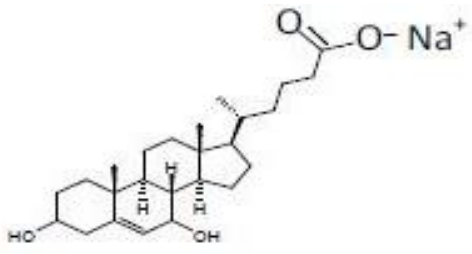


Fig.2 Sodium deoxycholate

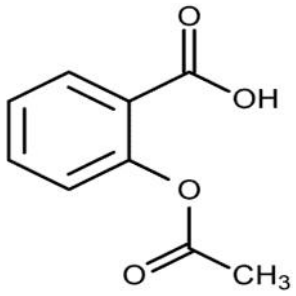


Fig. 3 Disprine

Method

State of human and animal rights-This article does not contain any studies with human or animal subjects performed by any of the authors.

Determination of critical micellization concentration value of binary mixtures

The critical micelle concentrations of the binary mixtures were studied using conductivity measurements, at different concentrations and different temperature. Prepared mixtures consisted concentration of 0.1-1 mM of Sodium cholate and Sodium deoxycholate and 0.1 mM of Disprine.

Conductivity measurement

Conductivity measurements were carried out on aqueous solutions of mixtures of Sodium cholate (SC) and Sodium deoxycholate (SDC) with Disprine at various temperatures.

Surfactants solutions were prepared by dissolving the relevant surfactants in deionised water. Conductivity was measured by gradual dilution of surfactants solutions with the deionised water. The data were acquired using Systronic direct reading conductometer (model number 306). The conductivity meter was caliberated with KCl solution of the appropriate concentration range. The cell containing solutions was immersed in a water bath where temperature varies (300-320 kelvin). The break in conductivity (Specific conductivity) concentration curve indicated the onset of micellization process [9].

Table I Experimentally obtained critical micelle concentrations of the Sodium deoxycholate with Disprine in various concentrations at room temperature.

Concentration of SDC (mM)	Concentration of Disprine (mM)	cmc (mM)	α
0.1	0.1	0.05	0.192
0.09	0.1	0.038	0.448
0.08	0.1	0.0325	0.438
0.07	0.1	0.04	0.6
0.06	0.1	0.0266	1.28
0.05	0.1	0.0187	0.2933
0.04	0.1	0.0327	0.0225
0.03	0.1	0.0216	0.0617
0.02	0.1	0.0171	0.076
0.01	0.1	0.016	0.053

Table II Experimentally obtained critical micelle concentrations of the Sodium cholate with Disprine in various concentrations at room temperature.

Concentration of SC (mM)	Concentration of Disprine (mM)	cmc (mM)	α
0.1	0.1	0.06	0.443
0.09	0.1	0.056	0.77
0.08	0.1	0.045	0.0204
0.07	0.1	0.04	0.0326
0.06	0.1	0.0314	0.0416
0.05	0.1	0.036	0.135
0.04	0.1	0.035	0.16
0.03	0.1	0.0325	0.892
0.02	0.1	0.0266	0.235
0.01	0.1	0.0244	0.124

Fig 1.1

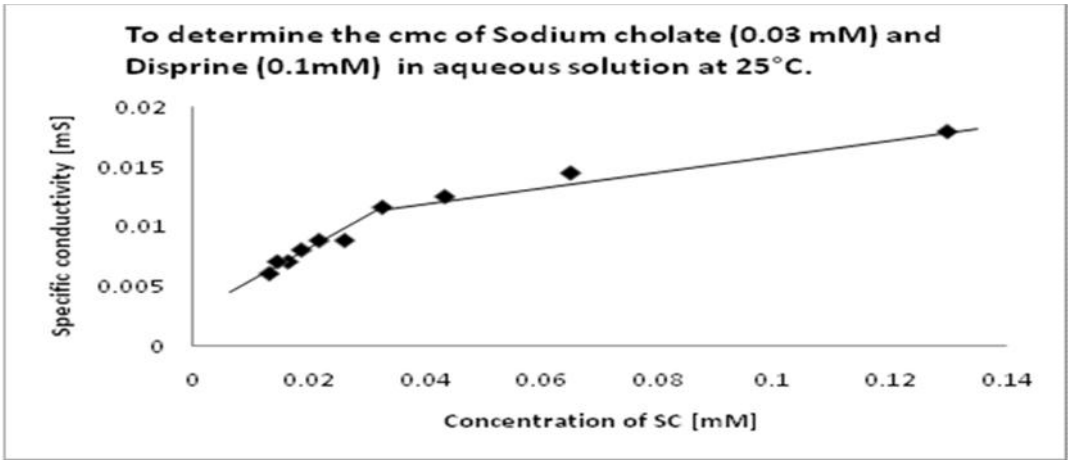


Fig 1.2

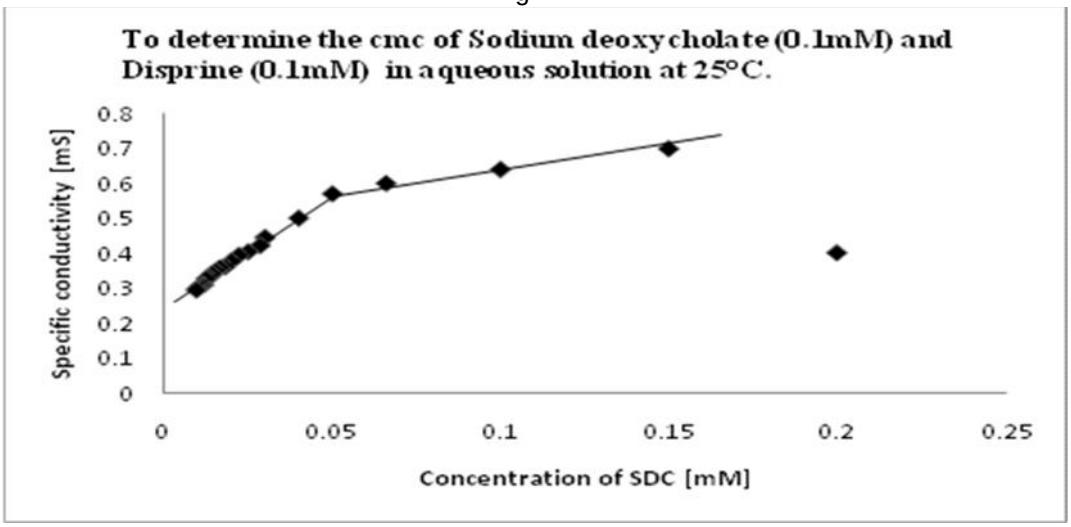


Fig 1.3

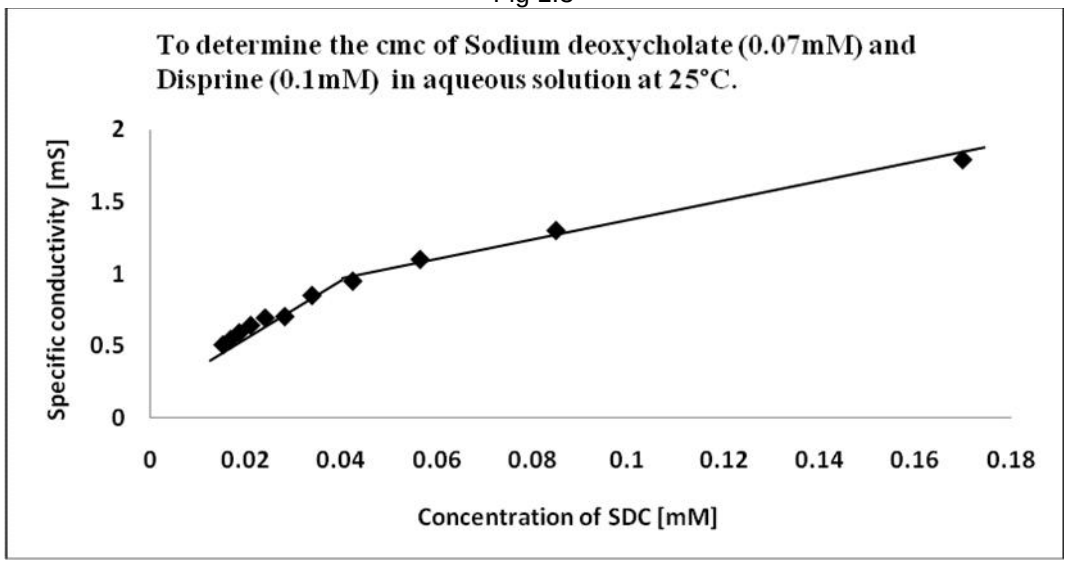


Fig 1.4

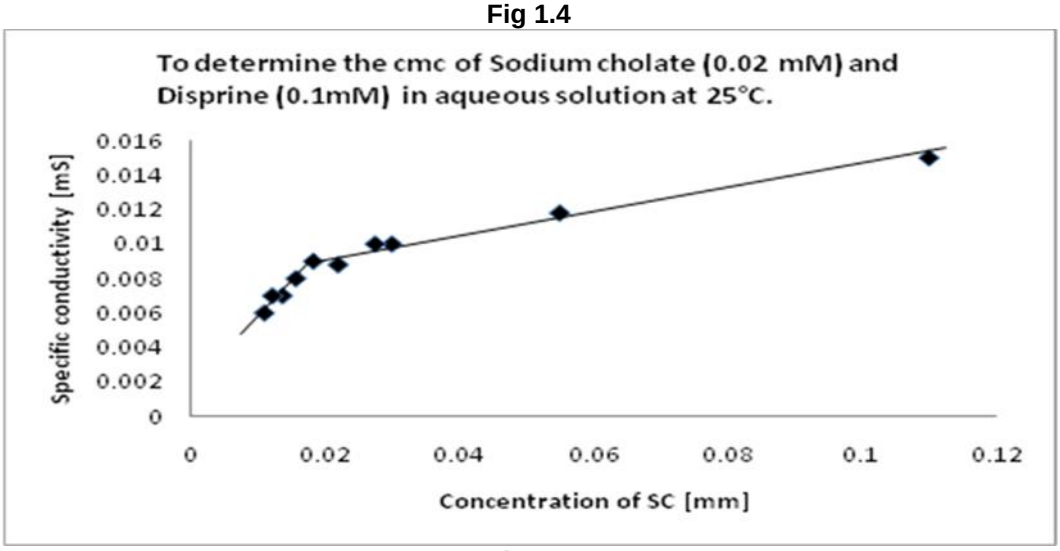


Fig 1.5

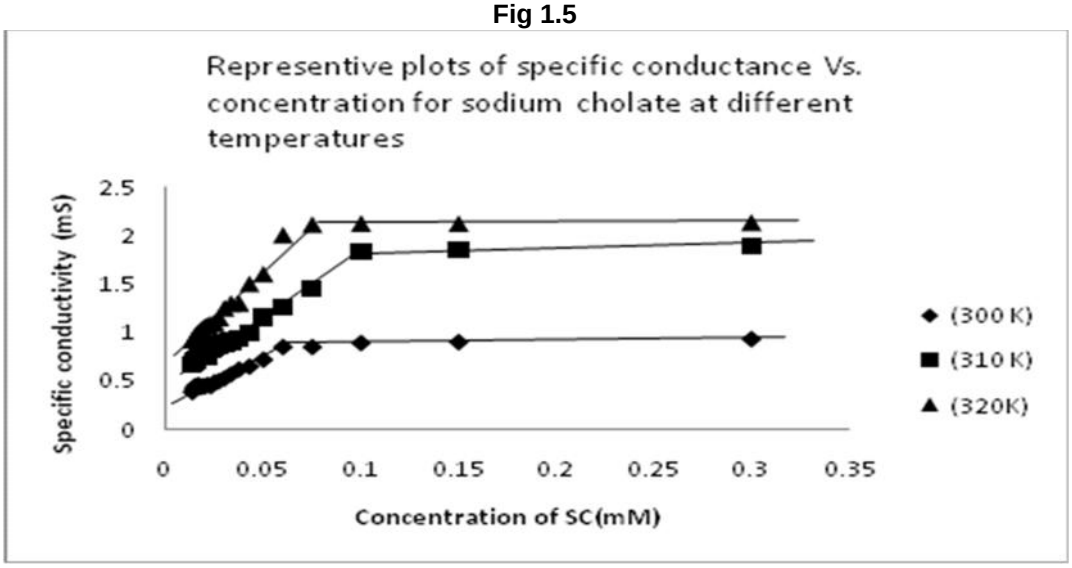
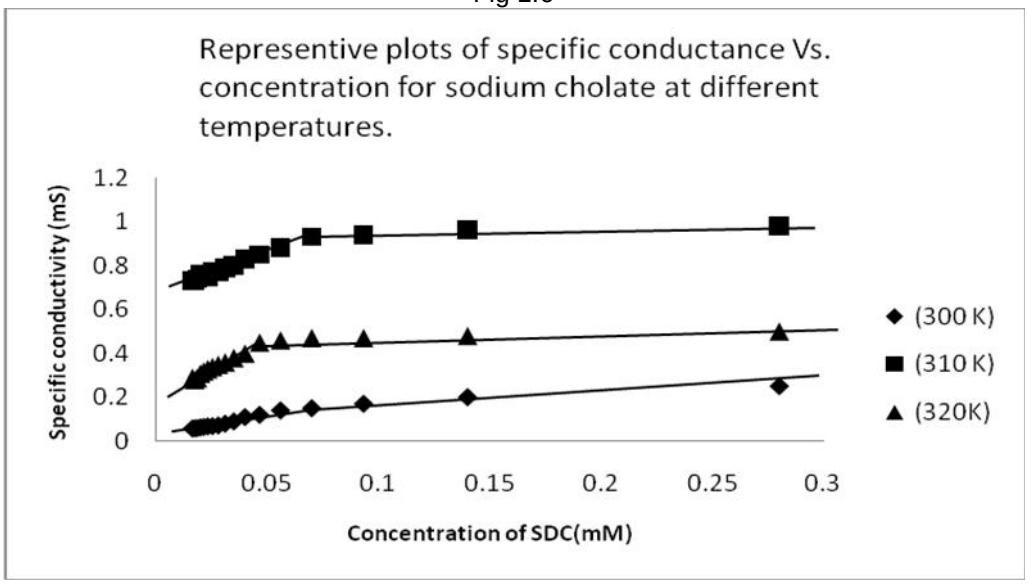


Fig 1.6



The cmc values for individual non-ionic surfactants and Disprine were obtained through conductometric measurements.

Table III Experimental critical micelle concentrations of the individual surfactants

Surfactants	SC	SDC	Disprine
cmc^{ex}/mM	12	6	0.977

Determination of the physico-chemical parameters

In order to study the influence of the structure of bile salts on the formation of mixed micelles with Disprine, the physico-chemical parameters of the micellar systems were calculated using experimentally obtained cmc values. The determined physico-chemical parameters are: the critical micelle concentration of ideal mixtures (cmc), mole fraction (α), Thermodynamic parameters (ΔG^o_m, ΔH^o_m, ΔS^o_m).

Result and Discussion

The critical micelle concentrations of the surfactqnts and drug solution were studied through conductivity measurements at different temperature prepares mixtures having different concentration plots; characterstics of micelle formation was observed (Fig 1.1 to 1.3). cmc of surfactants and drug is varies with the increase in temperature which is shown in fig 1.4 to 1.6. Table 1 and table 2 summarize the cmc values and mole fraction of sodium cholate and sodium deoxycholate experimentally obtained through conductivity measurements.

The thermodynamics parameters for micellization like Gibbs free energy (ΔG^o_m), enthalpy (ΔH^o_m), and entropy (ΔS^o_m) can be derived from the temperature dependence of the cmc. The trends of these parameter Table 6 and 7 at various temperature in all the solvent can give valuable insight in to the principle, which governs the formation of micelle.

The Gibbs free energy of micellization ΔG^o_m was calculated by using equation,

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

Where R is gas constant, T is temperature and $\ln X_{cmc}$ is cmc in mole fraction unit. The free energy decreases with rising temperature, this value show that the micellization process is spontaneous in aqueous solution at various temperatures (Table 6 and 7).

The standard enthalpy of micelle formation ΔH^o_m can be derived by the Von't Hoff equation.

$$\Delta H^{\circ}_{m} = -(2 - \alpha)RT^2 \left(\frac{d \ln X_{cmc}}{dT}\right)$$

The result also shows that standard enthalpy of micellization for all solvent is negative which indicates that the micellization process is exothermic.

The standard entropy of micelle formation ΔS^o_m was calculated from the obtained values of ΔH^o_m and ΔG^o_m equation and well-known relationship

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

The ΔS^o_m values are positive in all case, indicating that the micellization process is entropy dominated. The positive value of ΔS^o_m clearly indicates that the micellization of the studied surfactants in aqueous solution is governed mainly by hydrophobic interaction between the surfactants cation resulting in the breakdown of the structured water surrounding the hydrophobic groups [3].

Conclusion

We have studied a set of two bile salts sodium cholate (SC), sodium deoxycholate (SDC) to interact with drugs like Disprine, by conductometric method. It was observed that micellization tendency of SC and SDC decrease in the presence of various temperatures. 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. This suggests the micellization formation is becomes less spontaneous with increasing temperatures.

The entropy of micellization is positive indicated that the micellization process is somewhat entropy dominated.

Additionally, 7-oxo group of 7-oxodeoxycholate enhance attractive interactions with selected co-surfactants more than 7-hydroxyl group of sodium cholate. In the small intestine, co-administration of food and/or lipids leads to secretion of bile and digestive enzymes that produce a complex system of

intestinal colloidal phases designed to facilitate the digestion and absorption of dietary lipids. The increased concentration of bile and the presence of bile salt/ dietary lipid mixed micelles can improve the wetting of poor soluble drugs and increase their effective solubility via solubilization. Postprandial absorption may be improved by direct permeability enhancement or by solubilization that facilitates transport of lipophilic drugs across the aqueous diffusion layer. Intestinal lymphatic transport may also contribute to the absorption of highly lipophilic drugs.

Table IV Critical micelle concentrations 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 K		310 K		320 K	
		CMC	α	CMC	α	CMC	α
0.1	0.1	0.05	0.192	0.066	0.75	0.066	0.129
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 V Critical micelle concentrations 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 K		310 K		320 K	
		CMC	α	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 VI Thermodynamic parameters for the micellization of various concentration of sodium Deoxycholate (SDC) with Disprine

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	-31.5		0.066	-48.5	-30.1		0.066	-62.52	-41.4	
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 VII Thermodynamic parameters for the micellization of various concentration of sodium cholate (SC) with Disprine

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
0.0244	-52.31	-28.6	79	0.0314	-66.59	-29.09	120.9	0.0366	-68.65	-31.29	116.74

Acknowledgments

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