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Complex Behaviour of Bile Salts at Various Temperatures Under the Influence of Antidepressant Drug (Imipramine) in Aqueous Solution

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Abstract: The present method was based on the effect of bile salt (Sodium cholate and Sodium deoxy cholate) on the dissolution of Antidepressant drug like Imipramine. Sodium cholate and Sodium deoxycholate is a type of anionic surfactants form mixed micelle with Imipramine and influence its rate of dissolution. The micellization behavior of binary anionic bile salt surfactant mixtures was investigated by conductivity method and various thermodynamical parameters are calculated. The results of the study have been analyzed by using Clint's, Rubingh's, and Motomura's theories for mixed binary systems.

Keywords: Antideprassant Drug, Sodium Cholate, Sodium Deoxycholate, Conductometer, Critical Micelle Concentration, Counter Ion Dissociation

1. Introduction

Surfactants word is made up of three different word "surface active agent". It has two different part -water-loving or hydrophilic and water-hating or hydrophobic. Due to presence of its unique structure it is also known as amphiphilic or amphipathic molecules and due to its nature hydrophilic group of Surfactants forms hydrogen bonds with water molecules, while due to hydrophobic nature hydrocarbon chains aggregate and moving away from the water molecules. Due to these properties surfactants is soluble in water. In aqueous solutions, they form organized bunch like structures called micelles. Surfactants are further classifies in to various part according to functional group present in it is-Anionic, Cationic, Zwitter ionic, Nonionic and Gemini surfactants.

Surfactants play important role in almost every sector of industry like oil recover, pharmaceutical, physical and organic chemistry, cosmetic industry, food science etc. Micelles have importance property in various industries but basically it play important role in pharmaceutical industry because it have ability to dissurf solve sparingly soluble active substance like drug in aqueous solution. Important role of micelle is in delivery of drug towards targeted area and increase its bioavaibility. It also attempt to minimize drug degradation, its loss and to prevent its harmful side effects (16).

Micelles as drug carriers present some advantages when compared to other alternatives such as soluble polymers and liposomes. Micellar systems can solubilize poorly soluble drugs and thus increase their bioavailability, they can stay in the body (blood) long enough to provide gradual accumulation in the required area, and their sizes permit them to accumulate in areas with leaky vasculature (9).

In general, surfactants play an important role basically in pharmaceutical biotechnology fields, since they are largely utilized in various drug dosage forms to control wetting, stability, bioavailability, among other properties (1). It is important to notice that lyophobic colloids, such as polymers, require certain energy to be applied for their formation, are quite unstable from the thermodynamic point of view, and frequently form large aggregates. Association colloids such as micelles, on the other hand, can form spontaneously under certain conditions (self- assembling systems), and are

thermodynamically more stable towards both dissociation and aggregation (9).

In this work, we provide are view of micellar solubilisation of drugs in surfactant systems, blending it with basic information on surfactants structure and properties, as well as the applications for drug delivery. The main aim of our investigation was to study the influence of varying structures of the hydrophobic regions of selected anionic surfactants on the physico–chemical properties and the synergism effect in the bile salt and–anionic binary systems.

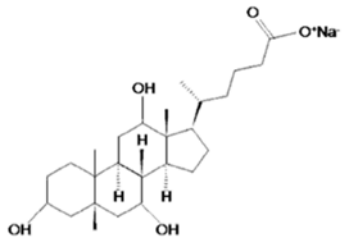

Fig. 1. *Sodium Cholate.*

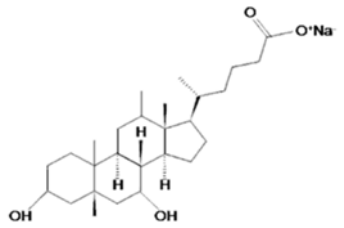

Fig. 2. *Sodium deoxycholate.*

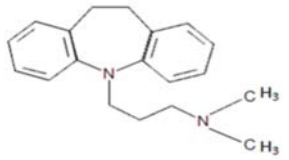

Fig. 3. *Imipramine.*

2. Experimental

2.1. Materials

The bile surfactants sodium cholate and sodium deoxycholate having anionic nature which is used in experiment was produced from LOBA Chemic and Imipramine. All the solutions were prepared in triple distilled water.

2.2. Determination of Critical Micellization Concentration Value of Binary Mixtures

In this experiment micellization tendency is determined by conductometric method because pure water or unionized water is a good insulator of electricity. If any charge or soluble ions present in it then it allow flowing current through aqueous solution. Thus the amount of current flow is used to calculate its ionic concentration.

Table 1. *Experimentally obtained critical micelle concentrations of the Sodium deoxy cholate with Imipramine in various concentrations.*

concentration of SDC(mM)	Concentration of Imipramine(mM)	CMC (mM)	α
0.1	0.1	0.016	0.0181
0.09	0.1	0.0189	$4.28X10^{-3}$
0.08	0.1	0.022	0.166
0.07	0.1	0.017	0.08
0.06	0.1	0.01	0.772
0.05	0.1	0.0375	$3.95X10^{-3}$
0.04	0.1		
0.03	0.1	0.0216	0.077
0.02	0.1	0.0075	1.7
0.01	0.1	0.00423	0.0272

Table 2. *Experimentally obtained critical micelle concentrations of the Sodium cholate with Imipramine in various concentration satroomtemperature.*

concentrationof SC(mM)	ConcentrationofImipramine(mM)	CMC (mM)	α
0.1	0.1	0.0166	0.0266
0.09	0.1	0.019	0.136
0.08	0.1	0.0225	0.031
0.07	0.1	0.0283	0.09
0.06	0.1	0.0133	0.225
0.05	0.1	0.0107	0.088
0.04	0.1	-	-
0.03	0.1	0.0092	0.109
0.02	0.1	0.01	0.148
0.01	0.1	0.00916	0.116

The CMC of the binary mixtures (Bile salt and Drugs) were studied using conductivity measurements, at different mole fractions and different temperature [6]. Prepared mixtures consisted of 0.1-1 mole fractions of Sodium cholate and Sodium deoxycholate and 0.1 mole fraction of Imipramine.

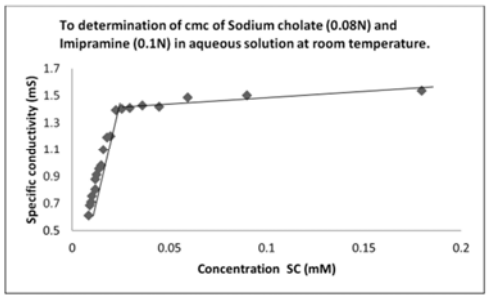

Fig. 4. *To determination of cmc of Sodium cholate and Imipramine in aqueous solution at room temperature.*

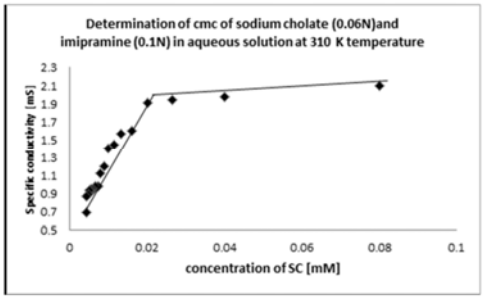

Fig. 5. *To determination of cmc of Sodium cholate and Imipramine inn ueoussolutionat310Ktemperature.*

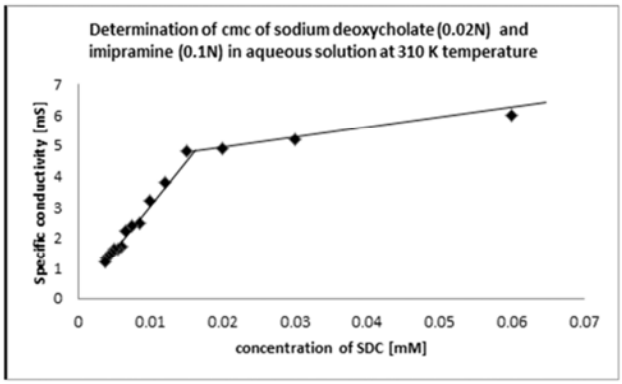

Fig. 6. *To determination of cmc of Sodium deoxycholate and Imipramine in aqueous solution at 310 K temperature.*

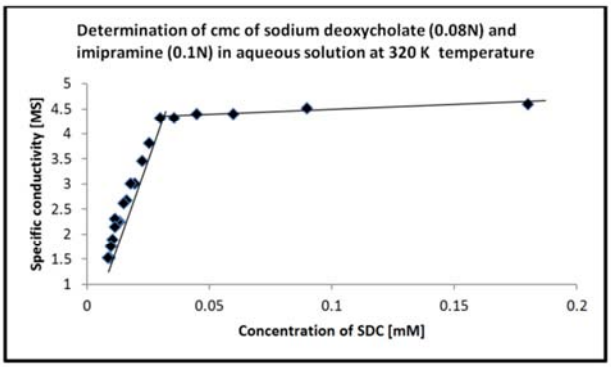

Fig. 7. *To determination of cmc of Sodium cholate and Imipramine in aqueous solution at 320 K temperature.*

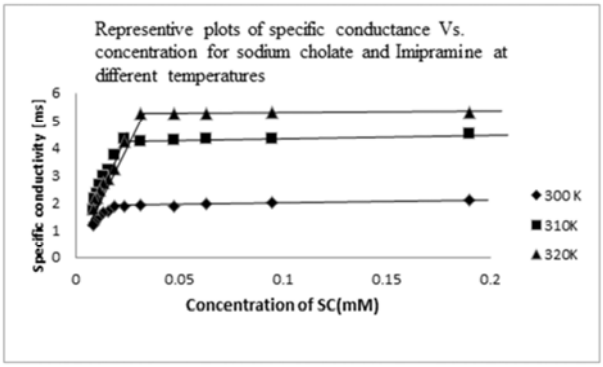

Fig. 8. *Representive plot of Specific conductivity and concentration of Sodium cholate and Imipramine at various temperature.*

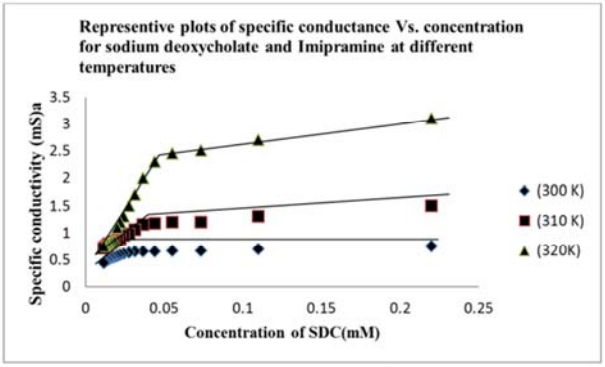

Fig. 9. *Representive plot of Specific conductivity and concentration for Sodium deoxycholate and Imipramine at various temperatures.*

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

Table 3. *Experimental critical micelle concentration of the individual surfactants.*

Surfactants	SC(mM)	SDC(mM)	Imipramine(mM)
Cmc^{ex}/mM	12	6	0.00909

2.3. Effect of Drugs on the Micellization Processs of BileSalts

Thermodynamics of micellization

Surfactant concentration is increases gradually after sometime it reaches at particular concentration which shows deviation between premiceller region and postmiceller region known as cmc, from where micelle form is spontaneous. This means the free energy of surfactants molecule of micelle is always beless than the monomeric surfactants molecule when dissolving in distilled water. All the thermodynamics parameters are temperature dependent.[34].

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

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

The Calculated value of parameter is shown in Table 4 and 5 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.[34] (Table 4 and 5).

The ΔH^o_m can be derived by the Von't Hoff equation.

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

The result also shows that standard enthalpy of micellization is negative which indicates that the micelle formation process is exothermic which show strong interaction between drug and bile salts [34].

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

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

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. [34, 5].

2.4. Development of Model

The present study provides an insight in to the mechanism of interaction of bile salts with various drugs like Imipramine. Based on the experimental findings it is possible to propose the concentration ranges involved with different stages of changes in the solubilisation of drugs by Sodium cholate and sodium deoxycholate. The experiments showed

that the concentration of a bile salt needed to bring about a certain change in the drugs is strongly dependent on the absolute concentrations of bile salt and not on their molar ratio. The bioavailability of orally administered drugs can be in fluenced by interacting with food constituent and by physico-chemical conditions in the upper gastrointestinal tract. Normally, bile salts enhance 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 [38].

Surfactant (bile salt) added in the drug and distilled water solution, then the dissolution rate of the Imipramine tablets increases (Shown in Table 1 and 2). It concludes that even presence of small concentration of bile salts is very helpful for the dissolution of various drugs [36].

In method to observing the influence of the structure of drug on formation of mixed micelles [4] with SDC and SC, physicochemical values of micelles and mixed micelle were calculated by using experimental cmc values which is shown in table 4- 5.

cmc^{id}, x^{id}, X_1 and the β parameter all were calculated by using following equation [6, 16].

The cmc^{id} parameter indicates non ideal behavior 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' stheory of ideal mixtures (cmc^{id})

$$\frac{1}{cmc^{id}} = \frac{\propto_i}{cmc_1} + \frac{1-\propto_i}{cmc_2}$$

The cmc^{id} values are presented and compared to the experimental cmc (cmc^{ex}) in Table 8 and 9 [3]. Deviation of the experimentally 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 being smaller than those predicted using models. The mole fraction of the more hydrophobic surfactant in the ideal mixed micelle (x^{id}) ,according to Motomura [4, 18], was calculated using the following relationship:

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

The x_1 value was calculated by using following relation:

$$1 = \frac{X_1^2 \ln(cmc^{ex} \propto / cmc_1 X_1)}{(1-x_1)^2 \ln[cmc^{ex}(1-\propto)/cmc_2(1-X_1)]}$$

The X^{id} and the X_1 values for the mixed micelles are presented in Table 8 and 9. Further according to Rubingh [5, 19], X_1 value was used to calculate the β interaction parameter, through the following equation:

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

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 [As referred in reference 5].

3. Conclusion

Binary combinations of bile salt and antidepressant drug (Imipramine) are studied. Aggregation of drug and bile salts as well as their tendency to form mixed micelles having CMC's different than ideal conditions, and the nonideality is more for the binary mixtures. The critical micelle concentration and thermodynamic parameters were studied using conductometric and surface tension method. The binary mixture of both surfactants and drug mixture was analysed by conductometer methods. 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 decreases 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 suggests that the micellization formation becomes less spontaneous with increasing amount of surfactants and solvents. The entropy of micellization is positive indicates that the micellization process is somewhat entropy dominated. Thus the values of CMC, ΔH^{ϑ}_m and ΔS^{ϑ}_m increase, while the value of ΔG^{ϑ}_m decrease with the increase of temperature.

The results of the study have been analysed using Clint's, Rubingh's, and Motomura's theories for mixed binary systems [7]. The critical micelle concentration of the ideal mixed micelle, the mole fraction of the more hydrophobic surfactant in the ideal mixed micelle, the mole fraction of the more hydrophobic surfactant in the real mixed micelle, and the β interaction parameter of the mixed micelles were calculated by using experimental values obtained [6]. It was concluded that increased synergistic interactions can be due to the large number of hydrophilic groups present in the bile salts.

Table 4. *Critical micelle concentration and α value of various concentrations of Sodium Deoxycholate (SDC) and Imipramine at different temperatures.*

SDC+Imipramineconcentration		Temperature(Kelvin)					
SDC(mM)	Imipramine(mM)	300		310		320	
		CMC(mM)	α	CMC(mM)	α	CMC(mM)	α
0.1	0.1	0.0166	0.0181	0.0181	0.27	0.02	0.266
0.09	0.1	0.019	$4.28X10^{-3}$	0.023	0.03	0.0316	$3.17X10^{-3}$
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	$2.9X10^{-3}$
0.06	0.1	0.01	0.772	0.0114	$9.01X10^{-3}$	0.016	0.14
0.05	0.1	0.0375	$3.95X10^{-3}$	0.0093	$4X10^{-3}$	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	$6.81X10^{-3}$	0.0061	0.01

Table 5. *Critical micelle concentration and α value of various concentrations of Sodium Cholate (SC)and Imipramine at different temperatures.*

SC+Imipramineconcentration		Temperature(Kelvin)					
SC(mM)	Imipramine(mM)	300		310		320	
		CMC (mM)	α	CMC(mM)	α	CMC(mM)	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 6. *Thermodynamic parameters for the micellization of various concentration of sodium deoxycholate (SDC) with Imipramine [34].*

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 7. *Thermodynamic parameters for the micellization of various concentration of sodium cholate (SC) with Imipramine [34].*

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 8. *Value of cmc^{id}/mM, Cmc^{ex}/mM, X^{id} & X_1 and the β of the mixed micelle so f Imipramine and anionic surfactants (SDC) at different mole fractions in aqueous solution [3].*

Imipramine+SDC					
α	**Cmc^{id}/mM**	**Cmc^{ex}/mM**	**X^{id}**	**X_1**	**β**
0.0181	$9.25X10^{-3}$	0.0166	$2.79X10^{-5}$	0.036	-7.07
$4.28X10^{-3}$	$9.13X10^{-3}$	0.019	$6.51X10^{-6}$	0.274	-18.8
0.166	0.01	0.0225	$3.01X10^{-4}$	0.081	-5.764
0.08	$9.87X10^{-3}$	0.017	$1.31X10^{-4}$	0.041	-5.65
0.772	0.039	0.01	$5.1X10^{-3}$	-0.543	-28.94
$3.95X10^{-3}$	$9.09X10^{-3}$	0.0375	$6X10^{-6}$	0.356	-23.09
-	-	-	-	-	-
0.077	$9.84X10^{-3}$	0.0216	$1.26X10^{-4}$	0.0796	-6.68
1.7	-0.013	0.0075	$-3.69X10^{-3}$	0.409	-15.05
0.0272	$9.35X10^{-3}$	0.00423	$41.23X10^{-5}$	-0.129	-11.61

Table 9. *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 [3].*

Imipramine+SC					
α	**Cmc^{id}/Mm**	**Cmc^{ex}/mM**	**X^{id}**	**X_1**	**β**
0.0266	$9.33X10^{-5}$	0.0166	$2.06X10^{-5}$	0.034	-7.32
0.136	0.0105	0.019	$1.19X10^{-4}$	0.048	-5.98
0.031	$9.38X10^{-5}$	0.0225	$2.42X10^{-5}$	0.073	-8.32
0.09	$9.98X10^{-5}$	0.0283	$7.49X10^{-5}$	0.109	-7.86
0.225	0.0117	0.0133	$2.19X10^{-4}$	0.159	-9.13
0.088	$9.96X10^{-5}$	0.0107	$7.30X10^{-5}$	0.106	-9.01
-	-	-	-	-	-
0.109	0.01	0.0092	$9.26X10^{-5}$	0.077	-8.01
0.148	0.0106	0.01	$1.31X10^{-4}$	0.078	-7.60
0.116	0.0102	0.00916	$9.93X10^{-5}$	0.437	-26.8

Parameters for thermodynamic micellization

ΔG^o_m= Gibbs free energy of micellization,

ΔH^o_m= Standard enthalpy of micelle formation

ΔS^o_m= Standard entropy of micellization

T= Temperature

R= Gas constant

X_{cmc}= Critical micelle concentration in mole fraction unit.

α= Conter ion dissociation

Parameters for development of model

cmc^{id}= Concentration of ideal mixtures

cmc^{ex}=Experimentally obtained critical micelle concentration

x^{id}= Mole fraction of the more hydrophobic surfactantin the ideal mixed micelle,

X_1=Mole fraction of the more hydrophobic surfactant in the real mixed micelle

β= Interaction parameter

cmc_1=Experimentally obtained cmc of the more hydrophobic (nonionic) surfactant (SDCandSC)

cmc_2=cmc of Imipramine drug

α = Mole fraction of the more hydrophobic surfactant in the solution.

α_i= Mole fraction of the more hydrophobic surfactant in the solution.

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