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The Effects of Additives on Micellar Behavior of Amitriptyline Hydrochloride Drug in Aqueous Solution at (298.15 to 313.15) K Temperature under Atmospheric Pressure

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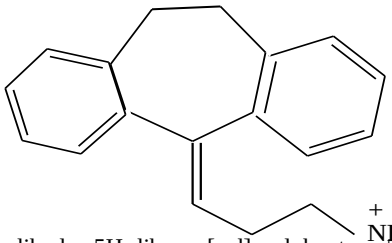
Abstract : *Micellar behavior of amitriptyline hydrochloride in aqueous media and presence of NaCl, glucose and urea has been investigated by conductivity measurement over the temperature range 298.15–313.15 K. The conductivity data were used to calculate critical micelle concentration (CMC), degree of counter ion association to the micelle (α) and degree of dissociation (β) of the micelle of AMT. Thermodynamic parameters viz., standard Gibbs free energy, ΔG_m^0, enthalpy, ΔH_m^0, entropy, ΔS_m^0 of micellization of AMT were estimated by applying the mass–action model.*

Keywords *- Amphiphilic drugs, Critical micelle concentration, Conductivity.*

I. Introduction

Amphiphilic drug molecules self-associate to form micelles in aqueous environment above their critical micelle concentration (*CMC*) [1-4]. Larger size of micelles affects their absorption across the cell membrane and thereby therapeutic effects. The potential of micelle solutions as functional molecular assemblies for use in many fields in pure and applied science is important because they can be used as models for several biochemical and pharmacological systems and they can solubilize water-insoluble substances (including certain medicines/ drugs) in their hydrophobic cores [5].

The self-association of amphiphilic drugs depends on the molecular structure of the drug, concentration, and physico-chemical conditions such as temperature, pH, ionic strength, and additive concentration [6]. In pharmacy, the interaction of small molecules with drugs is one of the most extensively studied. In this respect, many drugs, particularly those with local anesthetic, tranquillizer, antidepressant, and antibiotic actions, exert their activity by interaction with biological membranes, which can be considered as a complex form of amphiphilic bilayers. Therefore, a full knowledge of the mechanism of the interactions of drugs with other foreign materials is required before the actual application in human body. This is due to the fact that drugs are always used in the presence of a variety of additives (excipients).



Scheme 1. The molecular structure 3-(10,11-dihydro-5H-dibenzo[a,d]cycloheptane-5-ylidene)-N,N-dimethyl-1-propanamine hydrochloride (amitriptyline hydrochloride, AMT) used in the present study.

Amitriptyline hydrochloride is our studied amphiphilic drug. It is an antidepressant with neuroleptic activity, showing a large capacity to interact with biological membranes. AMT possesses a rigid hydrophobic ring system and a hydrophilic amine portion, which becomes cationic at low pH values and neutral at high pH values. Also, the pK_a value of this drug is 9.3 [7, 8]. AMT is often regarded as a model drug for the investigation of interactions between drugs and biological or model membranes [9]. Antidepressant drugs aggregate in a micelle-like manner with the value of N_{agg} (aggregation number) of the order of 6 to 15 [6, 7, 10]. Moreover, this types of drugs works in body with the ingredients of blood plasma, such as electrolytes, glucose, urea and others. The effects of NaCl on the micellar behavior of AMT are only investigated [3] at different temperatures.

Rational design and effective therapeutic dose of amphiphilic drugs require detail investigation of physico-chemical properties in aqueous media in presence of additives. With this view, micellar behaviors and thermodynamics of micellization of amitriptyline hydrochloride drug in water and in presence of additives have been studied conductometrycally.

II. Experimental

2.1. Chemicals and Their Pre-treatment

Amitriptyline hydrochloride (AMT) (purity ≥ 99.57%; Square Pharmaceuticals Ltd., Bangladesh), Sodium chloride (purity ≥ 99%; Merck, India), glucose anhydrous (purity ≥ 99.5%; Fluka, Switzerland), and urea (purity ≥ 99%; Loba Chemie PVT. Ltd., India) were used as received. Doubly distilled and deionized water (sp. cond. =1×10^{-6} to 2×10^{-6} μScm^{-1}) was used as the solvent.

2.2. Apparatus

An electric balance with an accuracy of ± 0.0001 g was used for weighing. A constant temperature water thermostat was used for the measurements of viscosity of solution. The temperature of the thermostat was maintained constant to an accuracy of ± 0.1 K. A conductivity meter (model 4310 Jenway) was used for the measurement of conductivity.

2.3. Conductivity measurements

The conductivity of amitriptyline hydrochloride (AMT) in water, and in 10, 30, 50, 70 $mmol.kg^{-1}$ aqueous NaCl, glucose and urea solutions were measured at different temperatures (viz., 298.15, 303.15, 308.15 and 313.15 K) by using conductivity meter (model 4310 Jenway) with cell constant 1.0 cm^{-1} . Water and 10, 30, 50, 70 $mmol.kg^{-1}$ NaCl, glucose and urea solutions were used as solvents Different concentrated solutions of amitriptyline hydrochloride (AMT) in the same solvent were taken in different test-tubes and those test-tubes were kept in thermostatic water bath with clamps for controlling temperature. Conductivity cell was dipped in solutions from the lowest to the highest concentrated solutions and each time the electrodes of conductivity cell were rinsed with solution of higher concentration.

3. Results and Discussion

3.1. Micellar Behaviors of AMT and with Additives in Aqueous Solution

In order to study the micellar behavior of amitriptyline hydrochloride (AMT) in water and with additives such as aqueous NaCl, glucose and urea solutions, the values of conductance of AMT in these systems were measured as a function of concentration (molality) at four temperatures of interval about 5 K ranging from 298.15 K to 313.15 K and shown in Table 1and Table 2. The experimental values of conductance of AMT as a function of concentration and temperature were illustrated in Fig. 1. This figure demonstrates that the conductance of all the selected systems increases linearly relatively at a higher rate up to certain concentration range with increasing the concentration of AMT. Beyond this concentration range the conductance increases relatively at a lower rate with increasing the concentration. It is apparent that the conductance versus concentration plots shows a clear breaking point, which is critical micelle concentration (*CMC*) [11]. Since the dilute surfactant solution behaves like electrolyte's solution, the addition of surfactant to an aqueous solution causes an increase in the number of charge carriers and consequently, an increase in the conductance up to the concentration of micelle formation. Further addition of surfactant increases the micelle concentration while the monomer concentration remains approximately constant. A micelle is much larger in size than a monomer surfactant it diffuses more slowly through solution and so is a less efficient charge carrier. It is, therefore, expected to change the dependence of conductance on the concentration of surfactant in aqueous solution, i.e., slope at the *CMC*. However, the determination of *CMC* point is a little bit tricky. Some authors [11, 12] have determined by manual interpolation method, which is subjected for large error, while others [13-14] have used second derivative of conductivity versus concentration data, which involves long mathematical calculations. In this presentation, the piecewise linear regression model is used for determining *CMC* point as shown in below

$$\left.\begin{aligned} y &= A(x - X) + C \qquad \text{if } x \le X \\ y &= B(x - X) + C \qquad \text{if } x \ge X \end{aligned}\right\} \tag{1}$$

where A and B are the slopes of pre- and post-critical micelle concentration curves respectively, X critical micelle concentration and C conductance at critical micelle concentration. The fitting was performed using the User-Defined module of Macrocal Origin Pro 8.5 software (OriginLab Corporation). The fitting values were included in Fig.1 along with the experimental conductance.

Table 1. Conductance of AMT in Water as a Function of Molality at 298.15 K, 303.15 K, 308.15 K and 313.15 K Temperatures.

Molality, $m/mol.kg^{-1}$	Conductance, C/mS			
	298.15 K	303.15 K	308.15 K	313.15 K
0.0000	0.00580	0.00910	0.01050	0.01240
0.0100	0.986	1.011	1.037	1.047
0.0151	1.460	1.503	1.535	1.570
0.0201	1.916	1.966	2.03	2.05
0.0250	2.32	2.44	2.47	2.54
0.0300	2.75	2.86	2.92	2.96
0.0351	3.14	3.28	3.36	3.41
0.0400	3.58	3.71	3.78	3.86
0.0502	4.26	4.47	4.58	4.71

0.0581	4.75	4.95	5.11	5.26
0.0699	5.32	5.64	5.79	5.94
0.0804	5.84	6.14	6.33	6.61

Table 2. Conductance of AMT in Water, Aqueous NaCl, Glucose and Urea Solutions as a Function of Molality at 298.15 K, 303.15 K, 308.15 K and 313.15 K Temperatures.

[AMT]/ mol.kg^{-1}	Conductance, C/mS				[AMT]/ mol.kg^{-1}	Conductance, C/mS			
	298.15 K	303.15 K	308.15 K	313.15 K		298.15 K	303.15 K	308.15 K	313.15 K
	AMT in 10 mmol.kg^{-1} NaCl solution					AMT in 50 mmol.kg^{-1} glucose solution			
0.0000	1.292	1.33	1.332	1.379	0.0000	0.00355	0.00449	0.00654	0.01123
0.0102	2.22	2.31	2.34	2.41	0.0107	1.053	1.072	1.090	1.112
0.0151	2.63	2.75	2.77	2.86	0.0151	1.454	1.488	1.515	1.543
0.0201	3.07	3.18	3.24	3.30	0.0201	1.933	1.981	2.04	2.07
0.0251	3.48	3.61	3.68	3.74	0.0251	2.35	2.44	2.47	2.49
0.0302	3.91	4.03	4.11	4.17	0.0302	2.79	2.87	2.92	2.94
0.0350	4.35	4.46	4.54	4.6	0.0352	3.20	3.32	3.36	3.40
0.0401	4.67	4.83	4.93	5.01	0.0401	3.59	3.68	3.77	3.80
0.0499	5.28	5.48	5.63	5.77	0.0518	4.30	4.51	4.59	4.73
0.0602	5.82	6.05	6.24	6.44	0.0601	4.79	4.99	5.13	5.29
0.0701	6.27	6.57	6.81	7.08	0.0700	5.27	5.53	5.74	5.88
0.0803	6.71	7.05	7.31	7.64	0.0805	5.78	6.03	6.35	6.47
	AMT in 30 mmol.kg^{-1} NaCl solution					AMT in 70 mmol.kg^{-1} glucose solution			
0.0000	3.70	3.81	3.89	3.97	0.0000	0.00296	0.00369	0.00503	0.00640
0.0100	4.54	4.67	4.77	4.88	0.0106	1.042	1.062	1.079	1.100
0.0150	4.93	5.10	5.19	5.29	0.0150	1.447	1.476	1.505	1.529
0.0200	5.32	5.48	5.59	5.67	0.0203	1.918	1.958	2.01	2.04
0.0251	5.69	5.87	6.01	6.09	0.0252	2.40	2.44	2.46	2.49
0.0301	6.12	6.28	6.40	6.49	0.0302	2.78	2.83	2.87	2.93
0.0350	6.45	6.63	6.75	6.86	0.0350	3.19	3.24	3.31	3.36
0.0402	6.76	6.98	7.14	7.27	0.0403	3.60	3.68	3.72	3.76
0.0496	7.24	7.51	7.69	7.86	0.0500	4.22	4.37	4.48	4.56
0.0600	7.76	8.03	8.27	8.48	0.0598	4.74	4.92	5.06	5.23
0.0698	8.17	8.50	8.76	9.00	0.0699	5.29	5.49	5.68	5.84
0.0803	8.68	9.01	9.31	9.61	0.0801	5.75	5.99	6.21	6.43
	AMT in 50 mmol.kg^{-1} NaCl solution					AMT in 10 mmol.kg^{-1} urea solution			
0.0000	6.15	6.28	6.32	6.44	0.0000	0.00434	0.00517	0.00747	0.00896
0.0100	6.92	7.07	7.20	7.28	0.0100	1.006	1.023	1.042	1.063
0.0151	7.29	7.40	7.57	7.69	0.0152	1.480	1.505	1.553	1.562
0.0200	7.60	7.75	7.85	7.98	0.0202	1.956	1.996	2.04	2.08
0.0250	8.00	8.20	8.29	8.43	0.0255	2.44	2.51	2.52	2.57
0.0301	8.40	8.57	8.69	8.82	0.0300	2.84	2.89	2.92	2.98
0.0350	8.67	8.87	9.00	9.13	0.0350	3.25	3.31	3.35	3.41
0.0400	8.95	9.15	9.31	9.48	0.0404	3.71	3.79	3.85	3.90

0.0501	9.43	9.66	9.88	10.09	0.0500	4.27	4.43	4.54	4.66
0.0601	9.75	10.09	10.32	10.60	0.0601	4.91	5.09	5.23	5.40
0.0697	10.16	10.53	10.80	11.10	0.0700	5.37	5.59	5.77	5.98
0.0799	10.61	10.96	11.27	11.61	0.0799	5.87	6.10	6.32	6.56
	AMT in 70 mmol.kg^{-1} NaCl solution					AMT in 30 mmol.kg^{-1} urea solution			
0.0000	8.28	8.46	8.58	8.71	0.0000	0.00600	0.00660	0.00856	0.01251
0.0103	9.04	9.18	9.34	9.46	0.0101	1.007	1.027	1.045	1.063
0.0151	9.34	9.55	9.72	9.86	0.0150	1.469	1.503	1.532	1.56
0.0202	9.70	9.91	10.10	10.23	0.0201	1.939	1.983	2.04	2.06
0.0248	10.05	10.24	10.45	10.58	0.0250	2.40	2.44	2.49	2.53
0.0299	10.38	10.54	10.71	10.82	0.0300	2.85	2.88	2.91	2.97
0.0350	10.64	10.84	11.08	11.19	0.0351	3.24	3.31	3.35	3.41
0.0401	10.90	11.12	11.35	11.50	0.0401	3.64	3.71	3.77	3.82
0.0500	11.28	11.57	11.82	12.05	0.0501	4.26	4.43	4.56	4.67
0.0600	11.65	12.01	12.28	12.58	0.0601	4.88	5.08	5.24	5.38
0.0699	12.01	12.39	12.70	13.04	0.0691	5.34	5.56	5.77	5.93
0.0801	12.41	12.86	13.20	13.49	0.0799	5.87	6.11	6.36	6.56
	AMT in 10 mmol.kg^{-1} glucose solution					AMT in 50 mmol.kg^{-1} urea solution			
0.0000	0.00330	0.00430	0.00487	0.00536	0.0000	0.00552	0.00574	0.00994	0.01108
0.0107	1.060	1.082	1.102	1.126	0.0102	0.996	1.022	1.040	1.058
0.0151	1.472	1.511	1.538	1.567	0.0152	1.475	1.515	1.543	1.574
0.0202	1.928	1.976	2.04	2.06	0.0202	1.955	2.00	2.05	2.09
0.0250	2.39	2.41	2.47	2.50	0.0251	2.43	2.47	2.49	2.52
0.0303	2.85	2.88	2.94	2.99	0.0302	2.89	2.93	2.94	2.99
0.0350	3.24	3.31	3.37	3.40	0.0350	3.24	3.31	3.35	3.40
0.0403	3.70	3.75	3.81	3.87	0.0398	3.52	3.67	3.71	3.84
0.0500	4.25	4.43	4.54	4.62	0.0500	4.03	4.17	4.31	4.46
0.0601	4.87	5.01	5.23	5.36	0.0593	4.54	4.73	4.90	5.13
0.0700	5.33	5.60	5.80	5.99	0.0701	5.08	5.34	5.53	5.79
0.0798	5.81	6.09	6.35	6.56	0.0801	5.53	5.83	6.08	6.36
	AMT in 30 mmol.kg^{-1} glucose solution					AMT in 70 mmol.kg^{-1} urea solution			
0.0000	0.00400	0.00494	0.00558	0.00662	0.0000	0.00766	0.00918	0.01021	0.01199
0.0107	1.061	1.078	1.100	1.116	0.0102	0.939	0.968	0.991	1.017
0.0151	1.453	1.492	1.523	1.547	0.0150	1.363	1.403	1.436	1.471
0.0202	1.914	1.968	2.03	2.04	0.0200	1.792	1.848	1.893	1.939
0.0250	2.34	2.40	2.47	2.48	0.0250	2.20	2.26	2.30	2.34
0.0300	2.78	2.87	2.91	2.95	0.0302	2.65	2.68	2.72	2.82
0.0351	3.21	3.30	3.36	3.39	0.0350	3.02	3.07	3.17	3.21
0.0402	3.60	3.73	3.78	3.82	0.0401	3.40	3.46	3.54	3.66
0.0503	4.26	4.42	4.53	4.68	0.0500	3.94	4.08	4.22	4.33
0.0600	4.83	5.02	5.16	5.31	0.0599	4.51	4.69	4.87	5.03
0.0703	5.34	5.58	5.77	5.95	0.0698	5.00	5.20	5.41	5.64
0.0799	5.79	6.04	6.30	6.52	0.0801	5.46	5.68	5.91	6.20

Table 3. The Physicochemical Parameters for AMT in Water, Aqueous NaCl, Urea and Glucose Solutions at Given Temperatures.

[additive]/ mmol.kg^{-1}	CMC/ mmol.kg^{-1}	α	β	ΔG_m^0 / kJ.mol^{-1}	ΔH_m^0 / kJ.mol^{-1}	ΔS_m^0 / kJ.mol^{-1}
			NaCl, T = 298.15 K			
0	44.13	0.42	0.58	-25.05	-2.29	0.08
10	38.77	0.42	0.58	-25.55	-1.09	0.08
30	36.65	0.43	0.57	-25.96	-3.81	0.07
50	34.27	0.43	0.57	-26.22	-1.80	0.08
70	32.79	0.44	0.56	-26.59	-2.56	0.08
			NaCl, T = 303.15 K			
0	44.57	0.39	0.61	-24.98	-2.33	0.07
10	38.96	0.40	0.60	-25.57	-1.11	0.08
30	37.68	0.40	0.60	-25.67	-3.84	0.07
50	34.47	0.41	0.59	-26.17	-1.83	0.08
70	32.93	0.41	0.59	-26.31	-2.58	0.08
			NaCl, T = 308.15 K			
0	45.21	0.36	0.64	-24.78	-2.36	0.07
10	39.10	0.37	0.63	-25.55	-1.13	0.08
30	38.19	0.38	0.62	-25.65	-3.91	0.07
50	34.63	0.39	0.61	-26.19	-1.86	0.08
70	33.39	0.39	0.61	-26.37	-2.63	0.08
			NaCl, T = 313.15 K			
0	45.56	0.34	0.66	-24.66	-2.40	0.07
10	39.40	0.35	0.65	-25.40	-1.14	0.08
30	38.76	0.35	0.65	-25.49	-3.96	0.07
50	34.71	0.36	0.64	-26.02	-1.88	0.08
70	33.96	0.36	0.64	-26.14	-2.66	0.08
			Urea, T = 298.15 K			
0	44.13	0.42	0.58	-25.05	-2.29	0.08
10	39.12	0.41	0.59	-25.36	-1.77	0.08
30	37.45	0.41	0.59	-25.50	-3.50	0.07
50	35.72	0.42	0.58	-25.88	-3.06	0.08
70	34.17	0.43	0.57	-26.23	-2.17	0.08
			Urea, T = 303.15 K			
0	44.57	0.39	0.61	-24.98	-2.33	0.07
10	39.32	0.39	0.61	-25.33	-1.80	0.08
30	38.83	0.40	0.60	-25.58	-3.59	0.07
50	36.33	0.40	0.60	-25.84	-3.10	0.07
70	34.71	0.41	0.59	-26.11	-2.21	0.08
			Urea, T = 308.15 K			
0	45.21	0.36	0.64	-24.78	-2.36	0.07
10	39.77	0.36	0.64	-25.29	-1.83	0.08
30	39.18	0.37	0.63	-25.44	-3.63	0.07
50	36.75	0.38	0.62	-25.80	-3.18	0.07
70	34.95	0.39	0.61	-26.17	-2.26	0.08
			Urea, T = 313.15 K			
0	45.56	0.34	0.66	-24.66	-2.40	0.07
10	40.09	0.34	0.66	-25.21	-1.86	0.07
30	39.49	0.35	0.65	-25.39	-3.69	0.07
50	37.35	0.36	0.64	-25.78	-3.22	0.07
70	35.28	0.37	0.63	-26.16	-2.30	0.08
			Glucose, T = 298.15 K			
0	44.13	0.42	0.58	-25.05	-2.29	0.08
10	39.34	0.41	0.59	-25.36	-1.56	0.08
30	39.00	0.42	0.58	-25.58	-1.68	0.08
50	38.76	0.43	0.57	-25.58	-1.36	0.08
70	38.58	0.44	0.56	-25.72	-1.33	0.08
			Glucose, T = 303.15 K			
0	44.57	0.39	0.61	-24.98	-2.33	0.07
10	39.62	0.38	0.62	-25.13	-1.58	0.08
30	39.43	0.39	0.61	-25.41	-1.70	0.08

50	39.11	0.39	0.61	-25.45	-1.37	0.08
70	38.72	0.40	0.60	-25.57	-1.35	0.08
			Glucose, T = 308.15 K			
0	45.21	0.36	0.64	-24.78	-2.36	0.07
10	39.96	0.33	0.67	-24.81	-1.58	0.08
30	39.78	0.39	0.61	-24.93	-1.69	0.08
50	39.27	0.35	0.65	-24.99	-1.37	0.08
70	38.97	0.35	0.65	-25.09	-1.34	0.08
			Glucose, T = 313.15 K			
0	45.56	0.34	0.66	-24.66	-2.40	0.07
10	40.21	0.30	0.70	-24.70	-1.58	0.07
30	40.01	0.31	0.69	-24.82	-1.71	0.07
50	39.55	0.32	0.68	-24.94	-1.39	0.07
70	39.31	0.33	0.67	-24.98	-1.36	0.08

3.1.1. Micellization of AMT in Aqueous Solution

Amphiphilic drugs are compounds with hydrophilic and hydrophobic moieties. They self-associate into micelles spontaneously when dispersed in water at a concentration above their critical micelle concentration. The pharmacokinetics and effectiveness of delivery of the drug to the site of action depend upon the size of the aggregate, as the micelle size might affect diffusion, transport across cell membranes, and interactions with enzymes, transport proteins and lipids. An understanding of the self-aggregation mechanism of amphiphilic drugs at the molecular level is crucial in the rational design of more effective drug [7]. The estimated *CMC* values of AMT in aqueous solution using equation 1 (shown in Table 3) are in good agreement with the values reported earlier [3, 4]. Frank and Evans introduced the idea that water molecules form 'icebergs' around non polar solutes [15-17]. Nemethy and Scheraga, on the other hand, used the term 'increased ice-likeness' [18, 19]. Ben-Naim also suggested a shift into the direction of the 'better order' form of water molecules upon introduction of a nobel gas [20]. According to all of these concepts, the water molecules become more ordered around the hydrophobic solute, with an increase in hydrogen bonding in this region. This situation is referred to as 'hydrophobic hydration' which occurs in very low concentration accompanied with positive free energy change. In order to minimize free energy, hydrocarbon cores tend to avoid water contact and aggregate through van der Waals interactions. The propensity of aggregation of hydrophobic solutes in water environment is termed as the 'hydrophobic interaction' and the condensation of the nonpolar solutes by the hydrophobic interaction is conventionally called the 'hydrophobic bond' [21]. The hydrophobic interaction plays crucial role for micelle formation. However, electrostatic repulsions among the charged heads that are formed from completely ionization of ionic amphiphilic molecules [22] in very dilute solution oppose the micellization process. As the concentration of solute increases, the degree of ionization reduce significantly and consequently diminish the electrostatic repulsion among the charged heads whose electrical charges are partially or fully neutralized due to the close proximities of their counter ions, while the condensation of hydrocarbon cores increases with solute concentration. Therefore, the attractive van der Waals interactions outweigh the electrostatic repulsions at certain solute concentration, which is critical micelle concentration. The micellization process is very complicated phenomena which may involve other factors like ion-pair formation, hydrophilic interactions, short range and long range interactions.

However, the micellization depends on the molecular structure of the drug, concentration, and physicochemical conditions such as temperature, pH, ionic strength, and additive concentration [23]. A full knowledge of the mechanism of the interactions of drugs with other foreign materials is required before the actual application in human body. The subsequent sub-sections concern with experimental studies of the effects of some additives such as NaCl, glucose and urea on the micellization of AMT in aqueous solution.

3.1.2. Effect of NaCl on Micellization of AMT in Aqueous Solution

The calculated *CMC*'s of AMT in aqueous NaCl solutions at different concentrations (10, 30, 50, 70 $mol.kg^{-1}$ NaCl) and temperatures using equation 1 presented in Table 3 are illustrated in Fig. 2. It is discernible that the *CMC* values decrease with increasing the concentration of NaCl. An increase in NaCl concentration increases the degree of counter ions and reduces the extent of ionization of drug molecules. The increased degree of counter ions serves to increase the degree of counter ion association to the micelle (α), while decreasing the extent of drug molecule ionization decreases the degree of dissociation of micelle (β), which are apparently evidenced by the experimental values of α and β . The value of β was determined from the ratio of the post micellar slope and the pre-micellar slope of conductance vs. molality data and α is equal to (1-β). The calculated values of α and β are given in Table 3. It is demonstrated from the table that the degree of counter ion association to micelles increases with increasing NaCl concentration, whereas the degree of dissociation of micelles decreases. These effects consequently reduce electrostatic repulsions among the ionic head groups and enhance the van der Waals attraction among the hydrocarbon cores. As a result, the electrostatic repulsions are balanced at a lower concentration of drug molecules by van der Waals attractive force, and thus NaCl decrease the *CMC*.

3.1.3. Effect of Glucose on Micellization of AMT in Aqueous Solution

The *CMC* values of AMT in 10, 30, 50, 70 $mmol.kg^{-1}$ aqueous glucose solutions are determined at different temperatures using equation 1 by conductance measurement and the data are listed in Table 3 and shown in Fig. 2. The *CMC* of AMT decreases with increasing glucose concentration. Because glucose molecule contains five hydroxyl groups in its cyclic structure and shows hydrophilic nature. With increasing glucose concentration it may be happened that partially negatively charge containing oxygen atoms of hydroxyl groups of glucose arrange around the cationic head groups of AMT and increase ion-dipole interaction, which reduce electrostatic repulsion among the charged head group and hence lower the

CMC. The values of degree of dissociation, β of the micelles in presence of glucose were also calculated, is presented in Table 3. These values indicate that glucose has the effect of reducing head group repulsion between the ionic head groups, and thus glucose decreases *CMC*.

3.1.4. Effect of Urea on Micellization of AMT in Aqueous Solution

The experimental *CMC* values of AMT in 10, 30, 50, 70 mmol.kg^{-1} aqueous urea solutions at 298.15, 303.15, 308.15 and 313.15 K temperatures are given in Table 3 and the results are presented in Fig. 2. It is found that the *CMC* values of AMT in presence of urea decrease with increasing urea concentration. Because the nature of urea is hydrophilic and it may be happened that an increase in urea concentration partial negatively charged oxygen atoms of urea molecules arrange around the cationic head groups of AMT and increase ion-dipole interaction which has the effect of reducing head group repulsion between the ionic head groups and hence lower the *CMC*. Besides the degree of dissociation, β of the micelles and degree of counter ion association, α to the micelles in presence of urea were also calculated that are shown in Table 3. These values indicate that urea reduces the head group repulsion between the ionic head groups, and thus decreases *CMC*. A similar behavior was observed by Naqvi et al [24].

3.2. Effect of Temperature on Micellization of AMT

The temperature dependence of *CMC* of AMT in aqueous solution, i.e., $\frac{d(CMC)}{dT}$ is illustrated in Fig. 2. It is seen that the *CMC* increases almost linearly with increasing the temperature. This is due to the fact that an increase in temperature increases the thermal agitation in the solution resulting in a decreasing adhesion between monomers. A similar behavior was observed by Alam *et al* [4].

The experimental *CMC*'s of AMT in water and presence of NaCl, glucose and urea at different temperature are presented in Fig. 2 and the data are shown in Table 3. In all cases, the *CMC*'s of AMT increase with increasing temperature. Because of increasing temperature, the thermal agitation in the solution is increased resulting in a decreasing adhesion between monomers. As a result, the degree of dissociation, β of the micelles of AMT increases with increasing temperature which is shown in Table 3. On the other hand, the degree of counter ion association, α to the micelles of AMT decreases which is presented in Table 3. So the electrostatic repulsion between ionic head groups of drug monomers is increased, and the *CMC* of AMT increases with increasing temperature.

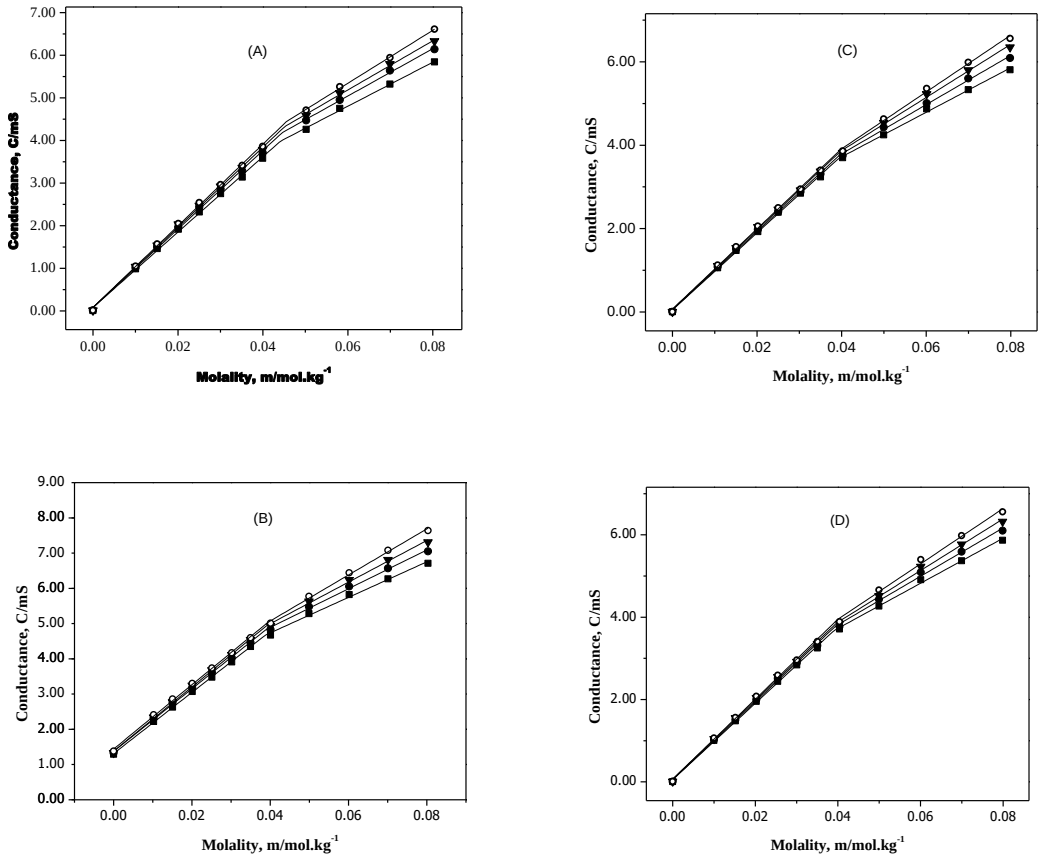


Figure 1. Variation of experimental conductance (indicated by symbols: ■ 298.15 K, ● 303.15 K, ▼ 308.15 K, ○ 313.15 K) as a function of molality of AMT in (A) water, aqueous (B) NaCl, (C) glucose and (D) urea solutions at different temperatures (solid lines refer to fitting values according to equation 1).

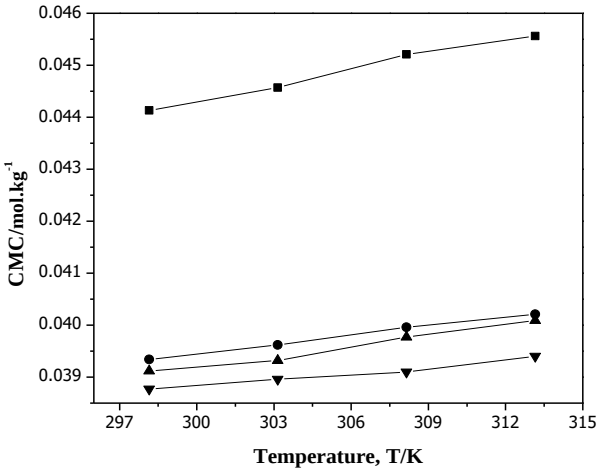


Figure 2. Variation of CMC's of AMT in ■ water, ●10 mmol.kg^{-1}glucose, ▲ 10 mmol.kg^{-1} urea, ▼ 10 mmol.kg^{-1} NaCl solutions as a function of temperature.

3.3. Thermodynamics of AMT in Absence and Presence of Additives

The thermodynamic parameters for micellization are inevitable for better understanding the aggregation process. Thermodynamic parameters for per mole of surfactant viz., standard Gibbs free energy ΔG_m^0, enthalpy (ΔH_m^0), and entropy (ΔS_m^0) of micellization of AMT in absence and presence of additives were calculated by using the following relations that were obtained from mass-action model [4]:

$$\Delta G_m^0 = (1 + \alpha)\, \mathrm{RT} \ln x_{CMC} \quad (2)$$

$$\Delta H_m^0 = -(1 + \alpha)\, \mathrm{RT}^2 (\mathrm{d} \ln x_{CMC} / \mathrm{dT}) \quad (3)$$

$$\Delta S_m^0 = (\Delta H_m^0 - \Delta G_m^0)/\mathrm{T} \quad (4)$$

where α is the degree of counter ion association to the micelles, which is given by (1 - β); β is the ratio of the post micellar slope of conductance versus concentration data to that of pre-micellar slope, x_{CMC} is the *CMC* in terms of mole fraction and other symbols have their usual meaning.

The calculated values of standard Gibbs free energy, ΔG_m^0, enthalpy, ΔH_m^0, and entropy, ΔS_m^0 of micellization of AMT in water are listed in Table 3 as a function of concentration and temperature. From the table it is seen that ΔG_m^0 and ΔH_m^0 are negative at studied temperature range, while ΔS_m^0 is positive at that temperature range and these thermodynamic parameters suggest that micellization is spontaneous process within the experimental temperature range. The spontaneity of micellization can be explained by considering the facts that in dilute solution water molecules form 'icebergs' around non polar solutes [15-17]. Nemethy and Scheraga, on the other hand, used the term 'increased ice-likeness' [18, 19]. According to all of these concepts, the water molecules become more ordered around the hydrophobic solute, with an increase in hydrogen bonding in this region. This situation is referred to as 'hydrophobic hydration', which causes negative entropy change, and negative enthalpy change as a consequence of extra strengthen hydrogen bonding of water molecules around the hydrophobic surface and multiple van der Waals interactions between water molecules and hydrophobic surface. Due to the hydrophobic hydration, free energy change becomes negative within the very limited concentration range afterwards that flips to positive free energy change. In order to minimize free energy, hydrocarbon cores tend to avoid water contact and aggregate through van der Waals interactions. The propensity of aggregation of hydrophobic solutes in water environment is termed as the 'hydrophobic interaction' and the condensation of the nonpolar solutes by the hydrophobic interaction is conventionally called the 'hydrophobic bond' [21]. The hydrophobic interaction plays crucial role for micelle formation. Aggregation through hydrophobic interaction renders negative entropy change. However, during aggregation ordered water molecules around hydrophobic cores detached to bulk water as monomers cause positive entropy change. The entropy change due to later process outweighs the previous one. As a result, the overall entropy change in micellization process becomes positive. On the other hand, aggregation produce a large negative enthalpy change due to multiple van der Waals interactions among hydrocarbon moieties, that overcomes the positive enthalpy change for breaking down ordered water structure around the hydrophobic hydration spheres. The combined effects of enthalpy and entropy changes make the free energy change negative.

The values of ΔG_m^0, ΔH_m^0 and ΔS_m^0 for micellization in presence of NaCl, glucose and urea were calculated, and are listed Table 3 as function of additives concentration and temperature. In all cases, ΔG_m^0 becomes more negative with increasing additives concentration, which indicates that addition of additives favors the micellization process. The values of ΔH_m^0 and ΔS_m^0 in presence of selected additives are negative and positive, respectively, within the studied concentration range, but random in nature. The causes of randomness are not clear and the precise measurements are very essential.

The data of temperature dependence of ΔG_m^0, ΔH_m^0 and ΔS_m^0 in absence and presence of these additives reveal that for all studied systems ΔG_m^0 becomes less negative, ΔH_m^0 more negative and ΔS_m^0 less positive with increasing temperature. These are due to the facts that ordered water structures around the hydrophobic part of AMT drug molecules are more temperature sensitive than that around the micelles. At higher temperature, water molecules around the hydrophobic part of AMT are less organized due to which aggregation process releases less amount of monomer water to bulk water and thereby less positive entropy change. Similarly, as the aggregation at high temperature expense less energy to break down less organized water structure around hydrophobic part of drug monomer, and consequently makes ΔH_m^0 more negative. The temperature sensitivity to ordered water structures to the surface of hydrophobic monomer make $T\Delta S_m^0$ larger than that of ΔH_m^0, and hence less negative change of free energy.

IV. Conclusion

The *CMC* values of AMT decrease with increasing the concentration of NaCl, glucose, urea. NaCl decreases *CMC* more than urea and urea decreases *CMC* more than glucose which is presented in Fig. 2. As a result the *CMC* decreasing order becomes NaCl > urea > glucose.

NaCl decreases *CMC* of AMT more than urea and glucose. Because NaCl is a strong electrolyte whereas, urea and glucose are non electrolytes. In case of urea and glucose, both of them are non electrolyte and hydrophilic in nature but urea decreases *CMC* of AMT more than glucose because of the dipole moment of urea is greater than glucose. Besides urea is more soluble than glucose in water and the size of urea molecule is smaller than glucose. So the radius of hydration sphere of urea is less than glucose. As a result greater number of urea molecules may be arranged around the cationic head groups of AMT and the partial negatively charged oxygen atoms of carbonyl group of urea molecules more closely interact with cationic head group of AMT compare to glucose which reduces the electrostatic repulsion between the ionic head groups compare to glucose and decreases *CMC* of AMT more than glucose. The *CMC*'s of AMT in presence and absence of NaCl, glucose and urea increases with increasing temperature.

The value of standard Gibbs free energy of micellization, ΔG_m^0 of AMT in water becomes negative. This indicates that the micellization process is spontaneous. In presence of NaCl, glucose and urea the ΔG_m^0 values of AMT become more negative and the negative value increases with increasing these additives concentration. This implies that AMT-NaCl, glucose, urea solutions are more stable. As a result, the micellization process becomes more favorable. In presence and absence of these additives the negative values of ΔG_m^0 decrease with increasing temperature then the micellization process becomes less spontaneous.

The ΔH_m^0 values of AMT in water and presence of NaCl, glucose and urea are negative and, as the temperature increases, it becomes more negative. Thus, the process of aggregation becomes more exothermic with an increase in temperature. The ΔS_m^0 values of AMT in absence and presence of these additives are positive and decrease with increasing temperature. The results would be useful in better designing of therapeutic agent and improving the efficiency of the drug molecule in physiological system.

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