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Micellar parameters and thermodynamics of interaction of fluoroquinolone drugs with cetyldimethylethylammonium bromide

Sk. Md. Ali Ahsan, Mohammed Delwar Hossain, Md. Anamul Hoque* & Mohammed Abdullah Khan

Department of Chemistry, Jahangirnagar University, Savar, Dhaka 1342, Bangladesh
Email: ahoque_ju@yahoo.com

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Interaction of fluoroquinolone antibiotic drugs, viz., ciprofloxacin hydrochloride, levofloxacin hemihydrate and lomefloxacin hydrochloride, with the cationic surfactant cetyldimethylethylammonium bromide (CDMEAB) has been studied by conductance measurements in water and in the presence of salts such as NaCl, Na_2SO_4 and $Na_3PO_4 \cdot 12H_2O$ over the temperature range of 298.15–318.15 K. Two critical micelle concentrations (c^*) are obtained for drug-CDMEAB systems in all the cases. The change of c^* values of CDMEAB due to the addition of the drugs is indicative of the interaction between drugs and CDMEAB. Favourable micellization of drug-CDMEAB systems is observed in the presence of salts. The ΔG^0_m values were negative in all the cases. The values of ΔH^0_m and ΔS^0_m reveal that the binding interactions between drug and CDMEAB in water are both electrostatic and hydrophobic in nature. The existence of linear correlation between ΔH^0_m and ΔS^0_m values is observed in all cases.

Keywords: Solution chemistry, Surfactants, Micellization, Drug-surfactant interactions, Surfactant-drug interactions, Hydrophobic interactions, Thermodynamic parameters, Cetyldimethylethylammonium bromide, Fluoroquinolones

Surfactants have been widely used in numerous fields such as foodstuffs, cleaning products, paints, cosmetics, oil recovery, waste water treatment, various separation process and pharmaceutical industry[1-4]. The affinity to aggregate in solutions to form micelles above a critical concentration, known as critical micelle concentration, is one of the characteristic properties of surfactants. Different physico-chemical phenomena such as micellar solubilization, micellar catalysis, reduction of surface tension, tertiary oil recovery, solute-sovent and solute-solute interactions are dependent on the critical micelle concentration[3,5]. Drug-membrane interactions are believed to be analogous to the interactions between drugs and surfactants. Surfactant micelles have thus been accepted as simplified model of biomembranes. In addition, surfactants are used to enhance the water solubility of many pharmaceutical components which is a difficult problem in formulation of an acceptable dosage form[6-8]. The interpretation of the interaction of drugs with surfactant micelles can be visualized as estimation for their interactions with biological surfaces. Also, characterization of drug-surfactant interactions is important in pharmacology and for developing better pharmaceutical formulations. The changes in surfactant structure and nature of the counter ions, added electrolytes, temperature, etc., can modify significantly the size, flexibility and type of interactions of surfactant micelles. Hence, interaction of drugs with surfactants has been studied by chemists and biochemists with increasingly growing research interest. Ismail *et al.*[9] investigated the interaction between tetracaine hydrochloride (THC) with sodium deoxycholate (SDC). They determined the critical micelle concentrations and observed synergistic behavior. They also observed that the mixed micelles appear to have spherical and prolate ellipsoidal shapes. In our early papers, we reported the interaction of cephalosporin drugs with ionic surfactants[10-14]. Literature survey reveals that a detail study regarding drug-surfactant interactions is still necessary.

Fluoroquinolones are broad spectrum synthetic antibiotics, which are advised as oral drugs to treat bacterial infections such as bronchitis, complicated urinary tract infections, respiratory tract infections bone and joint infections, intra-abdominal infections and to prevent urinary tract infections prior to surgery. In the present study, the interactions of fluoroquinolones drugs, namely, ciprofloxacin

hydrochloride (CPFH), levofloxacin hydrochloride (LVFH) and lomefloxacin hydrochloride (LMFH) with the cationic surfactant cetyldimethylethylammonium bromide (CDMEAB) have been undertaken using conductometric technique. To study the drug-CDMEAB interactions, values of critical micelle concentration (c^*), fraction of counter ion binding (β) and thermodynamic parameters such as ΔG^0_m, ΔH^0_m, ΔS^0_m and $\Delta C^0_{p,m}$ associated with the drug mediated CDMEAB micellization in pure water as well as in different salt solutions like NaCl, Na_2SO_4 and $Na_3PO_4.12H_2O$ have been determined.

Materials and Method

CDMEAB (Acros Organics, USA, 99%), USP standard sample of drugs such as CFH, LFH and LMFH (provided by General Pharmaceuticals Ltd., Bangladesh; 98%), NaCl (BDH, England, 99.5%), Na_2SO_4 (Merck, Mumbai, 99%) and $Na_3PO_4.12H_2O$ (Merck, Mumbai, 99%) were used as received All solutions were prepared by using distilled, deionized water of specific conductance 1.3-1.8 μS cm^{-1}.

The specific conductances of the drug-CDMEAB systems, both in water/water-salts mixed media, were measured using a 4510 conductivity meter (Jenway, UK) with a temperature-compensated cell (cell constant: 0.97 cm^{-1}) following the procedure reported in the literature[10-13,14,15]. Water/drug solution (20 mL) of a particular concentration was taken in a test tube immersed in a thermostatic water bath and then known volume of concentrated CDMEAB solution in water/ drug solution of same concentration was gradually added to the water/ drug solution with a pipette. After thoroughly mixing and allowing time for temperature equilibration, the conductance of the mixed system was recorded in each case. The temperature of the drug-CDMEAB systems was maintained with the help of Lauda water thermostated bath with precision of ±0.1 K. To study the effect of salts such as NaCl, Na_2SO_4, and $Na_3PO_4.12H_2O$ on interaction of the drugs with CDMEAB, the solutions of drug and CDMEAB were prepared in (water+salt) and in (water+drug+salt) media respectively in such a way that both solutions contained the same concentration of drug and salt. The critical micelle concentration (c^*) of drug-surfactant system was determined from the break point observed in the specific conductance (κ) versus concentration of surfactant (c_{CDMEAB}) plot.

Results and Discussion

Micellar parameters of drug-CDMEAB systems

The specific conductance (κ) value of CDMEAB solutions is found to change with the addition of drugs in water as well as in presence of salts as shown by a typical plot of κ versus concentration of CDMEAB (c_{CDMEAB}) for CFH–CDMEAB system in water at 303.15 K (Fig. 1). In this plot, two breakpoints are observed in both pure water and in aqueous solutions of salts. The c_{CDMEAB} corresponding to the breakpoints, i. e., critical micelle concentration, are labeled as c^*_1 and c^*_2 (refs 10-18). The c^*_1 reveals the concentration of surfactant at which association between drug and surfactant starts, while c^*_2 indicates CDMEAB micelle formation in presence of drug[11]. For different systems, more than one c^* value is also reported in the literature by others and us[11-15,17,18]. In our previous study, we reported the values of c^*_1 and c^*_2 of CDMEAB in water at 303.15 K to be 0.90 and 3.70 m*M* respectively[11]. The degree of ionization of micelles (α) was determined from the slopes of the straight lines above and below c^* (refs 10-18). The fraction of counter ion binding, β at c^* was determined by deducting the value of α from unity, i.e., $\beta = 1-\alpha$.

The values of c^* and β for the drug-CDMEAB system in water containing different concentrations of drugs at 303.15 K are shown in Fig. 2 (see also Supplementary Data, Table S1). The c^* values for CFH-CDMEAB are higher and lower than the pure CDMEAB systems in water at lower and higher CFH concentrations respectively at 303.15 K. In the case of LFH-CDMEAB and LMFH-CDMEAB

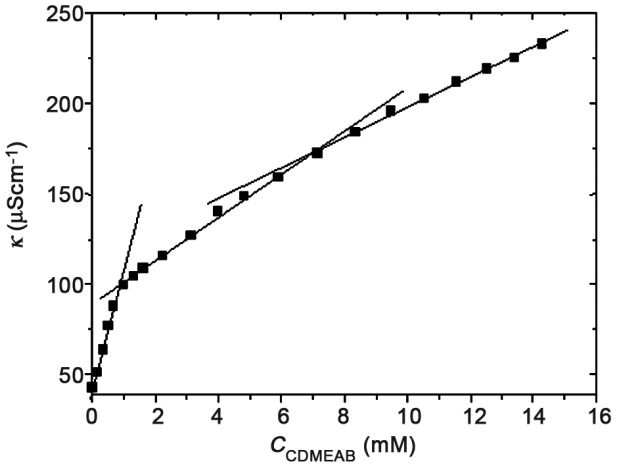

Fig. 1 – Specific conductivity (κ) versus concentration of CDMEAB for CFH-CDMEAB system in water at 303.15 K.

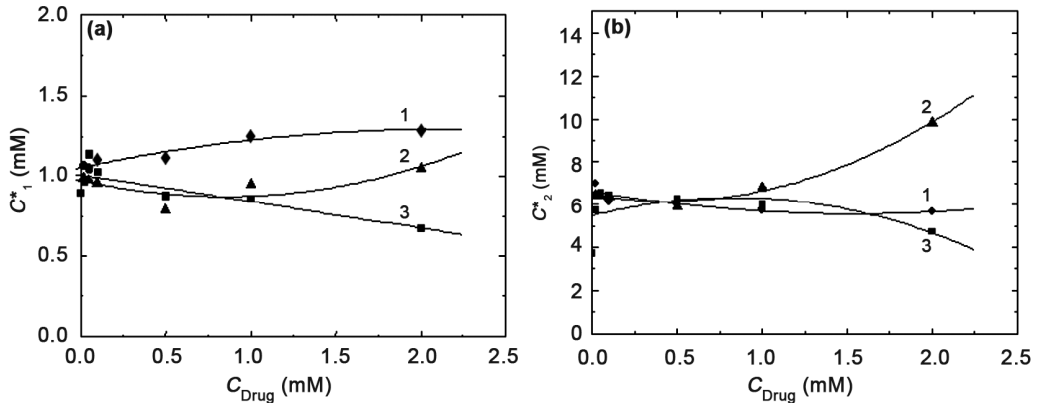

Fig. 2 – Values of (a) c^*_1 versus concentration of drug (c_{drug}) and (b) c^*_2 versus concentration of drug (c_{drug}) for LFH-CDMEAB (1, ♦), LMH-CDMEAB (2, ▲), and, CFH-CDMEAB (3, ■) systems in H_2O.

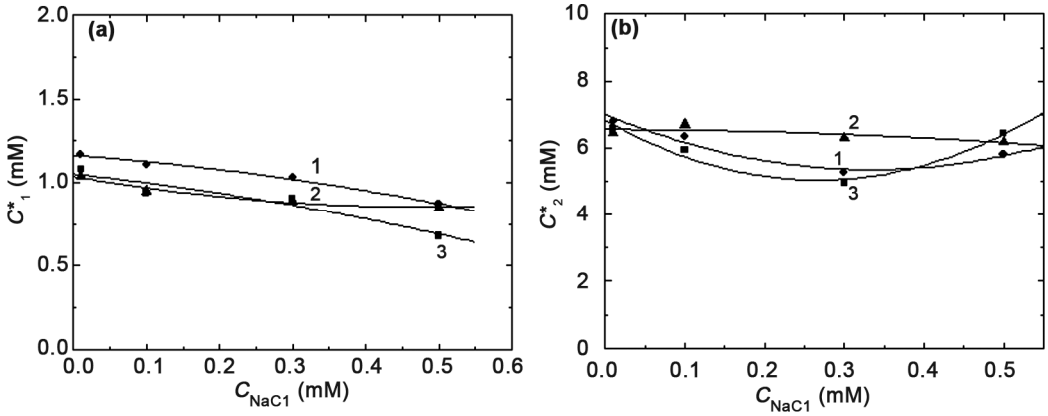

Fig. 3 – Values of (a) c^*_1 versus concentration of salt (c_{NaCl}) and (b) c^*_2 versus concentration of salt (c_{salt}) for LFH-CDMEAB (1, ♦), LMH-CDMEAB (2, ▲), and, CFH-CDMEAB (3, ■) systems in aqueous solution of NaCl.

systems, the c^* values are higher in magnitude than that of pure CDMEAB in water at 303.15 K, except the c^*_1 value for LMFH-CDMEAB system containing 0.5 m*M* drug. For CFH-CDMEAB system in water, the c^* values first increase with CFH concentration, attain a maximum and then the values tend to decrease with further increase in CFH concentration. For LFH-CDMEAB and LMFH-CDMEAB systems, the c^* values initially decrease with drug concentration, attain a minimum and then the values tend to increase with further increase in CFH concentration. The change of c^* values of CDMEAB with the addition of drugs show the interaction between drug and CDMEAB. At 303.15 K, the c^*_1 values of drug-CDMEAB systems containing 0.50 m*M* drug are found to follow the order: $c^*_{\text{LFH-CDMEAB}} > c^*_{\text{CFH-CDMEAB}} > c^*_{\text{LMFH-CDMEAB}}$, whereas c^*_2 values are found to follow the order: $c^*_{\text{CFH-CDMEAB}} > c^*_{\text{LFH-CDMEAB}} > c^*_{\text{LMFH-CDMEAB}}$. The differences of c^* values for drug-CDMEAB systems are due to the structural variation of the drugs used.

The c^* and β values for drug-CDMEAB systems at 303.15 K in aqueous solution of salts such as NaCl, Na_2SO_4 and Na_3PO_4 are shown in Figs 3-5 (see also Supplementary Data, Table S2). The c^*_1 values of drug-CDMEAB systems at 303.15 K in salts solution are found to decrease with increase of ionic strength (*I*) of salts except the c^*_1 value for LFH-CDMEAB system in aqueous solution of Na_2SO_4 having ionic strength of 0.50 m*M*. The c^*_2 values of drug-CDMEAB systems at 303.15 K in salts solution decrease up to a certain ionic strength of salts, attain minimum and then increase with increase of the ionic strength of salts. The c^*_1 values of CFH-CDMEAB system at 303.15 K at I = 0.50 m*M* of drug followed the order: $c_{NaCl} > c_{Na_2SO_4} > c_{Na_3PO_4}$, whereas c^*_2 values follow the order: $c_{NaCl} > c_{Na_3PO_4} > c_{Na_2SO_4}$ under the same experimental condition. This change of c^*

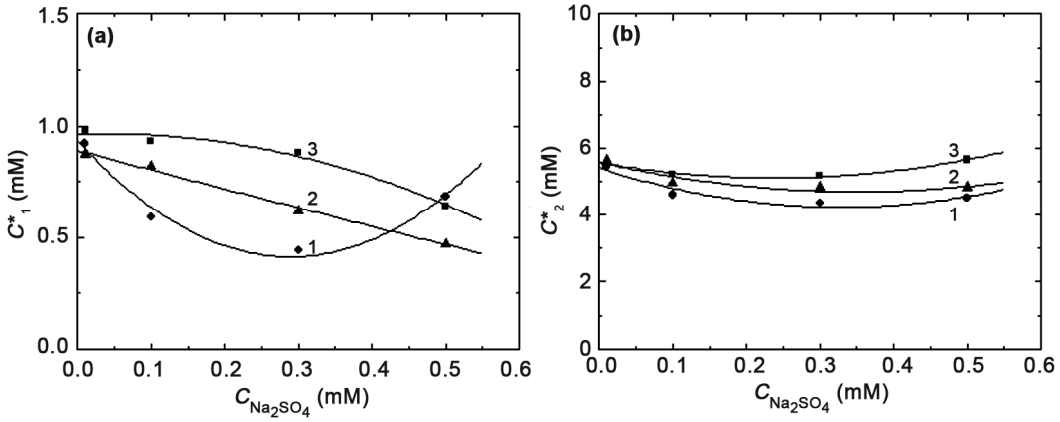

Fig. 4 – Values of c^*_1 versus concentration of salt ($c_{Na_2SO_4}$) and (b) c^*_2 versus concentration of salt ($c_{Na_2SO_4}$) for LFH-CDMEAB (1, ♦), LMH-CDMEAB (2, ▲), and, CFH-CDMEAB (3, ■) systems in aqueous solution of Na_2SO_4.

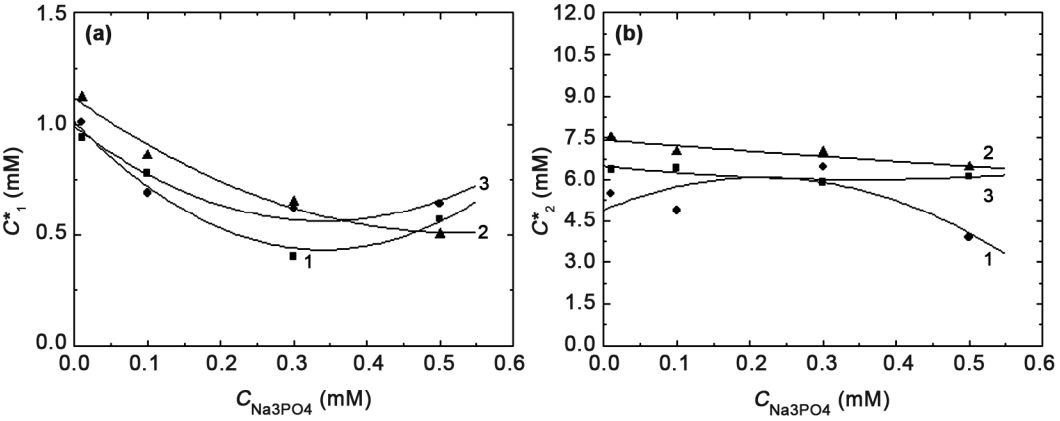

Fig. 5 – Values of c^*_1 versus concentration of salt ($c_{Na_3PO_4}$) and (b) c^*_2 versus concentration of salt ($c_{Na_3PO_4}$) for LFH-CDMEAB (1, ♦), LMH-CDMEAB (2, ▲), and, CFH-CDMEAB (3, ■) systems in aqueous solution of Na_3PO_4.

values may be due to the presence of ions of different nature. Chloride (Cl^-) ion is a moderate chaotrope, having a large singly charged ion with low charge density, ruptures water structures and weakens the stability of hydrophobic aggregates of surfactant molecules. Both sulfate and phosphate are strong kosmotropes, having small multi-charged ion with high charge density. They interact with water strongly as water structure makers and stabilize the hydrophobic aggregates of CDMEAB molecules. Thus, Na_2SO_4 and Na_3PO_4 salt out the hydrophobic chains of surfactants from aqueous medium and lower the c^* values of surfactant system significantly as compared to that of NaCl. The kosmotropic effect of the anions of sodium salts having ionic strength of I = 0.5 mM on the lowering of c^*_1 values follow the order: $PO_4^{-3} > SO_4^{-2}$. This is in good agreement with the observed results of the effect of salts on the critical micelle concentration of cetylpyridinium chloride[19]. With addition of salt, a decrease of c^* values was observed for the micellization of surfactants in the presence of drug[10-12, 20- 22]. The total effect of an electrolyte is the sum of its effects on the drug and surfactant molecule in association with the aqueous phase. Hydrophilic groups of the surfactant molecules are directed towards the aqueous phase both in the monomeric and micellar forms of the surfactant, while the hydrophobic groups are surrounded by water only in the monomeric form of surfactant molecules. Thus, the consequence of the electrolyte on the hydrophilic groups in the monomeric and micellar forms may eliminate each other and hence the effects of electrolyte on the hydrophobic groups of surfactant monomers play the dominating role.

The values of c^* and β at different temperatures for drug-CDMEAB systems in pure water and in the presence of salts such as NaCl, Na_2SO_4 and Na_3PO_4

are summarized in Fig. 6 (see also Supplementary Data, Tables S3 & S4 and Figs S1–S6). The c^*_1 values at different temperatures in pure water for CFH-CDMEAB and LFH-CDMEAB systems are found to increase gradually with increasing temperatures up to a certain temperature, attain a maximum value and then decrease with further increasing temperature. For LMFH-CDMEAB system, the c^*_1 values at different temperatures decrease gradually up to a maximum and thereafter the values gradually increase with further increasing temperature. The c^*_2 values for all the drug-CDMEAB systems initially decrease, pass a minimum value and then tend to increase with further increase of temperature. In the presence of NaCl, Na_2SO_4 and Na_3PO_4 salts, the c^* values for all the drug-CDMEAB systems are initially found to decrease, pass through a minimum and then tend to increase with further increase of temperature. Such a type of variation of the c^* values for different systems containing ionic surfactants and more often containing non-ionic surfactant are also reported in the literature[10-12,23]. In some cases the trend of gradual increase of c^* values with increasing temperature is also reported[16,24]. The change of c^* values with temperature can be explained with the change of the mode of hydration surrounding the surfactant monomers as well as the drug mediated CDMEAB micelles. In monomeric form of surfactant, both hydrophobic and hydrophilic hydrations are possible, whereas only hydrophilic hydration is possible for micellized CDMEAB. Both types of hydrations are expected to decrease with increase of temperature. A decrease in hydrophilic hydration favours the micelle formation, while a decrease of hydrophobic dehydration with the increase of temperature oppose the micelle formation[12,13,16,23,25]. Thus, the magnitude of these two factors determine whether the c^* values increase or decrease over a particular temperature range. The minimum in c^* versus temperature plots has been explained earlier considering the change in various factors like surfactant solubility, desolvation, change in solvent structure, etc., with temperature which may play an important role in this respect[16, 23, 26].

Thermodynamic parameters of drug-CDMEAB systems

Thermodynamic parameters are an effective tool to study the mode of interaction at the molecular level. The thermodynamic parameters of studied drug-CDMEAB systems containing 1:1 electrolyte surfactant were determined by Eqs (1-3)[10-15, 27-30],

$$\Delta G^0_m = (1+\beta)\, RT\ln(c^*) \quad \ldots(1)$$

$$\Delta H^0_m = -(1+\beta)\, RT^2\, (\partial \ln c^*/\partial T) \quad \ldots(2)$$

$$\Delta S^0_m = (\Delta H^0_m - \Delta G^0_m)/\mathrm{T} \quad \ldots(3)$$

where values of c^* are in mole fraction unit. Plot $\ln(c^*_2)$ versus T was nonlinear (Fig. 7) and the slope of the tangent drawn at each temperature of $\ln(c^*_2)$ versus T plot was taken as equal to $\partial \ln(c^*)/\partial T$ for the calculation of ΔH^0_m [31,32].

The values of thermodynamic parameters for drug-CDMEAB systems in pure water and in the presence of NaCl, Na_2SO_4 and Na_3PO_4 salts are presented in Tables 1 and 2. The $\Delta G^0_{1,m}$ and $\Delta G^0_{2,m}$ values for all the systems are found to be negative, which indicates that the micellization process is thermodynamically spontaneous.

For CFH-CDMEAB in water, the $\Delta H^0_{1,m}$ values are found to be positive and the values decrease with temperature and the sign of $\Delta H^0_{1,m}$ value changes from positive to negative at the elevated temperature.

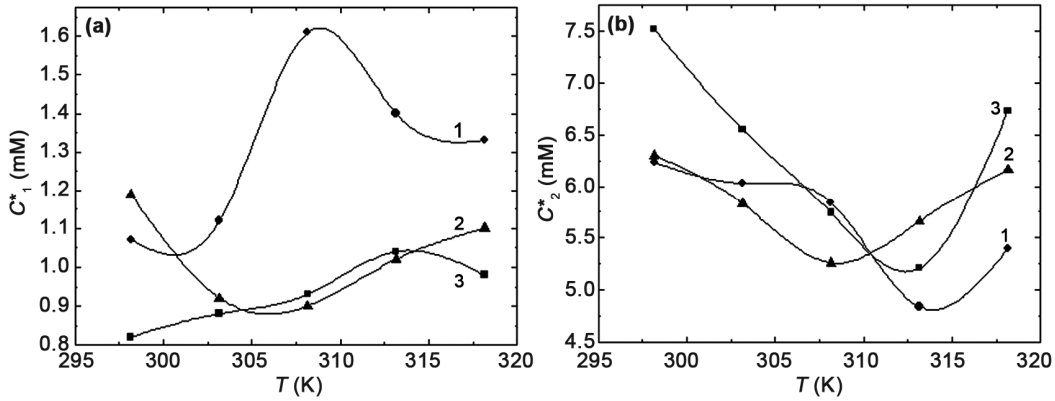

Fig. 6 – Plot of (a) c^*_1 vs. T and (b) c^*_2 vs. T for LFH-CDMEAB (1, ♦), LMH-CDMEAB (2, ▲), and, CFH-CDMEAB (3, ■) systems in water containing 0.50 mM drugs at different temperatures.

The values of $\Delta S^0_{1,m}$ are found to be positive and the values decrease gradually with increasing temperature. Thus, the first aggregation process was found to be entropy controlled at lower temperature and becomes both enthalpy and entropy controlled at higher temperature. For CFH-CDMEAB system in water, the $\Delta H^0_{2,m}$ values are negative and the values decrease with increasing temperature. The values of

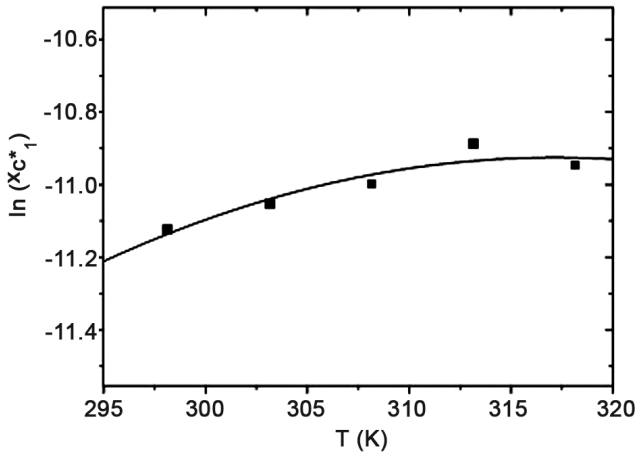

Fig. 7 – ln(c^*_1) versus T for CFH-CDMEAB system in water.

$\Delta S^0_{2,m}$ are negative at lower temperatures, and the sign changes from negative to positive with the positive values increasing with increase of temperature. Thus the CFH mediated CDMEAB micellization process is enthalpy controlled at lower temperatures and becomes both enthalpy and entropy controlled at higher temperatures. The results reveal that the binding interactions between CFH and CDMEAB are both electrostatic and hydrophobic in nature, although hydrophobic contribution plays the major role. In aqueous solution of NaCl salt, the $\Delta H^0_{1,m}$ values are found to be negative at lower temperatures and positive at higher temperatures. The $\Delta H^0_{2,m}$ values are found to be positive at lower temperatures and negative at higher temperatures. The values of $\Delta S^0_{1,m}$ and $\Delta S^0_{2,m}$ are positive, and the values increase gradually with increase of temperature. Thus, the first micellization at lower temperatures is both enthalpy and entropy controlled while at higher temperatures in presence of NaCl, it becomes entropy controlled. The second micellization process was entropy controlled at lower temperatures and becomes both entropy and enthalpy controlled at higher temperatures. The change of thermodynamic parameters in aqueous

Table 1 – Thermodynamic parameters[a] for the micellization of the drug-CDMEAB systems containing 0.50 m*M* drug in water at different temperatures

Systems	T	$\Delta G^0_{1,m}$	$\Delta G^0_{2,m}$[a]*	$\Delta H^0_{1,m}$	$\Delta H^0_{2,m}$[b]*	$\Delta S^0_{1,m}$	$\Delta S^0_{2,m}$	$\Delta C^0_{1,m}$	$C^0_{2,m}$
	(K)	(kJ mol^{-1})	(kJ mol^{-1})	(kJ mol^{-1})	(kJ mol^{-1})	(J mol^{-1} K^{-1})	(J mol^{-1} K^{-1})	(kJ mol^{-1} K^{-1})	(kJ mol^{-1} K^{-1})
CDMEAB	298.15	-46.60	-41.85	-61.38	-41.21	-49.57	2.18		
	303.15	-49.68	-43.59	-32.99	-23.02	55.03	67.87		
	308.15	-51.02	-44.76	-1.04	-2.01	162.2	138.7	6.51	4.23
	313.15	-51.00	-45.26	32.84	19.90	267.7	208.1		
	318.15	-51.23	-45.39	68.42	43.17	376.1	278.3		
CFH-CDMEAB	298.15	-50.34	-41.52	29.86	-8.24	268.9	-122.3		
	303.15	-50.59	-42.87	22.66	-7.23	241.6	-13.53		
	308.15	-50.95	-44.21	15.03	-5.4	214.1	98.73	-1.58	6.88
	313.15	-50.93	-44.92	6.84	-3.07	184.5	213.9		
	318.15	-52.09	-44.61	-1.68	0.69	158.4	327.2		
LFH-CDMEAB	298.15	-46.76	-41.61	67.99	-23.81	384.9	59.69		
	303.15	-47.31	-42.64	44.04	-19.53	301.3	76.25		
	308.15	-45.84	-42.97	17.79	-14.67	206.5	91.83	-5.37	0.98
	313.15	-47.91	-45.02	-9.62	-9.48	122.3	113.4		
	318.15	-49.59	-45.59	-39.34	-4.36	32.23	129.5		
LMFH-CDMEAB	298.15	-46.60	-41.85	-61.38	-41.21	-49.57	2.18		
	303.15	-49.68	-43.59	-32.99	-23.02	55.03	67.87		
	308.15	-51.02	-44.76	-1.04	-2.01	162.2	138.7	6.51	4.23
	313.15	-51.00	-45.26	32.84	19.90	267.7	208.1		
	318.15	-51.23	-45.39	68.42	43.17	376.1	278.4		

[a]The uncertainty of $\triangle G^0_m$, $\triangle H^0_m$, $\triangle S^0_m$ and ΔC^0_m values are: ±0.04–0.2 kJ mol^{-1}; ±0.03 kJ mol^{-1}; ±0.04–0.2 J mol^{-1} K^{-1} and 0.02–0.1 kJ mol^{-1} K^{-1} respectively.

Table 2 – Thermodynamic parameters[a] for the micellization of the drug-CDMEAB systems in 0.50 m*M* aqueous salt solutions at different temperatures

Systems[b]	T (K)	$\Delta G^0_{1,m}$ (kJ mol^{-1})	$\Delta G^0_{2,m}$ (kJ mol^{-1})	$\Delta H^0_{1,m}$ (kJ mol^{-1})	$\Delta H^0_{2,m}$ (kJ mol^{-1})	$\Delta S^0_{1,m}$ (J mol^{-1} K^{-1})	$\Delta S^0_{2,m}$ (J mol^{-1} K^{-1})	$\Delta C^0_{1,m}$ (kJ mol^{-1} K^{-1})	$C^0_{2,m}$ (kJ mol^{-1} K^{-1})
				H_2O-NaCl					
CFH–CDMEAB	298.15	-49.49	-41.86	-45.89	17.05	12.06	47.84		
	303.15	-51.9	-42.95	-19.22	3.76	107.79	90.72		
	308.15	-51.79	-44.15	9.3	-2.64	198.24	135.98	5.85	2.73
	313.15	-51.57	-44.73	39.61	-14.4	291.17	181.42		
	318.15	-51.86	-44.65	71.04	-28.26	386.3	225		
LFH–CDMEAB	298.15	-48.40	-41.47	-24.35	-44.06	80.67	-8.67		
	303.15	-49.79	-43.15	-8.55	-23.43	136.02	65.05		
	308.15	-49.55	-44.27	8.41	-1.18	188.08	139.83	3.50	4.65
	313.15	-50.34	-44.21	26.52	23.96	245.43	217.69		
	318.15	-50.99	-44.87	45.58	48.47	303.54	293.38		
LMFH–CDMEAB	298.15	-49.72	-41.95	-27.64	-26.84	74.06	50.68		
	303.15	-50.82	-43.01	-15.83	-14.61	115.44	93.69		
	308.15	-52.40	-44.24	-3.01	-0.99	160.29	140.34	2.62	2.76
	313.15	-52.48	-44.25	10.45	13.19	200.96	183.44		
	318.15	-52.44	-44.69	24.84	28.25	242.90	229.27		
				H_2O-Na_2SO_4					
CFH–CDMEAB	298.15	-49.19	-42.73	-50.51	12.31	-4.45	218.25		
	303.15	-50.79	-43.10	-30.12	5.77	68.17	176.01		
	308.15	-51.74	-43.77	-8.09	1.4	141.65	132.4	4.52	-2.72
	313.15	-52.23	-44.75	15.43	-2.53	216.09	88.47		
	318.15	-51.97	-45.74	39.68	-8.48	288.06	43.44		
LFH–CDMEAB	298.15	-49.09	-43.36	-0.16	11.65	164.10	184.53		
	303.15	-49.66	-43.88	16.75	9.73	219.07	176.85		
	308.15	-49.76	-44.55	34.87	7.70	274.63	169.56	3.67	-0.43
	313.15	-49.87	-45.31	54.83	5.38	334.32	161.86		
	318.15	-48.32	-45.29	72.45	3.05	379.62	151.92		
LMFH–CDMEAB	298.15	-50.28	-42.21	-73.71	-40.31	-78.57	6.37		
	303.15	-53.14	-43.43	-21.14	-22.65	105.56	68.56		
	308.15	-51.12	-43.93	35.18	-2.41	280.07	134.72	11.12	3.98
	313.15	-51.28	-44.70	94.68	18.17	466.11	200.75		
	318.15	-46.56	-42.74	146.31	38.68	606.24	255.91		
				H_2O-Na_3PO_4					
CFH–CDMEAB	298.15	-52.46	-43.30	47.59	-5.94	335.57	305.25		
	303.15	-52.25	-43.18	40.75	-5.64	306.78	213.92		
	308.15	-50.84	-43.65	33.53	-7.82	273.82	123.55	-1.44	-5.62
	313.15	-51.31	-44.27	26.44	-6.73	248.29	30.97		
	318.15	-51.02	-45.64	18.81	-5.52	219.48	-60.12		
LFH–CDMEAB	298.15	-48.48	-44.27	22.90	59.41	239.39	347.75		
	303.15	-49.79	-44.84	25.92	47.35	249.75	304.12		
	308.15	-49.74	-44.39	28.62	33.92	254.29	254.13	0.52	-2.80
	313.15	-50.08	-44.63	31.72	18.52	261.23	201.66		
	318.15	-48.01	-44.37	33.08	3.80	254.86	151.41		
LMFH–CDMEAB	298.15	-50.07	-42.51	-104.23	-23.69	-181.65	63.14		
	303.15	-51.13	-43.62	-58.11	-25.36	-23.00	60.22		
	308.15	-52.59	-44.77	-9.41	-26.94	140.12	57.85	9.92	-0.33
	313.15	-51.87	-45.78	40.30	-28.66	294.31	54.66		
	318.15	-51.83	-46.77	94.51	-30.32	459.99	51.69		

[a]The uncertainty of $\triangle G^0_m$, $\triangle H^0_m$, $\triangle S^0_m$ and ΔC^0_m values are: ±0.05–0.2 kJ mol^{-1}; ±0.05–0.2 kJ mol^{-1}; ±0.05–0.3 J mol^{-1} K^{-1} and 0.02–0.1 kJ mol^{-1} K^{-1} respectively.

[b]Drug = 0.50 m*M*.

solution of Na_2SO_4 is found to be almost similar to that in NaCl. However, the exothermic contribution on first aggregation process and the hydrophobic contribution on second micellization process are dominant at lower temperatures in the case of Na_2SO_4 as compared to that of NaCl. In presence of Na_3PO_4, the first micellization process is entirely entropy controlled, whereas the second micellization process is both entropy and enthalpy controlled within the temperatures studied. The variation of $\Delta H^0_{1,}$m and $\Delta H^0_{2,}$m with temperature (T) for the micellization of CFH-CDMEAB system in water and in aqueous solution of salts is shown in Figs S7 and S8 (Supplementary Data).

For LFH–CDMEAB system in water, the $\Delta H^0_{1,m}$ values are positive at lower temperatures. The values decrease with temperature, the sign changes from positive to negative and the negative values tend to increase gradually with increase of temperature. The and $\Delta H^0_{2,m}$ values are negative and the negative values are found to decrease gradually with increase of temperatures. The ΔS^0_m values over the range of temperatures studied are positive while the $\Delta S^0_{1,m}$ and $\Delta S^0_{2,m}$ values are found to decrease and increase respectively with increase of temperature. Thus, the micellization process is only entropy controlled at the lower temperatures while at higher temperatures there is also enthalpic contribution in addition to entropy effect. These results reveal that the binding interactions between LFH and CDMEAB are both electrostatic and hydrophobic in nature, while hydrophobic contribution plays the major role in the lower temperatures. In aqueous solution of salts, the ΔH^0_m and ΔS^0_m values reveal that the micellization processes are almost entropy controlled though there is some enthalpy effect at the lower temperatures in aqueous NaCl solution.

For LMFH–CDMEAB system in water, the $\Delta H^0_{1,m}$ and $\Delta H^0_{2,m}$ values are negative at lower temperatures, the sign changes from negative to positive and the positive values tend to increase gradually with increase of temperature. The value of $\Delta S^0_{1,m}$ at T = 298.15 K is negative, whereas the other $\Delta S^0_{1,m}$ and $\Delta S^0_{2,m}$ values are found positive with the values increasing gradually with increase of temperature. Thus, the micellization processes are both entropy and enthalpy controlled at lower temperatures, and become only entropy controlled at the elevated temperatures. The results reveal that the binding interactions between LMFH and CDMEAB are both electrostatic and hydrophobic in nature, while hydrophobic contribution plays the major role. In aqueous solution of salts, the change of ΔH^0_m and ΔS^0_m values follows almost the same trend as that in water. In some cases, the larger values of ΔH^0_m and ΔS^0_m reveal the enhanced binding interactions between LMFH and CDMEAB in aqueous salts solution.

The net ΔH^0_m is expected to be the sum of the change in enthalpies arising from hydrophobic interactions, electrostatic interactions and hydration of polar head groups. A negative ΔH^0_m may occur when second and third effects become dominant while the positive ΔH^0_m may arise when the first effect is stronger. The negative values of ΔH^0_m signify the importance of London-dispersion interactions as an attractive force of micellization between drug-surfactant systems[33], whereas the positive ΔH^0_m values indicate the breaking of structured water around the hydrophobic parts of the molecules[34]. The positive values of ΔS^0_m for drug mediated surfactant micellization can be explained considering two factors. These are: (i) transfer of hydrophobic chains from hydrated form in aqueous medium to the nonpolar interior of the micelle destroying iceberg structures, and, (ii) increase of rotational degree of freedom of hydrophobic chains in the micelle interior as compared to the aqueous environment[35,36]. The negative values of ΔS^0_m may occur when the formation of iceberg structure surrounding the drug and CDMEAB is dominant over the above two effects.

The enthalpy change with temperature, i.e., the molar heat capacity changes ($\Delta_m C^0_p$) for micelle formation, is an important sign of protein structural changes in response to different ligands which is obtained from the slope of the plot of ΔH^0_m versus temperature[37, 38].

$$\Delta_m C^0_p = ((\partial H^0_m)/\partial T)_p \quad ...(4)$$

The enthalpy change with temperature, i.e. the molar heat capacity, varies linearly with temperature for all the drug-CDMEAB systems in pure water as well as in the aqueous solution of salts. The values $\Delta_m C^0_p$ of the drug-CDMEAB systems were found to be positive in some cases and negative for others. The change in heat capacity associated with drug-CDMEAB binding is believed to be associated with motion restriction and is proportional to the change in the surface area

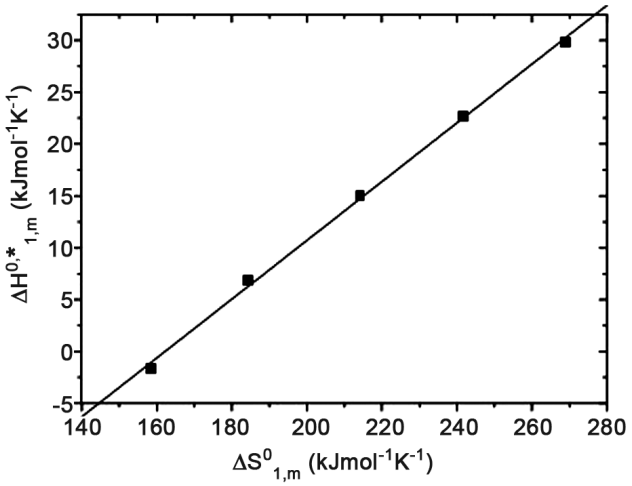

Fig. 8 – Enthalpy-entropy compensation plot for CFH-CDMEAB system in water with $R^2 = 0.99$.

accessible to the solvent[38]. However, the small $\Delta_m C^0_p$ and the positive binding entropy indicate minor structural rearrangement of CDMEAB micelle during binding with LMFH, whereas in the case of aggregation the effect was significant at lower temperatures.

A linear relationship between ΔH^0_m and ΔS^0_m, i.e., enthalpy-entropy compensation, with R^2 in the range of 0.993-0.999 was observed in all cases (Fig. 8) according to the following regression equation[39],

$$\Delta H^0_m = \Delta H^{0,*}_m + T_c \Delta S^0_m \quad \ldots(5)$$

where the slope, T_c the compensation temperature, describes the solvation part of the micellization process and is the basis of comparison for different examples of compensation behavior and the intercept $\Delta H^{0,*}_m$, is the intrinsic enthalpy gain. The intercept ΔH^{0*}_m characterizes the solute-solute interaction and is an index of the efficacy of the hydrophobic chain to participate in the micelle growth. The values of ΔH^0_m and T_c for both systems in pure water and in the presence of salts are shown in Table 3. The T_c values for drug-CDMEAB systems are slightly higher in the presence of salts than in pure water. The T_c value in the range of 275-581 K has been used as an indicator for the association of water in protein solution[40]. Higher negative ΔH^{0*}_m values indicates that the micellization of CDMEAB was facilitated even at $\Delta S^0_m = 0$. An increase in the negative $\Delta H^{0,*}_m$ values indicates the stability of the formation of the micelles.

Table 3 – Enthalpy-entropy compensation parameters for drug-CDMEAB systems in water and in 0.50 m*M* aqueous salt solutions

System[a]	$\Delta H^{0,*}_{1,m}$ (kJ mol^{-1})	$\Delta H^{0,*}_{2,m}$ (kJ mol^{-1})	$T_{c,1}$ (K)	$T_{c,2}$ (K)
		H_2O		
CFH-CDMEAB	–45.98	–42.20	283.44	305.19
LFH-CDMEAB	–47.36	–40.36	303.34	275.98
LMFH-CDMEAB	–48.48	–43.14	305.91	305.73
		H_2O-NaCl		
CFH-CDMEAB	–51.57	–43.09	314.08	306.99
LFH-CDMEAB	–50.60	–42.71	315.17	307.24
LMFH-CDMEAB	–51.44	–43.26	309.97	308.74
		H_2O-Na_2SO_4		
CFH-CDMEAB	–50.46	–44.95	308.25	311.65
LFH-CDMEAB	–56.20	–37.84	335.14	268.40
LMFH-CDMEAB	–52.22	–43.63	320.75	314.57
		H_2O-Na_3PO_4		
CFH-CDMEAB	–34.92	–44.85	246.92	307.81
LFH-CDMEAB	–86.20	–38.66	455.12	282.98
LMFH-CDMEAB	–50.13	–60.43	309.82	581.39

[a]Drug = 0.50 m*M*.

Conclusions

Interaction of three fluoroquinolone drugs with the cationic surfactant, CDMEAB, was studied by conductance measurements in water and in the presence of salts. The addition of drugs altered the micellization behaviour of CDMEAB. In addition, the effect of temperatures and presence of salts is also observed significantly. The thermodynamic parameters reveal that drug-CDMEAB interactions are mainly hydrophobic and electrostatic in nature.

Supplementary Data

Supplementary Data associated with this article, Figs S1-S8 and Tables S1-S4 are available in the electronic form at http://www.niscair.res.in/jinfo/ijca/IJCA_55A(02)160-169_SupplData.pdf.

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