

Micellization behavior of mixtures of amphiphilic promazine hydrochloride and cationic aniline hydrochloride in aqueous and electrolyte solutions

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Abstract—We studied the influence of cationic hydrotrope aniline hydrochloride on the micellization behavior of cationic amphiphilic phenothiazine drug promazine hydrochloride in the presence and absence of 50 mmol kg⁻¹ NaCl. The experimental critical micelle concentration (CMC) values came out to be lower than ideal CMC (CMC^{id}) values, signifying attractive interactions between the two components in mixed micelles. NaCl further decreases the CMC of pure PMZ and aniline hydrochloride as well as their mixture due to screening of the electrostatic repulsion among the polar head groups. The bulk properties of solution were examined by using different theoretical models for justification and comparison of results. The micellar mole fraction of aniline hydrochloride (X_1^{Rub} , X_1^M , X_1^{Rot} and X_1^{id}) was evaluated by different proposed models, showing greater contribution of hydrotrope in mixed micelle. The negative values of interaction parameter (β) indicate synergistic interactions and negative values of β further decrease by the addition of salt in mixed systems. From the CMC values as a function of temperature, various thermodynamic properties have been evaluated and discussed in detail.

Keywords: Phenothiazine Drug, Promazine Hydrochloride (PMZ), Critical Micelle Concentration (CMC), Hydrotrope, Interaction Parameter, Thermodynamic Parameters

INTRODUCTION

Amphiphilic molecules such as surfactants, drugs, hydrotropes, and polymers self-associate in aqueous solution to form micelles or related structures above a certain concentration known as critical micelle concentration (CMC) [1-7]. These micelles are of wide-spread use in pharmaceutical applications besides food, detergency, cosmetic industries and enhanced oil recovery and range of applications [8]. In many pharmaceutical formulations amphiphilic substances are often used together as active compounds or excipients, as interactions can influence the physico-chemical property of dosage form, which in turn may alter the stability of the formulation and the liberation of active compound at the target site. Numerous drug delivery and drug targeting systems have been studied in an attempt to minimize drug degradation and loss, to prevent harmful side effects and increase drug bioavailability [9-11]. One of the convenient ways to modulate the structures of micelles is by the addition of short chain amphiphiles known as hydrotropes. Due to their ability to dissolve insoluble organic compounds, most of the research has, however, been focused on the solubilization and separation with hydrotropes [12-14].

Hydrotropes have been identified as amphiphilic organic com-

pounds carrying a close structural similarity to classical surfactants (amphiphiles). The hydrotropes applied to short chain amphiphiles exhibit three common features: (a) They do not aggregate in well-arranged structures such as micelles but somewhat form dimers, trimers, etc. [15] (b) Above a bestowed concentration in water, hydrotropes make capable the solubilization of large quantities of hydrophobic compounds in water; the solubilization versus hydrotrope concentration curves pursue power series [16]. (c) Hydrotropes shatter ordered lyotropic phases shaped by amphiphiles at high concentration. The ability of hydrotropes to enhance the solubility of organics in water is often strongest when the hydrotrope concentration is enough to bring about the formation of associated structures [17]. The concentration at which self association begins is denoted as the minimum hydrotrope concentration (MHC) used in consonant with CMC [15,16] and is often indicated by changes in solution properties such as viscosity, conductivity, surface tension, or solubility.

Promazine hydrochloride (PMZ, 10-(3-dimethylamino-propyl) phenothiazine hydrochloride) is a medication that belongs to the phenothiazine class of antipsychotics. PMZ a phenothiazine drug that consists of two phenyl rings connected by sulfur and nitrogen atoms together with an aminopropyl chain (Fig. 1). Promazine can be used to calm your emotions particularly if you feel restless and agitated, particularly if you are an older person. PMZ consists of a planar rigid tricyclic ring system that behaves as hydrophobic part and an alkylamine side chain acts as hydrophilic head group part

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for that reason, PMZ aggregates in surfactant like manner and depends on the solution conditions (like pH, ionic strength, additive concentration, temperature, etc.) [18].

Although the pharmacological effect of this drug usually takes place at low concentrations where self aggregation is negligible, it is likely that the CMC of drug decreases in presence of additives and the drug may accumulate at certain sites in the body which may harm, or even prove fatal [19]. In contrast, the CMC of a mixture may increase/decrease depending upon the nature of the interactions of drug with amphiphiles when added to form mixed micelles. Increase in CMC may, in-vivo, result in disintegration of micelles when diluted in the body. This may perhaps also be the reason for unloading and accumulation of drug at a meticulous site. In most cases pharmacological activity of drugs appears at well below the CMC where aggregation is insignificant [18]. The incorporation of hydrotrope into an aggregate of an amphiphilic drug will affect its physicochemical properties such as the degree of ionization, reaction rates and clouding or phase separation [20,21]. In what way, during extended period of administration, drug accumulation takes place at certain sites which prevent the transport rate and cause several side effects, such as sedation, agitation, over-excitement, sleeplessness, confusion etc. To subdue these side effects the study of physicochemical properties of a drug is important from their implication point of view. In this context, we studied the micellization behavior of PMZ drug in presence of cationic hydrotrope aniline hydrochloride in absence and presence of inorganic salt (50 mmol kg⁻¹ NaCl) by determining various physicochemical parameters.

MATERIALS AND METHODS

1. Materials

Promazine hydrochloride, PMZ ($\geq 98\%$), supplied by Sigma, USA, was used as received. The cationic hydrotrope aniline hydrochloride (99.0%, Fluka, Switzerland) and sodium chloride (NaCl, 97%, BDH, England) were used as received.

Double-distilled water (DDW) with conductivity lower than $1 \cdot 6 \times 10^{-6} \text{ Scm}^{-1}$ was used to prepare the solutions. Stock solutions of salt were prepared by dissolving requisite amount of the compound in a known amount of DDW. This stock solution was then used as solvents.

2. Methods

Conductivity meter principle is a digital representation of solution conductivity with conduction current capacity. The conductance measurement were taken with a model 4510, Jenway, UK conductivity meter, equipped with a dip cell (glass electrode) having cell constant 1.026 cm^{-1} . The temperature in all the experiments was maintained by circulating water from an electronically controlled water bath (Julabo, Germany) with a temperature stability of $\pm 0.2 \text{ K}$. The stock solutions of drug PMZ (with or without aniline hydrochloride) in absence and presence of NaCl (salt) was prepared in double-distilled water (DDW). A known volume of concentrated stock solution was then added to water in case of no aniline hydrochloride or water containing fixed concentration of the aniline hydrochloride (hydrotrope) in absence and presence of salt with a micropipette and mixed thoroughly, followed by measurement of conductance. Similar process was repeated after every addi-

tion. A break in the specific conductivity versus amphiphiles concentration curve signals the onset of the micellization process is considered as the CMC of the solution. The uncertainty in specific conductance was found to be less than $\pm 2\%$.

RESULTS AND DISCUSSION

1. Effect of Aniline Hydrochloride on the CMC of the PMZ in Absence and Presence of 50 mmol kg⁻¹ NaCl

Critical micellar concentration (CMC) values in the present study have been computed from the breakpoint in the plot of specific conductance versus concentration of PMZ. The representative illustrations of specific conductance versus concentration of PMZ with and without aniline hydrochloride in absence and presence of salt at 303.15 K are shown in Fig. 2. The CMC values thus obtained with different mole fractions of the added aniline hydrochloride (α_1) in absence and presence of 50 mmol kg⁻¹ NaCl at different temperatures are given in Tables 1-2 together with the values of degree of counterion dissociation (g), interaction parameter (β) and activity coefficient. The *cmc* value of pure PMZ at 298.15 K was found to be $35.05 \text{ mmol kg}^{-1}$, which agreed with the literature value (36 mmol kg^{-1}) [18,22,23]. The MHC values of the pure aniline hydrochloride is presented in Tables 1-2 and found to be in good agree-

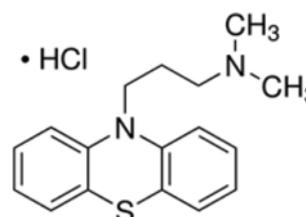


Fig. 1. Molecular model of promazine hydrochloride (PMZ).

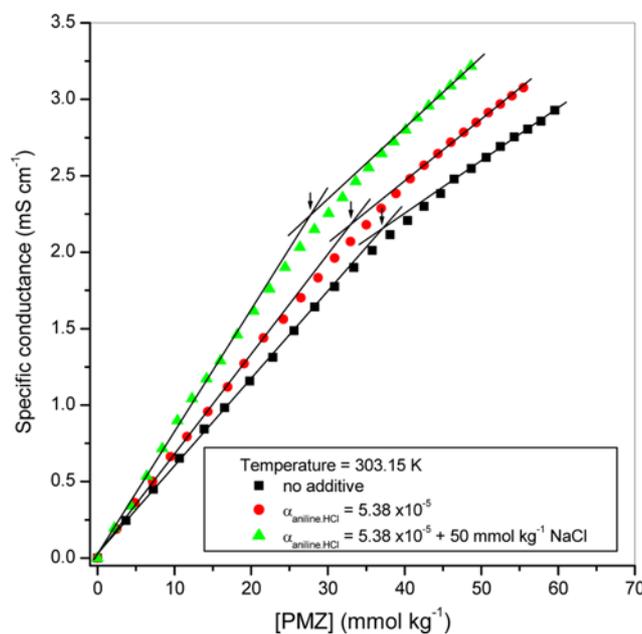


Fig. 2. Representative plots of specific conductance versus concentration of PMZ with and without additives at 303.15 K.

Table 1. The physicochemical parameters for PMZ-aniline hydrochloride mixed systems in aqueous solution at various temperature and concentration^a

α_1	CMC/mm \cdot kg $^{-1}$	CMC ^{id} /mm \cdot kg $^{-1}$	g	β	$f_1^{Rub}/f_1^M/f_1^{Rod}$	$f_2^{Rub}/f_2^M/f_2^{Rod}$
T=293.15 K						
0	33.25		0.59			
2.69×10^{-5}	31.30	33.24	0.58	-7.20	0.0014/0.0015/0.0012	0.9855/0.9825/0.9935
5.38×10^{-5}	29.25	33.23	0.57	-7.65	0.0015/0.0013/0.0011	0.9541/0.9664/0.9829
8.08×10^{-5}	27.15	33.22	0.56	-8.09	0.0015/0.0011/0.0010	0.9130/0.9550/0.9693
10.77×10^{-5}	25.0	33.21	0.55	-8.56	0.0015/0.0009/0.0009	0.8645/0.9517/0.9519
14.37×10^{-5}	22.80	33.20	0.54	-8.99	0.0015/0.0007/0.0008	0.8091/0.9894/0.9526
1.0	13.40		0.58			
T=298.15 K						
0	35.05		0.60			
2.69×10^{-5}	33.10	35.04	0.59	-7.13	0.0014/0.0016/0.0014	0.9868/0.9808/0.9885
5.38×10^{-5}	31.05	35.03	0.58	-7.55	0.0015/0.0014/0.0013	0.9579/0.9622/0.9728
8.08×10^{-5}	29.0	35.03	0.57	-7.95	0.0016/0.0012/0.0012	0.9209/0.9483/0.9554
10.77×10^{-5}	27.05	35.02	0.56	-8.33	0.0016/0.0011/0.0011	0.8804/0.9437/0.9397
14.37×10^{-5}	24.90	35.02	0.55	-8.72	0.0017/0.0009/0.0010	0.8303/0.9652/0.9327
1.0	14.20		0.62			
T=303.15 K						
0	37.0		0.61			
2.69×10^{-5}	35.05	36.99	0.60	-7.05	0.0015/0.0017/0.0015	0.9880/0.9818/0.9872
5.38×10^{-5}	33.05	36.98	0.59	-7.44	0.0016/0.0015/0.0014	0.9621/0.9653/0.9719
8.08×10^{-5}	31.10	36.97	0.58	-7.78	0.0017/0.0014/0.0013	0.9300/0.9541/0.9567
10.77×10^{-5}	29.05	36.97	0.57	-8.17	0.0017/0.0012/0.0012	0.8908/0.9458/0.9368
14.37×10^{-5}	26.85	36.96	0.56	-8.54	0.0018/0.0010/0.0011	0.8442/0.9613/0.9255
1.0	15.01		0.67			
T=308.15 K						
0	35.70		0.62			
2.69×10^{-5}	33.75	35.69	0.61	-7.18	0.0013/0.0015/0.0013	0.9871/0.9821/0.9893
5.38×10^{-5}	31.70	35.68	0.60	-7.60	0.0014/0.0013/0.0012	0.9589/0.9648/0.9745
8.08×10^{-5}	29.75	35.68	0.59	-7.97	0.0015/0.0012/0.0011	0.9247/0.9549/0.9614
10.77×10^{-5}	27.70	35.67	0.58	-8.38	0.0015/0.0010/0.0010	0.8827/0.9489/0.9434
14.37×10^{-5}	25.40	35.67	0.57	-8.79	0.0016/0.0008/0.0009	0.8316/0.9682/0.9322
1.0	15.65		0.74			
T=313.15 K						
0	34.20		0.63			
2.69×10^{-5}	32.25	34.19	0.62	-7.32	0.0012/0.0013/0.0011	0.9860/0.9810/0.9899
5.38×10^{-5}	30.20	34.19	0.61	-7.75	0.0013/0.0012/0.0010	0.9558/0.9627/0.9756
8.08×10^{-5}	28.15	34.18	0.60	-8.18	0.0013/0.0010/0.0009	0.9168/0.9496/0.9596
10.77×10^{-5}	26.10	34.18	0.59	-8.60	0.0013/0.0009/0.0009	0.8727/0.9441/0.9419
14.37×10^{-5}	24.0	34.17	0.58	-8.98	0.0014/0.0007/0.0008	0.8227/0.9718/0.9394
1.0	16.01		0.80			

^aStandard uncertainties (u) limits are u (CMC), u (g), are $\pm 2\%$ and $\pm 3\%$ respectively

ment with the literature value [24]. The drug structure shown in Fig. 1 clearly shows that the hydrophobic part of the drug molecule is short and rigid. Therefore, it forms aggregates at higher concentrations as compared to the aniline hydrochloride (hydrotrope) in the absence and presence of salt (50 mmol kg $^{-1}$ NaCl).

In the present study, concentrations of aniline hydrochloride (hydrotrope) used are lower than their MHC values. It means that the aniline hydrochloride would either form mixed micelles with

the drug molecules or would remain as monomers in the aqueous phase. Tables 1-2 and Fig. 2 data show that with increase in α_1 value the CMC of mixed systems decreases in absence and presence of 50 mmol kg $^{-1}$ NaCl. The CMC values of the mixed systems usually fall between the values of pure components. In our systems the same result is obtained. It suggests that the mixed micelles are formed due to attractive interactions between the two components. Aniline hydrochloride is tied to the positively charged amphiphilic

Table 2. The physico-chemical parameters for PMZ-aniline hydrochloride mixed systems in 50 mmol kg⁻¹ NaCl solution at various temperature and concentration^a

α_1	CMC/mm \cdot kg ⁻¹	CMC ^{id} /mm \cdot kg ⁻¹	g	β	$f_1^{Rub}/f_1^M/f_1^{Rod}$	$f_2^{Rub}/f_2^M/f_2^{Rod}$
T=293.15 K						
0	28.05		0.57			
2.69 $\times 10^{-5}$	26.05	28.04	0.56	-7.55	0.0011/0.0010/0.0008	0.9796/0.9811/0.9984
5.38 $\times 10^{-5}$	24.0	28.03	0.55	-8.08	0.0012/0.0009/0.0007	0.9385/0.9678/0.9976
8.08 $\times 10^{-5}$	21.90	28.03	0.53	-8.61	0.0012/0.0007/0.0006	0.8857/0.9646/0.9983
10.77 $\times 10^{-5}$	19.75	28.02	0.52	-9.19	0.0012/0.0006/0.0006	0.8229/0.9804/0.9926
14.37 $\times 10^{-5}$	17.15	28.01	0.51	-9.89	0.0011/0.0004/0.0005	0.7397/0.9975/0.9982
1.0	12.0		0.58			
T=298.15 K						
0	29.85		0.58			
2.69 $\times 10^{-5}$	27.90	29.84	0.57	-7.42	0.0012/0.0011/0.0008	0.9824/0.9975/0.9965
5.38 $\times 10^{-5}$	25.85	29.83	0.56	-7.92	0.0012/0.0009/0.0007	0.9453/0.9932/0.9945
8.08 $\times 10^{-5}$	23.65	29.82	0.54	-8.37	0.0014/0.0008/0.0007	0.8946/0.9919/0.9924
10.77 $\times 10^{-5}$	21.40	29.82	0.53	-8.14	0.0017/0.0006/0.0007	0.8960/0.9917/0.9915
14.37 $\times 10^{-5}$	18.90	29.81	0.52	-8.70	0.0016/0.0011/0.0006	0.8363/0.9865/0.9893
1.0	12.75		0.6			
T=303.15 K						
0	31.60		0.59			
2.69 $\times 10^{-5}$	29.70	31.59	0.58	-7.29	0.0012/0.0012/0.0009	0.9848/0.9849/0.9991
5.38 $\times 10^{-5}$	27.75	31.58	0.57	-7.74	0.0014/0.0011/0.0009	0.9529/0.9734/0.9964
8.08 $\times 10^{-5}$	25.70	31.58	0.56	-8.20	0.0014/0.0009/0.0008	0.9105/0.9665/0.9894
10.77 $\times 10^{-5}$	23.45	31.57	0.54	-8.74	0.0014/0.0008/0.0007	0.8556/0.9658/0.9731
14.37 $\times 10^{-5}$	21.0	31.56	0.53	-9.29	0.0014/0.0006/0.0007	0.7901/0.9891/0.9723
1.0	13.50		0.64			
T=308.15 K						
0	30.15		0.6			
2.69 $\times 10^{-5}$	28.20	30.14	0.59	-7.50	0.0011/0.0011/0.0008	0.9826/0.9817/0.9985
5.38 $\times 10^{-5}$	26.20	30.13	0.58	-7.97	0.0012/0.0009/0.0007	0.9470/0.9674/0.9950
8.08 $\times 10^{-5}$	24.15	30.12	0.57	-8.46	0.0012/0.0008/0.0007	0.9005/0.9601/0.9889
10.77 $\times 10^{-5}$	21.95	30.11	0.55	-9.01	0.0012/0.0006/0.0006	0.8437/0.9617/0.9750
14.37 $\times 10^{-5}$	19.60	30.10	0.54	-9.56	0.0012/0.0005/0.0005	0.7757/0.9916/0.9817
1.0	14.10		0.69			
T=313.15 K						
0	29.15		0.61			
2.69 $\times 10^{-5}$	27.20	29.14	0.60	-7.62	0.0010/0.0009/0.0007	0.9815/0.9837/0.9985
5.38 $\times 10^{-5}$	25.10	29.13	0.59	-8.17	0.0010/0.0008/0.0006	0.9416/0.9692/0.9985
8.08 $\times 10^{-5}$	23.0	29.12	0.58	-8.68	0.0011/0.0006/0.0005	0.8914/0.9654/0.9962
10.77 $\times 10^{-5}$	20.85	29.11	0.57	-9.23	0.0010/0.0005/0.0005	0.8324/0.9781/0.9983
14.37 $\times 10^{-5}$	18.25	29.11	0.55	-9.91	0.0010/0.0004/0.0004	0.7530/0.9987/0.9934
1.0	14.60		0.76			

^aStandard uncertainties (u) limits are u (CMC), u (g), are $\pm 2\%$ and $\pm 3\%$ respectively

ions, which is approved by the negative values of the interaction parameters (discussed ahead) and minimizes the head group area. As a result, micelles are formed at much lower concentration; thus, the decrease in CMC is dependent upon the concentration of aniline hydrochloride. Mukerjee [25] suggested that an additive which is functioning at hydrocarbon/water interface would be principally solubilized at the micellar surface and would assist micellar growth. With an increase in concentration of hydrotrope (aniline hydro-

chloride), CMC of PMZ decreases due to partitioning and preferential adsorption on the ionic head group of drug, thereby reducing the head group repulsions between the hydrophilic groups and favoring early micellization. The CMC value of the pure PMZ as well as their mixture with aniline hydrochloride in presence of 50 mmol kg⁻¹ NaCl was further decreased (Table 2). The further decrease in CMC value in the presence of salt is attributable to the screening effect of salt on the electrostatic repulsions between amphiphile

head groups in the micelle.

For ideal mixtures, CMC of mixed systems can be predicted using Clint's model [26]:

$$\frac{1}{\text{CMC}^{id}} = \frac{\alpha_1}{\text{CMC}_1} + \frac{(1-\alpha_1)}{\text{CMC}_2} \quad (1)$$

where CMC^{id} is the ideal state mixed CMC, α_1 (aniline hydrochloride) is the mole fraction of first component, CMC_1 and CMC_2 are the CMC values for the first (aniline hydrochloride) and second (drug) component, respectively. The Clint equation makes a difference between ideal and nonideal behavior of amphiphile mixtures. Any deviation from CMC^{id} would, however, account for interactions among amphiphiles. Deviation in positive and negative sides suggests antagonism and synergism, respectively, in the system. In the present study, the CMC values come out to be lower than CMC^{id} values (Tables 1-2). This indicates that PMZ-hydro-trope mixed micelles are formed by attractive interactions in between the PMZ and hydro-trope, which is also a signal of nonideal behavior of mixing. Hence, CMC^{id} values emerge to be more than experimental CMC values because of attractive interaction between the PMZ and hydro-trope. Occurrence of mixed micellization at lower concentration can be attributed to the weakening of head group repulsions in PMZ as aniline hydrochloride intercalates between the charged head groups of the drug molecules in absence and presence of 50 mmol kg⁻¹ NaCl. It is clear from Tables 1-2 that in the presence of salt the CMC of mixed system of PMZ and hydro-trope decreases more in comparison to salt-free solution at all mole fractions. It has been reported that the added inorganic salt is also responsible for the reduction in the CMC [27]. The reason behind that by the addition inorganic salt, is that electrostatic repulsion between the polar head group of amphiphiles will decrease with increasing ionic strength of the aqueous medium due to increased sufficient shielding of the electrostatic repulsion by the ionic atmosphere around each charged site [28]. Therefore, the charge on the micellar head group becomes neutralized due to the added salt. Hence, at all mole fractions of hydro-trope (aniline hydrochloride), the interaction between these two amphiphiles is higher by the addition of salt, which correlates well with our findings (Tables 1-2).

2. Effect of Temperature on CMC and MHC of the PMZ and Aniline Hydrochloride, Respectively, as well as Their Mixture in Absence and Presence of 50 mmol kg⁻¹ NaCl

There are two opposing forces that govern the micellar phenomenon: (a) van der Waals forces between the hydrophobic part of an amphiphile that stabilizes the micelles, and (b) hydration of the hydrophilic part that destabilizes the micelles at a particular temperature. The CMC values of surfactants are known to show a complex behavior with temperature. CMC of nonionic surfactants decreases with increasing temperature as the hydrophilicity of the molecules decreases [29]; in contrast, the effect of temperature on the CMC of ionic surfactants is more complex. The CMC of ionic surfactants generally passes through a minimum with increasing temperature [30]. Tables 1-2 show the temperature dependence of CMC of the mixed systems in absence and presence of 50 mmol kg⁻¹ NaCl.

Generally, the effect of temperature on the CMC value of amphiphile in aqueous solution is complex and is discussed in terms of hydrophobic and hydrophilic hydrations [8]. In monomeric form

of amphiphile, both the hydrophobic and hydrophilic hydrations are attainable, whereas just hydrophilic hydration is plausible for micellized amphiphile system. Both types of hydrations are known to reduce with increase in temperature [31]. Only hydrophilic dehydration favors the micelle formation at lower temperature, while with the increase in temperature; hydrophobic dehydration disfavors the micelle formation [32,33]. As a result, the magnitude of these two factors determines whether the CMC values increase/decrease at a particular temperature. The first factor dominates usually in low temperature range. Above a certain temperature, the second factor starts dominating. However, the literature also contains examples of continuous increase in CMC with temperature [34,35].

In our case of micellization of aniline hydrochloride, the gradual increase of MHC values with increase in temperature may be due to the dominance of second factor only. From another opinion, it has been viewed that with increase in temperature, the thermal motions of amphiphile and solvent molecules increase so that the formation of ordered micelle structures becomes complicated, i.e., the thermal motions may be more important than the breakage of water structure at high temperatures. The enhancement of temperature further makes the kinetic energies increase and the ordered micellar structures destroyed, causing decrease in the micelle aggregation number but the MHC value increases.

Even though, the drug is ionic in nature but performs in a different way contrary to normal surfactant. CMC value of the drug increases up to 303.15 K, which means that disruption of structured water around the hydrophobic parts governs over dehydration of hydrophilic part. On the other hand, at 308.15 K and above, a reduction in CMC is observed, which denotes dehydration of hydrophilic part of drug is the overlooked factor over the disruption of water molecules around the hydrophobic portion. Seemingly, the key lies in the different degree of hydration between the saturated and aromatic hydrocarbon part of the drug (PMZ) molecule. Strong discharge of water, which is possibly the water linked with the aromatic ring of PMZ, takes place. Alike inverted U-shaped behavior has also been viewed in case of nonionic surfactants [36] and other amphiphilic drugs [37,38]. Analogous behavior has been found in case of drug-aniline hydrochloride mixed systems as clear from the tables that very small mole fraction of aniline hydrochloride is present in the mixture; therefore, its effect is not shown on micellization with variation of temperature. A decrease in CMC values is observed, which is because of the release of water associated with aromatic rings of the drug molecules, which raises the drug's hydrophobicity, which in turn results in increased micellization.

3. Degree of Dissociation in Absence and Presence of Salt (g)

Ionic amphiphiles bind a considerable amount of counterions, which can be estimated by electrochemical measurements. The degree of dissociation (g) of pure and mixed micelles has been evaluated from the ratio of the postmicellar and premicellar slopes obtained from the plots of specific conductance of the solutions versus the concentration of drug (Fig. 2). The extent of binding (association) of the counterion (α) increases with the increase in valence and polarizability of the ion and with decrease in hydrated radius. Hence, degree of association ($\alpha=(1-g)$) decreases. The degree of dissociation (g) decreases with increase in electrolyte concentration [39] and may decrease with micellar growth [40]. Also, with the increase

in temperature, CMC values increase and micellar growth decreases. Therefore, we can safely conclude that with the increase in temperature, an increase in g is expected, which is also observed in the case of ionic surfactants [41,42]. Our values show a similar trend (Tables 1-2). Note the relationship between CMC and g , where it can be observed that maximum of CMC corresponds to maximum of g . It means that the degree of dissociation of counterion has an effect on the attractive or repulsive forces in mixed micelle formation between the two amphiphiles. The lower the g value, the easier is the micellization to occur. In other words, the micellization process takes place at a lower concentration. In our study also, the values of g are lower for PMZ+aniline hydrochloride mixtures as of pure PMZ; it means micellization takes place early in the mixture of PMZ+aniline hydrochloride in comparison to drug only. The value of g obtained in presence of 50 mmol kg⁻¹ NaCl in mixed systems is shown in Table 2, and the values permit us to evaluate the effect of salt on the degree of counterion dissociation on the aggregates' surface of the systems. A decrease in g values in presence of salt can be seen, signifying better packed aggregates of amphiphiles, which is related to the increase in charge density of the stern layer of the micelles formed, thereby increasing the number of chloride ions bound to micelles [43].

4. Composition and Interaction of Mixed Micelles in Absence and Presence of Salt

Regular solution theory (RST) has been used to explain the values of amphiphile molecular interaction parameter (β) observed in mixed micelles. The β parameter estimates the strength and interactions between two components (drug and aniline hydrochloride). The types of molecular interactions in amphiphiles include electrostatic, ion-dipole, steric and van der Waals interactions, etc. The CMC values of PMZ-aniline hydrochloride mixed systems signify micellization between the two components. The nonideality in mixed micelles of PMZ-aniline hydrochloride mixtures in absence and presence of 50 mmol kg⁻¹ NaCl can be evaluated by using the regular solution theory (RST), given by Rubingh based on the phase separation model of micellization [44]. The elementary equation is

$$\frac{(X_1^{Rub})^2 \ln[(\alpha_1 CMC/X_1^{Rub} CMC_1)]}{(1-X_1^{Rub})^2 \ln[(1-\alpha_1)CMC/(1-X_1^{Rub})CMC_2]} = 1 \quad (2)$$

where X_1^{Rub} is the micellar mole fraction of aniline hydrochloride in the mixture and CMC_1 and CMC_2 are the CMC values of the pure aniline hydrochloride and PMZ, respectively. The equation was solved iteratively to obtain the value of X_1^{Rub} , from which the interaction parameter β was evaluated using the following equation which is discussed later in the present study.

$$\beta = \frac{\ln(CMC\alpha_1/CMC_1X_1^{Rub})}{(1-X_1^{Rub})^2} \quad (3)$$

The obtained results have been also evaluated by using Motomura's theory [45]. Their theory evaluates the composition of monomeric and micellar phases from the variation of CMC with the composition of the mixed solution. Motomura's model foretells that the molar fraction of a component in the mixed micelle can be reckoned as a function of the CMC and the molar fraction of the components in the solution.

The following equations are used:

$$X_1^M = \frac{\overline{\alpha_1\alpha_2}/\overline{CMC}(\partial\overline{CMC}/\partial\overline{\alpha_1})_{T,P}}{1 - \frac{\delta v_{1,c} \cdot v_{2,d}}{v_{1,c}v_2\overline{\alpha_1} + v_{2,d}v_1\overline{\alpha_2}}} \quad (4)$$

$v_{1,c}$ means component 1 (aniline hydrochloride) dissociate into a -ions and c -ions. $v_{2,d}$ means component 2 (PMZ) dissociate into b -ions and d -ions (c and d -ions are the counterparts of the respective component) where

$$\overline{CMC} = (v_1\alpha_1 + v_2\alpha_2)CMC, \text{ and} \quad (5)$$

$$\overline{\alpha_i} = \frac{v_i\alpha_i}{v_1\alpha_1 + v_2\alpha_2} \quad (i=1, 2) \quad (6)$$

In the above equations, X_1^M is the micellar mole fraction of the hydrotrope, $\overline{\alpha_i}$ is the bulk mole fraction and v_i is the number of ions dissociated by the i^{th} component. δ is the Kronecker delta which is equal to 1 for identical counterions and 0 for different counterions. The model of Motomura is independent of the nature of the additive and their counterions and is suitable in the forecast of micellar composition when the CMC of the mixed micelle is measured as a function of temperature and pressure.

The experimental data were further analyzed using another model projected by Rodenas [46]. Rodenas's treatment is based on Lange's model [47] and considers the Gibbs-Duhem equation, then is not subjected to the restrictions of the regular theory of real solution. From this approach, the micellar mole fractions of the components can be evaluated if the CMC of the mixtures is known as a function of bulk stoichiometric mole fractions, from the expression:

$$X_1^{Rod} = -(1-\alpha_1)\alpha_1 \frac{d\ln CMC}{d\alpha_1} + \alpha_1 \quad (7)$$

The micellar mole fraction of mixed systems in the ideal state X_1^{id} , has been computed using the equation

$$X_1^{id} = \frac{\alpha_1 CMC_2}{\alpha_1 CMC_2 + \alpha_2 CMC_1} \quad (8)$$

The micellar mole fractions of component 1 (aniline hydrochloride) evaluated using different proposed models (X_1^{Rub} , X_1^M and X_1^{Rod} (as well as X_1^{id})) are significantly larger than the corresponding stoichiometric mole fraction (α_1) in absence and presence of salt (Table 3). This shows that the added aniline hydrochloride replaces some of the drug molecules from the mixed micelles, and therefore the contribution of aniline hydrochloride is more in mixed micelles than it should be in ideally mixed systems. All X_1^{Rub} , X_1^M and X_1^{Rod} (as well as X_1^{id}) values for mixed systems increase with increase in the aniline hydrochloride concentration (Table 3). The values of micellar mole fraction (X_1) are in the order of $X_1^{id} < X_1^M < X_1^{Rub} < X_1^{Rod}$ at lowest α_1 but, at higher α_1 , the order is $X_1^{id} < X_1^{Rub} < X_1^{Rod} < X_1^M$ in almost all cases in absence of salt. This difference can be ascribed to screening of repulsions between head groups of the cationic amphiphilic drug (PMZ). X_1^{id} values decrease with temperature in all systems, signifying the thermal impediment of micellar growth. We can realize from the results that aniline hydrochloride partitions into micelles of drug, thus strengthening the hydrophobic environment in the mixed state and resulting in onset of micelliza-

Table 3. Values of micellar mole fraction (X_1) of aniline hydrochloride for PMZ-aniline hydrochloride mixed systems at various temperature and concentration^a

α_1	$10^4 \cdot X_1^{id}$	$X_1^{Rub}/X_1^M/X_1^{Rod}$										
PMZ+aniline hydrochloride mixture in aqueous solution												
	293.15 K			298.15 K			303.15 K			308.15 K		
2.69×10^{-5}	0.69	0.044/0.041/0.052	0.66	0.043/0.037/0.044	0.64	0.041/0.035/0.040	0.62	0.042/0.037/0.044	0.57	0.043/0.038/0.047		
5.38×10^{-5}	1.34	0.078/0.089/0.105	1.33	0.075/0.079/0.089	1.33	0.072/0.074/0.081	1.23	0.074/0.079/0.088	1.15	0.076/0.082/0.094		
8.08×10^{-5}	2.01	0.106/0.145/0.157	2.00	0.101/0.127/0.134	1.99	0.096/0.119/0.121	1.84	0.099/0.127/0.133	1.73	0.103/0.133/0.142		
10.77×10^{-5}	2.67	0.130/0.210/0.210	2.66	0.123/0.182/0.178	2.66	0.118/0.170/0.162	2.46	0.122/0.182/0.177	2.30	0.125/0.191/0.189		
14.37×10^{-5}	3.57	0.153/0.307/0.280	3.55	0.146/0.264/0.238	3.54	0.141/0.245/0.216	3.28	0.144/0.265/0.236	3.07	0.147/0.278/0.253		
PMZ+aniline hydrochloride mixture in 50 mmol·kg ⁻¹ NaCl solution												
	293.15 K			298.15 K			303.15 K			308.15 K		
2.69×10^{-5}	0.63	0.052/0.053/0.072	0.63	0.048/0.051/0.069	0.63	0.045/0.045/0.059	0.57	0.048/0.047/0.063	0.54	0.049/0.051/0.070		
5.38×10^{-5}	1.26	0.088/0.116/0.145	1.26	0.084/0.102/0.138	1.26	0.078/0.097/0.118	1.15	0.082/0.101/0.126	1.08	0.085/0.111/0.141		
8.08×10^{-5}	1.89	0.118/0.190/0.218	1.89	0.115/0.165/0.208	1.89	0.106/0.158/0.178	1.73	0.111/0.165/0.190	1.61	0.115/0.182/0.212		
10.77×10^{-5}	2.52	0.145/0.281/0.290	2.52	0.116/0.241/0.277	2.52	0.133/0.231/0.237	2.30	0.137/0.243/0.253	2.15	0.140/0.268/0.283		
14.37×10^{-5}	3.36	0.174/0.432/0.387	3.36	0.143/0.355/0.369	3.36	0.159/0.345/0.316	3.07	0.162/0.362/0.337	2.87	0.169/0.409/0.378		

^aStandard uncertainties (u) are u (T)=0.2K, u (X_1)=2%

tion at lower concentration in comparison to pure state.

On adding NaCl in mixed system of drug and aniline hydrochloride, the micellar mole fraction (X_1) calculated by all models as well as ideal mole fraction (X_1^{id}) values increases as compared to that in absence of salt. This increment is due to the reduction in the repulsive interactions between the aniline hydrochloride-aniline hydrochloride head groups, PMZ-PMZ head groups and PMZ-aniline hydrochloride head groups with increasing ionic strength of the aqueous medium due to increased adequate shielding of the electrostatic repulsion by the ionic atmosphere around each charged site. For that reason, the charge on the micellar head group becomes neutralized due to the added salt. Thus, the interaction between these two amphiphiles (drug and aniline hydrochloride) is higher in presence of salt and is responsible for lowering the CMC as well as increasing the value of micellar mole fraction (X_1) (Table 3).

The sign and magnitude of the β parameter is representative of the type and extent of interaction, respectively. According to Rubingh [44], a negative β value indicates an attractive interaction or synergism, a positive value indicates a repulsive interactions or antagonism, and zero value means no interaction in the mixture or ideal mixing. Repulsive interactions are found only in mixtures of hydrocarbon chain and fluorocarbon chain surfactants of the same sign. The larger the absolute negative value of β the greater is the strength of the interaction between the two molecules. However, it has been established that the attractive interactions in mixed systems may be called as 'synergistic', if these two conditions are fulfilled [8]: (a) β must be negative, and (b) $|\beta| > |\ln(\text{CMC}_1/\text{CMC}_2)|$. In our systems, although the first condition is fulfilled, the second one fails. It is, therefore, appropriate to use the term 'attractive interaction' rather than 'synergism' in the studied cases where a negative deviation from the CMC^{id} is obtained. Our results show that β values are negative which increase with increase in concentration of aniline hydrochloride (Tables 1-2). This can be attributed to the interaction between the head groups leading to electrostatic stabilization,

as aromatic counter ions are more effective to penetrate into the head group region, which leads to the reduction of head group repulsions and makes micellar growth easier. The average β values, β_{av} , fall between -7 to -9.

On adding NaCl the attractive interaction between the two amphiphiles (PMZ and aniline hydrochloride) was further increased (β becomes more negative) (Table 2). For the mixture of opposite charged ionic amphiphiles, the contributions to the interaction between the amphiphiles are from the van der Waals interaction between the tails of the amphiphiles and the attractive interaction between the head groups due to opposite charge therefore interaction between the tails as well as between heads are negative. With the addition of NaCl, the interaction between the charged head groups further increases because of high ionic strength in the solution, which in turn makes β more negative [48].

With the knowledge of the micellar interaction parameters (β) for the mixed micelles, it is possible to determine the activity coefficients of amphiphiles in the mixed micelles. Using the nonideal solution theory, the activity coefficients (f_1^{Rub} and f_2^{Rub}) of aniline hydrochloride and PMZ (drug), respectively, in mixed micelles are related to β by the following relations:

$$f_1^{Rub} = \exp\{\beta(1 - X_1^{Rub})^2\} \quad (9)$$

$$f_2^{Rub} = \exp\{\beta(X_1^{Rub})^2\} \quad (10)$$

The activity coefficient (f_1 and f_2) were also calculated from Motomura and Rodenas models:

$$f_1 = \frac{\alpha_1 \text{CMC}}{X_1^a \text{CMC}_1} \quad (11)$$

$$f_2 = \frac{(1 - \alpha_1) \text{CMC}}{(1 - X_1^a) \text{CMC}_2} \quad (12)$$

X_1^a is X_1^M for Motomura model and X_1^{Rod} for Rodenas model.

Table 4. The thermodynamic parameters (ΔG_m^0 (kJ mol⁻¹), ΔH_m^0 (kJ mol⁻¹), and ΔS_m^0 (JK⁻¹ mol⁻¹)) for PMZ-aniline hydrochloride mixed systems at various temperatures (evaluated on the basis of conductance measurements)^a

α_1	$\Delta G_m^0/\Delta H_m^0/\Delta S_m^0$				
PMZ+aniline hydrochloride mixture in aqueous solution					
	293.15 K	298.15 K	303.15 K	308.15 K	313.15 K
0	-25.49/-10.75/50.27	-25.52/-11.03/48.61	-25.65/-11.35/47.15	-25.95/8.55/111.99	-26.32/8.76/112.04
2.69×10^{-5}	-25.89/-11.47/49.18	-25.95/-11.78/47.51	-25.99/-12.09/45.85	-26.37/9.13/115.21	-26.77/9.36/115.38
5.38×10^{-5}	-26.30/-12.47/47.20	-26.36/-12.81/45.44	-26.39/-13.15/43.68	-26.78/9.95/119.24	-27.20/10.21/119.47
8.08×10^{-5}	-26.75/-13.96/43.62	-26.78/-14.34/41.72	-26.79/-14.72/39.80	-27.20/11.08/124.27	-27.65/11.36/124.61
10.77×10^{-5}	-27.23/-15.54/39.86	-27.22/-15.97/37.74	-27.23/-16.39/35.74	-27.66/11.99/128.69	-28.12/12.30/129.10
14.37×10^{-5}	-27.74/-17.04/36.50	-27.71/-17.51/34.20	-27.70/-17.98/32.08	-28.17/12.66/132.53	-28.63/12.98/132.93
1	-28.82/-9.02/67.54	-28.30/-9.07/64.49	-27.42/-9.0/60.76	-26.18/-8.78/56.48	-25.46/-8.70/53.52
PMZ+aniline hydrochloride mixture in 50 mmol kg ⁻¹ NaCl solution					
	293.15 K	298.15 K	303.15 K	308.15 K	313.15 K
0	-26.46/-12.35/48.14	-26.50/-12.68/46.33	-26.55/-13.02/44.63	-26.97/8.91/116.46	-27.33/9.14/116.49
2.69×10^{-5}	-26.90/-13.48/45.77	-26.92/-13.85/43.86	-26.96/-14.21/42.04	-27.40/9.78/120.68	-27.78/10.03/120.76
5.38×10^{-5}	-27.37/-15.03/42.11	-27.38/-15.44/40.06	-27.40/-15.85/38.08	-27.86/11.24/126.91	-28.27/11.53/127.11
8.08×10^{-5}	-28.08/-16.79/38.50	-28.09/-17.25/36.33	-27.87/-17.59/33.88	-28.36/12.51/132.66	-28.79/12.83/132.96
10.77×10^{-5}	-28.64/-18.15/35.81	-28.64/-18.64/33.54	-28.59/-19.14/31.16	-29.11/13.45/138.12	-29.36/13.69/137.52
14.37×10^{-5}	-29.35/-21.55/26.61	-29.29/-22.14/23.99	-29.19/-22.73/21.31	-29.73/16.17/148.97	-30.28/16.58/149.66
1	-29.20/-9.94/65.70	-29.07/-10.14/63.50	-28.52/-10.18/60.49	-27.78/-10.13/57.26	-26.61/-9.91/53.33

^aStandard uncertainties (u) limits are u (ΔG_m^0), u (ΔS_m^0), and u (ΔH_m^0), are $\pm 3\%$, $\pm 3\%$, and $\pm 4\%$ respectively

It is evident from Tables 1-2 that the values of activity coefficients (f_1 and f_2), calculated by Rubingh, Motomura and Rodenas models are less than unity at all mole fractions and temperatures, which signifies nonideal behavior and thus attractive interactions between PMZ and aniline hydrochloride hydrotrope in the mixed micelles in the absence and presence of salt. The very low activity coefficients (f_1) values of aniline hydrochloride molecules in the mixed micelles possibly indicate that these components in the mixed micelle are far away from their standard states (i.e., pure aniline hydrochloride), where the activity coefficients should be unity; and the other reason is that its mole fraction is also very low in the mixtures in absence and presence of salt. On the other hand, the higher activity coefficients of PMZ in PMZ-aniline hydrochloride mixtures indicate that these are very near their standard state (i.e., pure PMZ). Sum of the activity coefficient values i.e. (f_1 and f_2) observed for the mixed micelles is less than unity, which supports the existence of attractive interactions between PMZ and aniline hydrochloride in absence and presence of salt in the mixed state. In the presence of inorganic salt (50 mmol.kg⁻¹ NaCl) in the aqueous solution of drug and aniline hydrochloride mixtures the values of activity coefficient reduces, showing that nonideality of mixed systems increases more in comparison to their absence (Tables 1-2).

5. Thermodynamics of Micellization in Absence and Presence of Salt

The phenomena of micellization of drug with aniline hydrochloride (hydrotrope) in absence and presence of salt can be quantified with the help of various thermodynamic parameters. According to the pseudo-phase separation model [8], the standard Gibbs energy of micellization (ΔG_m^0) for ionic uni-univalent amphiphiles can be evaluated by taking into consideration of degree of dissociation (g) of the counterion to the micelle

$$\Delta G_m^0 = (2-g)RT \ln X_{CMC} \quad (13)$$

where X_{CMC} is the CMC in mole fraction units and g is the degree of dissociation. R and T are the gas constant and absolute temperature, respectively. There are various possible interactions between the entities of the solutions. Based on that, complete accounts of the thermodynamic parameters associate are not possible as various factors, such as, charges, polarity, hydrophobicity, etc., are associated with them and due to these factors the uncertainties in values are large. The ΔG_m^0 values are all negative and vary slightly with increase in temperature, additive concentration, and types (Table 4). As usual, the micellization process is thus directed primarily by the entropy gain associated with the propensity of the hydrophobic group of amphiphile to transfer from the aqueous environment to the interior of micelle. In case of pure aniline hydrochloride, the magnitude of ΔG_m^0 decreases with the increase in temperature, thus making micellization less spontaneous at higher temperature. The ΔG_m^0 values for pure components agree well with literature data [18,22-24]. For drug-aniline hydrochloride mixed systems, ΔG_m^0 becomes increasingly more negative, suggesting ease of micelle formation in mixed systems (Table 4). Gibbs energy of micellization (ΔG_m^0) is always more negative in presence of salt as compared in pure water, indicating easy facilitation of the aggregation process by the addition of salt because driving force for micellization was significantly increased in presence of salt in compare to salt free solution (Table 4).

The associated standard enthalpy (ΔH_m^0) and entropy (ΔS_m^0) can then be calculated using Eqs. (14) and (15):

$$\Delta H_m^0 = -(2-g)RT^2 \left[\frac{d \ln X_{CMC}}{dT} \right] \quad (14)$$

$$\text{and } \Delta S_m^0 = \frac{\Delta H_m^0 - \Delta G_m^0}{T} \quad (15)$$

The ΔH_m^0 values for micellization of pure aniline hydrochloride are negative at all temperature and do not vary significantly with temperature, proposing no significant variation in the environment surrounding the hydrocarbon chain of the amphiphilic molecule with temperature variation (Table 4). However the ΔH_m^0 values of pure PMZ (drug) change from negative to positive on increasing the temperature from 293.15 to 308.15 K (the process is exothermic at 293.15 K and it becomes endothermic as the temperature increases to 308.15 K). The negative values of ΔH_m^0 suggest the importance of the London-dispersion interactions as an attractive force for micellization [49], whereas positive values mean the breaking of structured water around the hydrophobic parts of the molecule [50]. Similar trend was found for mixed systems with difference in magnitude of ΔH_m^0 (Table 4). At higher temperature, endothermicity may be because of dehydration of water associated with the aromatic ring of PMZ. While we are not sure about the reason for this reversal in behavior, the release of water molecules from hydrophobic portion may be the cause of endothermicity as well as decrease in CMC at 308.15 K and above. In presence of 50 mmol kg⁻¹ NaCl, the magnitude of ΔH_m^0 increases in case of pure amphiphiles as well as their mixtures at different concentration and temperature; this difference in behavior can be attributed to the fact that micellization of PMZ and aniline hydrochloride as well as their mixtures in aqueous solution is relatively more entropy driven than in 50 mmol kg⁻¹ NaCl solution. This may be interpreted to mean that transferring of PMZ and aniline hydrochloride as well as their mixtures in aqueous solution molecule to micellar region is accompanied with a greater disruption of the solvent structure, explaining $\Delta S_m^0 > 0$. The addition of NaCl to aqueous solutions of PMZ and aniline hydrochloride as well as their mixture has at least two effects. The first is the partial reduction of the water of hydration around the alkyl chain of the non-associated amphiphilic molecule. The reduced ordering of that water leads to a decrease in the energy needed for breaking down this structure during the process of micelle formation and to a decrease in the endothermic contribution to the value of ΔH_m^0 . The second consequence of the presence of salt appears to be related to the influence of counterion binding on the structure of the micelles. This process is accompanied by an increase in the average number of counterions bound to the surface of the micelle, which results in a large exothermic effect. The above two factors determined the enthalpy change at a particular temperature range.

The ΔS_m^0 value for micellization of pure aniline hydrochloride is positive and decreases with increasing temperature, and the decrease in ΔS_m^0 values with temperature is due to decrease in the degree of hydration of hydrophobic parts at high temperature (Table 4). Hydrophobic hydration causes vibrations of hydrophobic chains to be restricted in solution. The more ordered structure of water molecules around hydrophobic chains and restriction on vibrations of hydrophobic groups leads to decrease in entropy of system. The entropy of micellization (ΔS_m^0) is positive at all temperatures, indicating that the micellization process is entropy dominated in these systems, mainly when entropy change is high. Although entropy

of micellization (ΔS_m^0) is positive at all temperatures for pure drug (PMZ), but the trend is different from pure hydrotrope aniline hydrochloride, i.e., the values are small at 293.15-303.15 K and increase sharply with increase in temperature at 308.15 and above. Obviously, this is caused by the particular structure of PMZ, which is the major component of the mixed micelles. Actually, the key lies in the difference in the hydration between the saturated and aromatic hydrocarbon portions of the drug molecule. The high increase in entropy indicates a strong discharge of water, which possibly is the water associated with the aromatic ring of drug. This,

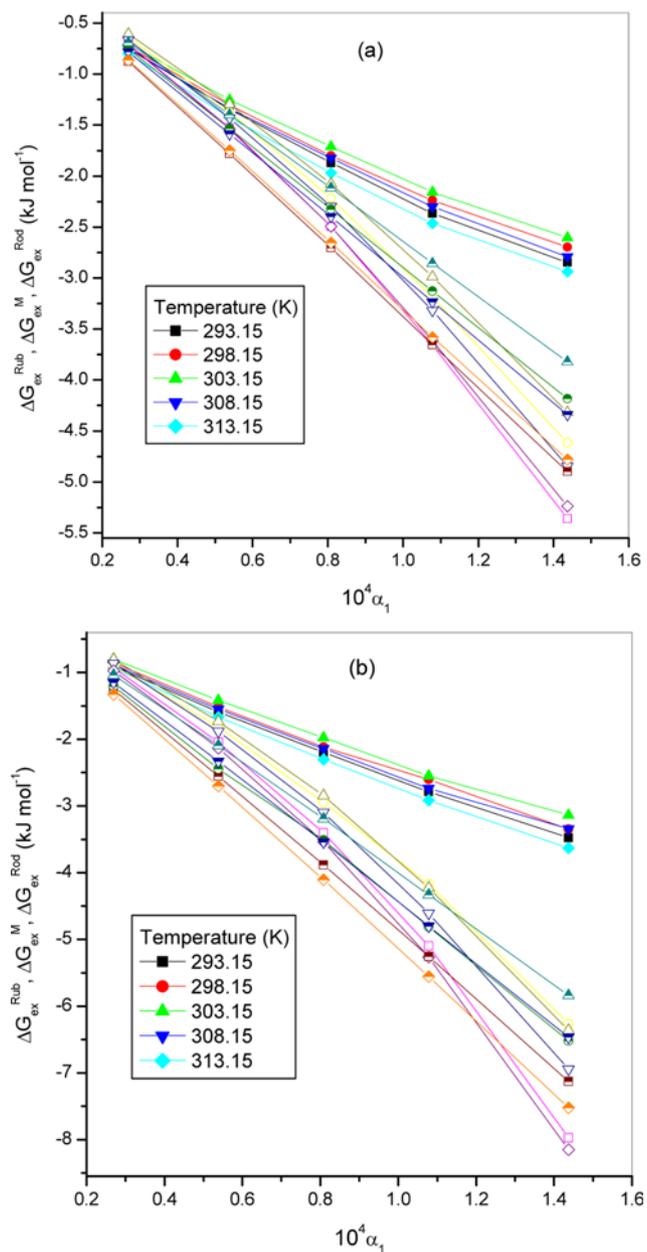


Fig. 3. Variations of ΔG_{ex}^{Rub} , ΔG_{ex}^M , and ΔG_{ex}^{Rod} versus mole fraction of aniline hydrochloride (α_1) in PMZ-aniline hydrochloride mixtures at different temperatures in absence (a) and presence of salt (b). The models used were: Rubingh (filled symbols), Motomura (open symbols), Rodenas (half-filled symbols).

in turn, must enhance the hydrophobicity of drug molecules, causing decrease of CMC. Similar behavior is also found in case of PMZ-hydrotrope mixtures. As is clear from Table 4, the magnitude of ΔS_m^0 is higher in presence of aniline hydrochloride comparative to their absence; it means the presence of aniline hydrochloride increases the randomness in the system. In the presence 50 mmol kg^{-1} NaCl the magnitude of ΔS_m^0 increases for pure amphiphile as well as their mixtures because in the presence of salt the system produces more disorder in comparison to their absence.

We have also evaluated the excess free energy of micellization (G_{ex}) by considering Rubingh's, Motomura's and Rodenas' approaches through the equations given elsewhere for the additional information about the mixed systems [51-55]. The ΔG_{ex} values estimated for drug+aniline hydrochloride mixtures in aqueous as well as in 50 mmol kg^{-1} NaCl solutions are shown in Fig. 3. The excess free energy is found to be zero for an ideal system. These values come out to be negative and their magnitude increases with the increase in aniline hydrochloride concentrations. This confirms that the mixed micelles formed are more stable than the micelles of individual components and their stability increases with increase in concentration of aniline hydrochloride, i.e., large introduction of aniline hydrochloride makes the micelles more stable, which is well supported by their interaction parameters. This shows that hydrotrope aniline hydrochloride reduces the repulsion between the ionic head groups of drug and increases hydrophobic interactions which, in turn, enhances the stability of micelles. There is no significant effect of temperatures on the ΔG_{ex} values (Fig. 3). Mixed micelles have fairly different physicochemical properties from those of pure micelles of individual components. From the application point of view, mixed micelles are of great importance in biological, technological, pharmaceutical and medicinal formulation, enhanced oil recovery process for the purpose of solubilization, suspension, dispersion, etc. It was found that the CMC of mixed amphiphiles was lower than either of the individual amphiphiles, which is very valuable because it decreases the total amount of amphiphile used in meticulous purpose leading in lessening of cost and environmental affect. Therefore, micelle formed by mixing of two components is more stable in contrast to micelle formed by single component. The ΔG_{ex} values evaluated by all proposed models used in the present study were found to be more in magnitude in presence of 50 mmol kg^{-1} NaCl in comparison to their absence, which means mixed micellization formation is more stable in presence of salt. On the addition of inorganic salts, electrostatic repulsion between the polar head group of ionic amphiphile will decrease with increasing ionic strength of the aqueous medium due to increased sufficient shielding of the electrostatic repulsion by the ionic atmosphere around each charged site [26]. Therefore, micelle formed by mixing of two components is more stable in contrast to micelle formed by single component, and their stability increases in the presence of salt.

CONCLUSIONS

A detailed physicochemical investigation of interactions between cationic amphiphilic phenothiazine drug promazine hydrochloride and a hydrotrope aniline hydrochloride in the absence and presence of 50 mmol kg^{-1} NaCl has been done. The following con-

clusions can be drawn:

1. PMZ forms mixed micelles with aniline hydrochloride through attractive interactions as indicated by the CMC and CMC^{id} values.
2. Addition of 50 mmol kg^{-1} NaCl in solution shows that the electrostatic repulsion between the positive head groups of PMZ and aniline hydrochloride gets decreased, hence CMC of mixed systems further decreases in comparison to mixtures in pure aqueous solution.
3. X_1 values calculated by Rubingh, Motomura and Rodenas models show higher contribution of aniline hydrochloride in the mixed micelles. These values are higher than X_1^{id} .
4. β values calculated using Rubingh approach also suggest attractive interactions among micelles. This study also has confirmed that synergism in mixed micelle formation can be enhanced by adding salt.
5. For PMZ-aniline hydrochloride mixed systems, ΔG_m^0 becomes increasingly more negative, suggesting micelle formation in mixed systems to be easier.
6. The ΔS_m^0 values at lower temperatures are small, whereas at 308.15 K and above, the magnitude increases sharply; the sign remains positive for all systems.
7. The magnitude of different thermodynamic parameters evaluated in the present study is higher in presence of NaCl relative to that in their absence.

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