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Thermodynamics of Amphiphilic Drug Imipramine Hydrochloride in Presence of Additives

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1. Introduction

In aqueous environment, amphiphilic molecules (*viz.*, surfactants, drugs, polymers, etc.) or ions are frequently assemble at interfaces and self-associate in an attempt to sequester their apolar regions from contact with the aqueous phase (Attwood & Florence, 1983, Atherton & Barry, 1985, Attwood et al, 1989, Schreier et al, 2000, Attwood, 1995a,1995b, Mandal & Nair, 1988, 1991, Mandal et al, 1987, 1993, Geetha et al, 1993, 2003, Mandal, 1993, Mandal & Jayakumar, 1994, Geetha & Mandal, 1997a, 1997b, 2000, Rose & Mandal, 1996, Taboada et al, 2000, 2001, Junquera et al, 2001, Rodriguez et al, 2004, Misra et al, 2009, 2010, James et al, 2011, James & Mandal 2011, Mandal et al, 2010, Tiwary et al, 2011, Alam et al, 2007, Khan et al, 2009, 2010). A large number of drug molecules are amphiphilic and self-associate in aqueous solution to form small aggregates. These surface-active behavior among many diverse classes of drugs has been reported and attempts have been made to correlate surface activity and biological activity (Attwood & Florence, 1983, Atherton & Barry, 1985, Attwood et al, 1989, Schreier et al, 2000, Taboada et al, 2000, Junquera et al, 2001, Attwood, 1995, Geetha et al, 2003, Alam et al, 2007, 2008). The aggregation of the above drugs follows the same principles as of conventional surfactants (Schreier et al, 2000, Taboada et al, 2000, Junquera et al, 2001, Attwood, 1995, Geetha et al, 2003, Alam et al, 2007, 2008). The self-association of drug depends on the molecular structure of the drug, its concentration and the experimental conditions such as temperature, pH and salt concentration (Atherton & Barry, 1985, Taboada et al, 2000, Junquera et al, 2001, Attwood, 1995, Geetha et al, 2003, Alam et al, 2007, 2008). The "surfactant-like" behavior of these drugs is due to the presence of an almost planar tricyclic ring system and a short hydrocarbon chain carrying a terminal nitrogen atom (Taboada et al, 2000, Junquera et al, 2001).

The self-assembly and self-organization are natural and spontaneous processes, occurring mainly through non-covalent interactions such as, van der Waals, hydrogen-bonding,

hydrophilic/hydrophobic, electrostatic, donor and acceptor, and metal-ligand coordination networks (Whitesides & Grzybowski, 2002). The interest in micelle solutions stems from their potential as functional molecular assemblies for use in many fields in pure and applied sciences, because they can be used as models for several biochemical and pharmacological systems and can solubilize water-insoluble substances (including certain medicines/drugs) in their hydrophobic cores (Barzykin et al, 1996).

The colloidal properties of amphiphilic drugs are largely determined by the nature of the aromatic ring system of their hydrophobic moieties, and such drugs are useful in probing the relationship between the molecular architecture and physicochemical properties (Attwood & Florence, 1983). 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, antidepressant, tranquillizer, and antibiotic actions, exert their activity by interaction with biological membranes, which can be considered as 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 presence of a variety of additives (excipients).

Thermodynamic parameters of some amphiphilic drugs (viz. amitriptyline hydrochloride, imipramine hydrochloride, chlorpromazine hydrochloride, and promethazine hydrochloride) in presence of additives have recently been evaluated (Alam et al, 2010a, 2010b, 2010c, 2010d, 2010e). Micellar characteristics of various peptides, collagens, polymers in aqueous and non-aqueous media and their interactions with various surfactant micelles have widely been studied (Mandal et al, 1987, 1993, Mandal & Jayakumar, 1994, Jayakumar, et al, 1994, Geetha & Mandal, 1995, 1996, Jayakumar & Mandal, 1993, Ramya, et al, 2003, 2004, Khan et al, 2010a, 2010b) in light of aggregation, H-bonding, geometry, correlation times, conformation, hydrodynamic and thermodynamic studies.

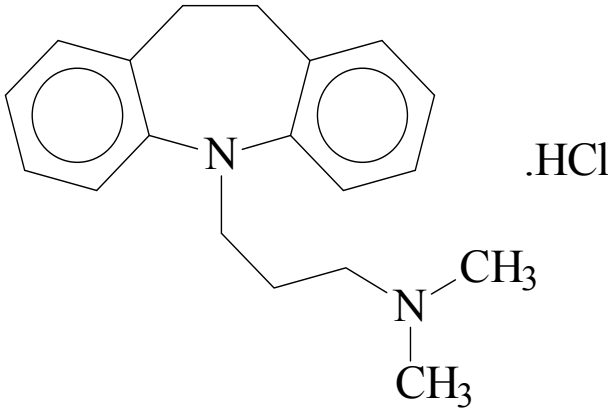
It has been established from earlier studies on these drugs that aggregates of approximately 6–12 monomers are formed in water above the critical micelle concentration (cmc). The pK_a values of these drugs lie between 9.1-9.4 (Katzung, 2004), and depending upon the solution pH, the drug monomers may acquire cationic (i.e., protonated) or neutral (i.e., deprotonated) form (Kim, 2002).

It is well known that cmc of amphiphiles varies in presence of additives, because the interfacial and micellar properties of these compounds in solutions are governed by a delicate balance of hydrophobic and hydrophilic interactions. These characteristics can be modified in two ways: (i) through specific interactions with the amphiphile and (ii) by changing the nature of solvent (Ruiz & Sanchez, 1994). As drugs are used in combination with additives (e.g., surfactants), it is necessary to have a knowledge of additive effect on the cmc and their thermodynamics of amphiphilic drugs.

Clouding is a well-known phenomenon observed in non-ionic surfactants. The clouding phenomenon can be induced by changing the temperature of the solution. The temperature at which a clear, single phase becomes cloudy and phase-separates occur upon heating is known as the cloud point (CP) (Gu & Galera-Gomez, 1999). The mechanism of clouding in non-ionic surfactants, however, is not yet very clear, and continues to be a source of controversy among different research groups. However, the occurrence of CP in charged micelle (i.e., ionic surfactants) solutions is not usual except under special conditions, e.g., high salt concentration (Gomati et al, 1987, Kumar et al, 2000, 2001, 2002, 2003, Panizza et al, 1998), salt free aqueous solutions of certain surfactants with large headgroups (Kumar et al,

2001, Panizza et al, 1998) or large counterions (Kumar et al, 2001, 2003), and some mixed cationic and anionic surfactant solutions (Kim & Shah, 2002, 2003). The CP appearance in these systems is explained in terms of increased hydrophobic interactions, dehydration of hydrophilic group, and formation of large aggregates/clusters. Like ionic surfactants, some amphiphilic drugs undergo pH-, concentration-, and temperature- dependent phase separation (Kim & Shah, 2002, 2003, Kumar et al, 2006, Alam et al, 2006a, 2006b, 2007a, 2007b, 2007c, 2007d, 2008a, 2008b, 2008c, 2010a, 2010b, 2010c, Alam & Kabir-ud-Din, 2008a, 2008b). It was observed that their CP can vary with additives.

5-[3- (dimethylamino) propyl]- 10,11-dihydro -*5H*-dibenz[*b,f*]azepine hydrochloride (imipramine hydrochloride, IMP) is a tricyclic antdepressant amphiphilic drug with neuroleptic activity, showing a large capacity to interact with biological membranes and sometimes be used as a local anesthetic (Seeman, 1972). IMP possesses a rigid hydrophobic ring system and a hydrophilic amine portion, which becomes cationic at low pH values and neutral at high pH values (Scheme 1). Moreover, the pK_a value of this drug is 9.3 (Katzung, 2004). IMP is often regarded as a model drug for the investigation of interactions between drugs and biological or model membranes (Schreier el al, 2000). Amphiphilic antidepressant drugs aggregate in a micelle-like manner and the value of N_{agg} (aggregation number) being of the order of 6-15 (Attwood & Florence, 1983, Attwood, 1995, Schreier el al, 2000). As clouding is concentration, pH and temperature dependent, it is essential to have a knowledge of clouding behavior of the drug under varying conditions.



Scheme 1. The molecular structure of amphiphilic tricyclic antidepressant drug, 5-[3-(dimethylamino)propyl]-10,11-dihydro-*5H*-dibenz[*b,f*]azepine hydrochloride (imipramine hydrochloride, IMP) used in the present study.

In the present work, we report the micellization and clouding of an amphiphilic tricyclic antidepressant drug, IMP (see Scheme 1) in absence and presence of additives (KCl and TX-100). The work presented here is aimed at obtaining a better understanding of the role of the presence of additives in the thermodynamic quantities of micellization and clouding of the drug in absence and presence of additives. With this viewpoint surface tension, conductivity measurements and dye solubilization studies have been performed on aqueous solutions of IMP to determine the cmc of these drugs in presence of different additives. The surface

properties (in water and in presence of varying mole fraction of TX-100) of IMP and the micellar and surface parameters *viz.*, cmc, Γ_{max} (maximum surface excess concentration at air/water interface) and A_{min} (minimum area per surfactant molecule at the air/water interface), interaction parameter, β^m, activity coefficeients (f_1, f_2) were evaluated. Using these data, we had evaluated Gibbs energies viz., Gibbs energies at air/water interface ($G_{min}^{(s)}$), the standard Gibbs energy of micellization ($\Delta_{mic}G^0$), the standard Gibbs free energy change of adsorption ($\Delta_{ads}G^0$), and the excess Gibbs energy change of micellization (ΔG_{ex}). We report the micellization and clouding of IMP in absence and presence of KCl. The thermodynamic parameters are evaluated (in micellization and at CP) in presence and absence of electrolyte (KCl). The results have relevance in drug delivery/model drug delivery.

2. Materials and methods

2.1 Materials

IMP (≥ 98 %, Sigma, USA), polyethylene glycol *t*-octylphenyl ether, TX-100 (≥ 99 %, Fluka, Switzerland), and KCl (≥ 99.9 %, Ranbaxy, India) were used as received. Doubly distilled and deionized water (sp. cond. = 1-2 μS·cm^{-1}) was used as the solvent. Trisodium phosphate dodecahydrate (TSP), and sodium dihydrogen phosphate monohydrate (SDP) were of reagent grades obtained from Merck. 10 mM Sodium phosphate (SP) buffer solutions were used throughout as solvent. The pH of the IMP solutions was measured with an ELICO pH meter (model LI 120) using combined electrode.

2.2 Methods

2.2.1 Surface tension measurements

The cmc values of the drugs (with and without additives) in pure water were determined by measuring the surface tension (ST) of pure drug, as well as drug + additive (TX-100), solutions of various concentrations at ~ 300 K. The cmc values were obtained by plotting ST *vs* log [drug]. The ST values decrease continuously and then remain constant along a wide concentration range (see Figure 1). The point of break, when the constancy of ST begins, was taken as the cmc of the drug.

2.2.2 Conductivity measurements

GLOBAL conductivity meter (model DCM 900) and dip cell (cell constant 1.0 cm^{-1}) was employed to perform the conductivity measurements at different temperatures (viz., 293.15 , 303.15, 313.15 and 323.15 K). The stock solutions of IMP (with or without a fixed concentration of KCl) were prepared in double distilled water. The conductivity was measured by successive addition of concentrated solution in pure water (in case of without KCl) or in a fixed concentration of KCl solutions. A break in the specific conductivity versus drug concentration curve signals the onset of the micellization process (Figure 2).

2.2.3 Cloud point measurements

All CPs were obtained by placing Pyrex glass tubes (containing the drug solution) into a temperature controlled bath, the temperature was ramped at the rate of 0.1 K / min near the CP and onset of clouding was noted by visual inspection. The temperature, as the clouding commences, was taken as CP (Gu & Galera-Gomez, 1999, Kim & Shah, 2002, Kumar et al, 2006, Alam et al, 2006a, 2007a, 2008a, 2010a, Alam & Kabir-ud-Din, 2008a). The uncertainty in the measured CP was ± 0.5 K.

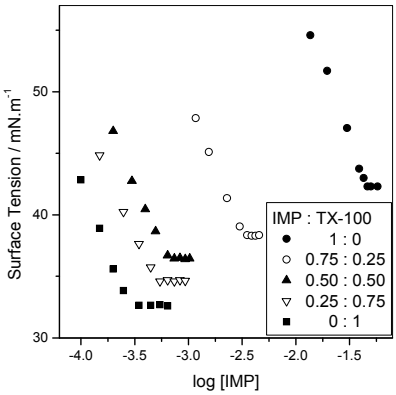


Fig. 1. Plots of surface tension *vs.* log [IMP].

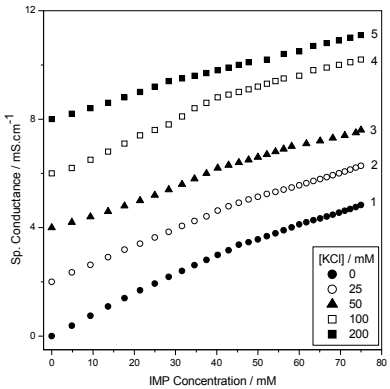


Fig. 2. Representative plots of specific conductance versus [IMP] in absence and presence of different fixed KCl concentrations at 303.15 K. The curves 2, 3, 4, and 5 have been shifted by 2, 4, 6, and 8 scale units (mS · cm^{-1}), respectively.

2.2.4 Dye solubilization measurements

Dye solubilization experiments for the aqueous drug solutions (with and without electrolyte) were performed at room temperature. The sample solutions with Sudan III dye (kept for 24 h) were filtered and then the spectra were recorded using a UV-visible Shimadzu spectrophotometer (model UV-1800).

3. Results and discussion

3.1 Micellization

3.1.1 Surface tension measurements

The value for pure drug has been found to be in good agreement with the literature value (Attwood & Florence, 1983), whereas the values decrease in the presence of additive (TX-100

– see Figure 3). The values of the surface pressure at the cmc (Π_{cmc}) were obtained by using the equation

$$\Pi_{cmc} = \gamma_0 - \gamma_{cmc} \tag{1}$$

where γ_0, and γ_{cmc} (see Figure 1) are the surface tension of the solvent and the surface tension of the mixture at the cmc, respectively. With increasing the additives concentration, the values of Π_{cmc} increase, indicating that the efficiency increases (Table 1).

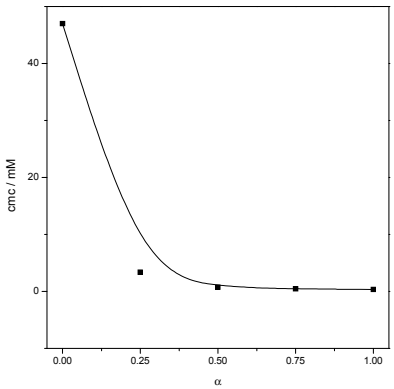


Fig. 3. Effect of additive (TX-100) on the cmc of amphiphilic drug IMP at 300.15 K.

It is well known that the air/solution interface of an amphiphile solution is well populated (Clint, 1992) by the adsorbed molecules. Accordingly, it has been shown that the concentration of the surfactant is always greater at the surface due to adsorption over and above the concentration of surfactant in the bulk. For calculation of Gibbs free energy changes, required different surface properties (e.g., the surface excess concentration, Γ_{max}, minimum area per surfactant molecule at the air/water interface, A_{min} etc.). The surface excess concentration is an effective measure of the Gibbs adsorption at liquid/air interface, which was calculated by applying equation (Chattoraj & Birdi, 1984)

$$\Gamma_{max} = -\frac{1}{2.303nRT}(d\gamma / d\log c)_T \tag{2}$$

where γ, R, T and c are surface tension, gas costant, absolute temperature and concentration, respectively. The variable n is introduced to allow for the simultaneous adsorption of cations and anions. The expression used in the calculation of n was that proposed by Matejevic and Pethica (Matijevic & Pethica, 1958). $n = 1 + m/(m+m_s)$, where m_s is the concentration of the added electrolyte. Thus, n has a value of 2 in water and approaches 1 in the presence of excess inert electrolyte. The slope of the tangent at the given concentration of the γ *vs* log c plot was used to calculate Γ_{max}, and A_{min} was evaluated using the relation (Anand et al, 1991)

$$A_{min} = 10^{16} / N_A \Gamma_{max} \, (\text{Å}^2) \tag{3}$$

where N_A is Avogadro number.

The data show the expected area decrease with increasing additive concentration. This is due to progressive charge shielding and closer packing of the drug ions in the surface. The low values of A_{min} suggest that the orientation of the surfactant molecule at the interface is almost perpendicular to the interface (Anand et al, 1991). The values of A_{min} for the drug are similar to those reported for other antidepressants (Taboada et al, 2001) and phenothiazines (Zografi & Zarenda, 1966).

X_{IPM}	cmc / mM	$10^{10} \bullet \Gamma_{max}$ / mol•m^{-2}	A_{min} / Å^2	Π_{cmc} / mN·m^{-1}
1	47.78	1.95	87.34	29.7
0.75	3.47	1.99	85.81	33.7
0.5	0.76	2.06	82.69	35.6
0.25	0.48	2.12	80.52	37.4
0	0.31	2.23	76.31	39.4

Table 1. Effect of additive concentrations on the cmc (determined by surface tension measurements), Γ_{max}, A_{min} and Π_{cmc} values of amphiphilic drug IMP in aqueous solutions at ~300 K.

Sugihara *et al* (Sugihara et al, 2003, 2004) have proposed a thermodynamic quantity for the evaluation of synergism in mixing, i.e., the free energy of the given air/water interface $G_{min}^{(s)}$ which is defined as follows:

$$G_{min}^{(s)} = A_{min} \cdot \Pi_{cmc} \cdot N_A \tag{4}$$

$G_{min}^{(s)}$ regard as the work needed to make an interface per mole or the free energy change accompanied by the transition from the bulk phase to the surface phase of the solution components. In other words, the lower the values of $G_{min}^{(s)}$, the more thermodynamically stable surface is found. The $G_{min}^{(s)}$ values are decreased with increasing the additive concentration/mole fraction (Figure 4).

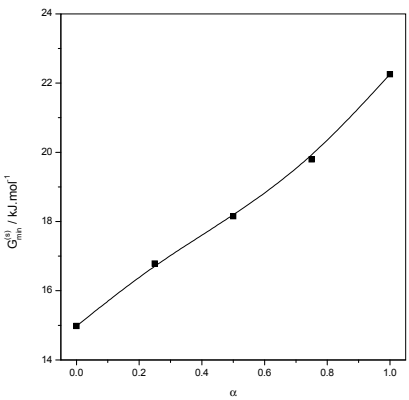


Fig. 4. Variation of Gibbs free energy at the air/water interface, $G_{min}^{(s)}$ of the amphiphilic drug IMP at different concentration (mole fraction) of TX-100.

To quantify the effect of additives in the mixture on the micellization process, the standard Gibbs free energy change of micellization, $\Delta_{mic}G^0$, and the standard Gibbs energy of adsorption, $\Delta_{ads}G^0$, were calculated by using equations (5) and (6),

$$\Delta_{mic}G^0 = RT \ln \mathrm{cmc_m} \tag{5}$$

($\mathrm{cmc_m}$ is the cmc of the mixture of the two components at a given mole fraction)

$$\Delta_{ads}G^0 = \Delta_{mic}G^0 - \Pi_{\mathrm{cmc}} / \Gamma_{\mathrm{max}} \tag{6}$$

Figures 5 illustrates that $\Delta_{mic}G^0$ and $\Delta_{ads}G^0$ decrease with increasing the additive concentrations, respectively. The standard state for the adsorbed surfactant is a hypothetical monolayer at its minimum surface area per molecule, but at zero surface pressure. The last term in equation (6) expresses work involved in transferring the surfactant molecule from a monolayer at a zero surface pressure to the micelle. In all cases (in abcence and presence of additive), $\Delta_{mic}G^0$ values are negative and decreases with increasing additive concentration/mole fraction. This indicates that the micellization takes place more spontaneously in presence of additive (TX-100) (Figure 5). All the $\Delta_{ads}G^0$ values are negative, which implies that the adsorption of the surfactants at the air/mixture interface takes place spontaneously (see Figure 5).

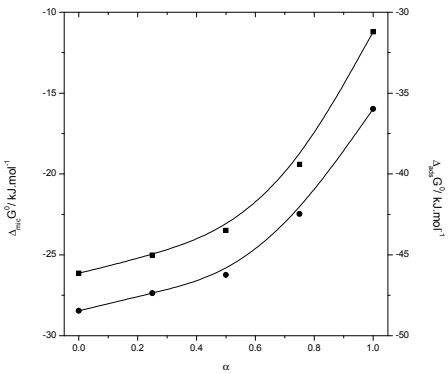


Fig. 5. Variation of the standard Gibbs energy change of micellization, $\Delta_{mic}G^0$ and the standard Gibbs free energy change of adsorption, $\Delta_{ads}G^0$ of the amphiphilic drug at different concentration/mole fraction of TX-100.

It has been reported that surfactants form mixed micelles with the drugs (Rodriguez et al, 2004, Alam et al, 2007). Mixed micelles are known to possess quite different physicochemical properties from those of pure micelles of the individual components. The micellar aggregation number and the association of counterions with micelles change dramatically with composition in mixed micelles. The degree of counterion association of an ionic micelle is about 0.7 for monovalent counterions. However, when an ionic surfactant is mixed with a non-ionic surfactant, the degree of the association falls to zero as the mole fraction of the non-ionic surfactant in the micelle increases (Meyer & Sepulveda, 1984, Jansson & Rymden,

1987). Most cmc's of binary mixtures fall between the cmc's of the two components but some are above (Sugihara et al, 1988) or below (Nguyen et al, 1986) this range. Our results for the cmc of drug in presence of TX-100 show the same behavior (Table 1). Addition of TX-100 assists in micelle formation of drug. TX-100 (by penetrating into the micelles) lowers the repulsive forces between the polar head groups of the drug (IMP).

Rodriguez et al (Rodriguez et al, 2004) who studied the effect of dodecyltrimethylammonium bromide concentration on the cmc of amitrityline hydrochloride in aqueous solution by conductivity and static fluorescence measurements explained their results on the basis of mixed micelle formation. Theoretical calculations predicted an apparent ideal but non-synergistic behavior of the mixed micelles. Our results do indicate mixed micelle formation (Table 1).

The nature and strength of the interactions between the two components (amphiphilic drug IMP and surfactant TX-100) can be determined by calculating the values of their β parameters (Rubingh, 1979).

The intermicellar interaction coefficient in the mixed micelles is calculated from:

$$\frac{[(x_1^{\mathrm{m}})^2 \cdot \ln(\mathrm{cmc} \cdot \alpha_1 / \mathrm{cmc}_1 \cdot x_1^{\mathrm{m}})]}{[(1-x_1^{\mathrm{m}})^2 \cdot \ln\{(\mathrm{cmc} \cdot (1-\alpha_1)/\mathrm{cmc}_2 \cdot (1-x_1^{\mathrm{m}})]} = 1 \tag{7}$$

and

$$\beta^m = \ln(cmc \cdot \alpha_1 \cdot x_1^m) / (1-x_1^m)^2 \tag{8}$$

where x_1^m is the mole fraction of component 1 in the micelles and cmc_1 ; cmc_2 and cmc are the cmc's for component 1, component 2 and their mixture at mole fraction of component1, a_1, in the solution.

Equation (7) was solved iteratively for x_1^m, which was then substituted into equations (8) to calculate β^m values.

The activity coefficients f_1^m and f_2^m are related to β^m as

$$f_1^m = \exp\{\beta^m \cdot (1-x_1^m)^2\} \tag{9}$$

$$f_2^m = \exp\{\beta^m \cdot (x_1^m)^2\} \tag{10}$$

The evaluated parameters (x_1^m , f_1^m , f_2^m and β^m) are given in Table 2.

a_1	x_1^m	β^m	f_1^m	f_2^m
0.25	0.324	-3.14	0.043	0.486
0.50	0.447	-3.42	0.033	0.107
0.75	0.568	-3.5	0.03	0.002

Table 2. Micellar composition (x_1^m), interaction parameter (β^m), and activity coefficients (f_1^m , f_2^m) of binary mixtures of drug IMP and TX-00 at different mole fractions of IMP (a_1).

The composition of the adsorbed mixed monolayer of binary component systems in equilibrium with the singly dispersed components can be evaluated using Rosen's equations (Li et al, 2001, Zhou & Rosen, 2003). From analogy, using the derivation of Rubingh's equations for mixed micelles, the mole fraction of component 1, x_1^σ, in the mixed monolayer is related to a_1 as

$$\frac{[(x_1^\sigma)^2 \cdot \ln(\mathrm{cmc} \cdot \alpha_1 / \mathrm{cmc}_1 \cdot x_1^\sigma)]}{[(1-x_1^\sigma)^2 \cdot \ln\{(\mathrm{cmc} \cdot (1-\alpha_1)/\mathrm{cmc}_2 \cdot (1-x_1^\sigma)]} = 1 \tag{11}$$

and

$$\beta^\sigma = \ln(cmc \cdot \alpha_1 \cdot x_1^\sigma) / (1-x_1^\sigma)^2 \tag{12}$$

where cmc_1, cmc_2 and cmc are the molar concentrations of components 1, 2 and their mixture, at α_1, required to produce a given surface tension reduction (corresponds to γ = 45 mN•m^{-1}, determined from the plots of γ *vs* log [drug]), and β^σ is the interaction parameter for mixed monolayer formation at the aqueous solution/air interface.

Equation (11) was solved iteratively for x_1^σ, which was then substituted into equations (12) to calculate β values.

The activity coefficients f_1^σ and f_2^σ are related to β^σ as

$$f_1^\sigma = \exp\{\beta^\sigma \cdot (1-x_1^\sigma)^2\} \tag{13}$$

$$f_2^\sigma = \exp\{\beta^\sigma \cdot (x_1^\sigma)^2\} \tag{14}$$

The evaluated parameters (x_1^σ, f_1^σ, f_2^σ and β^σ) are given in Table 3.

a_1	x_1^σ	β^σ	f_1^σ	f_2^σ
0.25	0.394	-3.33	0.036	0.244
0.50	0.522	-3.58	0.028	0.014
0.75	0.633	-3.61	0.027	2.19E-05

Table 3. Monomer composition (x_1^σ), interaction parameter (β^σ), and activity coefficients (f_1^σ, f_2^σ) of binary mixtures of drug IMP and TX-00 at different mole fractions of IMP (a_1).

3.1.1.1 Significance of β

β indicates not only the degree of interaction between the two components but also accounts for the deviation from ideality. β assumes a value of zero for ideal mixing of two components. Positive β values means repulsion among mixed species. A negative β value implies an attractive interaction; the more negative its value, the greater the interaction. The β^m values are negative at all mole fractions of the mixed system (Tables 2 and 3), suggest that the interaction between the two components is more attractive in the mixed micelle than the self-interaction of the two components before mixing. As the mole fraction of

additive (TX-100) increases, β^m values become more negative. This indicates an increase in the attractive interaction with the increase in additive concentration is also evident from the cmc values, which decrease with increasing additive concentration.

β^σ also follows similar trend (Tables 2 and 3). The mixtures of drugs/surfactants show stronger attractive interaction at the air/water interface. These interactions are stronger than in mixed micelles as evidenced by the fact that β^σ are more negative than β^m values. This is due to the steric factor, which is more important in micelle formation than in monolayer formation at a planar interface. Increased bulkiness in the hydrophobic group causes greater difficulty for incorporation into the curved mixed micelle compared to that of accommodating at the planar interface (Rosen et al, 1994).

The excess free energy change of micellization, ΔG_{ex}, calculated by the equation (15)

$$\Delta G_{ex} = [x_1^m \cdot \ln f_1 + (1 - x_1^m) \cdot \ln f_2]RT \tag{15}$$

and shown in Figure 6. The values of ΔG_{ex} are negatives for all mole fraction/concentration of additives and the magnitude increases (ΔG_{ex} become more negative) with increasing the additives mole fractions/concentrations, indicating stability of the micelles (Figure 6).

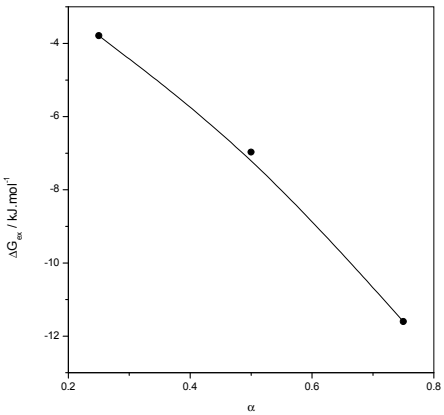


Fig. 6. Variation of the excess free energy change of micellization, ΔG_{ex} of the amphiphilic drug IMP at different concentration/mole fraction of TX-100.

3.1.2 Conductivity measurements

The cmc of IMP in absence and presence of fixed concentrations of KCl (25, 50, 100 and 200 mM) were determined by conductivivity method at different temperatures (293.15, 303.15, 313.15, and 323.15 K). Figure 2 shows the representative plots of specific conductivity vs. [IMP]. The cmc values of IMP are measured in absence as well as presence of a fixed concentration of KCl at different temperatures and listed in Table 4. The cmc values of IMP decrease with increasing the KCl concentration (see Figure 7), whereas the effect of temperature shows an opposite trend for all systems (i.e., increase with increasing temperature) (Figure 8).

The value of the cmc is dependent upon a variety of parameters including the nature of the hydrophilic and hydrophobic groups, additives present in the solution, and external influences such as temperature. The micellization takes place where the energy released as a result of association of hydrophobic part of the monomer is sufficient to overcome the electrostatic repulsion between the ionic head groups and decrease in entropy accompanying the aggregation. The cmc can also be influenced by the addition of a strong electrolyte into the solution. This serves to increase the degree of counterion binding, which has the effect of reducing head group repulsion between the ionic head groups, and thus decrease the cmc. This effect has been empirically quantified according to (Corrin & Harkins, 1947)

$$\log \text{cmc} = -\, a \log C_t + b \tag{16}$$

where a and b are constants for a specific ionic head group ant C_t denotes the total conunterion concentration.

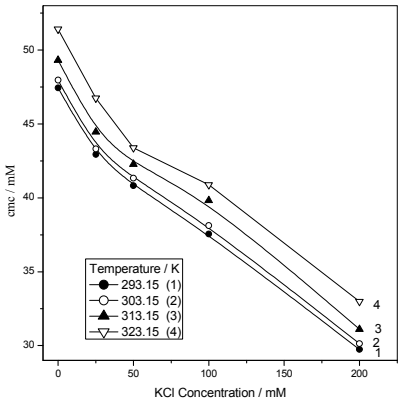


Fig. 7. Effect of KCl concentrations on the cmc of IMP solutions.

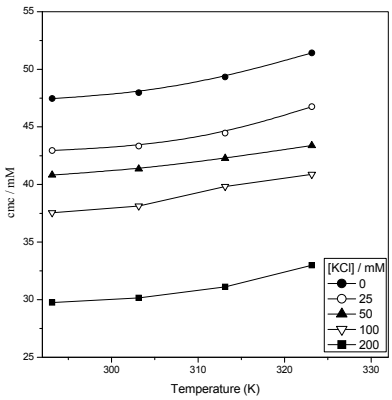


Fig. 8. Effect of temperature on the cmc of IMP solutions.

The degree of dissociation, x of the micelles was determined from the specific conductance vs. concentration of surfactants plot. Actually, x is the ratio of the post micellar slope to the premicellar slope of these plots. The counter ion association, y of the micelles is equal to (1 – x). The results of cmc and y values obtained for IMP micelles in absence and presence of KCl at different temperatures are given in Table 4. It is found that the cmc of IMP in aqueous solution increased with increase in temperature, whereas the cmc of IMP decreased in the presence of additive (KCl) at all temperatures mentioned above (see Table 4). The increase in cmc and decrease in y values for IMP micelles in aqueous solution suggest that the micelle formation of IMP is hindered with the increase in temperature. However, the micelle formation of IMP is more facilitated in the presence of KCl even at higher temperatures showing lower cmc and higher y values (see Table 4).

[KCl] mM	cmc mM	y	ΔG_m^0 (kJ·mol^{-1})	ΔH_m^0 (kJ·mol^{-1})	ΔS_m^0 (kJ·K ·mol^{-1})
293.15 K					
0	47.45	0.3126	-29.07	-1.31	0.095
25	42.94	0.3231	-29.30	-1.05	0.096
50	40.82	0.3277	-29.42	-1.51	0.095
100	37.55	0.3682	-29.04	-1.76	0.093
200	29.74	0.3246	-30.77	-1.60	0.100
303.15 K					
0	47.97	0.3278	-29.74	-3.54	0.086
25	43.32	0.3169	-30.37	-3.34	0.089
50	41.34	0.3284	-30.36	-2.87	0.091
100	38.12	0.3377	-30.53	-5.54	0.082
200	30.14	0.3341	-31.58	-4.03	0.091
313.15 K					
0	49.32	0.3618	-29.98	-5.56	0.078
25	44.46	0.3571	-30.51	-6.72	0.076
50	42.28	0.3462	-30.93	-3.46	0.088
100	39.82	0.3520	-31.08	-3.53	0.088
200	31.11	0.3722	-31.74	-7.74	0.077
323.15 K					
0	51.42	0.4251	-29.57	-5.70	0.074
25	46.75	0.4343	-29.79	-6.82	0.071
50	43.38	0.4355	-30.09	-3.49	0.082
100	40.88	0.4268	-30.50	-3.59	0.083
200	32.98	0.4182	-31.58	-8.01	0.073

Table 4. The cmc and Various Thermodynamic Parameters for IMP Solutions in Absence and Presence of Different Fixed KCl Concentrations at Different Temperatures; Evaluated on the Basis of Conductivity Measurements.

3.1.2.1 Thermodynamics

In the van't Hoff method, the cmc of a surfactant is measured at different temperatures and the energetic parameters can be evaluated by the mass-action and pseudo-phase models (Attwood & Florence, 1983, Moroi, 1992, Moulik et al, 1996, Chaterjee et al, 2001, 2002, Dan et al, 2008, 2009). For calculating thermodynamic parameters, we have used the following equations:

$$\Delta G_m^0 = (2-\alpha)RT\ln\chi_{cmc} \tag{17}$$

$$\Delta H_m^0 = -(2-\alpha)RT^2\left(\frac{\partial \ln\chi_{cmc}}{\partial T}\right)_P \tag{18}$$

And

$$\Delta S_m^0 = \frac{\Delta H_m^0 - \Delta G_m^0}{T} \tag{19}$$

where ΔG_m^0, ΔH_m^0 and ΔS_m^0 are the standard Gibbs free energy, enthalpy and entropy of micellization, expressed per mole of monomer unit, respectively. The y, R, T and χ_{cmc} are the counterion association, universal gas constant, temperature in absolute scale and cmc in mole fraction unit, respectively. In the present case, all the ΔG_m^0 values are negative, which increase with increasing the electrolyte concentration (Table 4); this implies that the drug-electrolyte solutions are more stable. The values of ΔH_m^0 and ΔS_m^0 also agree with the low randomness and more stability (Table 4).

3.2 Clouding phenomena

3.2.1 Effect of KCl on the cloud point

The CP of the IMP solutions has been found highly sensitive to the solution pH (see Figure 9). The results show that the CP decreases as the value of pH increases (whether or not an electrolyte is present). In the pH range employed, this decrease in the CP is due to changes in the micellar surface charge. The ionization constant, pK_a, of IMP in free molecular state is 9.3 (Attwood & Florence, 1983, Katzung, 2004). The tricyclic part of IMP molecule (Scheme 1) is hydrophobic and the *t*-amine portion is hydrophilic. The protonation is highly dependent upon the solution pH. At low pH, the *t*-amine becomes protonated (i.e., cationic) and at high pH, the *t*-amine becomes deprotonated (i.e., neutral). The number of un-ionized (deprotonated) IMP molecules in micelles increases with the increase in solution pH. This, in turn, reduces both intra- as well as inter-micellar repulsions, leading to an increase in micellar aggregation and a decrease in CP (Schreier et al, 2000, Kim & Shah, 2002, Wajnberg et al, 1988, Mandal et al, 2010).

Figure 10 illustrates the variation of CP of 100 mM IMP solutions with KCl addition at different fixed pHs, prepared in 10 mM SP buffer. Here, the pH was varied from 6.5 to 6.8. It is seen that, as before (see Figure 9), CP decreases with increasing pH at all KCl concentrations (due to decrease in repulsions, as discussed above for Figure 3). The behavior of CP increases with increasing KCl concentration is found to follow a similar trend at all pH values. As discussed above, both charged and uncharged fractions of IMP molecules would be available for aggregate (so-called IMP micelle) formation. Thus, each micelle

would bear a cationic charge. Increasing the amount of KCl would, therefore, cause the micellar size to increase progressively with the concomitant increase in CP (Kim & Shah, 2002).

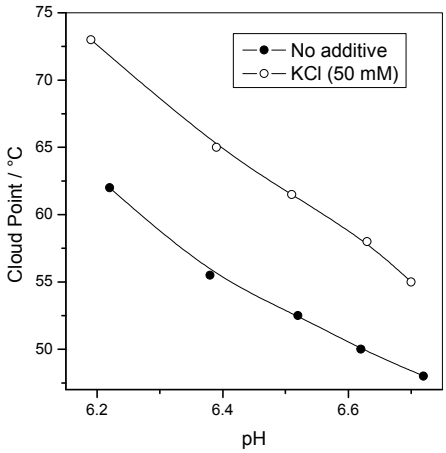


Fig. 9. Effect of pH on the CP of 100 mM IMP solution, prepared in 10 mM sodium phosphate buffer, containing no or a fixed KCl concentration (50 mM).

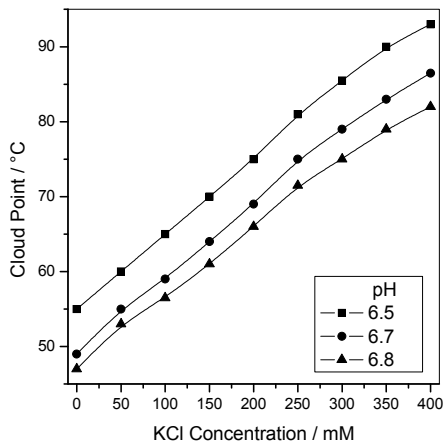


Fig. 10. Effect of KCl concentration on the CP of 100 mM IMP solution, prepared in 10 mM sodium phosphate buffer at different pHs.

Figure 11 displays the effect of KCl addition on the CP of IMP solutions of different fixed concentrations of the drug (100, 125 and 150 mM). At a constant KCl concentration, increase in drug concentration increases both the number and charge of micelles. This increases both inter- and intra-micellar repulsions, causing increase in CP.

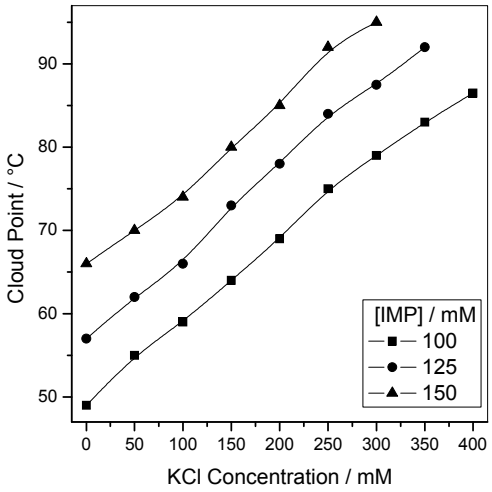


Fig. 11. Effect of KCl concentration on the CP of different fixed concentrations of IMP solution, prepared in 10 mM sodium phosphate buffer (pH = 6.7).

3.2.2 Thermodynamics at CP

As the clouding components above CP release their solvated water and separate out from the solution, the CP of an amphiphile can be considered as the limit of its solubility. Hence, the standard Gibbs energy of solubilization (ΔG_s^0) of the drug micelles can be evaluated from the relation

$$\Delta G_s^0 = -RT \ln \chi_s \tag{20}$$

where χ_s is the mole fraction concentration of additive at CP, R is gas constant and T is the clouding temperature in Kelvin scale.

The standard enthalpy and entropy of clouding, ΔH_s^0 and $T\Delta S_s^0$, respectively, can be calculated by

$$\Delta H_s^0 = \frac{\partial(\Delta G_s^0 / T)}{\partial(1/T)} \tag{21}$$

$$T\Delta S_s^0 = \Delta H_s^0 - \Delta G_s^0 \tag{22}$$

The energetic parameters were calculated using eqs. (20) to (22). The thermodynamic data of clouding for the drug IMP in the presence of KCl are given in Table 5. For IMP with and without KCl, the thermodynamic parameters, ΔG_s^0, ΔH_s^0 and $T\Delta S_s^0$ are found to be positive.

$\chi_{PMT} \cdot 10^3$	CP K	ΔG_s^0 kJ·mol^{-1}	ΔH_s^0 kJ·mol^{-1}	$T\Delta S_s^0$ kJ·K^{-1}·mol^{-1}
x = 0				
1.80	322.15	16.93	21.58	4.65
2.25	330.15	16.74		4.84
2.69	339.15	16.68		4.9
x = 50				
1.80	328.15	17.25	23.49	6.24
2.24	335.15	16.99		6.5
2.69	343.15	16.88		6.61
x = 100				
1.80	332.15	17.46	24.82	7.36
2.24	339.15	17.2		7.62
2.69	347.15	17.08		7.74
x = 150				
1.79	337.15	17.73	25.67	7.94
2.24	346.15	17.56		8.11
2.69	353.15	17.38		8.29
x = 200				
1.79	342.15	17.99	25.92	7.93
2.24	351.15	17.81		8.11
2.69	358.15	17.63		8.29
x = 250				
1.79	348.15	18.31	26.36	8.05
2.24	357.15	18.12		8.24
2.69	365.15	17.97		8.39
x = 300				
1.79	352.15	18.52	27.26	8.74
2.23	360.65	18.3		8.96
2.68	368.15	18.13		9.13
x = 350				
1.79	359.65	18.92	28.72	9.8
2.23	365.15	18.53		10.2

Table 5. Cloud Point (CP) and Energetic Parameters for Clouding of different fixed concentration (100, 125 and 150 mM) of IMP Prepared in 10 mM Sodium Phosphate Buffer Solutions (pH = 6.7) in Presence of x mM KCl.

3.3 Dye solubilization measurements

An important property of micelles that has particular significance in pharmacy is their ability to increase the solubility of sparingly soluble substances (Mitra et al, 2000, Kelarakis et al, 2004, Mata et al, 2004, 2005). A number of approaches have been taken to measure the solubilizing behavior of amphiphiles in which the solubilization of a water insoluble dye in the surfactant micelles was studied. The plots illustrated in Figure 12 clearly demonstrate that, in the presence of additives, micelle size increases due to the fact that more dye can solubilize in the aggregates.

The absorbance variations with KCl concentration in the absence as well as presence of different fixed concentrations of IMP are illustrated in Figure 12. The amount of solubilized dye depends on the state of aggregation. We see that the solubilizing power of the drugs markedly increases in the presence of additives. Figure 6 shows the visible spectra of Sudan III solubilized in 50 mM IMP in water containing different fixed amounts of the additive (KCl) concentrations. One can see that the absorbance increases on addition of KCl, increasing the concentration of KCl increases the absorbance. Addition of KCl raises the aggregation number of ionic micelles due to electrostatic effects (Evans & Wennerstrom, 1999). The absorbance increase with increasing concentration of KCl suggests that the micellar growth is substantial with KCl addition.

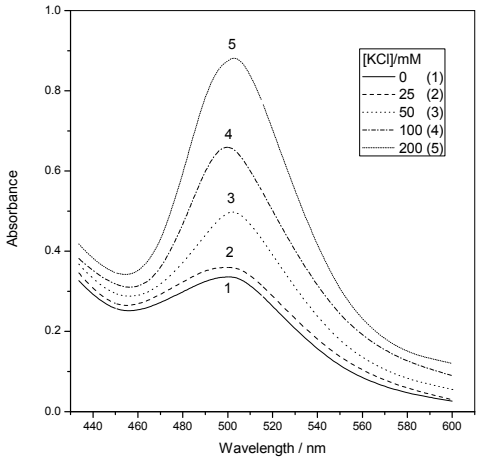


Fig. 12. Visible spectra of Sudan III solubilized in the PMT (50 mM) containing no or a fixed concentration of KCl.

4. Conclusion

We have studied the thermodynamics of a tricyclic antidepressant drug imipramine hydrochloride (IMP). The mixed micelles of IMP and non-ionic surfactant polyethylene glycol *t*-octylphenyl ether (TX-100) has been investigated using surface tension measurements and evaluated Gibbs energies (at air/water interface ($G_{min}^{(s)}$), the standard Gibbs energy change of micellization ($\Delta_{mic}G^0$), the standard Gibbs energy change of adsorption ($\Delta_{ads}G^0$), the excess free energy change of micellization (ΔG_{ex})). The micellization at different fixed temperatures (*viz.*, 293.15, 303.15, 313.15 and 323.15 K), and clouding behavior of IMP in absence and presence of KCl. The *critical micelle concentration* (*cmc*) of IMP is measured by conductivity method and the values decrease with increasing the KCl concentration, whereas with increasing temperature the *cmc* values increase. The thermodynamic parameters *viz.*, standard Gibbs energy (ΔG_m^0), standard enthalpy (ΔH_m^0), and standard entropy (ΔS_m^0) of micellization of IMP are evaluated, which indicate more stability of the IMP solution in presence of KCl. IMP undergoes concentration-, pH-, and

temperature-dependent phase separation, also known as "*clouding*", which is a well known phenomenon with non-ionic surfactants. The temperature at which phase separation occurs is called '*cloud point*' (CP). Studies on the CP of IMP have been made to see the effect of KCl. Strong dependence on the concentration of the KCl has been observed. A pH increase in the presence as well as in the absence of electrolyte decreased the CP. Drug molecules become neutral at high pH and therefore, head group repulsion decreases which lead to CP decrease. Effect of KCl at different fixed drug concentrations showed that at all electrolyte concentrations the CP value was higher for higher drug concentrations. However, variation of pH produced opposite effect: CP at all KCl concentrations decreased with increasing pH. The results are interpreted in terms of micellar growth. Furthermore, the thermodynamic parameters are evaluated at CP.

The surface properties, Gibbs energies of an amphiphilic drug IMP in water are evaluated in absence and presence of additive (TX-100), and the micellization and clouding behavior of IMP in absence and presence of KCl have studied and the results obtained are as:

i. With TX-100, increase in Γ_{max} and decrease in cmc/A_{min} are due to the formation of mixed micelles with the drug.
ii. The drug/surfactant systems show an increase in synergism with the increase in surfactant concentration.
iii. Rosen's approach reveals increased synergism in the mixed monolayers in comparision to in the mixed micelles.
iv. In all cases (in presence and absence of additive) the G^{s}_{min} values decrease with increasing the additives concentrations, indicating thermodynamically stable surface.
v. The $\Delta_{mic}G^0$ values are negative and decreases with increasing the additive concentration indicate that the micelle formation takes place spontaneously.
vi. The negative $\Delta_{ads}G^0$ values indicate that the adsorption of the surfactant at the air/solution interface takes place spontaneously.
vii. The values ΔG_{ex} are negative for all mole fractions of additives indicating the stability of the micelles.
viii. Knowledge of self-aggregation and clouding behavior of amphiphilic drugs and effect of additives on clouding will allow the better designing of effective therapeutic agents.
ix. The critical micelle concentration (cmc) of IMP decreases with increasing KCl concentration, whereas with increasing temperature the cmc values increases.
x. The thermodynamic parameters are evaluated, which indicate more stability of the IMP solution in presence of KCl.
xi. The IMP also shows phase-separation. The cloud point (CP) of IMP decreases with increase in pH of the drug molecules because of deprotonation.
xii. The CP values increase with increasing KCl and IMP concentrations leading to micellar growth.

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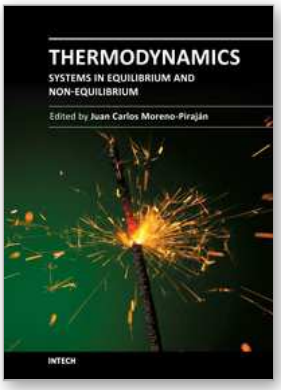

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Thermodynamics is one of the most exciting branches of physical chemistry which has greatly contributed to the modern science. Being concentrated on a wide range of applications of thermodynamics, this book gathers a series of contributions by the finest scientists in the world, gathered in an orderly manner. It can be used in post-graduate courses for students and as a reference book, as it is written in a language pleasing to the reader. It can also serve as a reference material for researchers to whom the thermodynamics is one of the area of interest.

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