Surface and Micellar Properties of Some Amphiphilic Drugs in the Presence of Additives

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In this study, the surface properties (in water and in the presence of varying concentrations of NaCl, CTAB, and TX-100) of four amphiphilic drugs are presented. The parameters evaluated are cmc (critical micelle concentration), Γ_{max} (maximum surface excess concentration at the air/water interface), and A_{min} (minimum area per surfactant molecule at the air/water interface). Γ_{max} increases and cmc/A_{min} decreases with increasing concentration of the additives. The cmc values calculated using a dye solubilization method for the systems also follow the same trend. The behavior is explained on the basis of counterion adsorption and mixed micelle formation.

Introduction

Self-association of amphiphilic compounds is a possible way of eliminating the energetically unfavorable contact between the nonpolar part of the compound and water while simultaneously retaining the polar part in an aqueous environment. A large number of drug molecules, such as the one used in the present studies (Scheme 1), are amphiphilic and self-associate in aqueous environments to form small aggregates. Their "surfactant-like" behavior is due to the presence of an almost planar tricyclic ring system and a short hydrocarbon chain carrying a terminal nitrogen atom.[1,2] Self-association depends on the molecular structure of the drug, concentration, and physicochemical conditions such as temperature, pH, ionic strength, and additive concentration.[3] It has been established from earlier studies on these drugs that aggregates of approximately 6 to 12 monomers are formed in water above the critical micelle concentration (cmc). The pK_a values of these drugs lie between 9.1 and 9.4,[4] and depending upon the solution pH, the drug monomers may acquire the cationic (i.e., protonated) or neutral (i.e., deprotonated) form.[5]

It is well-known that the cmc of amphiphiles varies in the presence of additives because the interfacial and micellar properties of these compounds in solution 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 the solvent.[6] As drugs are used in combination with additives (e.g., surfactants), it is necessary to have a knowledge of the additive effect on the cmc of amphiphilic drugs.

With this viewpoint, surface tension and dye solubilization studies have been performed on aqueous solutions of four amphiphilic drugs, AMT and IMP (antidepressants) and CPZ and PMT (phenothiazines), to determine the cmc of these drugs in the presence of different additives, viz., NaCl, CTAB, and TX-100. Surface properties, namely, maximum surface excess concentration (Γ_{max}) and minimum area per molecule (A_{min}), are calculated. The compositions of mixed micelles/mixed monolayers formed with CTAB/TX-100 and mixed micelle/mixed monolayer interactions are also estimated.

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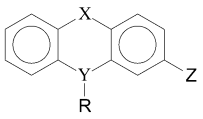
Scheme 1. Molecular Structure of Amphiphilic Drugs Used in the Present Studies



Amitriptyline (AMT) : X = CH_2CH_2, Y = C, Z = H, R = $C_3H_5N(CH_3)_2H^+Cl^-$
Imipramine (IMP) : X = CH_2CH_2, Y = N, Z = H, R = $C_3H_6N(CH_3)_2H^+Cl^-$
Chlorpromazine (CPZ) : X = S, Y = N, Z = Cl, R = $C_3H_6N(CH_3)_2H^+Cl^-$
Promethazine (PMT) : X = S, Y = N, Z = H, R = $C_3H_6N(CH_3)_2H^+Cl^-$

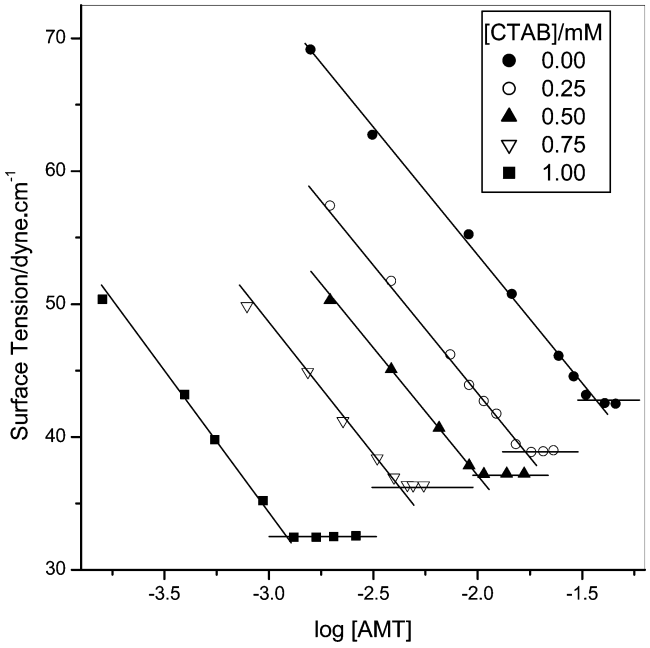


Figure 1. Plots of surface tension vs logarithm of AMT concentration at different fixed concentrations of CTAB.

Materials and Methods

AMT hydrochloride (≥ 98 %, Sigma, USA), IMP hydrochloride (≥ 98 %, Sigma), PMT hydrochloride (≥ 98 %, Sigma), CPZ hydrochloride (≥ 95.0 %, Fluka, Switzerland), NaCl (≥ 99.9 %, BDH, England), cetyltrimethylammonium bromide (CTAB; ≥ 99 %, BDH), and polyethylene glycol

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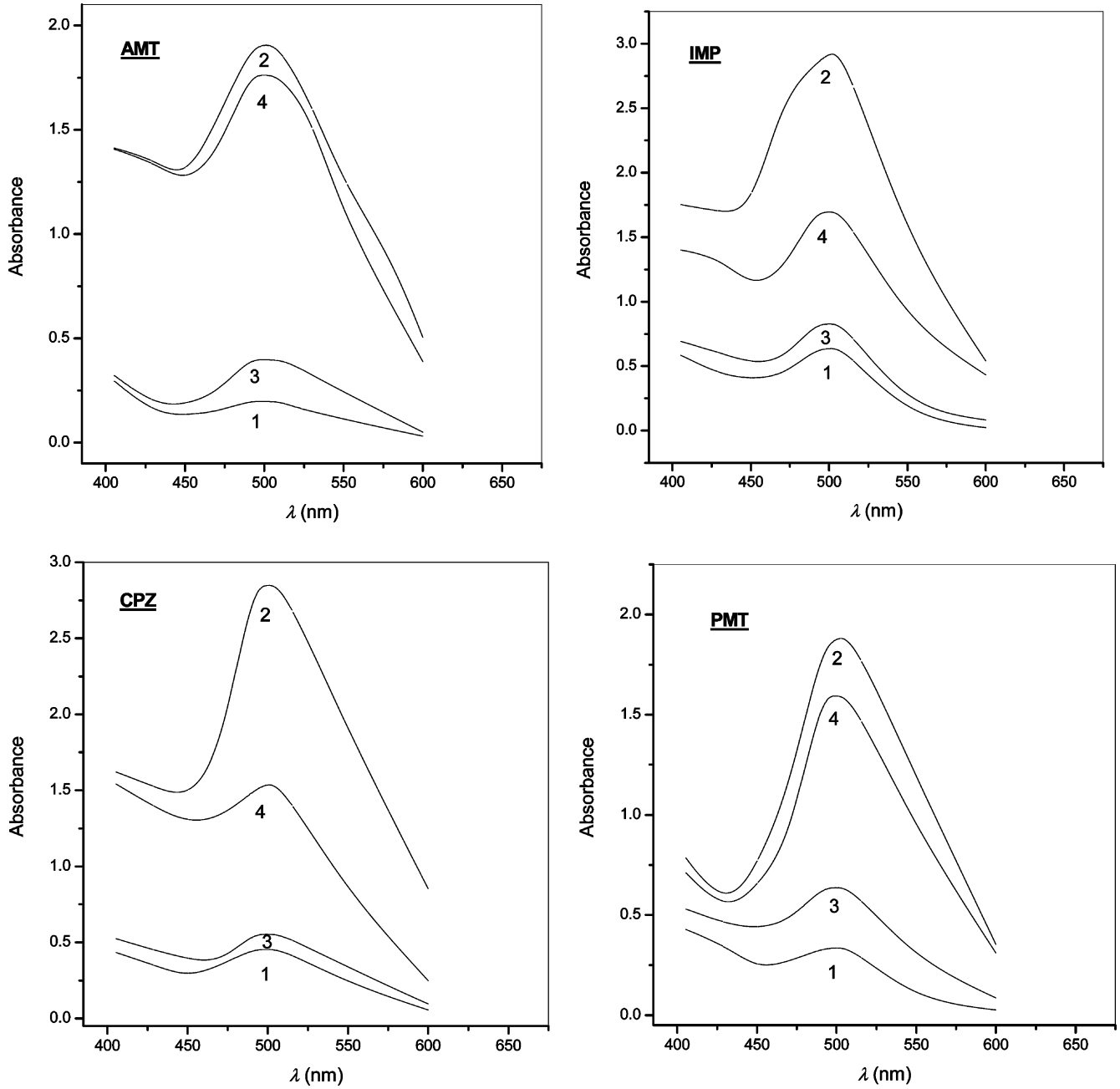

Figure 2. Spectra of Sudan III solubilized in the amphiphilic drugs (50 mM) containing no or a fixed concentration of additives: 1, [additive] = none; 2, 400 mM NaCl; 3, 1.0 mM CTAB; 4, 0.3 mM TX-100.

t-octylphenyl ether (TX-100; ≥ 99 %, Fluka) were used as received. Doubly distilled and deionized water (sp. cond. = (1 to 2)·10^{-6} S·cm^{-1}) was used as the solvent.

(a) Surface Tension Measurements. The cmc's of the drugs (with and without additives) in pure water were determined by measuring the surface tension (ST) of the pure drug as well as of drug + additive (NaCl, CTAB, 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, as an example, Figure 1). The point of break, when the constancy of ST begins, was taken as the cmc of the drug.

The ST values were measured by the ring detachment method using an S. D. Hardson tensiometer (Kolkata, India).

(b) Dye Solubilization. Dye solubilization experiments for the aqueous drug solutions (with and without additives) were performed at room temperature. The sample solutions with Sudan III dye were kept for 24 h and filtered, and then the spectra were recorded using a UV−visible spectrophotometer (Cintra 5, GBC Scientific Equipment, Australia). The wavelengths of maximum absorption (λ_{max}) for the dye in the drug (50 mM) were found to lie between (500 and 510) nm (Figure 2). For evaluating the cmc by the dye solubilization method, absorbances were recorded at the corresponding λ_{max} values (as an example, see Figure 3).

Results and Discussion

The cmc values for pure drugs have been found to be in good agreement with the literature values,[7] whereas the values decrease in the presence of additives (NaCl, CTAB, TX-100) (Table 1). Counterions are bound to micelles primarily by the strong electrical field created by the head groups and by the

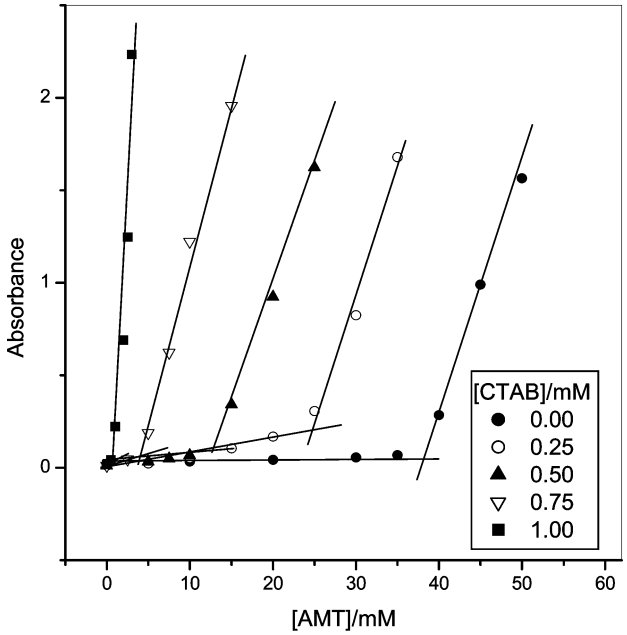

Figure 3. Evaluation of cmc of the amphiphilic drug AMT by the dye (Sudan III) solubilization method.

specific interactions that depend upon the head group and the counterion type. Two mechanisms have been proposed: in one mechanism, inorganic salts affect the solvent property of water, and in another, ions affect the micelles directly by adsorbing/desorbing to the head group region of the micelles.[8,9] Counterion binding plays a role in deciding the effective charge on the micelles and hence their formation, shape, and mutual interaction.[10] Added Cl^- ions (in the form of NaCl) follow the second mechanism and adsorb to the cationic head group region of the drug monomers. This adsorption decreases the electrostatic repulsion among head groups, and less electrical work is required to form micelles. With CTAB and TX-100, the cmc also shows a decrease. The concentrations of these surfactants were lower than or equal to their cmc values (which are 1 mM for CTAB and 0.36 mM for TX-100[11]). Further, it has been reported that surfactants form mixed micelles with the drugs.[12,13]

Mixed micelles are known to possess physicochemical properties quite different 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 nonionic surfactant, the degree of the association falls to zero as the mole fraction of the nonionic surfactant in the micelle increases.[14,15] Most cmc's of binary mixtures fall between the cmc's of the two components, but some are above[16] or below[17] this range. Our results for the cmc of drugs in the presence of TX-100 or CTAB show the same behavior (Table 1). Addition of TX-100 assists in micelle formation of drugs. TX-100 (by penetrating into the micelles) lowers the repulsive forces between the polar head groups of the drugs.

Rodriguez et al.[12] who studied the effect of dodecyltrimethylammonium bromide concentration on the cmc of AMT 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 nonsynergistic behavior of the mixed micelles. Though the slope of cmc decrease is lower in the case of CTAB, our results do indicate mixed micelle formation (Table 1). The nature and strength of the interactions between the two components (drugs and surfactants) can be determined by calculating the values of their β parameters.[18]

The intermicellar interaction coefficient in the mixed micelles is calculated from

$$\frac{[(X_1^{\,m})^2 \cdot \ln(\mathrm{cmc} \cdot \alpha_1/\mathrm{cmc}_1 \cdot X_1^{\,m})]}{[(1 - X_1^{\,m})^2 \cdot \ln\{\mathrm{cmc} \cdot (1 - \alpha_1)/\mathrm{cmc}_2 \cdot (1 - X_1^{\,m})\}]} = 1 \quad (1)$$

and

$$\beta^m = \ln(\mathrm{cmc} \cdot \alpha_1/\mathrm{cmc}_1 \cdot X_1^{\,m})/(1 - X_1^{\,m})^2 \quad (2)$$

where X_1^m is the mole fraction of component 1 in the micelles; cmc_1, cmc_2, and cmc are the cmc's for component 1, component 2, and their mixture at the given mole fraction; and β^m is the interaction parameter for mixed micelle formation in an aqueous medium.

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.[19,20] 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 α_1 as

$$\frac{[(X_1^{\,\sigma})^2 \cdot \ln(C \cdot \alpha_1/C_1 \cdot X_1^{\,\sigma})]}{[(1 - X_1^{\,\sigma})^2 \cdot \ln\{C \cdot (1 - \alpha_1)/C_2 \cdot (1 - X_1^{\,\sigma})\}]} = 1 \quad (3)$$

and

$$\beta^\sigma = \ln(C \cdot \alpha_1/C_1 \cdot X_1^{\,\sigma})/(1 - X_1^{\,\sigma})^2 \quad (4)$$

where C_1, C_2, and C are the molar concentrations of components 1 and 2 and their mixture, at α_1, required to produce a given surface tension reduction (corresponds to $\gamma = 45$ dyne·cm^{-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.

Equations 1 and 3 were solved iteratively for X_1 which was then substituted into eqs 2 and 4 to calculate the β values.

The activity coefficients f_1 and f_2 are related to β as

$$f_1 = \exp\{\beta \cdot (1 - X_1)^2\} \quad (5)$$

$$f_2 = \exp\{\beta \cdot X_1^{\,2}\} \quad (6)$$

β not only indicates 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 mean 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), suggesting 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 additives (CTAB or TX-100) increases, β^m values become more negative. This indicates an increase in the attractive interaction with the increase in additive concentration which is also evident from the cmc values, which decrease with increasing additive concentration.

β^σ also follows a similar trend (Tables 2 and 3). The mixtures of drugs/surfactants show stronger attractive interaction at the

Table 1. Effect of Additive Concentrations on the cmc (Determined by Surface Tension Measurements) and A_{min} as Well as Γ_{max} Values of Amphiphilic Drugs in Aqueous Solutions at ~300 K

	AMT			IMP			CPZ			PMT		
[additive]	cmc	$10^{10}\cdot\Gamma_{max}$	A_{min}	cmc	$10^{10}\cdot\Gamma_{max}$	A_{min}	cmc	$10^{10}\cdot\Gamma_{max}$	A_{min}	cmc	$10^{10}\cdot\Gamma_{max}$	A_{min}
mM	mM	mol·m^{-2}	Å^2	mM	mol·m^{-2}	Å^2	mM	mol·m^{-2}	Å^2	mM	mol·m^{-2}	Å^2
					NaCl							
0	38.08 (36.0)[7]	1.5808	105.03	47.46 (47.0)[7]	1.9506	85.12	16.86 (19.0)[7]	1.8975	87.50	45.14 (44.0)[7]	2.0985	79.12
100	29.22	3.4661	47.90	37.24	4.1604	39.91	11.55	3.9554	41.98	36.28	4.256	39.01
200	24.44	3.4992	47.45	30.47	4.0647	40.85	9.28	3.9792	41.72	29.56	4.3466	38.19
300	21.81	3.5375	46.93	27.14	4.2439	39.12	7.48	4.0752	40.74	23.82	4.4214	37.55
400	18.58	3.5879	46.27	21.58	4.3205	38.43	6.43	4.3188	38.44	18.32	4.5345	36.61
					CTAB							
0.25	17.10	3.2922	50.43	37.84	3.9168	42.39	8.82	3.9533	41.99	29.98	4.3309	38.34
0.50	10.36	3.3479	49.59	22.94	3.9439	42.11	6.72	4.0004	41.50	22.56	4.4597	37.23
0.75	4.23	3.4471	48.16	9.06	3.9725	41.79	2.55	4.0264	41.24	8.49	4.5606	36.41
1.00	1.18	3.6279	45.76	3.20	4.0212	41.29	1.52	4.0821	40.67	2.09	4.8008	34.58
					TX-100							
0.075	14.95	1.5538	106.90	33.32	2.0454	81.17	9.55	1.9679	84.37	31.05	2.1133	78.57
0.150	9.49	1.61997	102.50	22.56	2.0819	79.75	7.12	1.9828	83.74	21.38	2.1742	76.36
0.225	2.94	1.7601	94.33	10.31	2.1420	77.51	3.35	2.0115	82.54	6.86	2.2038	75.34
0.300	0.95	1.9062	87.10	4.32	2.2464	73.91	2.23	2.0306	81.76	2.24	2.2760	72.95

Table 2. Micellar Compositions (X_1^m, X_1^σ), Interaction Parameters (β^m, β^σ), and Activity Coefficients (f_1^m, f_2^m, f_1^σ, f_2^σ) of Binary Mixtures of Drugs and CTAB at Different Mole Fractions of CTAB (α_1)

α_1	X_1^m	β^m	f_1^m	f_2^m	X_1^σ	β^σ	f_1^σ	f_2^σ
				AMT				
0.005	0.335	−3.086	0.255	0.707	0.433	−3.618	0.313	0.507
0.010	0.417	−4.122	0.246	0.489	0.496	−5.239	0.264	0.277
0.015	0.466	−7.039	0.134	0.217	0.516	−8.022	0.152	0.119
0.020	0.489	−11.664	0.047	0.062	0.524	−14.236	0.039	0.021
				IMP				
0.005	0.197	−0.062	0.961	0.998	0.406	−0.504	0.837	0.921
0.010	0.393	−1.484	0.578	0.796	0.525	−2.293	0.596	0.532
0.015	0.472	−4.507	0.284	0.367	0.537	−6.066	0.272	0.174
0.020	0.497	−8.181	0.126	0.133	0.538	−10.482	0.107	0.048
				CPZ				
0.005	0.311	−4.120	0.142	0.671	0.362	−3.736	0.218	0.613
0.010	0.369	−4.311	0.180	0.556	0.432	−4.629	0.224	0.422
0.015	0.441	−7.874	0.086	0.216	0.475	−8.331	0.101	0.152
0.020	0.453	−9.104	0.066	0.155	0.491	−10.580	0.064	0.078
				PMT				
0.005	0.268	−1.079	0.560	0.926	0.400	−1.035	0.689	0.847
0.010	0.380	−1.384	0.588	0.819	0.505	−1.999	0.618	0.595
0.015	0.471	−4.719	0.267	0.351	0.532	−5.629	0.291	0.203
0.020	0.494	−9.743	0.083	0.092	0.530	−10.795	0.092	0.048

Table 3. Micellar Compositions (X_1^m, X_1^σ), Interaction Parameters (β^m, β^σ), and Activity Coefficients (f_1^m, f_2^m, f_1^σ, f_2^σ) of Binary Mixtures of Drugs and TX-00 at Different Mole Fractions of TX-100 (α_1)

α_1	X_1^m	β^m	f_1^m	f_2^m	X_1^σ	β^σ	f_1^σ	f_2^σ
				AMT				
0.0015	0.351	−3.668	0.213	0.637	0.435	−4.551	0.233	0.423
0.0030	0.422	−4.482	0.223	0.451	0.489	−6.206	0.199	0.226
0.0045	0.471	−8.459	0.094	0.154	0.509	−10.744	0.075	0.061
0.0060	0.489	−12.46	0.039	0.051	0.515	−15.495	0.026	0.016
				IMP				
0.0015	0.256	−0.772	0.652	0.951	0.422	−0.965	0.725	0.842
0.0030	0.394	−1.525	0.571	0.789	0.512	−2.494	0.553	0.519
0.0045	0.471	−3.984	0.328	0.413	0.535	−6.411	0.249	0.159
0.0060	0.497	−6.924	0.173	0.181	0.605	−15.648	0.087	0.003
				CPZ				
0.0015	0.299	−3.735	0.159	0.716	0.362	−4.157	0.184	0.579
0.0030	0.364	−4.032	0.195	0.587	0.424	−4.740	0.208	0.426
0.0045	0.427	−10.484	0.095	0.055	0.468	−7.546	0.118	0.191
0.0060	0.450	−7.660	0.098	0.212	0.485	−9.240	0.087	0.113
				PMT				
0.0015	0.254	−0.885	0.611	0.944	0.395	−1.404	0.598	0.803
0.0030	0.386	−1.582	0.551	0.789	0.497	−2.623	0.515	0.523
0.0045	0.469	−5.396	0.219	0.304	0.522	−6.826	0.209	0.156
0.0060	0.495	−9.433	0.090	0.099	0.525	−11.531	0.074	0.042

air/water interface. These interactions are stronger than in mixed micelles as evidenced by the fact that β^σ values 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.[21]

It is well-known that the air/solution interface of an amphiphile solution is well populated[22] 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 the surfactant in the bulk.

The surface excess concentration, Γ_{max}, is an effective measure of the Gibbs adsorption at the liquid/air interface which was calculated by applying the following equation[23]

$$\Gamma_{max} = -\frac{1}{2.303nRT}(\mathrm{d}\gamma/\mathrm{d}\log c)_T \qquad (7)$$

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,[24] $n = 1 + m/(m + m_s)$, where m and m_s are the concentrations of drug and the added electrolyte, respectively. 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}.

The Table 1 data show that Γ_{max} increases with an increase in the concentration of additives. The drug solutions with additives, compared to a pure drug solution, have greater preference to be adsorbed at the air/water interface. The presence of additives decreases the repulsion among head groups, and more drug molecules can adsorb at the interface which is also confirmed by low values of A_{min}.

Table 4. Effect of Additive Concentrations on the cmc Values of Amphiphilic Drugs in Aqueous Solutions at ~300 K (Determined by the Dye Solubilization Method)

[additive]	cmc/mM			
mM	AMT	IMP	CPZ	PMT
		NaCl		
0	38.75	48.33	18.22	47.40
100	33.98	43.43	14.46	39.74
200	32.71	38.57	12.46	38.27
300	28.29	35.81	11.20	34.10
400	23.25	33.12	7.95	30.17
		CTAB		
0.25	24.20	38.00	12.23	37.54
0.50	11.75	27.64	9.27	25.61
0.75	5.40	14.74	4.02	12.15
1.00	1.64	3.78	1.63	3.28
		TX-100		
0.075	23.53	38.44	12.17	36.77
0.150	12.50	25.63	9.02	25.14
0.225	6.60	13.99	4.31	12.62
0.300	2.17	3.22	1.39	2.83

A_{min} was evaluated using the relation[25]

$$A_{min} = 10^{16}/N_A\Gamma_{max}\ (\text{Å}^2) \quad (8)$$

where N_A is Avogadro's 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.[25] The values of A_{min} for these drugs are similar to those reported for other antidepressants[26] and phenothiazines.[27]

An important property of micelles that has particular significance in pharmacy is their ability to increase the solubility of sparingly soluble substances.[28−30] 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.[31] The plots illustrated in Figure 2 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 AMT concentration in the absence as well as presence of different fixed concentrations of CTAB are illustrated in Figure 3 (similar plots were obtained in the presence of the remaining drug−additive combinations). The plots reveal that the amount of the dye solubilized slowly rises to the cmc of the drug, and thereafter a sudden and steep rise occurs with the formation of micelles. 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. The cmc values, recorded in Table 4, were estimated from Figure 3 (and similar plots obtained with the three drugs). Differences between the cmc values obtained by surface tension (Table 1) and dye solubilization techniques (Table 4) arise because the techniques measure different underlying phenomena.

Conclusions

Surface properties of four amphiphilic drugs are investigated in water and in different additives (NaCl, CTAB, TX-100), and the results obtained were as follows:

(i) With NaCl, an increase in Γ_{max} and a decrease in cmc/A_{min} are due to binding of the Cl^- counterion to the drug micelles, thereby decreasing repulsion among the charged head groups.

(ii) With CTAB and TX-100, although the trend of the decrease/increase of cmc and A_{min} and Γ_{max} is similar, the explanation is different. These additives form mixed micelles with the drugs.

(iii) The drug/surfactant systems show an increase in synergism with the increase in surfactant concentration.

(iv) Rosen's approach reveals increased synergism in the mixed monolayers in comparison to in the mixed micelles.

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