Journal of Molecular Liquids xxx (2013) xxx–xxx

Contents lists available at ScienceDirect

Journal of Molecular Liquids

journal homepage: www.elsevier.com/locate/molliq

A study of the interaction between a phenothiazine drug promazine hydrochloride with cationic surfactants

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ARTICLE INFO

Article history:
Received 27 July 2011
Received in revised form 5 September 2013
Accepted 5 September 2013
Available online xxxx

Keywords:
Promazine hydrochloride
Cationic surfactants
Critical micelle concentration
Interaction parameters
Activity coefficients

ABSTRACT

A tensiometric study at 303.15 K was made to study the binary mixed systems of a phenothiazine drug promazine hydrochloride with six cationic surfactants (decyl-, dodecyl-, tetradecyl-, hexadecyltrimethylammonoium bromides, and cetylpyridinium bromide/chloride). Relevant parameters were evaluated by using the Regular Solution Theory and Motomura treatment for binary mixed systems. Clint's model was also used to explain the nonideal behavior of the systems. The synergistic behavior (i.e., non-ideal behavior) for binary mixtures is explained by the deviation of critical micelle concentration (*cmc*) from ideal critical micelle concentration (*cmc**), micellar mole fraction (X_1^m) from ideal micellar mole fraction (X_1^{ideal}), the values of interaction parameter (β) and activity coefficients (f_i) (for both mixed micelles and mixed monolayer). The excess free energy (ΔG_{ex}) explains the stability of mixed micelles in comparison to micelles of pure drug; the stability decreases with the increase in alkyl chain length of the surfactant. Interfacial parameters, i.e., Gibbs surface excess (Γ_{max}), minimum head group area at air/water interface (A_{min}), free energy of micellization (ΔG_m^o), and standard Gibbs energy of adsorption (ΔG_{ads}^o) were also evaluated for the systems.

1. Introduction

The dual nature of amphiphilic compounds (because of the hydrophilic and hydrophobic parts) is the foundation of their relation to both external and internal interfaces in solutions. In recent years, studying the mixed amphiphilic systems is in vogue [1–4] owing to their better performance than the pure individual components. The nonideality of mixing may cause synergism in the properties of amphiphilic mixtures that may be exploited in many ways to their end use applications [5]. For example, in dermatological preparations, the surfactant mixture synergism can minimize the total surfactant monomer concentration, which, in turn, reduces skin irritation [6]. Micelles can only be used as drug carriers and not as targeting systems due to their labile nature, although evidences are there that suggest possibility to alter the biodistribution of a drug by administering it in a micellar solution [7]. A large number of drugs from many pharmacological groups of compounds exhibit typical colloidal behavior [8–10]. Phenothiaznes act on a wide range of receptors in the nervous system and have been found to be versatile anticholinergic and antihistamine compounds. The micellar mode of association and the discontinuity in the physicochemical properties of phenothiazine drugs in the aqueous solutions have been studied by several workers [11–13]. As mentioned earlier the mixed micellar systems have been widely studied, but mixtures of drug–cationic surfactant have been less frequently examined [14–16]. Here we used the surface tension measurements to determine the critical micelle concentration (cmc) of various drug–cationic surfactant binary systems wherein the effect of chain length and head group of n-alkyltrimethylammonium bromides and n-alkylpyridinium halides on the physico-chemical properties of a phenothiazine drug promazine hydrochloride (PMZ) by was studied using the various solution and thermodynamic theories [17–24]. The effect of alkyl chain length on the toxicity and pharmacology of a series of C_{10}–C_{20} has been studied in the female rat [25], and toxicity decreases with the increasing length of alkyl chain up to C_{16}. Cetyltrimethylammonium bromide (CTAB) has also been found to be non-carcinogenic in rats [26]. Cationic (CTAB) and a nonionic ($C_{12}E_{23}$) reduced the degradation of several penicillins by the factor 4 to 12, while anionic surfactant (NaLS) increased the rate of degradation [27].

Meakin et al. [28] concluded that when CTAB increases the rate of hydrolysis, it is likely that the site of interaction is the surface, where the ester linkage would be in a region of high hydroxyl ion concentration. For mixed micellar solutions, the theoretical models rely on the equilibrium between micelles and monomers in solution. The phenomenon of mixed micelle formation described by the Clint's model [17] is used to estimate the deviation of mixed micellar systems from the ideal behavior. The extent of deviation from ideal behavior is quantified via the dimensionless interaction coefficient β, originally introduced by Holland and Rubingh [18]. The Motomura treatment [19] has been used to determine the composition of mixed micelles from the variation of experimental cmc values with the change in composition of binary surfactant mixtures.

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0167-7322/$ – see front matter © 2013 Published by Elsevier B.V.
http://dx.doi.org/10.1016/j.molliq.2013.09.003

2. Experimental

2.1. Materials

The phenothiazine drug promazine hydrochloride (PMZ) (≥98%, Sigma, USA, CAS registry no. 53-60-1) and cationic surfactants, i.e., decyltrimethylammonium bromide (≥98%, TCI, Japan), dodecyltrimethylammonium bromide (≥98%, TCI, Japan), tetradecyltrimethylammonium bromide (≥99%, Sigma, USA), cetyltrimethylammonium bromide (≥99%, Merck, Germany), cetylpyridinium bromide (≥99%, Merck, Germany), and cetylpyridinium chloride (98%, BDH, England) were used without further purification. The γ vs. logC plots of pure surfactants showed no minima which ascertained their purity. Their aqueous stock solutions were prepared in doubly distilled water.

2.2. Surface tension measurements

The ring detachment method (Du Noüy Tensiometer) was used to measure surface tension (γ). The ring used in the measurement was cleaned by washing with doubly distilled water followed by heating through alcohol flame. Different mole fractions of mixed systems were prepared from stock solutions of different concentrations of PMZ and cationic surfactants. The γ at each mole fraction was measured by successive addition of concentrated solution of the mixture in pure water at 303.15 K. In order to determine the values of critical micelle concentration (cmc), two linear fits were used for each of the isotherms. The first line was fitted to the interval of concentration characterized by linear decrease of the surface tension and the second one to the region of concentration with nearly constant surface tension. The cmc values were determined from the break point of the surface tension vs log C curves and accuracy on the individual surface tension reading is approximately $\pm 0.5 \mathrm{mNm}^{-1}$. The cmc values agree well with the literature (Table 1). Further, in conformity to the observations of Mandal and Nair [29], we too obtained slightly lower cmc value for CPB than CPC. Seemingly, the higher counterion association of CPB (as the larger the hydrated radius of the counterion, the weaker is the degree of binding) [29,30] results in CPB micelles with more rigid surface.

Table 1
Variation of critical micelle concentration (*cmc*) and ideal critical micelle concentration (*cmc**) with mole fraction of surfactants.

Mole fraction of surfactants	*cmc* (mM)	*cmc** (mM)	Mole fraction of surfactants	*cmc* (mM)	*cmc** (mM)
0	33		0	33	
DeTAB			CTAB		
0.1	5.90	34.45	0.1	3.40	7.03
0.5	29.5	41.80	0.5	1.52	1.70
0.7	34.5	46.79	0.7	1.20	1.23
0.9	38.9	53.14	0.9	0.96	0.96
1	57.0		1	0.87	
DTAB			CPB		
0.1	15.0	28.97	0.1	3.55	4.55
0.5	14.0	19.46	0.5	1.12	1.02
0.7	12.0	16.72	0.7	0.81	0.74
0.9	11.7	14.65	0.9	0.66	0.58
1	13.8		1	0.52	
TTAB			CPC		
0.1	6.9	15.55	0.1	3.16	4.78
0.5	5.0	4.99	0.5	0.10	1.08
0.7	4.1	3.73	0.7	0.89	0.78
0.9	3.8	2.97	0.9	0.79	0.61
1	2.7		1	0.55	

3. Theoretical approach

3.1. Composition of mixed films and micelles

The composition of mixed adsorbed layers and micelles differs from that of pure components because of their mutual interactions. Using Motomura theory, which is based on the Gibbs–Duhem equation [31–33], the composition of mixed micelles is determined by use of Eq. (1)

$$X_{M,1}^{m} = \alpha_1^0 - \frac{\left(\alpha_1^0\alpha_2^0/cmc^0\right)\left(\partial cmc^0/\partial\alpha_1^0\right)}{1-\frac{\delta\nu_{1,c}\nu_{2,d}}{\nu_{1,c}\nu_2\alpha_1^0+\nu_{2,d}\nu_1\alpha_2^0}} \quad (1)$$

Where

$$cmc^0 = (\nu_1\alpha_1+\nu_2\alpha_2)cmc \quad (2)$$

and

$$\alpha_1^0 = \frac{\nu_i\alpha_i}{\nu_1\alpha_1+\nu_2\alpha_2}(i=1,2) \quad (3)$$

In Eq. (1), $X_{M,1}^{m}$ is the micellar mole fraction of the surfactant, ν_i is the number of ions dissociated by the *i*th component, and δ is the Kronecker delta which is equal to 1 for identical counterions and 0 for different counterions. By using Eqs. (2) & (3) and δ value, the Eq. (1) for PMZ–cationic surfactant systems reduces to

$$X_{M,1}^{m} = \alpha_1 - \left(\frac{\alpha_1\alpha_2}{2cmc}\right)\left(\frac{\partial cmc^0}{\partial\alpha_1}\right)_{T,P} \quad (4)$$

Similarly, for mixed adsorbed layer Eq. (1) modifies to

$$X_{M,1}^{\sigma} = \alpha_1 - \left(\frac{\alpha_1\alpha_2}{2C}\right)\left(\frac{\partial C^0}{\partial\alpha_1}\right)_{T,P} \quad (5)$$

where $X_{M,1}^{\sigma}$ is the mole fraction of the surfactant in the mixed adsorbed layer, *C* is concentration of the surfactant at $\gamma = 49\ \mathrm{mNm}^{-1}$ and

$$C^0 = 2C$$

Fig. 1 (a–d) shows the variation of α_1, $X_{M,1}^{m}$ and α_1, $X_{M,1}^{\sigma}$ with respect to cmc^0 and C^0, respectively. In all the systems $X_{M,1}^{m}$ and $X_{M,1}^{\sigma}$ values are higher than the corresponding α_1 values with respect to cmc^0 and C^0, except in the case of mixed micelles of the drug and DeTAB where $X_{M,1}^{\sigma}$ values are lower than α_1. It is also observed from Fig. 1 (a–d) that with the increase in alkyl chain length of the surfactant, the difference of $X_{M,1}^{m}$ and $X_{M,1}^{\sigma}$ values with α_1 also increases. Variation of α_1 and $X_{M,1}^{\sigma}$ with cmc^0 for drug–CPB (Fig. 1 (e)), shows the same pattern as in case of drug–CTAB mixed micelles but the decrease is more in cmc^0 in case of the former. It suggests that despite of totally different molecular dynamics (spin lattice relaxation time, T_1, values) [29] there is no significant effect of pyridinium head group if replaced by trimethylammonium head group of CTAB in the mixed micelles.

3.2. Interaction between molecules in mixed adsorbed film and micelle

The properties of ideal or nonideal behavior of mixed micelles of PMZ–cationic surfactants are investigated by the pseudo phase model. According to this model, micelles are considered to be macroscopic phase in equilibrium with a solution containing corresponding monomers. As such, the ideal cmc is related to individual cmc's by Eq. (6) [34]

$$\frac{1}{cmc*} = \frac{\alpha_1}{cmc_1} + \frac{(1-\alpha_1)}{cmc_2} \quad (6)$$

Please cite this article as: Kabir-ud-Din, et al., J. Mol. Liq. (2013), http://dx.doi.org/10.1016/j.molliq.2013.09.003