Z. Phys. Chem. **227** (2013) 441–458 / **DOI** 10.1524/zpch.2012.0340

Interaction between Zwitterionic Surfactants and Amphiphilic Drug: A Tensiometric Study

By Wajid H. Ansari*, Sahar Noori, Andleeb Z. Naqvi*, and Kabir-ud-Din

Department of Chemistry, Aligarh Muslim University, Aligarh-202002, India

(Received August 13, 2012; accepted in revised form November 13, 2012)
(Published online January 28, 2013)

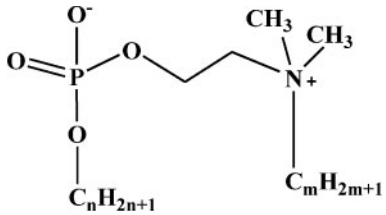
Amitriptyline Hydrochloride / Zwitterionic Gemini Surfactants / Surface Tension / Mixed Micelles

The physicochemical properties, viz, critical micelle concentration (cmc), surface excess concentration (Γ_{max}), minimum area per head group (A_{min}) of zwitterionic surfactants (designated as $n(-)$-2-$m(+)$; $n = 8$, 10, 12 and $m = 12$, 14, 16) and their mixtures with amphiphilic antidepressant drug amitriptyline hydrochloride (AMT) were determined by using surface tension measurements. The cmc and ideal cmc (cmc_{id}) values along with interaction parameters, β^m and β^σ (calculated using Rubingh's and Rosen's models), suggest attractive interactions among the components. The Krafft temperature measurements also indicate strong attractive interactions. Γ_{max} (or A_{min}) increases (or decreases) with the addition of gemini surfactant; the values being closer to that of the drug. These values and micellar mole fraction (X_1^m-calculated from Rubingh's model and X_1^{Moto}-calculated from Motomura's model) indicate larger contribution of gemini surfactants in mixed micelles and smaller contribution at air/solution interface (as mole fraction values at interface, X_1^σ, are slightly smaller than X_1^m). The standard Gibbs energy of micellization (ΔG°_{mic}) and adsorption (ΔG°_{ad}) as well as excess energy of mixing (ΔG^m_{ex}) are all negative. All these results suggest higher stability of the mixed systems. UV absorbance results also suggest that the mixed micelles are stable for several days.

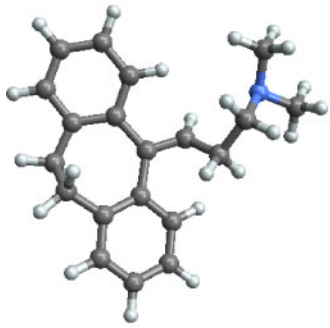
1. Introduction

The aqueous solubility of solid drugs is a major problem and, hence, an important subject for pharmaceutical scientists. Knowledge of aqueous solubility of drugs helps in choosing the best solvent for dissolving drugs and designing drug formulation. Drug solubility affects the pharmacokinetics such as transport, release and absorption [1]. Drugs with low aqueous solubility often show inadequate or variable bioavailability which hampers their applicability. Two main aspects of successful drug formulation are its solubility and stability. The solubilizing system must be able to solubilize the required concentration of the drug. Also, the system must be such that the drug remains stable in it. Some of the methods used to modify drug solubility are micronization [2], complexation [3], use of prodrugs [4], cosolvency [5], pH adjustment [6],

* Corresponding authors. E-mail: naqviaz@gmail.com; wajidhusain.chem@gmail.com



(A)



(*n*=8, 10, 12; *m*=12, 14, 16)

(B)

Scheme 1. Molecular structures of zwitterionic heterogeminis (**A**) and AMT (**B**).

hydrotropy [7] and solubilization in micelles/microemulsions [8,9]. However, many of these methods have limitations and cannot be used for all active drugs [9–13].

Colloidal drug carrier systems such as micelles and mixed micelles show great promise in drug delivery as with these systems size of the carrier as well as the amount of drug loading can be optimized. Also, these systems are easy to prepare, have long shelf life and low toxicity [14]. The most commonly used surfactants include Cremophor EL, Tween 20, Tween 80 and sodium lauryl sulphate [12,15]. However, Tweens are known to be toxic, although less than Tritons [16]. Cremophor EL, which is used to solubilise various drugs like anaesthetics, photosensitizers, immunosuppressive agents, sedatives, anticancer and antitumor drugs, is reported to have side effects like severe anaphylactic hypersensitivity reactions, abnormal lipoprotein patterns, hyperlipidaemia and peripheral neuropathy [17–19].

Gemini surfactants can be 10 to 100 times more surface active than conventional ones and, hence, are gaining wide attention in both academic and industrial research [20,21]. These surfactants have shown great promise in skin care [22], drug entrapment and release [23], gene therapy [24] and antibacterial regimens [25] as well as in various analytical processes [26]. The most widely used gemini surfactants are the *m-s-m* type, *i.e.*, symmetrical ones: two hydrophobic chains of equal length connected by a spacer at the level of head groups, with same charge on both heads. Charge on head groups may be either positive (cationic gemini) or negative (anionic gemini) [27]. Cationic geminis with the same head group but different tails are also reported

in literature [28,29]. Studies on these types of surfactants indicated that unsymmetrical geometry may give interesting properties to the surfactant self-assembly.

Another type of gemini surfactants is the heterogemini surfactants [30–32] in which the head groups are of different types. Among these types anionic-cationic ones, also known as zwitterionic, are the most interesting and important. Presence of a cationic and an anionic group in the same molecule gives the surfactant a nature intermediate to ionic and non-ionic ones [33]. Depending upon the type of head groups these surfactants may show pH-dependent or pH-independent behavior. These surfactants are known to be less skin irritating. The zwitterionic geminis contain no counterions and when mixed with ionic amphiphiles they may produce strong synergism.

In this paper we present results of mixed micellization studies of AMT with nine zwitterionic surfactants which contain a negatively charged phosphodiester and a positively charged quaternary ammonium head. The two head groups are separated by two methylene groups. The lengths of the two tails vary between 8–12 and 12–16 (Scheme 1A). AMT is an amphiphilic drug which possesses a rigid, almost planar tricyclic ring system bound to a short alkyl chain with a terminal nitrogen atom (Scheme 1B). This drug suffers from anticholinergic, cardiovascular and antiarrhythemic side effects. However, these side effects can be reduced by using AMT with a carrier.

Although there exists a few reports on the physicochemical properties of these surfactants [30,34–37], this is probably the first detailed study of mixed systems of these surfactants with a drug.

2. Experimental section

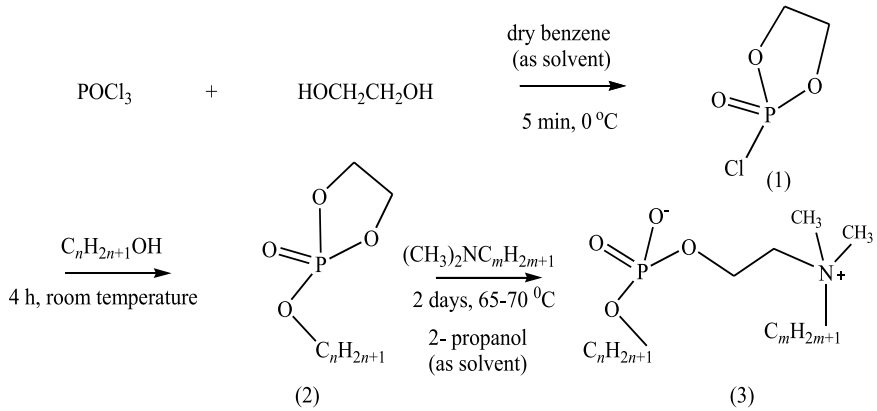
2.1 Materials

The antidepressant drug amitriptyline hydrochloride (98%, Sigma Aldrich, St. Louis, USA, CAS: 594-18-8), phosphoryl chloride (99%, Otto, Mumbai, India, CAS: 10025-87-3), ethylene glycol (≥ 99%, Sigma Aldrich, USA, CAS: 107-21-1), 1-octanol (≥ 99%, Merck, Hohenbrunn, Germany, Cat. No.: 8209311000), 1-decanol (99%, Otto, Mumbai, India, CAS: 112-30-1), 1-dodecanol (99%, Otto, Mumbai, India, CAS: 112-53-8), *N*,*N*-dimethyldodecylamine (95%, Acros Organics Mumbai, India, CAS: 112-18-5), *N*,*N*-dimethyltetradecylamine (≥ 95%, Aldrich, USA, CAS: 112-75-14), *N*,*N*-dimethylhexadecylamine (≥ 95%, Fluka, France, CAS: 112-69-6) were used without further purification.

2.2 Synthesis of gemini surfactants (one pot synthesis)

The zwitterionic geminis (designated as *n*(−)-2-*m*(+) throughout this text) were synthesized according to the procedure given in literature [30,36].

The synthesis was carried out in two steps: In the first step, a solution of phosphoryl chloride (0.025 mol) was added to a cooled (0 °C) solution of ethylene glycol (0.03 mol) in dry benzene. After the addition, the reaction mixture was stirred for 5 min and to this cyclic ethylene chlorophosphate (1) formed was added the solution of alkylalcohol (0.025 mol) in dry benzene. The reaction mixture was stirred continuously for



Scheme 2. Synthesis of the zwitterionic gemini surfactants ($n = 8$, 10, 12; $m = 12$, 14, 16).

4 h at room temperature. The solvent was then removed under reduced pressure to get the precursor (2).

In the second step, *N*,*N*-dimethylalkylamine (0.025 mol) was added to a solution of precursor (2) in 2-propanol and heated to 65–70 °C with stirring for 2 days. After removal of the solvent under diminished pressure, the desired gemini surfactant (3) was obtained. The compound was finally purified by recrystallization with acetone. The structures of the geminis were ascertained by ^{1}H NMR spectral studies.

^{1}H-NMR (300 MHz, $CDCl_3$, δ scale); 0.86–0.88 (*t*, 6H, 2C*H*$_3$– tail alkyl chains), 1.25–1.34 (*m*, 28–44H, –C*H*$_2$– both tail alkyl chains), 1.83 (*m*, 2H, N$^+$–C–C*H*$_2$– tail alkyl chain), 3.00 (*t*, 2H, N$^+$–C*H*$_2$–C– tail alkyl chain), 2.82 (*s*, 6H, N$^+$(C*H*$_3$)$_2$), 1.65 (*m*, 2H, O–C–C*H*$_2$– tail alkyl chain), 3.95 (*t*, 2H, O–C*H*$_2$–C– tail alkyl chain), 4.08 (*t*, 2H, O–C*H*$_2$–C–N$^+$), 3.78 (*t*, 2H, N$^+$–C*H*$_2$–C–O).

2.3 Tensiometric measurements

The tensiometric measurements were performed using a platinum ring by the ring detachment method with a S. D. Hardson tensiometer. Different mole fractions of mixed systems were prepared from stock solutions of zwitterionic gemini surfactants and AMT. The instrument was calibrated each time measurements were made. The surfactant concentration was varied by using Hamilton-Bonaduz, SCHWEIZ, microsyringe and readings were taken after thorough mixing and temperature equilibration. The cmc values were obtained from surface tension versus logarithm of surfactant concentration plots.

2.4 Krafft temperature measurements

The Krafft temperature measurements of pure gemini surfactants and their mixtures with AMT were made at concentration 5 and 50 mM, respectively. The clear experimental solutions were kept in a refrigerator for at least a day, when the precipitation of solid surfactant-hydrate crystals occurred. The temperature was raised slowly with

Table 1. Solution properties (cmc, Γ_{max}, A_{min}, pC_{20}, ΔG°_{mic}, ΔG°_{ad}, G_{min} and K_T)[a] of pure amphiphiles.

Amphiphiles	cmc (mM)	$\Gamma_{max} \pm 1$ 10^7 (mol m^{-2})	A_{min} (Å^2)	pC_{20}	ΔG°_{mic} (kJ mol^{-1})	ΔG°_{ad} (kJ mol^{-1})	G_{min} (kJ mol^{-1})	K_T (K)
AMT	36.22	21	80 ± 4	1.92	−18.4 ± 0.2	−34.0 ± 0.3	19.1 ± 0.9	
8(−)-2-12(+)	0.148	43	38 ± 1	4.71	−32.3 ± 0.3	−41.8 ± 0.4	7.3 ± 0.2	
8(−)-2-14(+)	0.061	24	68 ± 3	5.55	−34.5 ± 0.3	−50.2 ± 0.5	12.9 ± 0.5	
8(−)-2-16(+)	0.057	24	70 ± 3	5.74	−34.7 ± 0.3	−52.0 ± 0.5	13.2 ± 0.5	292.0
10(−)-2-12(+)	0.144	27	61 ± 2	4.13	−32.3 ± 0.3	−41.2 ± 0.4	16.7 ± 0.6	
10(−)-2-14(+)	0.070	33	49 ± 1	5.32	−34.1 ± 0.3	−47.1 ± 0.5	8.9 ± 0.2	278.0
10(−)-2-16(+)	0.041	31	53 ± 2	5.37	−35.5 ± 0.3	−49.4 ± 0.5	9.3 ± 0.3	294.5
12(−)-2-12(+)	0.073	21	77 ± 3	5.77	−34.0 ± 0.3	−53.2 ± 0.5	14.2 ± 0.6	
12(−)-2-14(+)	0.041	20	83 ± 4	6.26	−35.5 ± 0.3	−56.3 ± 0.6	15.0 ± 0.7	279.0
12(−)-2-16(+)	0.032	44	38 ± 1	5.22	−35.9 ± 0.4	−45.1 ± 0.4	6.9 ± 0.1	298.0

[a] equations used for calculation: $\Gamma_{max} = \frac{1}{2.303nRT}(\partial\gamma/\partial \log C)$, $A_{min} = (N_A \Gamma_{max})^{-1} \times 10^{20}$, $pC_{20} = -\log C_{20}$, $\Delta G^{\circ}_{mic} = RT \ln X_{cmc}$, $\Delta G^{\circ}_{ad} = \Delta G^{\circ}_{mic} - \frac{\pi_{cmc}}{\Gamma_{max}}$ and $G_{min} = \gamma_{cmc} A_{min} N_A$.

continuous stirring until the solution became clear and readings were taken by visual inspection. The process was repeated three times to check the reproducibility of the measurements. The estimated error was within ±0.5 °C.

2.5 Micellar stability

The stability of mixed system was obtained by measuring their absorbance with a UV-vis spectrophotometer (SHIMADZU-model UV mini 1240). The absorbance of one mole fraction (0.075) of gemini surfactants with the drug and pure AMT were taken above the cmc.

3. Results and discussion

On dissolution, an amphiphile first saturates the interface, and then the excess molecules tend to self-associate in the bulk solution to form micelles and surface tension becomes constant. This concentration is taken as critical micelle concentration (cmc, Fig. 1).

3.1 Surface and micellar properties

3.1.1 Critical micelle concentration

Data in Table 1 record the cmc values of pure drug and *n*(−)-2-*m*(+) surfactants along with other parameters. The drug cmc comes out to be 36 mM which agrees well with the literature value [38–40]. As is clear from Scheme 1, the hydrophobic part of the drug is short. Hence, its cmc value is very high. As for the heterogemini surfactants compared to conventional ones, their cmc values are remarkably low. This arises mainly due to the presence of two hydrophobic tails which transfer at the same time from aqueous to micellar phase. In agreement with the published values [36], cmc of 0.073 mM

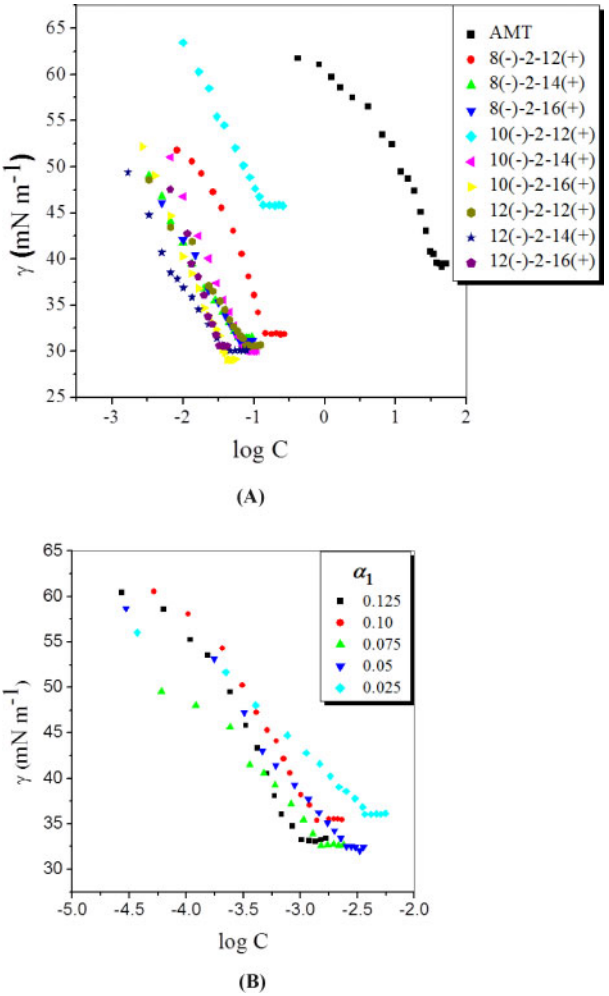


Fig. 1. Variation of surface tension (γ) *vs.* log C of pure amphiphiles (**A**) and 8(−)-2-12(+)-AMT mixed systems (**B**) at different mole fraction (α_1, indicated) of 8(−)-2-12(+).

for 12(−)-2-12(+) is observed (see Table 1). Dodecyltrimethylammonium bromide (DTAB), which is the monomeric analog of the heterogemini 12(−)-2-12(+) and symmetrical cationic gemini ethylenediyl-α,ω-bis(dimethyldodecylammonium bromide) (12-2-12), has cmc value (15.3 mM [41]) more than 15 times higher than that of 12-2-12 (cmc value is 0.83 mM [42]), which is again 11 times higher than that of 12(−)-2-12(+). Mainly two factors affect the process of micellization: effect of tails which favors micelle formation and effect of head groups which opposes it. Although 12-2-12 and 12(−)-2-12(+) both contain two equal chains, their cmc values are more than 10 times different from each other. Due to the opposite charges on the head groups of 12(−)-2-12(+), the effect of head group (which opposes the micellization) decreases.

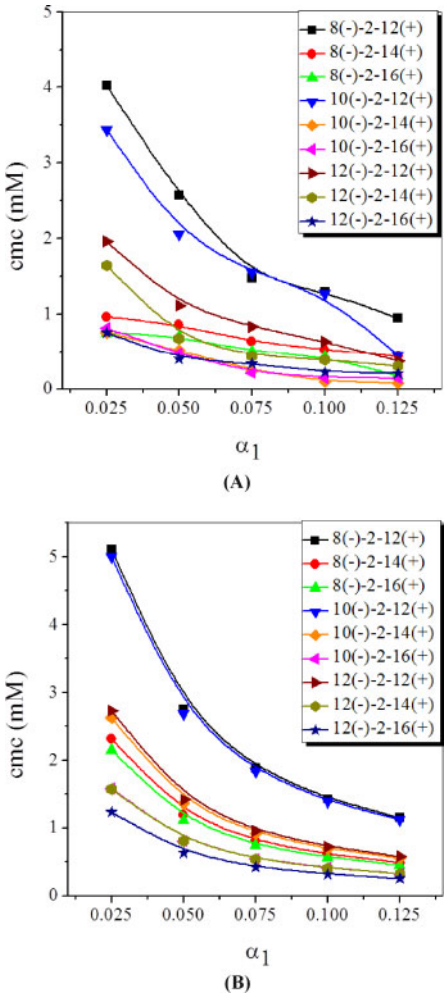


Fig. 2. Variation of experimental (**A**) and ideal cmc (**B**) values with mole fraction (α_1) of gemini surfactants.

This, in turn, decreases the cmc. Among geminis with the same spacer, the trend in cmc in the present case is as: with the increase in total number of carbon atoms in the two tails (*i.e.*, $n+m$), cmc decreases, the two exceptions being 8(−)-2-14(+) and 8(−)-2-16(+). As the number of $-CH_2-$ groups in the tail increases, hydrophobicity of the molecule also increases and the cmc decreases. For the 8(−)-2-14(+) and 8(−)-2-16(+) geminis, the chain length difference makes micellization easier. One shorter chain makes room for the other long chain making tail adjustment in the core much easier and cmc values decrease remarkably.

Figure 2A exhibits the variation of cmc values of the mixed drug-gemini surfactant systems with the stoichiometric mole fraction of gemini surfactant (α_1). The cmc

values decrease sharply as the surfactants are added (at $\alpha_1 = 0.025$, cmc values drop from 36 mM to ≤ 4 mM). The decrease becomes slower at higher α_1 values. All the values of cmc fall in between the values of single components. This indicates that the two components form mixed micelles through attractive interactions. The mixing of two homologous amphiphiles is considered as an ideal mixing. However, amphiphiles with different structures usually mix nonideally. In order to investigate the ideality in mixed systems the pseudophase thermodynamic model proposed by Clint [43] can be used. This model relates the stoichiometric mole fraction of the mixed components (α_i) with their cmc values (cmc_i) as

$$\frac{1}{cmc_{id}} = \frac{\alpha_1}{cmc_1} + \frac{\alpha_2}{cmc_2} \tag{1}$$

where 1 and 2 stand for surfactant and drug, respectively, and cmc_{id} is the cmc at ideal mixing. The difference in experimentally obtained cmc values (cmc) and cmc_{id} gives an idea about the extent of the nonideality in the solution. cmc_{id} values decrease with increase in α_1 (shown in Fig. 2B); the magnitude always remains higher than cmc values. To further analyse the extent of deviation, we have evaluated another parameter, *i.e.*, equivalent deviation which may be defined as the ratio of difference between cmc_{id} and cmc to cmc_{id} values. The magnitude of $\Delta cmc/cmc_{id}$ is the highest for 8(−)-2-14(+) and 8(−)-2-16(+) (Table 2). Due to incompatible and unequal tails these two surfactants make micelles at very low concentration and greatest deviation, as expected, is shown by these two surfactants.

3.1.2 Surface excess concentration

The surface excess concentration under the condition of surface saturation (Γ_{max}) can be used as a measure of surface adsorption. Γ_{max} can be calculated using the well known Gibbs adsorption equation [44].

$$\Gamma_{max} = \frac{1}{2.303nRT}\,(\partial\gamma/\partial \log C) \tag{2}$$

The value of n, the number of ions whose concentration at the interface changes with amphiphile concentration, is taken as 1 for gemini, 2 for drug and 3 for drug-gemini mixtures. The values of pure components and mixed systems are given in Tables 1 and 2. The value of Γ_{max} for AMT is slightly higher than the value found in literature [45]. Although the Γ_{max} values for mixture are always smaller than that of pure components, they increase with increase in gemini surfactant content in the mixture. May be the negative charge on gemini is interacting attractively with the positive one on the drug resulting in compact surface and increase in Γ_{max}.

3.1.3 Minimum area per molecule

The minimum area per molecule (A_{min}) in Å can be calculated by $(N_A\ \Gamma_{max})^{-1} \times 10^{20}$ (where N_A is Avogadro's number). The trend is opposite of Γ_{max}, *i.e.*, with increase in α_1, A_{min} decreases. The values of mixture are always greater than single components. The ideal mixing values, A^{id}, calculated from the relation $A^{id} = X_1^{\sigma} A_1 + X_2^{\sigma} A_2$ (where

Table 2. Surface parameters of zwitterionic gemini surfactant-AMT mixed systems.

Surfactant mole fraction (α_1)	$\Gamma_{max} \pm 1$ 10^7 (mol m^{-2})	A_{min} (Å^2)	A^{id} (Å^2)	Δcmc/ cmc$_{id}$	pC_{20}	β^σ	f_1^σ	f_2^σ	X_1^σ
				8(−)-2-12(+)					
0.125	15	110 ± 7		0.179	3.66				
0.10	14	120 ± 8		0.092	3.61				
0.075	9	181 ± 18	46	0.216	3.80	−4.034	0.860	0.072	0.807
0.05	8	189 ± 19	45	0.065	3.87	−2.863	0.923	0.137	0.833
0.025	7	228 ± 27	44	0.214	3.39	−1.291	0.976	0.382	0.863
				8(−)-2-14(+)					
0.125	16	102 ± 13	69	0.107	4.61	−4.663	0.957	0.022	0.903
0.10	10	156 ± 16		0.145	4.34				
0.075	9	172 ± 19		0.216	4.22				
0.05	8	186 ± 27	70	0.286	4.61	−5.312	0.843	0.027	0.821
0.025	7	229 ± 49	69	0.584	4.29	−2.565	0.974	0.126	0.898
				8(−)-2-16(+)					
0.125	14	113 ± 7	74	0.621	4.22	−15.315	0.054	0.007	0.564
0.10	13	123 ± 8	74	0.232	4.05	−12.089	0.106	0.019	0.569
0.075	9	178 ± 17	74	0.334	4.32	−14.733	0.05	0.011	0.549
0.05	9	179 ± 17	74	0.365	3.43	−7.978	0.213	0.081	0.560
0.025	9	182 ± 18	75	0.650	3.31	−7.559	0.182	0.124	0.525
				10(−)-2-12(+)					
0.125	11	144 ± 11	68	0.600	3.94	−10.182	0.216	0.022	0.612
0.10	11	146 ± 12	65	0.092	3.32	−2.276	0.891	0.255	0.775
0.075	11	157 ± 12	64	0.155	3.03	−1.293	0.949	0.437	0.800
0.05	6	249 ± 32		0.234	3.16				
0.025	6	277 ± 39		0.312	2.65				
				10(−)-2-14(+)					
0.125	15	109 ± 6	59	0.860	4.80	−11.752	0.335	0.003	0.695
0.10	14	114 ± 7	58	0.861	4.75	−10.518	0.400	0.005	0.705
0.075	9	182 ± 18		0.733	3.57				
0.05	13	123 ± 8		0.623	3.68				
0.025	8	209 ± 23	56	0.713	3.87	−3.909	0.851	0.083	0.797
				10(−)-2-16(+)					
0.125	13	130 ± 9	57	0.568	4.60	−5.718	0.912	0.013	0.873
0.10	10	156 ± 13	58	0.635	4.75	−7.063	0.773	0.009	0.809
0.075	10	167 ± 15	58	0.604	4.60	−5.790	0.856	0.017	0.836
0.05	14	116 ± 7		0.411	3.82				
0.025	8	192 ± 19		0.484	3.80				
				12(−)-2-12(+)					
0.125	9	177 ± 17		0.358	4.23				
0.10	8	201 ± 21	77	0.125	4.83	−5.828	0.866	0.016	0.843
0.075	5	310 ± 49	78	0.135	5.31	−10.050	0.449	0.007	0.718
0.05	4	367 ± 66	78	0.216	5.64	−14.268	0.172	0.002	0.649
0.025	4	409 ± 81	78	0.282	5.17	−10.378	0.314	0.010	0.666
				12(−)-2-14(+)					
0.125	10	169 ± 16		0.075	4.41				
0.10	9	181 ± 18		0.057	4.81				
0.075	8	207 ± 23		0.195	4.56				
0.05	7	250 ± 33		0.176	3.95				
0.025	6	285 ± 42		0.089	3.16				
				12(−)-2-16(+)					
0.125	10	169 ± 15	47	0.189	5.04	−8.237	0.686	0.006	0.786
0.10	7	231 ± 28	50	0.289	5.25	−11.841	0.359	0.003	0.706
0.075	6	258 ± 28	47	0.201	4.78	−7.640	0.681	0.010	0.776
0.05	5	314 ± 50	49	0.369	5.31	−9.058	0.496	0.009	0.722
0.025	8	207 ± 23		0.393	3.76				

X_1^σ is the mole fraction of surfactant in mixed monolayer and $X_2^\sigma = 1 - X_1^\sigma$) are also given in Table 2 along with A_{min} values. A^{id} values are always smaller than A_{min} values. This expansion of area after mixed monolayer formation has been observed by other researchers also [46,47]. Although the mixed layer formation is due to attractive interactions, the expansion of area as compared to A^{id} is due to the insertion of gemini surfactant in the monolayer formed by drug molecules. It is also clear from Table 2 that A_{min} values are highest for geminis with longest tail attached to the phosphate head group (*i.e.*, 12(−)-2-*m*(+)).

3.1.4 Surface activity

It is a measure of surface activity of amphiphile in terms of its concentration required to decrease the surface tension of the solvent by 20 mN m^{-1}. The values of pC_{20} (p$C_{20} = -\log C_{20}$), given in Tables 1 and 2, indicate that the drug is less active than the gemini surfactants and the mixtures show intermediate surface activity. This is what we have expected as the cmc results also suggest similar behavior. As the head groups in all the surfactants are same, the values of pC_{20} (or C_{20}) are not very different from each other.

3.1.5 Micellar mole fractions

The results of cmc and cmc_{id} indicate attractive interactions between the components. To further analyze for the ideality/nonideality of interactions, the regular solution theory is used [48]. In this theory type and extent of interactions are characterized by an interaction parameter (β^m) which is also related to the activity coefficients (f_i^m) of the two components. The fundamental equations are:

$$\frac{(X_1^m)^2 \ln[\text{cmc}\,\alpha_1/\text{cmc}_1 X_1^m]}{(1-X_1^m)^2 \ln[\text{cmc}(1-\alpha_1)/\text{cmc}_2(1-X_1^m)]} = 1 \tag{3}$$

and

$$\beta^m = \frac{\ln(\text{cmc}\alpha_1/\text{cmc}_1 X_1^m)}{(1-X_1^m)^2} \tag{4}$$

where X_1^m is the micellar mole fraction of gemini surfactants. Equation (3) is solved iteratively for X_1^m. These values are then used to calculate f_1^m values as

$$f_1^m = \exp\left\{\beta^m (1-X_1^m)^2\right\} \tag{5}$$

$$f_2^m = \exp\left\{\beta^m (X_1^m)^2\right\} \tag{6}$$

Motomura [49] considered mixed micelles as a macroscopic bulk phase and proposed that the energetics of such systems should be evaluated in terms of excess thermodynamic quantities. The composition of mixed micelles is evaluated by the relationship:

$$X_1^{Moto} = \overline{\alpha_1} - \frac{(\overline{\alpha_1}\,\overline{\alpha_2}/\overline{\text{cmc}})\,(\partial\overline{\text{cmc}}/\partial\overline{\alpha_1})_{T,P}}{1 - \dfrac{\delta_d^c \nu_{1,c}\nu_{2,d}}{\nu_{1,c}\nu_2\,\overline{\alpha_1} + \nu_{2,d}\,\nu_1\overline{\alpha_2}}} \tag{7}$$

where

$$\overline{\text{cmc}} = (\nu_1\alpha_1 + \nu_2\alpha_2)\text{cmc} \tag{8}$$

and

$$\overline{\alpha_i} = \frac{\nu_i\alpha_i}{\nu_1\alpha_1 + \nu_2\alpha_2} \quad (i = 1, 2) \tag{9}$$

ν_i is the number of ions dissociated by the i^{th} component, $\nu_i = \nu_1 + \nu_2$, where $\nu_1 = \nu_{1a} + \nu_{1c}$ and $\nu_2 = \nu_{2b} + \nu_{2d}$ (c and d are counterions).

In the above equation, X_1^{Moto} is the micellar mole fraction of surfactant, $\overline{\alpha_i}$ the bulk mole fraction. $\delta_{\text{d}}^{\text{c}}$ is Kronecker delta which is equal to 1 for identical counterions (d = c) and 0 for no or different counterions (d ≠ c).

For zwitterionic gemini-drug systems Eq. (10) reduces to

$$X_1^{\text{Moto}} = \overline{\alpha}_1 - \left(\frac{\overline{\alpha_1}\,\overline{\alpha_2}}{\overline{\text{cmc}}}\right)\left(\frac{\partial\overline{\text{cmc}}}{\partial\overline{\alpha_1}}\right)_{\text{T,P}} \tag{10}$$

Analogous to Rubingh's theory, Rosen proposed a model for mixed monolayers [47] in which, instead of cmc values, concentrations (of pure components and their mixtures required to produce a given surface tension value) are used.

Both X_1^{m} and X_1^{Moto} values for mixed systems increase with increase in α_1. With the increase in mole fraction of zwitterionic surfactant in mixed systems, contribution of surfactants in mixed micelles also increase. It seems that the added surfactant replaces some of the drug molecules from mixed micelles resulting in some reduction in steric hindrance in the micellar core. The values obtained for our systems are given in Table 3. For few systems equation for X_1^{σ} is non-convergent. In most of the cases, X_1^{m} values are slightly higher than X_1^{σ}. As the surfactants contain two hydrophobic tails, they prefer to form micelles and, hence, mixed micelles are rich in gemini surfactants. The drug molecules, on the other hand, due to the rigid hydrophobic moiety, prefer to adsorb on the air/water interface (as it is difficult for them to accommodate in curved areas). The mixed monolayer is thus richer in the drug. With the increase in α_1, in most of the cases, X_1^{m} values increase whereas X_1^{σ} values decrease. With the increase in α_1, more and more surfactant contributes in mixed micelles (*i.e.*, X_1^{m} increases) and its contribution in mixed monolayer (*i.e.*, X_1^{σ}) decreases.

The micellar mole fraction in the ideal mixing state (X_1^{id}) for the respective mixtures can be computed using the equation:

$$X_1^{\text{id}} = \frac{\alpha_1\text{cmc}_2}{(\alpha_1\text{cmc}_2 + \alpha_2\text{cmc}_1)} \tag{11}$$

These values are also given in Table 3. In all the cases, $X_1^{\text{id}} > X_1^{\text{m}}$, *i.e.*, the mixed micelles are poorer in surfactants over their values in ideal mixtures. As the gemini surfactants are more hydrophobic than the drug, ideally the micelles should contain surfactant upto 90–95%. However, mixed micelles contain some drug molecules also, may be because of the negative charge on one of the head groups of zwitterionic surfactants. As the length of the two tails of the surfactants increases the behavior of a few systems

Table 3. Solution properties of gemini surfactant-AMT mixed systems.

Surfactant mole fraction (α_1)	ΔG_{ex}^{m} (kJ mol^{-1})	X_1^m	X_1^{Moto}	X_1^{id}	K_T (K)	ΔH_f° (kJ mol^{-1})	β^m	f_1^m	f_2^m
				8(−)-2-12(+)					
0.125	−0.87	0.849		0.972			−2.716	0.939	0.141
0.10	−0.39	0.892		0.964			−1.616	0.981	0.276
0.075	−0.95	0.813		0.951			−2.488	0.916	0.193
0.05	−0.23	0.878	0.991	0.927			−0.853	0.987	0.518
0.025	−0.72	0.747	0.317	0.862			−1.524	0.907	0.427
				8(−)-2-14(+)					
0.125	−0.61	0.905		0.988			−2.807	0.975	0.100
0.10	−0.78	0.879		0.984			−2.929	0.958	0.104
0.075	−1.15	0.838	0.688	0.979			−3.356	0.915	0.095
0.05	−1.43	0.798	0.342	0.968			−3.534	0.865	0.105
0.025	−0.3	0.681	0.151	0.937			−5.475	0.573	0.079
				8(−)-2-16(+)					
0.125	−0.42	0.719		0.989	289	77.15	−8.243	0.521	0.014
0.10	−1.32	0.838		0.986	288.5	35.36	−3.877	0.903	0.065
0.075	−1.85	0.792	0.876	0.980	288	40.76	−4.467	0.824	0.060
0.05	−1.90	0.771	0.415	0.971	286.5	32.89	−4.273	0.799	0.079
0.025	−3.56	0.667	0.192	0.942			−6.359	0.494	0.059
				10(−)-2-12(+)					
0.125	−3.52	0.703		0.972			−6.697	0.554	0.036
0.10	−0.40	0.893		0.965			−1.666	0.981	0.265
0.075	−0.64	0.844		0.953			−1.940	0.954	0.251
0.05	−0.94	0.787	0.647	0.929			−2.222	0.904	0.252
0.025	−1.14	0.714	0.196	0.865			−2.227	0.833	0.321
				10(−)-2-14(+)					
0.125	−7.17	0.648		0.986			−12.473	0.213	0.005
0.10	−7.04	0.643		0.982			−12.168	0.212	0.006
0.075	−4.82	0.673		0.976			−8.701	0.394	0.019
0.05	−3.59	0.69	0.853	0.964			−6.669	0.527	0.041
0.025	−4.02	0.644	0.291	0.929			−6.965	0.413	0.055
				10(−)-2-16(+)					
0.125	−3.89	0.739		0.992	285.5	23.49	−7.999	0.58	0.012
0.10	−4.35	0.716		0.989	285	24.54	−8.498	0.503	0.013
0.075	−3.91	0.718		0.986	284	21.94	−7.672	0.543	0.019
0.05	−2.31	0.764	0.930	0.978	283	16.22	−5.078	0.753	0.051
0.025	−2.48	0.722	0.273	0.957			−4.916	0.684	0.077
				12(−)-2-12(+)					
0.125	−2.13	0.791		0.985			−5.108	0.800	0.041
0.10	−0.69	0.889		0.982			−2.771	0.966	0.112
0.075	−0.64	0.875		0.975			−2.321	0.964	0.169
0.05	−1.00	0.822	0.430	0.962			−2.708	0.918	0.160
0.025	−1.16	0.766	0.125	0.926			−2.576	0.868	0.220
				12(−)-2-14(+)					
0.125	−0.46	0.93		0.992			−2.834	0.986	0.086
0.10	−0.33	0.941		0.989			−2.375	0.992	0.122
0.075	−1.10	0.855	0.783	0.986			−3.528	0.928	0.076
0.05	−0.92	0.857	0.347	0.978			−2.974	0.941	0.112
0.025	−0.36	0.888	0.086	0.957			−1.452	0.982	0.318
				12(−)-2-16(+)					
0.125	−1.28	0.869		0.993	287	9.07	−4.480	0.925	0.034
0.10	−1.86	0.824		0.992	286	11.43	−5.092	0.854	0.031
0.075	−1.25	0.858	0.621	0.989	285	8.32	−4.075	0.921	0.049
0.05	−2.12	0.783	0.351	0.983	284.5	12.77	−4.962	0.791	0.047
0.025	−2.02	0.758	0.097	0.966			−4.376	0.773	0.081

changes: X_1^m decreases which may be due to the overcrowding of chains in the micellar core.

3.1.6 Interaction parameters

The β parameters measure the interaction between two amphiphiles after mixing relative to the self-interaction of those amphiphiles before mixing under the same conditions. Negative β values indicate synergism while positive values mean antagonism. β values close to zero mean almost ideal mixing. In our systems both the interaction parameters for mixed micelles (β^m) and mixed monolayers (β^σ) are negative indicating synergism in the systems. These values are shown in Tables 2 and 3. The values (both β^m and β^σ) should, however, remain constant for a given amphiphile pair. The nonconstancy of β with composition have been reported previously also [50]. β^σ is greater than β^m for the systems in which either the tails are small or the difference in length of two tails is small.

3.1.7 Activity coefficients

The values of activity coefficients are given in Tables 2 and 3. These values are always less than unity indicating the mixing to be nonideal. Both f_1^m and f_1^σ are much greater than f_2^m and f_2^σ and are close to unity which means that surfactants in the mixed systems are near to their standard state.

3.2 Krafft temperature behaviour

Tables 1 and 3 contain the values of K_T for pure surfactant and some mixed systems. We could not obtain the K_T value for some pure as well as mixed systems as they were below 0 °C. With the increase in mole fraction of surfactant K_T increases. As the total number of carbon atom in the hydrophobic tail increases, K_T increases, but for the same number of carbon atoms, the greater the difference in tail lengths the higher is the K_T value. These values were used to evaluate the heat of fusion of solid surfactant hydrate to liquid hydrates (ΔH_f°) as [51]

$$\Delta H_f^\circ = -R \ln X_1^m \left[\frac{TT_1^0}{T_1^0 - T} \right] \tag{12}$$

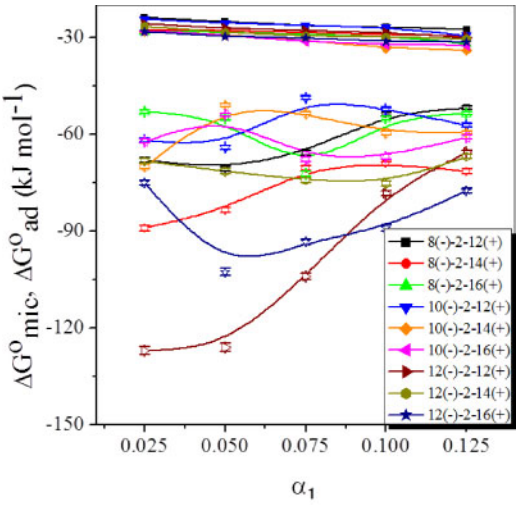
where T_1^0 and T are the Krafft temperatures of pure surfactant and its mixtures, respectively. The ΔH_f° values show large variation with increasing α_1 in 8(−)-2-16(+) systems, again confirming strong synergism in the mixed micelles (Table 3).

3.3 Thermodynamics of mixing

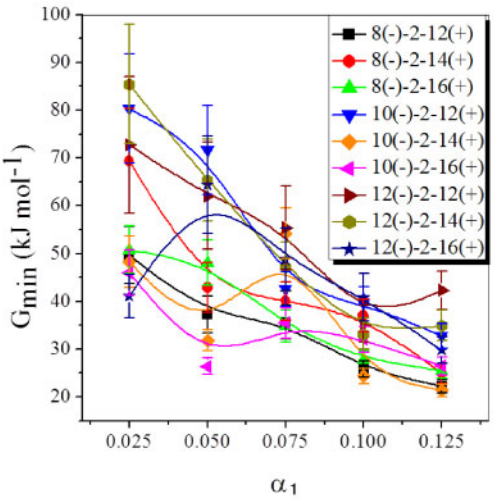
3.3.1 Standard Gibbs energy of micellization

The standard Gibbs energy of micellization, ΔG_{mic}°, was calculated using the well known equation

$$\Delta G_{mic}^\circ = RT \ln X_{cmc} \tag{13}$$



(A)



(B)

Fig. 3. Plots of ΔG°_{ad} (filled symbols) and ΔG°_{mic} (unfilled symbols) *vs.* mole fraction (α_1) of gemini surfactants (**A**) and G_{min} *vs.* mole fraction (α_1) of gemini surfactants (**B**).

where X_{cmc} is the mixture cmc in the mole fraction units. The values are shown in Fig. 3A. For pure components, these values are given in Table 1. The values are all negative confirming that the process of micellization is spontaneous. The magnitude of ΔG°_{mic} values varies with the type and mole fraction of the gemini surfactants. The magnitude is smaller for drug in comparison to that of gemini surfactants. Due to its short hydrophobic portion, the drug is less hydrophobic than the gemini surfactants.

The values for mixtures are intermediate to those of single components. Presence of a gemini surfactant makes the process of micellization more spontaneous than for pure drug.

3.3.2 Standard Gibbs energy of adsorption

The standard Gibbs energy of adsorption is given by [52]

$$\Delta G^{\circ}_{ad} = \Delta G^{\circ}_{mic} - \frac{\pi_{cmc}}{\Gamma_{max}} \tag{14}$$

where π_{cmc} is the surface pressure at the cmc. These values are shown in Fig. 3A which are also negative indicating the process of adsorption to be spontaneous. Moreover, the absolute values of ΔG°_{ad} are greater than that of ΔG°_{mic}. This means that the hydrophobicity of the molecules leads them towards the air/solution interface and after surface adsorption, micellization takes place.

3.3.3 Minimum free energy of adsorption

The values of molar free energy at the maximum adsorption attained at cmc, G_{min}, are calculated according to Eq. (15) [53]

$$G_{min} = \gamma_{cmc} A_{min} N_A \tag{15}$$

In other words, G_{min} is the minimum free energy of the given surface with fully adsorbed amphiphile molecules. The smaller is the value of G_{min}, the more stable surface forms. Hence, as expected, the values of G_{min} for surfactants are smaller than that of drug and for mixtures the values decrease with the increase in gemini surfactant content in the solution (Fig. 3B).

3.3.4 Excess free energy of mixing

Excess free energy of mixing, ΔG^{m}_{ex}, was calculated from the values of f^{m}_{1} and f^{m}_{2} by

$$\Delta G^{m}_{ex} = RT[X^{m}_{1} \ln f^{m}_{1} + (1 - X^{m}_{1}) \ln f^{m}_{2}] \tag{16}$$

The values are all negative (Table 3) suggesting mixed micelles to be relatively more stable than the micelles of individual components. Except in one or two cases, the absolute value decreases with the increase in α_1. Thus, increasing concentration of gemini surfactants increases the stability of mixed micelles.

3.4 Stability of mixed micelles

Figure 4 depicts the UV spectra of pure drug as well as its mixtures with zwitterionic surfactants. The spectra recorded at different time intervals (just after preparation and after 3, 7 and 15 days) show absorption maxima at around 210 to 260 nm. There is hardly any change in spectra even after 15 days implying that the mixed micelles are quite stable for the period.

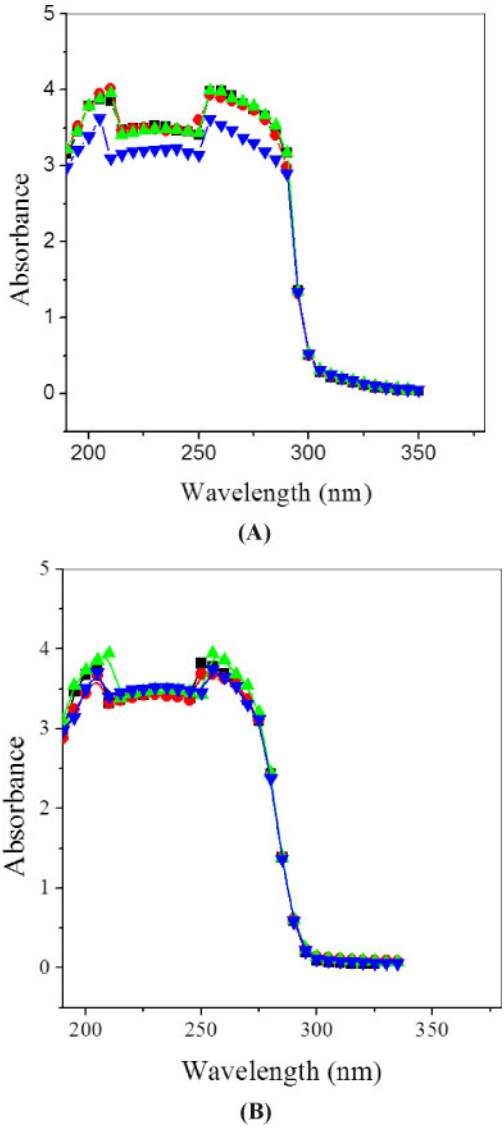


Fig. 4. UV-vis spectra of pure AMT (**A**) and 8(−)-2-12(+)-AMT mixed systems (**B**) at $\alpha_1 = 0.075$, just after preparation (■), 3 (●), 7 (▲) and 15 (▼) days.

4. Conclusions

We have investigated the interactions among an amphiphilic drug amitriptyline hydrochloride (AMT) and nine zwitterionic heterogemini surfactants which have a phosphodiester (anionic) and a quaternary ammonium (cationic) polar heads (denoted as $n(-)$-2-$m(+)$, $n = 8$, 10, 12 and $m = 12$, 14, 16). To the best of our knowledge, this

is the first report dealing with detailed physicochemical investigations on mixed micellization involving AMT and zwitterionic heterogemini surfactants. The mixed systems have cmc values lower than the individual components and ideal cmc values. The cmc values and interaction parameters (β^{m}) suggest strong attractive interactions in the mixed micelles. The results get support from Krafft temperature measurements as ΔH_{f}° values (calculated from K_{T} values) show variations. The surface excess (Γ_{max}) increases and minimum area per head group (A_{min}) decreases with increasing stoichiometric mole fraction (α_1) of the surfactant. The values are closer to that of the pure drug. Application of the Rubingh's, Motomura's and Rosen's theoretical approaches also shows synergism in all the drug-surfactant systems. Micellar mole fraction (X_1^{m}) values indicate larger contribution from surfactants. Micellar mole fraction (X_1^{Moto}) evaluated from Motomura's model, are in line with that obtained by Rubingh's model. Mole fraction values at mixed interface (X_1^{σ}) are slightly smaller than X_1^{m} which means that the drug participates more in monolayer formation than in micelle formation. Rigid ring system of the drug makes easier for it to adjust at the planar air/solution interface. The UV-spectra of pure drug as well as its mixtures show maxima in absorption at 210 to 260 nm in all systems that remain constant upto 15 days. This suggests that the mixed micelles remain stable after long time.

Acknowledgement

Sahar Noori is thankful to MANF for financial support and Kabir-ud-Din thanks the UGC for awarding BSR-Faculty Fellowship. Andleeb Z. Naqvi acknowledges financial assistance under DST's SERC Scheme (SR/FT/CS-82/2011).

References

1. U. Gupta, H. B. Agashe, A. Asthana, and N. K. Jain, Biomacromolecules **7** (2006) 649.
2. N. Blagden, M. de Matas, P. T. Gavan, and P. York, Adv. Drug Deliv. Rev. **59** (2007) 617.
3. M. E. Brewster and T. Loftsson, Adv. Drug Deliv. Rev. **59** (2007) 645.
4. V. J. Stella and K. W. Nti-Addae, Adv. Drug Deliv. Rev. **59** (2007) 603.
5. A. Avdeef, Adv. Drug Deliv. Rev. **59** (2007) 568.
6. S. Agharkar, S. Lindenbaum, and T. Higuchi, J. Pharm. Sci. **5** (1976) 161.
7. A. M. Saleh, S. A. Khalil, and L. K. El-Khordagui, Int. J. Pharm. **5** (1980) 161.
8. A. Sparreboom, L. van Zuylen, E. Brouwer, W. J. Loos, P. de Bruijin, B. Gelderblom, M. Pillay, K. Nooter, G. Stoter, and J. Verweij, Cancer Res. **59** (1999) 1454.
9. M. Kreilgaard, Adv. Drug Deliv. Rev. **54** (2002) S77.
10. T. Loftsson and M. E. Brewster, J. Pharm. Sci. **93** (2004) 1091.
11. R. A. Rajewski and A. J. Stella, J. Pharm. Sci. **85** (1996) 1142.
12. R. G. Strickley, Pharm. Res. **21** (2004) 201.
13. S. H. Yalkowsky, J. F. Krzyzaniak, and G. H. Ward, J. Pharm. Sci. **87** (1998) 787.
14. C. O. Rangel-Yagui, H. W. L. Hsu, A. Pessoa Jr., and L. C. Tavares, Braz. J. Pharm. Sci. **41** (2005) 237.
15. M. J. Lawrence, Chem. Soc. Rev. **23** (1994) 417.
16. M. Cornelis, C. Dupont, and J. Wepierre, Toxic. in Vitro **6** (1992) 119.
17. M. S. Huttel, A. S. Olesen, and E. Stoffersen, Br. J. Anaesth. **52** (1980) 77.
18. K. Woodburn and D. Kessel, J. Photochem. Photobiol. B **22** (1994) 197.
19. A. J. Windebank, M. D. Blexrud, and P. C. Degroen, J. Pharmacol. Exp. Ther. **268** (1994) 1051.
20. M. Dreja, S. Gramberg, and B. Tieke, Chem. Commun. (1998) 1371.

21. C. Hu, R. Li, H. Yang, and J. Wang, J. Colloid Interface Sci. **356** (2011) 605.
22. D. Shukla and V. K. Tayagi, J. Oleo Sci. **55** (2006) 381.
23. C. Bombelli, G. Caracciolo, P. D. Profio, M. Diociaiuti, P. Luciani, G. Mancini, C. Mazzuca, M. Marra, A. Molinari, D. Monti, L. Toccacieli, and M. Venanzi, J. Med. Chem. **48** (2005) 4882.
24. P. Camilleri, A. Kermer, A. J. Edwards, K. H. Jannings, O. Jenkins, I. Marshall, C. McGregor, W. Neville, S. Q. Rice, R. J. Smith, M. J. Wilkinson, and A. J. Kirby, Chem. Commun. (2000) 1253.
25. M. Pavlikova, I. Lacko, F. Devinsky, and D. Mlynarcik, Collect. Czech. Chem. Commun. **60** (1995) 1213.
26. F. Wang and S. Hua, Colloids Surf. B. **63** (2008) 262.
27. R. Zana, Adv. Colloid Interface Sci. **97** (2002) 205.
28. R. Oda, I. Huc and S. J. Candau, Chem. Commun. (1997) 2105.
29. R. Oda, I. Huc, J. C. Homo, B. Heinrich, M. Schutz, and S. J. Candau, Langmuir **15** (1999) 2384.
30. A. V. Peresypkin and F. M. Menger, Org. Lett. **1** (1999) 1347.
31. E. Alami and K. Holmberg, J. Colloid Interface Sci. **239** (2001) 230.
32. E. Alami, K. Holmberg, and J. Eastoe, J. Colloid Interface Sci. **247** (2002) 447.
33. R.G. Laughlin, Langmuir **7** (1991) 842.
34. V. Seredyuk, E. Alami, M. Nyden, K. Holmberg, A. V. Peresypkin, and F. M. Menger, Langmuir **17** (2001) 5160.
35. V. Seredyuk, E. Alami, M. Nyden, K. Holmberg, A. V. Peresypkin, and F. M. Menger, Colloids Surf. A **203** (2002) 245.
36. Y. Sun, Y. Feng, H. Dong, Z. Chen, and L. Han, Cent. Europ. J. Chem. 5 (2007) 620.
37. M. Lukac, L. Timko, M. Mrva, F. Ondriska, J. Karelovska, J. Valentove, and I. Lacko, Heteroatom Chem. **21** (2010) 203.
38. M. S. Alam and A. B. Mandal, J. Mol. Liq. **168** (2012) 75.
39. Kabir-ud-Din, M. A. Rub, and A. Z. Naqvi, J. Phys. Chem. B,**114** (2010) 6354.
40. Kabir-ud-Din, M. A. Rub, and A. Z. Naqvi, Colloids Surf. B: Biointerfaces **92** (2012) 16.
41. A. C. F. Ribeiro, V. M. M. Lobo, A. J. M. Valente, E. F. G. Azevedo, M. da G. Miguel, and H. D. Burrows, Colloid Polym. Sci **283** (2004) 277.
42. M. Nilsson, C. C. Lago, A. J. M. Valente, and O. Soderman, Langmuir **22** (2006) 8663.
43. J. H. Clint, J. Chem. Soc. Faraday Trans. **171** (1975) 1327.
44. D. K. Chattoraj and K. S. Birdi, *Adsorption and the Gibbs Surface Excess*, Plenum Press, New York, (1984).
45. Kabir-ud-Din, A. Z. Naqvi, and A. B. Khan, Tens. Surf. Det. **47** (2010) 318.
46. H. Matsubara, S. Muroi, M. Kameda, I. Ikeda, A. Ohta, and M. Aratona, Langmuir **17** (2001) 7752.
47. Q. Zhou and M. J. Rosen, Langmuir **19** (2003) 4555.
48. D. N. Rubingh, Mixed micelles solutions, in: *Solution Chemistry of Surfactants*. Vol. 1, K. L. Mittal, (Ed.), Plenum press, New York, (1979), p. 337.
49. (a) K. Motomura, M. Yamanaka, and M. Aratono, Colloid Polym. Sci. **262** (1984**)** 948; (b) M. Aratono, M. Villeneuve, T. Takiue, N. Ikeda, and H. Iyota, J. Colloid Interface Sci. **200** (1998) 161.
50. S. Ghosh, D. Khatua, and J. Dey, Langmuir **27** (2011) 5184.
51. M. S. Bakshi and K. Singh, J. Colloid Interface Sci. **287** (2005) 288.
52. M. J. Rosen and S. Aronson, Colloids Surf. **3** (1981) 201.
53. G. Sugihara, A. M. Miyazono, S. Nagadome, T. Oida, Y. Hayashi, and J. S. Ko, J. Oleo Sci. **52** (2001) 449.