Journal of Saudi Chemical Society (2015) **19**, 292–300

King Saud University

Journal of Saudi Chemical Society

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ORIGINAL ARTICLE

Influence of additives (inorganic/organic) on the clouding behavior of amphiphilic drug solutions: Some thermodynamic studies

Malik Abdul Rub [a,*], Abdulrahman O. Al-Youbi [a,b], Abdullah M. Asiri [a,b], Anish Khan [a], Aftab Aslam Parwaz Khan [a], Naved Azum [a], Kabir-ud-Din [c]

[a] *Center of Excellence for Advanced Materials Research, King Abdulaziz University, Jeddah 21589, Saudi Arabia*
[b] *Chemistry Department, Faculty of Science, King Abdulaziz University, Jeddah 21589, Saudi Arabia*
[c] *Department of Chemistry, Aligarh Muslim University, Aligarh 202 002, India*

Received 31 December 2011; accepted 3 April 2012
Available online 24 April 2012

KEYWORDS

Amphiphilic antidepressant drug;
Amitriptyline hydrochloride;
Cloud point;
Inorganic salts;
Amino acids

Abstract Herein we provide a detailed result about the effect of various additives, viz. inorganic salts, quaternary ammonium bromides (QABs) and amino acids on clouding behavior of amphiphilic drug amitriptyline hydrochloride (AMT). The continuous increase in the cloud point (*CP*) of drug by increase in inorganic salt concentration and the magnitude of increases rely upon the position of the salts in Hofmeister series and hydrated radii. The QABs also influence continuous increase in the *CP*, which is illustrated in terms of the alkyl chain length of peculiar QAB. The effect of amino acids on *CP* of the drug solution is dependent upon the characteristics (acidic, basic, polar or nonpolar) of particular amino acids. The overall behavior of additives has been analyzed and discussed on the basis of electrostatic repulsion or interaction, micellar growth, and mixed micelle formation between the ingredients. In addition to this, thermodynamic parameters are also evaluated.

1. Introduction

Like surfactant many amphiphilic drug molecules (analgesics, phenothiazines, tranquillizers, peptides, tricyclic antidepressants, antibiotics, etc.) also self-associate in aqueous solution to form small aggregates so called micelles (Taboada et al., 1999; Schreier et al., 2000; Krishnan et al., 2003; Mandal et al., 2010; Tiwary et al., 2011; James and Mandal, 2011; James et al., 2011). Micelle formation can be regarded as a choice mechanism to adsorption at the interfaces for dismissal of hydrophobic groups from contact with water, thereby diminishing the free energy of the systems. It is well known that amphiphilic molecules act differently when present in

* Corresponding author. Tel.: +966 563671946.
E-mail addresses: malikrub@gmail.com, malik_rub2000@yahoo.com (M.A. Rub).
Peer review under responsibility of King Saud University.

ELSEVIER Production and hosting by Elsevier

http://dx.doi.org/10.1016/j.jscs.2012.04.005
1319-6103

micelles than as free monomers in solution. As amphiphilic drug molecules bear an ionic or nonionic polar headgroup and a hydrophobic portion, their self-association powerfully depends on a number of parameters, involving (a) structure of amphiphile (b) presence of salt, cosolute, etc. and (d) temperature (Rosen, 2004). The concept of micelle solutions originates from their ability of becoming as functional molecular assemblies for use in many fields in pure and applied science. They can be used as template for various biochemical and pharmacological schemes and can solubilize water-insoluble materials (including particular medicines and drugs) in their hydrophobic cores (Barzykin and Tachiya, 1996). Although aggregation of the drugs could act as their own carriers and it has been also claimed that the drug vesicle formation is able to be carried out (Vaizoglu and Speiser, 1986), even though, most drugs are not lipophilic to sufficient degree to form vesicles so that they require drug delivery systems to implement them into the body. Therefore, over the years, micelles have been of interest to pharmacological scientists either as drug delivery or as targeting systems (Lawrence and Rees, 2000).

Nonionic surfactants are thought to be true to owe their solubility in water through hydrogen bonding; on heating, these weak hydrogen bonds break and by means of that turn down the surfactant solubility in water. Hence, cloud point (*CP*) phenomenon is usually observed in aqueous nonionic surfactant solutions when the temperature of the surfactant solution is elevated to a particular value (Al-Ghamdi and Nasr-El-Din, 1997; Gu and Galera-Gomez, 1999; Schott, 2001; Shigeto et al., 2001). The phase separation occurs within a temperature range that is moderately constant for surfactant concentrations within a narrow range (Nakagawa and Shinoda, 1963). The phases that come into view are composed of an almost micelle-free dilute solution of the nonionic surfactant and a surfactant-rich micellar phase. The phase separation is reversible and, on cooling, the two phases merge to form a clear solution. In what way, for ionic surfactants, occurring of the clouding phenomenon is unusual because electrostatic repulsions among charged micelles impede occurrence of phase separation. In these systems, the happening of clouding (under unique situations) is illustrated, in terms of charge neutralization and raised hydrophobic interactions (Kumar et al., 2000, 2002, 2003).

Clouding happens in many amphiphilic drug solutions too. As additives change solution properties, their presence have an affinity to effect the clouding. Many workers have deliberated the effect of various additives on the cloud point of amphiphilic drugs recently (Kim and Shah, 2002, 2003; Alam et al., 2010a,b,c,d, 2011; Kabir-ud-Din et al., 2010a,b; Naqvi et al., 2011). In the present study, amitriptyline hydrochloride (AMT – a tricyclic antidepressant) was considered as a model drug. It contains a tricyclic ring and alkyl amine side chain (Fig. 1). The tricyclic part of AMT molecule is hydrophobic and alkyl amine part is hydrophilic. The pharmacological undertaking of these drugs comes into view at low concentrations where aggregation is insignificant (Attwood, 1995). However, the agglomeration of drug can occur at particular site of organism after long period of administration, giving rise to making of aggregates that are lacking ability to pass by way of membranes; decreasing transport rate and, as a result, leading to hostile effect on health. Thus, the study of physico-chemical properties of an amphiphilic drug is significant from physical, chemical, biological and pharmaceutical outlook for their implication. AMT feel pain from distinct drawbacks such as anticholinergic, cardiovascular and antiarrhythmic side effects. These side effects may be lessened if the drug is properly targeted to the organism. Here, we give an account the effect of various additives like inorganic salts, quaternary ammonium salts, and amino acids, on *CP* behavior of AMT solution prepared in 2.5 mM CTAB + 10 mM sodium phosphate (SP) buffer solution (pH = 6.7).

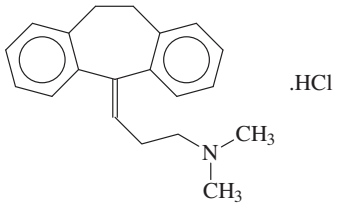

Figure 1 Molecular structure of amitriptyline hydrochloride (AMT).

2. Materials and methods

AMT (⩾98%, CAS Registry No. 113-52-0, Sigma, USA), lithium chloride, LiCl (98%, Loba Chemie, India), lithium bromide, LiBr (99.4%, Riedel–deHaen, Germany), sodium fluoride, NaF (97%, BDH, England), sodium chloride, NaCl (99.9%, BDH, England), potassium chloride, KCl (99.8%, BDH, India), sodium bromide, NaBr (99.8%, Loba Chemie, India), potassium bromide, KBr (99%, Merck, India), ammonium chloride, NH_4Cl (99%, Merck, India), ammonium bromide, NH_4Br (99%, Loba Chemie, India), tetramethylammonium bromide, TMeAB (⩾97%), tetraethylammonium bromide, TEtAB (⩾98%), tetra-*n*-propylammonium bromide, TPrAB (⩾98%), tetra-*n*-butylammonium bromide, TBuAB (⩾99%), tetra-*n*-pentylammonium bromide, TPeAB (⩾99%), (all Fluka, Switzerland), aspartic acid (⩾99.0%), glutamic acid (⩾99.0%), glycine (⩾99.5%), phenylalanine (⩾99.0%), alanine (⩾99.0%), (all SISCO, India), leucine (⩾99.9%, E. Merck, Germany), asparagine (⩾99.0%, Reanal, Hungary), threonine (⩾98.5%, BDH, England), lysine monohydrochloride (⩾99.0%, s.d. fine, India), arginine monohydrochloride (99.0%, Loba Chemie, India), were used as received without any further purifications. Trisodium phosphate dodecahydrate (TSP) and sodium dihydrogen phosphate monohydrate (SDP) were of reagent grade procured from Merck, India.

All the solutions were prepared in double-distilled water with specific conductivity: $(1–2) \times 10^{-6}$ S cm^{-1} at 30 °C. Combination of TSP and SDP were used to fix the pH of the sample solutions (Britton, 1942). The drug solutions were prepared in cetyltrimethylammonium bromide (CTAB) and sodium phosphate (SP) buffer solutions (pH = 6.7).

For determining the *CP*, the sample solution was taken in a Pyrex glass tube, which was then stoppered and put in a controlled heating set-up. The temperature was elevated slowly, at the rate of 0.5 °C/min near the *CP*, and the beginning of surprising clouding in the solution was noted. The temperature was subsequently lowered until the sample became clear again. The temperature was cycled (twice) in this way to get the mean *CP*. Uncertainty in *CP* measurements was ±0.5 °C. Unless referred to under other circumstances, the pH and drug

concentration of the solutions were fixed at 6.7 and 50 mM, respectively. The pH measurements were done with an ELICO pH meter (model LI 120, India) used in uniting with combination electrode CL 51 B (ELICO).

3. Results and discussion

The critical micelle concentration (cmc) of aqueous AMT solution determined by conductivity measurement was found to be 32.60 mM at 25 °C which is in good agreement with literature value (Schreier et al., 2000). The cloud point (*CP*) of pure AMT (50 mM) in 10 mM SP buffer (pH = 6.7) solution was found to be 24 °C (Alam et al., 2006), which increased to 35 °C on supplement of 2.5 mM CTAB. The pK_a value of AMT in water is 9.4 (Katzung, 2004). CTAB was present in all the solutions as surfactants are most frequently used as carriers. Drug and CTAB concentration used in the present study are above their cmc, therefore, mixed micelles (drug + CTAB) are formed in the system (Kabir-ud-Din et al., 2010a,b; Tiwary et al., 2011). Monomers of the components (surfactant and drug) are positively charged, the mixed micelles are united due to the electrostatic head-head repulsions. Water molecules cave into the micellar head group region and the *CP* is therefore higher (comparative to the case of pure micelles restraining only drug monomers). An enormous number of additives of desperate nature and properties were attempted at different concentrations to examine the stability or phase separation (clouding) of AMT by variation of temperature.

3.1. Effect of pH

It is confirmed from Fig. 2 that *CP* of the AMT solutions was found highly able to perceive sensation to the pH of drug solution. At different fixed pHs, AMT solutions with NaCl/NaBr addition show that on increasing pH, the *CP* decreases, at all salt concentrations. As discussed before, the hydrophobic portion of AMT molecule (Fig. 1) is tricyclic and the *t*-amine part is hydrophilic. Protonation of hydrophilic part of the AMT is highly relying upon the solution pH: at low pH, the *t*-amine becomes cationic (i.e., protonated) while, at high pH, it becomes neutral (i.e., deprotonated). Increasing pH of solution increases the number of un-ionized (deprotonated) AMT molecules in micelles and, therefore, reduces the repulsion between the head groups and brings about inter-micellar compactness directing to a decrease in *CP* and an increase in micellar aggregation (Kim and Shah, 2002; Mata et al., 2004). The increase in amount of NaCl/NaBr would, hence, cause the micellar size to increase successively (Evans and Wennerstrom, 1999) with the continuous increase in *CP*.

3.2. Effect of electrolytes

Fig. 3 shows the *CP* variation of drug solutions prepared in 10 mM SP buffer keeping CTAB surfactant fixed at 2.5 mM (pH = 6.7), as a function of the concentration of added inorganic salts. The increase in *CP* follows the manner NaF < NaCl < NaBr. The halide ions interact electrostatically with the positively charged drug micelles. The degree of binding of halide ions to drug micelles influences size and shape of micelles (Attwood and Florence, 1983; Rosen, 2004). Traditionally, the efficiency of inorganic anions into influencing micellization has been ascribed to their influence on the structure of water through their location in the lyotropic (Hofmeister) series: $F^- < Cl^- < Br^-$. The F^- ion is cosmotrope (small ions with high charge density considered as "water making structure", thus with a large hydration shell), while Cl^- and Br^- on the right of the lyotropic series are named chaotropes (large ions with small charge density and high polarizability, considered as "water breaking structure", thus having a thin hydration layer ($Cl^- < Br^-$)). Models developed by Collins (Collins, 1997) describe ion pairing as a critical parameter influencing the micellar properties. Specifically, it is suggested that chaotropes form ion pairs only with other chaotropes,

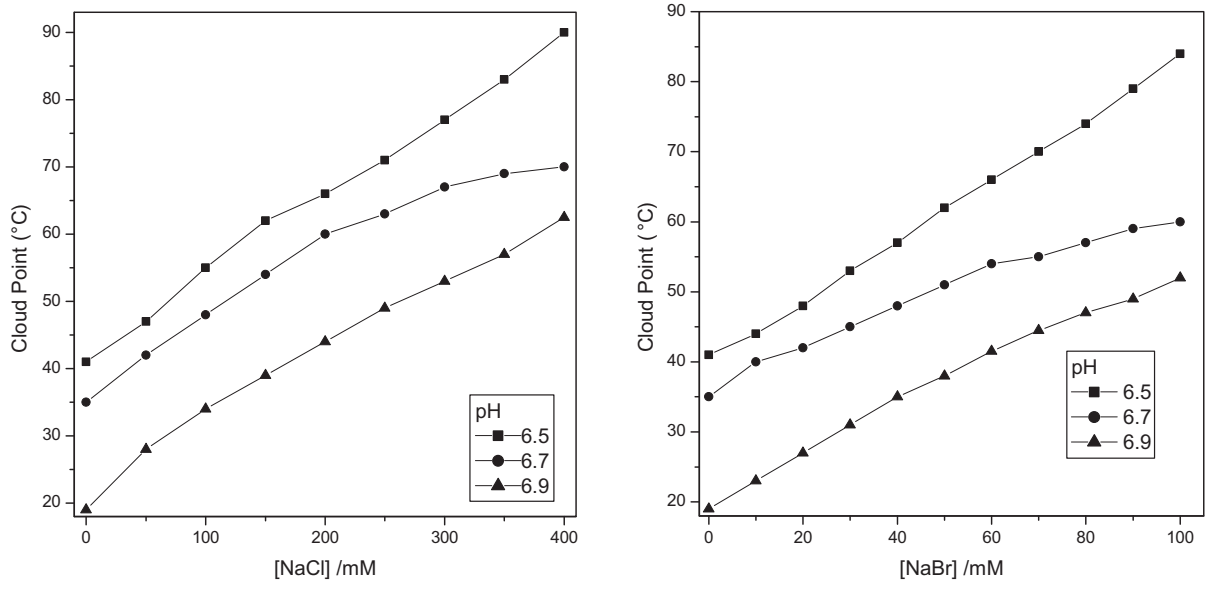

Figure 2 Effect of NaCl and NaBr concentration on the *CP* of 50 mM AMT solutions, prepared in 2.5 mM CTAB + 10 mM SP buffer of different pH values.

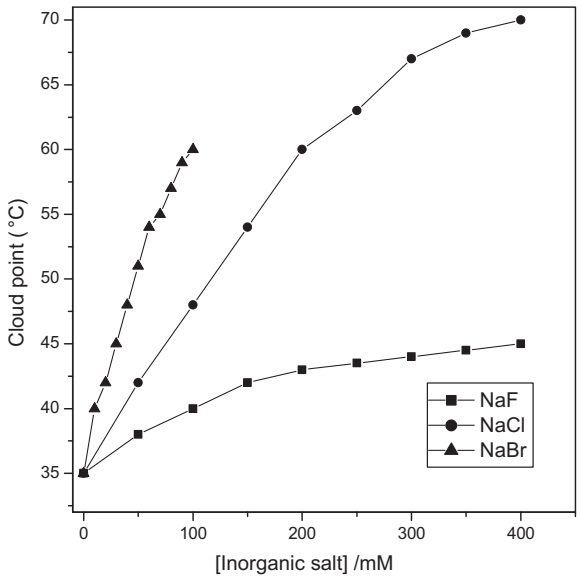

Figure 3 Effect of addition of inorganic salts on the cloud point of 50 mM AMT prepared in 2.5 mM CTAB + 10 mM SP buffer (pH = 6.7).

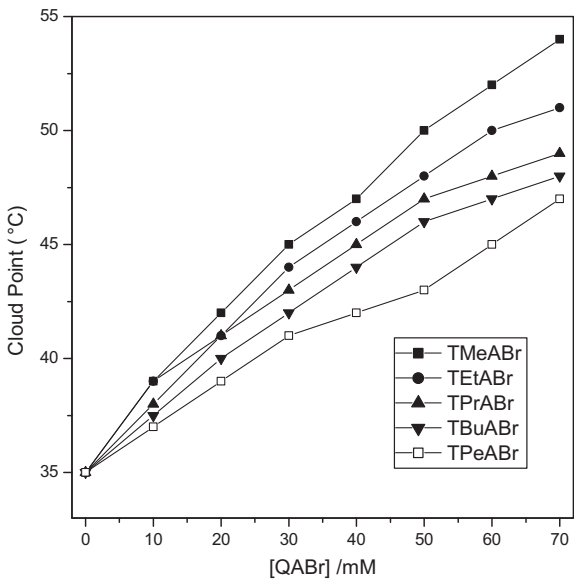

Figure 5 Effect of addition of quaternary ammonium salts on the cloud point of 50 mM AMT prepared in 2.5 mM CTAB + 10 mM SP buffer (pH = 6.7).

while cosmotropes would pair only with other cosmotropes, always with a preference for a counterion with a matching absolute free energy of hydration (Collins, 1999). Hence bromide ion binds powerfully to the micelles and increases the size of micelles as compared to chloride and fluoride ions because it has a large size and small hydrated radius (3.30 Å). In case of fluoride ion, the binding to cationic head group is weak, because it has large hydrated radius (3.52 Å) and small size and, therefore, with NaF addition micelle size/shape changes slowly and *CP* increase is slow. The size of chloride ion (hydrated radius 3.32 Å) is in intermediate to fluoride ion and bromide ion; therefore *CP* increase is intermediate to both ions.

The similar fashion of increasing the *CP* was found with MBr/MCl (M = Li, Na, K or NH_4) addition which are shown in Fig. 4. It is observed that the order of impressiveness of *CP* increase is $Li^+ < Na^+ < K^+ < NH_4^+$. According to their hydrated radii and salting-out strength, ions are classified into Hofmeister series (Hofmeister, 1888). Salts which are on left hand side of the series are water structure-makers and therefore decrease the solute solubility while salts on right hand side are considered to be water-structure breakers so they increase the solute solubility in water (Franks, 1978). Another mechanism of Hofmeister series considers the salting-in and salting-out phenomena directly to adsorption/desorption of ions to the

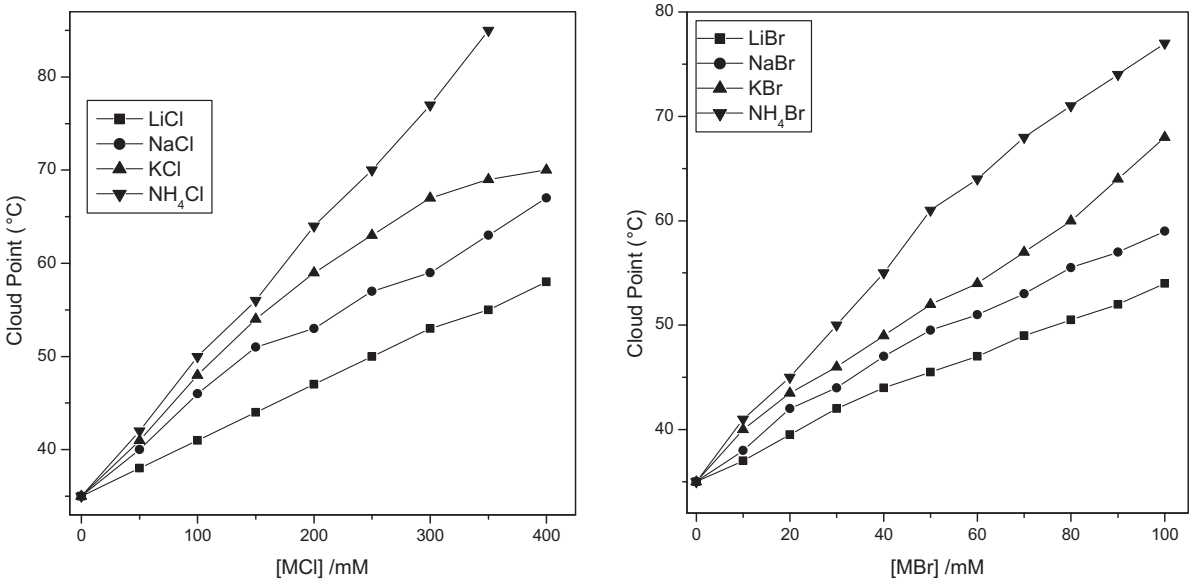

Figure 4 Effect of cationic co-ions: MCl and MBr on the *CP* of 50 mM AMT solutions, prepared in 2.5 mM CTAB + 10 mM SP buffer (pH = 6.7).

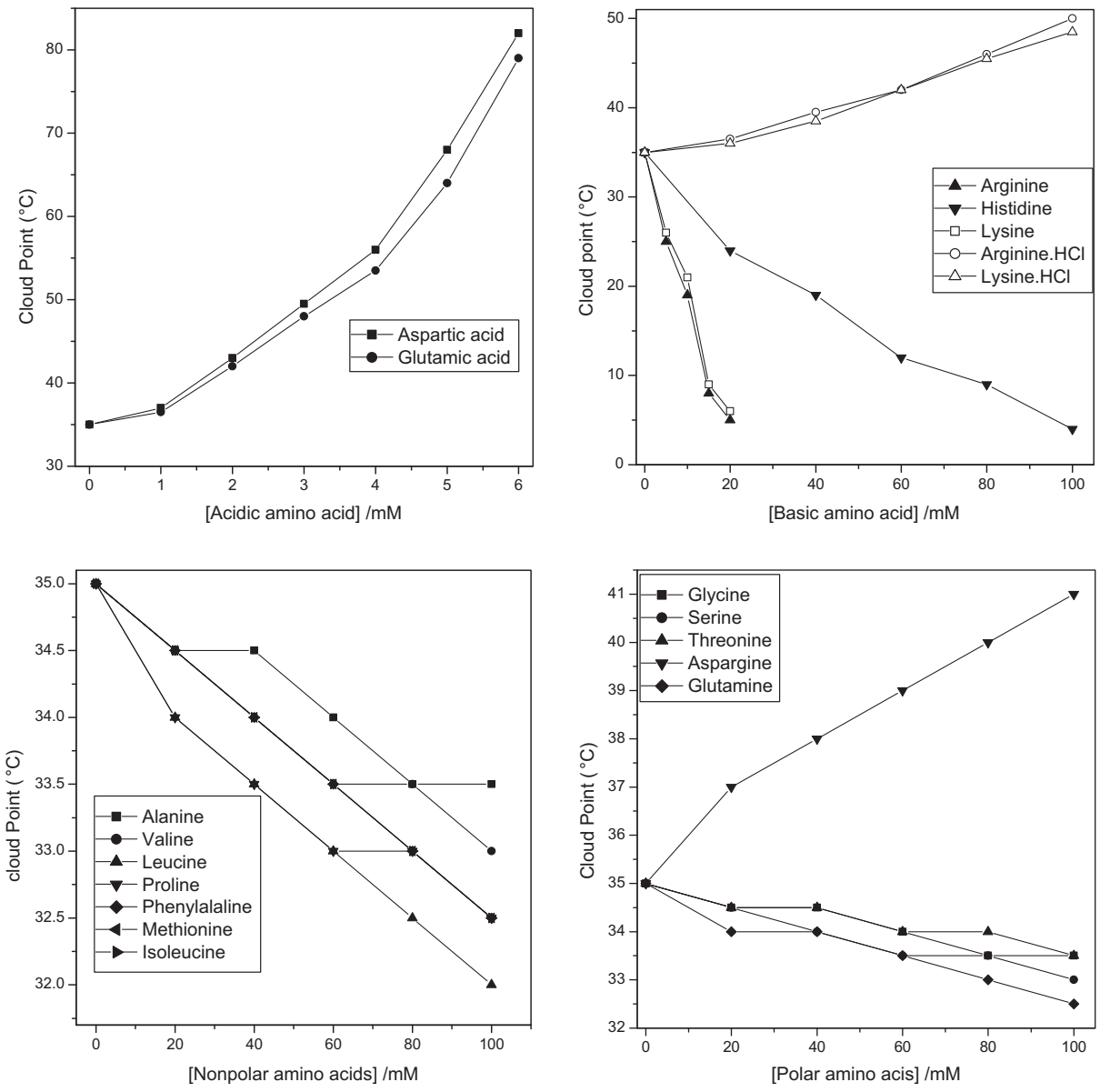

Figure 6 Effect of addition of amino acids on the cloud point of 50 mM AMT prepared in 2.5 mM CTAB + 10 mM SP buffer (pH = 6.7).

hydrophilic parts (Hall, 1991). In MCl/MBr salts series, Li^+ is highly hydrated (r_h = 3.82 Å) and would act as a water-structure promoter, by decreasing the availability of the water to the micelles which bring about slower increase in *CP*. K^+ or $NH)_4^+$ (r_h = 3.31 Å) are relatively less hydrated than Li^+, hence, to remove water from micelles needs much energy causing a sharp increase in *CP*. Na^+ (r_h = 3.58 Å) shows mediatory effect on *CP* of AMT due to the fact that its hydrated radius is intermediate to Li^+ and K^+ or NH_4^+ ions.

3.3. Quaternary ammonium bromides (QABs)

The effects of QABs on the variation of *CP* are shown in Fig. 5. QAB salts increase the *CP* in the following order: TMeAB > TEtAB > TPrAB > TBuAB > TPeAB. QAB salts are less hydrated than inorganic salts (Kabir-ud-Din et al., 1998). Tetraalkylammonium ions are water-structure maker; so that *CP* increases with increase in alkyl chain length of QAB. However, it is not observed by experiment due to the adsorption/mixed micelle maker factor command over water-structure maker (Zana, 2002). Hence, micelles would endure greater inter-micellar repulsions and, as a result, higher *CP*. In fact, it was found so, experimentally (Fig. 5).

3.4. Effect of amino acids

Fig. 6 shows the effects of amino acids on the variation of *CP* of drug. Amino acids contain carboxylic acids as well as an amine function. The most important aspect of amino acids is that they share the common characteristics of being α-amino acids, and their side chains are different. Peptide bonds allot the structure of proteins, but it is the side chain that is mainly

Table 1 Thermodynamic parameters for clouding of 50 mM AMT prepared in 2.5 mM CTAB + 10 mM SP buffer in presence QABs.

Mole fraction of additive × 10^4	ΔG_c° (kJ mol^{-1})	ΔH_c° (kJ mol^{-1})	$T\Delta S_c^\circ$ (kJ mol^{-1})	Mole fraction of additive × 10^4	ΔG_c° (kJ mol^{-1})	ΔH_c° (kJ mol^{-1})	$T\Delta S_c^\circ$ (kJ mol^{-1})
QABs							
TMeAB				TEtAB			
1.80	−22.31	−92.42	−70.01	1.80	−22.31	−104.45	−82.01
3.60	−20.72		−71.62	3.60	−20.73		−83.65
5.40	−19.95		−72.53	5.40	−19.82		−84.54
7.20	−19.26		−73.15	7.20	−19.25		−85.12
8.99	−18.88		−73.54	8.99	−18.74		−85.63
10.79	−18.42		−73.96	10.79	−18.36		−86.05
12.59	−18.13		−74.27	12.59	−17.95		−86.45
TPrAB				TBuAB			
1.80	−22.31	−126.33	−103.91	1.80	−22.21	−145.55	−123.21
3.60	−20.73		−105.52	3.60	−20.69		−124.84
5.40	−19.75		−106.53	5.40	−19.77		−125.72
7.20	−19.13		−107.13	7.20	−19.18		−126.43
8.99	−18.66		−107.67	8.99	−18.64		−126.86
10.79	−18.22		−108.12	10.79	−18.13		−127.33
12.59	−17.80		−108.44	12.59	−17.82		−127.64
TPeAB							
1.80	−22.28	−186.74	−164.46				
3.60	−20.53		−166.12				
5.40	−19.64		−167.04				
7.20	−18.94		−167.76				
8.99	−18.45		−168.23				
10.79	−18.07		−168.63				
12.59	−17.72		−168.99				

being the primary cause for their properties. The major differences between amino acid side chains are of interest: (i) size and shape, and (b) electronic characteristics and their effects on the capableness of side chains to engage the attention or efforts in ionic bonding, hydrogen bonding, covalent bonding, van der Waals forces, and acid–base chemistry. Therefore, the effect of amino acids is prescribed by their polar/non-polar characteristics of the side chains and also by their acidic/basic nature. Acidic amino acids (negatively charged side chains) and also hydrochloride salts of basic amino acids, to act on each other with the amine group of AMT molecules; admitting entry of water ensuing in more hydrated micelles, this causes to increase in *CP*, whereas non-polar and uncharged polar amino acids persist much less effective because they are solubilized in bulk water or micellar interior and would not affect the micellar morphology. Hence *CP* alterations are insignificant in their presence. The nature and structure of molecule of the amino acid apparently play a role. Basic amino acids behave in a fashion opposite to that of acidic ones. They favor polar environment and thus they would partition in the head group region. This would replace certain amount of water from the head group, ensuing in dehydration of micelles and hence decrease in *CP* is detected.

3.5. Effect of drug concentration

Fig. 7 presents comparison of the effect of NaCl/NaBr addition on the variation of *CP* of three different concentrations of AMT drug solution. As accounted earlier, Br^- causes significant growth; therefore, its presence affects more than Cl^- at each concentration. The values of *CP* are higher for higher drug concentration but conduct is similar for all concentrations. Increase in drug concentration (50–100 mM) increases the number, size and charge of micelles that enhances both inter- and intra-micellar repulsions, getting increase in *CP* at every fixed NaCl/NaBr concentration.

3.6. Thermodynamic of clouding phenomenon

Despite of the mechanism of *CP* not yet be resolved, it is supposed that dehydration of micellar head group part is the main reason of the happening of *CP* (Karlstrom, 1985; Tasaki, 1996). The *CP* value of amphiphile may be dealt as the temperature at which phase separation takes place. The clouding constituents free their solvated water and separate out from the solution. Considering *CP* as a boundary of solubility of the amphiphile, the standard free energy change of clouding (ΔG_c°) can be calculated from Eq. (1):

$$\Delta G_c^\circ = RT \ln X_c \tag{1}$$

where X_c is the mole fraction of clouding species at *CP*, *R* and *T* have their usual meaning. The standard enthalpy change of clouding, ΔH_c°, and the standard entropy change of clouding, ΔS_c°, can then be calculated by applying the following equations:

$$\Delta H_c^\circ = \frac{\partial(\Delta G_c^\circ/T)}{\partial(1/T)} \tag{2}$$

$$\Delta S_c^\circ = (\Delta H_c^\circ - \Delta G_c^\circ)/T \tag{3}$$

The thermodynamic parameters thus evaluated indicate that for all the additives, ΔG_c° is negative (Tables 1 and 2). The values of ΔG_c° increase as the concentrations of QABs

Table 2 Thermodynamic parameters for clouding of AMT prepared in 2.5 mM CTAB + 10 mM SP buffer solutions in presence NaCl/NaBr.

mole fraction of AMT $\times 10^4$	ΔG_c° kJ mol^{-1}	ΔH_c° kJ mol^{-1}	$T\Delta S_c^\circ$ kJ mol^{-1}	mole fraction of AMT $\times 10^4$	ΔG_c° kJ mol^{-1}	ΔH_c° kJ mol^{-1}	$T\Delta S_c^\circ$ kJ mol^{-1}
			NaCl				
	0 mM				50 mM		
8.99	−17.96	−29.14	−11.17	8.99	−18.37	−31.33	−12.95
13.49	−17.47		−11.66	13.49	−17.75		−13.57
17.98	−17.24		−11.89	17.98	−17.50		−13.82
	100 mM				150 mM		
8.99	−18.72	-32.88	−14.15	8.99	−19.07	−33.91	−14.83
13.49	−18.11		−14.76	13.49	−18.41		−15.49
17.98	−17.87		−15.01	17.98	−18.11		−15.79
	200 mM				250 mM		
8.99	−19.42	-34.93	−15.50	8.99	−19.60	−35.68	−16.07
13.49	−18.60		−16.32	13.49	−18.82		−16.85
17.98	−18.40		−16.52	17.98	−18.69		−16.98
	300 mM				350 mM		
8.99	−19.83	−36.19	−16.35	8.99	−19.95	−37.03	−17.07
13.49	−19.01		−17.17	13.49	−19.23		−17.79
17.98	−18.87		−17.31	17.98	−19.03		−17.99
	400 mM						
8.99	−20.06	−37.89	−17.82				
13.49	−19.45		−18.43				
17.98	−19.24		−18.64				
			NaBr				
	10 mM				20 mM		
8.99	−18.25	−31.81	−13.55	8.99	−18.37	−32.92	−14.54
13.49	−17.58		−13.22	13.49	−17.75		−14.16
17.98	−17.37		−13.43	17.98	−17.50		−14.41
	30 mM				40 mM		
8.99	−18.55	−33.85	−15.29	8.99	−18.72	−34.99	−16.26
13.49	−17.91		−14.93	13.49	−18.05		−16.93
17.98	−17.63		−15.21	17.98	−17.74		−17.24
	50 mM				60 mM		
8.99	−18.90	−36.85	−17.94	8.99	−19.07	−38.36	−19.28
13.49	−18.19		−18.65	13.49	−18.27		−20.08
17.98	−17.87		−18.92	17.98	−17.98		−20.37
	70 mM				80 mM		
8.99	−19.13	−39.66	−20.52	8.99	−19.25	−40.73	−21.47
13.49	−18.41	−39.66	−21.24	13.49	−18.52	−40.73	−22.20
17.98	−18.08	−39.66	−21.57	17.98	−18.19	−40.73	−22.53
	90 mM				100 mM		
8.99	−19.36	−41.01	−21.64	8.99	−19.48	−42.45	−22.96
13.49	−18.63		−22.37	13.49	−18.79		−23.65
17.98	−18.29		−22.71	17.98	−18.42		−24.02

increase, which suggests that the process is comparatively more spontaneous at lower concentrations of the QABs (Table 1). The ΔH_c° and $T\Delta S_c^\circ$ values are negative for all QABs, at all concentrations (Table 1). The added QABs exist in the solution as monomers, or mixed micelles and the values of ΔH_c° and $T\Delta S_c^\circ$ are negative due to enhancement in the intermicellar repulsion, which is mainly assured by enthalpy with a substantial ordering of the system. With increase in alkyl chain length of QABs, values of ΔH_c° and $T\Delta S_c^\circ$ decreases, as short chain length form larger micelles and less effective charge would produce less repulsion, developing lower values of $T\Delta S_c^\circ$. The difference between the negative values of ΔH_c° and $T\Delta S_c^\circ$ becomes minuter with increase in additive concentration with uninterrupted increase in $T\Delta S_c^\circ$, i.e., the entropy factor starts dominating but the overall process is still a compromise of both with a major donation from the enthalpy factor (Table 1). With increase in additive concentration the value of entropy decreases but the decreases in case of QABs is much more pronounced (Table 1) as compared to NaCl/NaBr (Table 2) where the decrease in negative value of entropy is not significant. The values of $T\Delta S_c^\circ$ and ΔH_c° come out to be negative which hinders the micellar aggregation due to increase in inter-

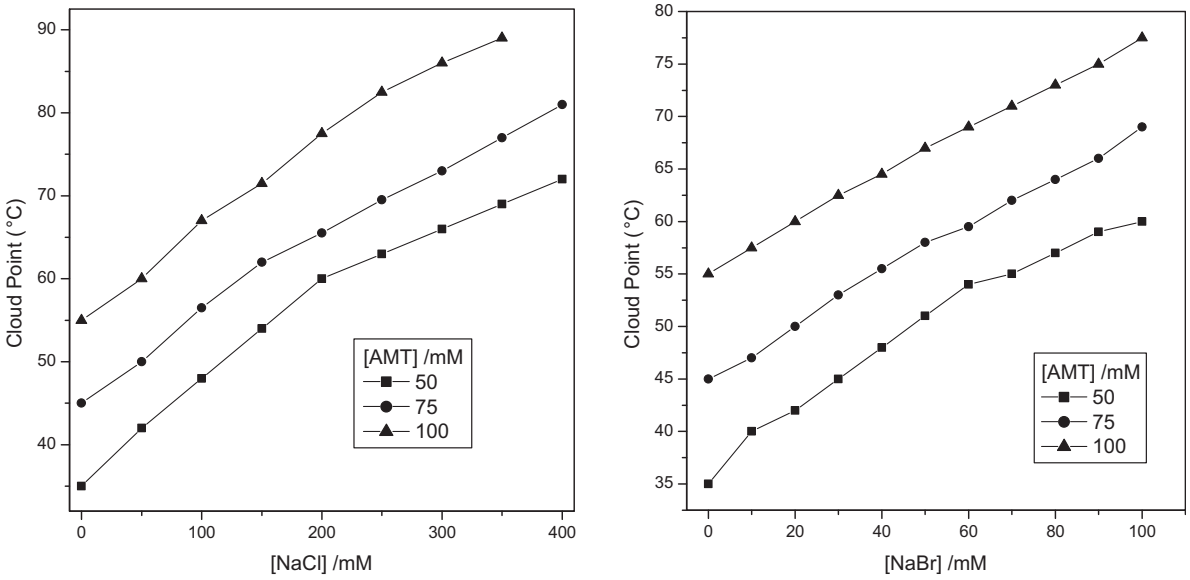

Figure 7 Effect of NaCl and NaBr concentration on the *CP* of AMT solutions of different fixed concentrations, prepared in 2.5 mM CTAB + 10 mM SP buffer (pH = 6.7).

micellar repulsion. The driving force for the overall process is enthalpy-driven as shown by large negative values of ΔH_c° in both the cases of QABs and NaBr/NaCl.

Effect of NaCl/NaBr on clouding behavior of drug at different concentrations (50–100 mM) has showed that the magnitude of negative values of ΔG_c° is higher in presence of salt showing that the process is more spontaneous with salt (NaCl/NaBr) but the values are higher for NaBr (Table 2). The negative values of ΔH_c° and $T\Delta S_c^\circ$ are higher for NaBr than NaCl; supporting the fact that bromide ion binds strongly to the micelles because of its large size and small hydrated radius as compared to chloride ion. The negative values of ΔH_c° and $T\Delta S_c^\circ$ decrease with increase in the concentration of NaCl/NaBr but these negative values are always more with the presence of NaBr.

4. Conclusions

Herein, we report the *CP* behavior of an amphiphilic antidepressant drug amitriptyline hydrochloride (AMT) in presence of several additives like inorganic salts, QABs and amino acids. By addition of inorganic salts, increase in *CP* is detected due to the micellar growth leading to electrical repulsion. With quaternary salts, increase in *CP* is found due to the adsorption/mixed micelle formation. With acidic amino acids and hydrochloride salts of basic amino acids, increase in *CP* occurs. Other amino acids do not show any significant impression. Thermodynamic parameters show that the values are negative in presence of all the additives.

Acknowledgment

The authors are thankful to the Council of Scientific and Industrial Research (CSIR), New Delhi, India for research Grant (No. 01(2208)/08/EMR–II).

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