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Effect of KCl on the Micellization and Clouding Phenomenon of the Amphiphilic Phenothiazine Drug Promethazine Hydrochloride: Some Thermodynamic Properties

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Supporting Information

ABSTRACT: In the present paper, we report the micellization at different fixed temperatures [(293.15, 303.15, 313.15, and 323.15) K] and the clouding behavior of the phenothiazine drug 10-[2-(dimethylamino)propyl]phenothiazine hydrochloride (promethazine hydrochloride, PMT) in the absence and presence of KCl. The critical micelle concentration (cmc) of PMT was measured by the conductivity method. The cmc values decrease with increasing the KCl concentration, whereas with increasing temperature, the cmc values increase. The thermodynamic parameters, namely, the standard Gibbs energy ($\Delta_m G°$), standard enthalpy ($\Delta_m H°$), and standard entropy ($\Delta_m S°$) of micellization of PMT were evaluated, and they indicate greater stability of the PMT solution in the presence of KCl. PMT shows phase separation also. The cloud point (CP) of PMT decreases with increasing pH because of deprotonation of the drug molecules. The CP values increase with increasing KCl as well as PMT concentration because of micellar growth. Furthermore, the thermodynamic parameters were evaluated at the CP.

INTRODUCTION

In an aqueous environment, amphiphilic molecules (e.g., surfactants, drugs, polymers, etc.) can form micelles, a kind of self-organized molecular assembly, above their *critical* micelle concentration (cmc).[1−5] The self-assembly and self-organization are natural and spontaneous processes, occurring mainly through noncovalent interactions such as van der Waals, hydrogen-bonding, hydrophilic/hydrophobic, electrostatic, donor/acceptor, and metal−ligand coordination networks.[6] The interest in micelle solutions stems from their potential as functional molecular assemblies for use in many fields in pure and applied science because they can be used as models for several biochemical and pharmacological systems and can solubilize water-insoluble substances (including certain medicines and drugs) in their hydrophobic cores.[7]

Many drug molecules are amphiphilic and self-associate in aqueous environments to form small aggregates like surfactants.[8−15] The colloidal properties of amphiphilic drugs are largely determined by the nature of the aromatic ring system of their hydrophobic moieties, and such drugs are useful in probing the relationship between the molecular architecture and the physicochemical properties.[8] In pharmacy, the interaction of small molecules with drugs is one of the most extensively studied areas. In this respect, a large number of drugs (especially those with local anesthetic, tranquilizer, antidepressant, and antibiotic actions) exert their activity by interaction with biological membranes, which can be considered as a complex form of amphiphilic bilayer. Therefore, a full knowledge of the mechanism of the interactions of drugs with other foreign materials is required before their actual application in human body. This is due to the fact that drugs are always used in the presence of a variety of additives (excipients).

The thermodynamic parameters of some amphiphilic drugs (amitriptyline hydrochloride, imipramine hydrochloride, chlorpromazine hydrochloride, and promethazine hydrochloride) in the presence of additives have recently been evaluated.[16−20] Micellar characteristics of various peptides, collagens, and polymers in aqueous and nonaqueous media and their interactions with various surfactant micelles have widely been studied[21−26] in light of aggregation, H-bonding, geometry, correlation times, conformation, and hydrodynamic and thermodynamic studies.

Clouding is a well-known phenomenon observed in nonionic surfactants. The clouding phenomenon can be induced by changing the temperature of the solution. The temperature at which a clear, single phase becomes cloudy and undergoes phase separation upon heating is known as the cloud point (CP).[27] However, the mechanism of clouding in nonionic surfactants is not yet very clear and continues to be a source of controversy among different research groups. On the other hand, the occurrence of CPs in charged micelle (i.e., ionic surfactant) solutions is not usual except under special conditions, such as high salt concentration,[28−31] salt-free aqueous solutions of certain surfactants with large headgroups[29,31] or large counterions,[29,30] and some mixed cationic and anionic surfactant solutions.[32] The CP appearance in these systems is explained in terms of increased hydrophobic interactions, dehydration of the hydrophilic group,[30] and formation of large aggregates/clusters.[31] Like ionic surfactants, some amphiphilic drugs undergo pH-, concentration-, and temperature-dependent phase separation.[33−45] It was observed that their CPs can vary with additives.

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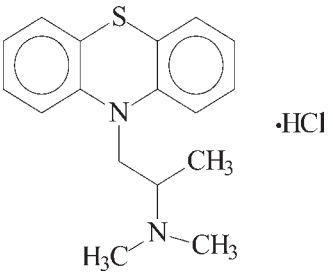
Scheme 1. Molecular Structure of the Amphiphilic Phenothiazine Drug 10-[2-(Dimethylamino)propyl]-phenothiazine Hydrochloride (Promethazine Hydrochloride, PMT)



10-[2-(Dimethylamino)propyl]phenothiazine hydrochloride (promethazine hydrochloride, PMT) is an amphiphilic phenothiazine drug with neuroleptic activity that shows a large capacity to interact with biological membranes and is sometimes used as a local anesthetic.[46] PMT possesses a rigid hydrophobic ring system and a hydrophilic amine portion, which becomes cationic at low pH values and neutral at high pH values (Scheme 1). Moreover, the pK_a value of this drug is 9.1.[47] PMT is often regarded as a model drug for the investigation of interactions between drugs and biological or model membranes.[9] Phenothiazine drugs aggregate in a micelle-like manner, and the value of the aggregation number (N_{agg}) is on the order of 6 to 15.[8,9] As clouding is concentration-, pH-, and temperature-dependent, it is essential to have a knowledge of the clouding behavior of the drug under various conditions.

In the present paper, we report the micellization and clouding of PMT in the absence and presence of KCl. The thermodynamic parameters have been evaluated (in micellization and at the CP) in the presence and absence of electrolyte (KCl). The results have relevance to drug delivery processes.

MATERIALS AND METHODS

Materials. PMT hydrochloride ($\chi \geq 0.980$, CAS no. 58-33-3; Sigma) and potassium chloride, KCl ($\chi \geq 0.999$, CAS no. 7447-40-7; Ranbaxy, India) were used as received. Trisodium phosphate dodecahydrate (TSP) and sodium dihydrogen phosphate monohydrate (SDP) were reagent-grade and obtained from Merck.

The water used was doubly distilled and deionized [specific conductivity = (1 to 2)·10^{-6} S·cm^{-1}]. Buffer solutions containing 10 mmol·kg^{-1} sodium phosphate (SP) were used throughout as the solvent. The pH of the PMT solutions was measured with an ELICO pH meter (model LI 120) using combined electrode.

Methods. *Conductivity Measurements.* A conductivity meter (Global Electronics, model DCM 900) and dip cell (cell constant = 1.0 cm^{-1}) were used to perform the conductivity measurements at different temperatures [(293.15, 303.15, 313.15, and 323.15) K]. The stock solutions of PMT (with or without a fixed concentration of KCl) were prepared in doubly distilled water. The conductivity was measured by successive addition of a concentrated solution to pure water (in the case of no KCl) or a KCl solution with fixed concentration. A break in the specific conductivity versus drug concentration curve signals the onset of the micellization process (see Figure 1). The conductivity meter cell was calibrated using the instruction manual of the instrument.

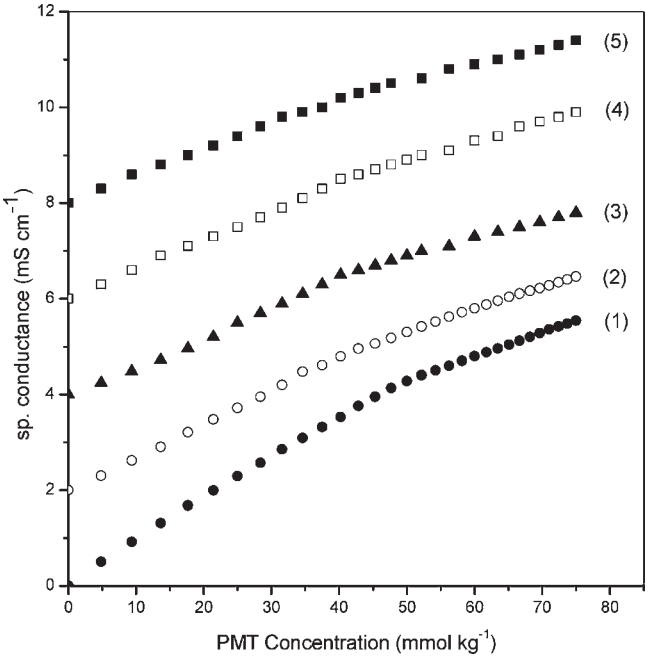


Figure 1. Representative plots of specific conductance vs PMT concentration at different fixed KCl concentrations [(1), 0 mmol·kg^{-1}; (2), 25 mmol·kg^{-1}; (3), 50 mmol·kg^{-1}; (4), 100 mmol·kg^{-1}; (5), 200 mmol·kg^{-1}] at 313.15 K. For clarity, curves 2, 3, 4, and 5 have been shifted upward by (2, 4, 6, and 8) mS·cm^{-1}, respectively.

The degree of dissociation of the micelles (x) was determined from the plot of specific conductance versus surfactant concentration. Actually, x is the ratio of the postmicellar slope to the premicellar slope in such a plot. The counterion association of the micelles (α) is equal to $(1 - x)$.

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

Cloud Point Measurements. All CPs were obtained by placing a Pyrex glass tube containing the drug solution into a temperature-controlled bath and then ramping the temperature at a rate of 0.1 K·min^{-1} near the CP; the onset of clouding was noted by visual inspection. The temperature when the clouding commenced was taken as the CP.[45−50] The uncertainty in the measured CP was ± 0.5 K.

The uncertainties of the evaluated quantites were as follows: (1.10 to 4.95)·10^{-6} mol·kg^{-1} for the cmc; (1.10 to 4.95)·10^{-5} for α; (1.10 to 4.95)·10^{-3} kJ·mol^{-1} for $\Delta_m G°$, $\Delta_m H°$, $\Delta_s G°$, $\Delta_s H°$, and $T\Delta_s S°$; and (1.10 to 4.95)·10^{-3} kJ·K^{-1}·mol^{-1} for $\Delta_m S°$.

RESULTS AND DISCUSSION

Micellization. Values of the cmc of PMT in the absence of KCl or in the presence of a fixed concentration of KCl [(25, 50, 100, or 200) mmol·kg^{-1}] were determined by the conductivivity method at different temperatures [(293.15, 303.15, 313.15, and

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Table 1. Critical Micelle Concentrations (cmc) and Values of Various Thermodynamic Parameters for PMT Solutions at Different Fixed KCl Concentrations (m_{KCl}) at Various Temperatures Evaluated on the Basis of Conductivity Measurements

m_{KCl}	cmc		$\Delta_m G°$	$\Delta_m H°$	$\Delta_m S°$
mmol·kg^{-1}	mmol·kg^{-1}	α	kJ·mol^{-1}	kJ·mol^{-1}	kJ·K^{-1}·mol^{-1}
		293.15 K			
0	45.75	0.306	−29.34	−0.32	0.09
25	41.92	0.328	−29.31	−0.28	0.09
50	39.84	0.308	−29.87	−0.18	0.10
100	36.10	0.379	−29.01	−0.38	0.09
200	28.12	0.245	−32.47	−0.89	0.11
		303.15 K			
0	45.87	0.329	−29.91	−3.70	0.09
25	42.02	0.297	−30.86	−4.32	0.09
50	39.90	0.288	−31.24	−4.35	0.09
100	36.22	0.418	−29.26	−9.92	0.06
200	28.32	0.204	−34.33	−8.54	0.08
		313.15 K			
0	47.22	0.419	−29.12	−5.03	0.08
25	43.44	0.357	−30.61	−6.93	0.08
50	41.25	0.426	−29.54	−3.28	0.08
100	39.32	0.322	−31.69	−2.14	0.09
200	30.14	0.400	−31.33	−6.91	0.08
		323.15 K			
0	49.10	0.465	−29.01	−5.19	0.07
25	45.75	0.400	−30.54	−7.19	0.07
50	42.32	0.436	−30.19	−3.48	0.08
100	39.94	0.407	−30.99	−2.16	0.09
200	31.78	0.418	−31.74	−7.27	0.08

323.15) K]. Figure 1 shows representative plots of specific conductivity versus PMT concentration. The cmc values of PMT measured at various fixed concentrations of KCl at different temperatures are listed in Table 1 and plotted in Figure 2. The cmc values of PMT decrease with increasing KCl concentration, whereas the effect of temperature shows the opposite trend (i.e., an increase with increasing temperature) for all of the systems (Figure 2).

The value of the cmc is dependent upon a variety of parameters, including the nature of the hydrophilic and hydrophobic groups, additives present in the solution, and external influences such as temperature. The micellization takes place when the energy released as a result of association of the hydrophobic parts of the monomers is sufficient to overcome the electrostatic repulsion between the ionic head groups and the decrease in entropy accompanying the aggregation. The cmc can also be influenced by the addition of a strong electrolyte to the solution. This serves to increase the degree of counterion binding, which has the effect of reducing the headgroup repulsion between the ionic head groups and thus decreasing the cmc. This effect has been empirically quantified according to the equation[48]

$$\log \text{cmc} = -a \log C_t + b \qquad (1)$$

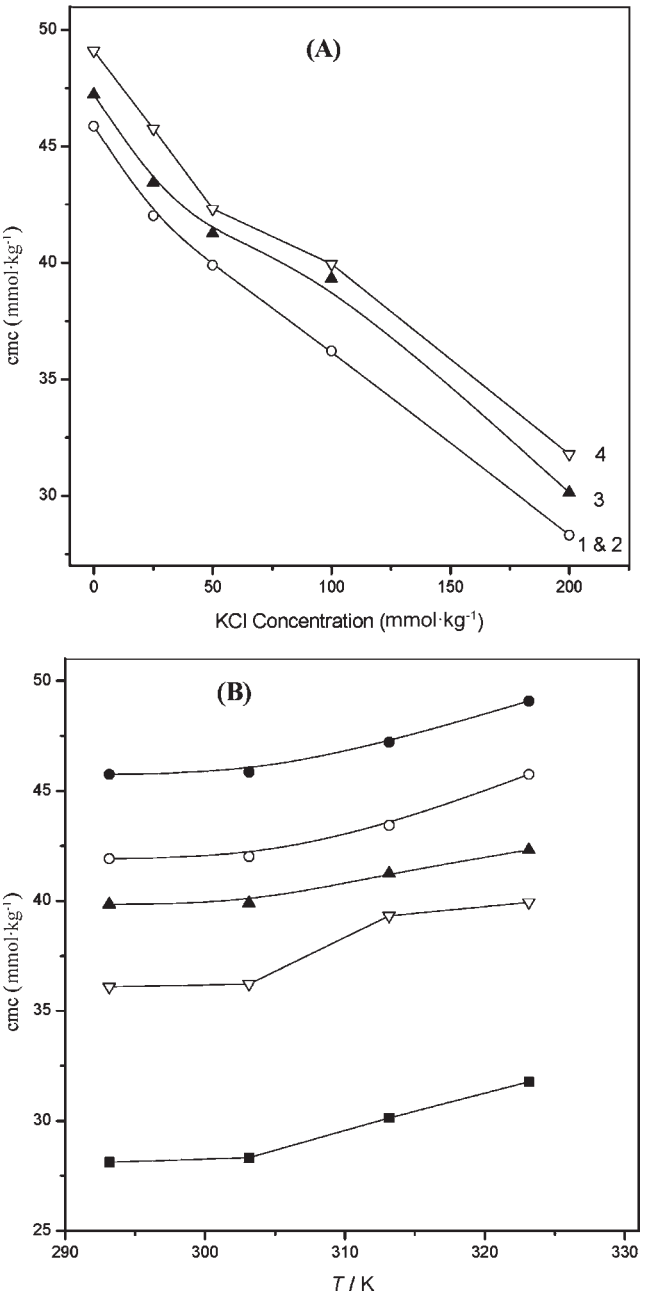

Figure 2. Effect of (A) KCl concentration at different temperatures [(1), 293.15 K; (2), 303.15 K; (3), 313.15 K; (4), 323.15 K] and (B) temperature at different fixed concentrations of KCl (●, 0 mmol·kg^{-1}; ○, 25 mmol·kg^{-1}; ▲, 50 mmol·kg^{-1}; △, 100 mmol·kg^{-1}; ■, 200 mmol·kg^{-1}) on the cmc of PMT solutions.

where a and b are constants for a specific ionic headgroup ant C_t denotes the total counterion concentration.

The cmc and α values obtained for PMT micelles in the absence and presence of KCl at various temperatures are given in Table 1. It was found that the cmc of PMT in aqueous solution increased with increasing temperature, whereas the cmc of PMT decreased in the presence of the additive (KCl) at all temperatures mentioned above (see Table 1). The increase in cmc and decrease in α for PMT micelles in aqueous solution suggest that micelle formation of PMT is hindered with increasing temperature. However, formation of PMT micelles is facilitated in the

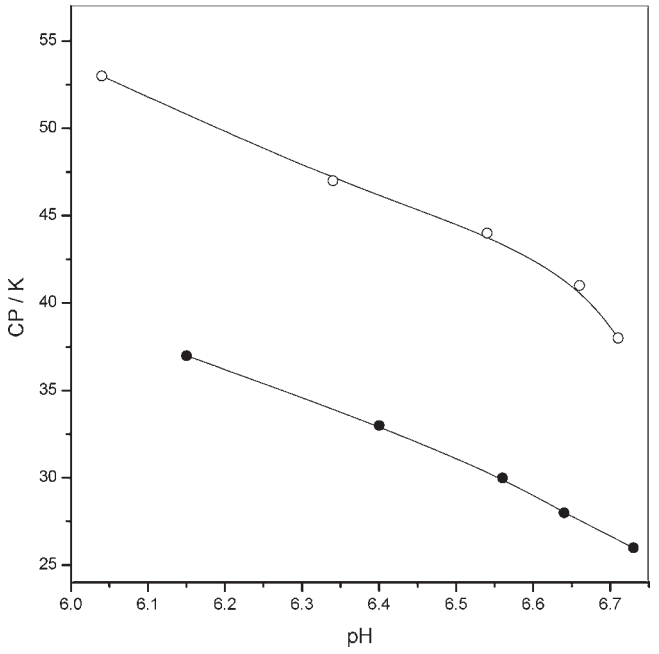

Figure 3. Effect of pH on the CP of 50 mmol·kg^{-1} PMT solutions prepared in 10 mmol·kg^{-1} sodium phosphate buffer containing (●) no KCl or (○) a fixed KCl concentration of 100 mmol·kg^{-1}.

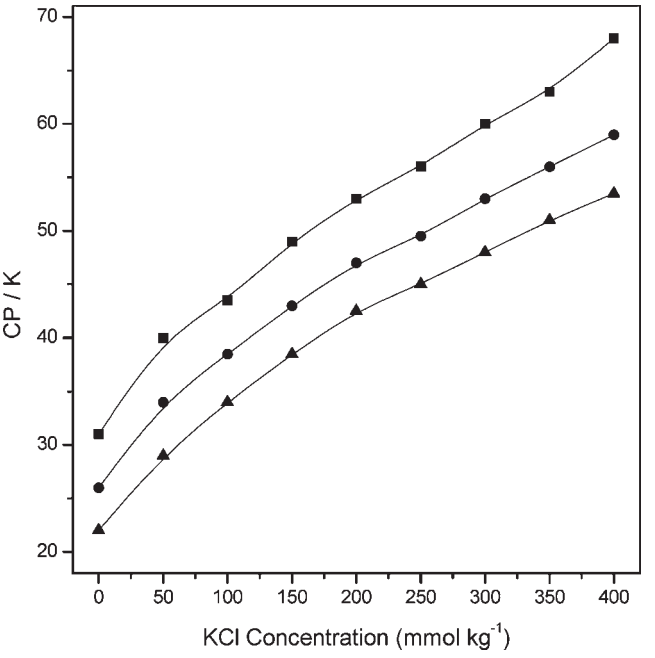

Figure 4. Effect of KCl concentration on the CP of 50 mmol·kg^{-1} PMT solutions prepared in 10 mmol·kg^{-1} sodium phosphate buffer at different pH: ■, 6.5; ●, 6.7; ▲, 6.8.

presence of KCl even at higher temperatures, as shown by the lower cmc and higher α values (see Table 1).

Thermodynamics. In the van't Hoff method, the cmc of a surfactant is measured at different temperatures, and the energetic parameters can be evaluated by the mass-action and pseudophase models.[8,49−54] For calculating values of the thermodynamic parameters for the micellar systems, we used the following equations:

$$\Delta_m G^\circ = (2-\alpha)RT \ln \chi_{cmc} \quad (2)$$

$$\Delta_m H^\circ = -(2-\alpha)RT^2 \left(\frac{\partial \ln \chi_{cmc}}{\partial T}\right)_P \quad (3)$$

$$\Delta_m S^\circ = \frac{\Delta_m H^\circ - \Delta_m G^\circ}{T} \quad (4)$$

where $\Delta_m G^\circ$, $\Delta_m H^\circ$, and $\Delta_m S^\circ$ are the standard Gibbs free energy, enthalpy, and entropy of micellization expressed per mole of monomer unit, respectively, and α, R, T, and χ_{cmc} are the counterion association, universal gas constant, absolute temperature, and mole-fraction cmc, respectively. All of the $\Delta_m G^\circ$ values are negative and increase with increasing electrolyte concentration (Table 1); this implies that the drug/electrolyte solutions are more stable. The values of $\Delta_m H^\circ$ and $\Delta_m S^\circ$ also agree with the low randomness and more stability (Table 1).

Effect of KCl on the Cloud Point. The CP of the PMT solutions was found to be highly sensitive to the solution pH (see Figure 3). The results show that the CP decreases as the pH increases in the presence and in the absence of KCl. In the pH range employed, this decrease in the CP is due to changes in the micellar surface charge. The ionization constant (pK_a) of PMT in the free molecular state is 9.1.[47] The tricyclic part of the PMT molecule (Scheme 1) is hydrophobic, and the tertiary amine portion is hydrophilic. The protonation is highly dependent upon the solution pH. At low pH, the tertiary amine becomes protonated (i.e., cationic), and it is deprotonated (i.e., neutral) at high pH. The number of nonionized (deprotonated) PMT molecules in micelles increases with increasing solution pH. This in turn reduces both intra- as well as intermicellar repulsions, leading to an increase in micellar aggregation and a decrease in the CP.[9,33,55]

Figure 4 illustrates the variation of the CP of 50 mmol·kg^{-1} PMT solutions prepared in 10 mM SP buffer upon addition of KCl at different fixed pH. Here the pH was varied from 6.5 to 6.8. It can be seen that as before (see Figure 3), the CP decreases with increasing pH at all KCl concentrations as a result of the decrease in repulsions (as discussed above for Figure 3). The increase in CP with increasing KCl concentration was found to follow a similar trend at all pH values. As discussed above, both charged and uncharged fractions of PMT molecules would be available for formation of aggregates (so-called PMT micelles). Thus, each micelle would bear a cationic charge. Increasing the amount of KCl would therefore cause the micellar size to increase progressively, with a concomitant increase in the CP.[33]

Figure 5 displays the effect of KCl addition on the CP of PMT solutions containing different fixed concentrations of the drug [(50, 75, and 100) mmol·kg^{-1}]. At a constant KCl concentration, the increase in drug concentration increases both the number and charge of the micelles. This increases both the inter- and intramicellar repulsions, causing the increase in the CP.

Figure 6 shows the visible spectra of Sudan III solubilized in 50 mmol·kg^{-1} aqueous PMT solution containing different fixed concentrations of KCl. One can see that the absorbance increases upon addition of KCl and that increasing the concentration of KCl increases the absorbance. Addition of KCl increases the aggregation number of ionic micelles because of electrostatic effects.[56] With addition of more KCl, the size of the micelles increases, which causes the absorbance to increase. The

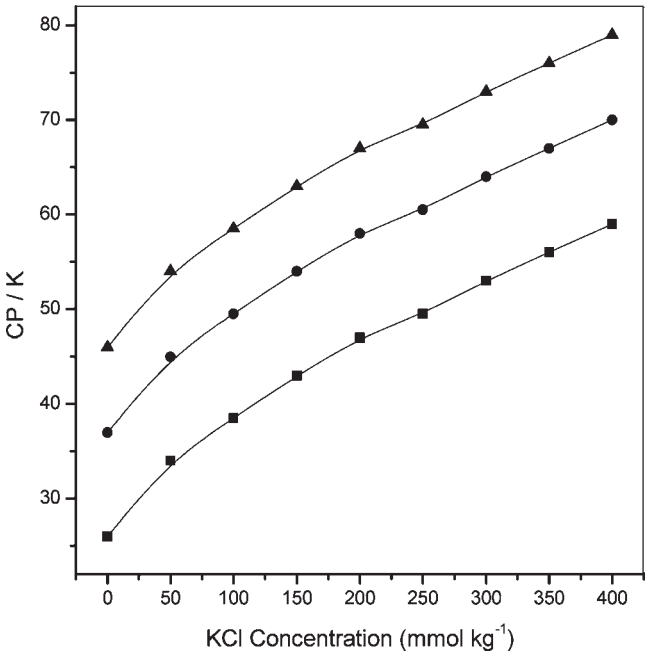

Figure 5. Effect of KCl concentration on the CP of PMT solutions having different fixed PMT concentrations (■, 50 mmol·kg^{-1}; ●, 75 mmol·kg^{-1}; ▲, 100 mmol·kg^{-1}) prepared in 10 mmol·kg^{-1} sodium phosphate buffer (pH 6.7).

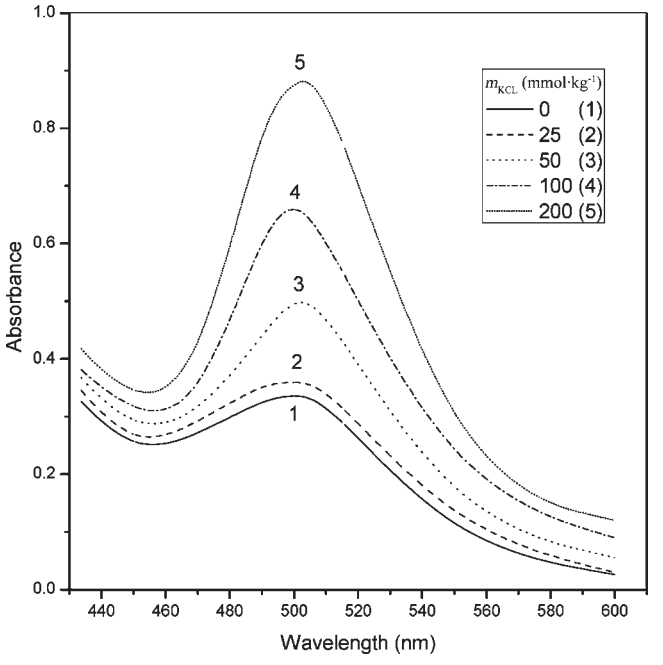

Figure 6. Visible spectra of Sudan III solubilized in an aqueous PMT solution (50 mmol·kg^{-1}) containing various fixed concentrations of KCl: (1), 0 mmol·kg^{-1}; (2), 25 mmol·kg^{-1}; (3), 50 mmol·kg^{-1}; (4), 100 mmol·kg^{-1}; (5), 200 mmol·kg^{-1}.

absorbance increase with increasing concentration of KCl suggests that the micellar growth with KCl addition is substantial.

Thermodynamics at the CP. Since the clouding components above the CP release their solvated water and separate out from the solution, the CP of an amphiphile can be considered as the limit of its solubility. Hence, the standard Gibbs energy of solubilization ($\Delta_sG°$) of the drug micelles can be evaluated from the relation[53,54]

$$\Delta_sG° = -RT \ln \chi_s \quad (5)$$

where χ_s is the mole fraction of the additive at the CP and T is the clouding temperature.

Table 2. Cloud Points (CP) and Values of Energetic Parameters of Clouding in 50 mmol·kg^{-1} PMT Solutions Prepared in 10 mmol·kg^{-1} Sodium Phosphate Buffer (pH 6.7) in the Presence of x mmol·kg^{-1} KCl

	CP	$\Delta_sG°$	$\Delta_sH°$	$T\Delta_sS°$
$\chi_{PMT}\cdot10^4$	K	kJ·mol^{-1}	kJ·mol^{-1}	kJ·mol^{-1}
		$x = 0$		
8.99	299.15	17.44	27.52	10.08
13.49	310.15	17.04		10.48
17.98	319.15	16.77		10.75
		$x = 50$		
8.99	307.15	17.91	28.96	11.05
13.48	318.15	17.48		11.48
17.97	327.15	17.19		11.77
		$x = 100$		
8.98	311.65	18.18	29.79	11.61
13.47	322.65	17.73		12.06
17.95	331.65	17.43		12.36
		$x = 150$		
8.98	316.15	18.44	30.63	12.19
13.46	327.15	17.98		12.65
17.93	336.15	17.67		12.96
		$x = 200$		
8.97	320.15	18.68	31.39	12.71
13.44	331.15	18.20		13.19
17.92	340.15	17.89		13.50
		$x = 250$		
8.96	322.65	18.83	31.87	13.04
13.43	333.65	18.34		13.53
17.90	342.65	18.02		13.85
		$x = 300$		
8.95	326.15	19.03	32.54	13.51
13.42	337.15	18.54		14.00
17.89	346.15	18.21		14.33
		$x = 350$		
8.94	329.15	19.21	33.12	13.91
13.41	340.15	18.71		14.41
17.87	349.15	18.37		14.75
		$x = 400$		
8.94	332.15	19.39	33.71	14.32
13.40	343.15	18.87		14.84
17.85	352.15	18.53		15.18

The standard enthalpy and entropy of clouding, $\Delta_s H^\circ$ and $T\Delta_s S^\circ$, respectively, can be calculated using the equations

$$\Delta_s H^\circ = \frac{\partial(\Delta_s G^\circ/T)}{\partial(1/T)} \quad (6)$$

and

$$T\Delta_s S^\circ = \Delta_s H^\circ - \Delta_s G^\circ \quad (7)$$

The energetic parameters were calculated using eqs 5 to 7. The thermodynamic data of clouding for the drug PMT in the presence of KCl are given in Table 2. For PMT with and without KCl, the thermodynamic parameters $\Delta_s G^\circ$, $\Delta_s H^\circ$, and $T\Delta_s S^\circ$ were found to be positive. It is interesting that all of the $\Delta_m G^\circ$ values are negative whereas the $\Delta_s G^\circ$ values are positive; this indicates that micelle formation is spontaneous whereas the clouding process is nonspontaneous (as it is caused by desolvating the species using temperature). Increasing the electrolyte concentration enhances the spontaneity/nonspontaneity of the drug/electrolyte systems.[16−18,53,54]

CONCLUSIONS

We have studied the micellization and clouding behavior of the phenothiazine drug promethazine hydrochloride (PMT) in the absence and presence of KCl. Knowledge of the self-aggregation and clouding behavior of amphiphilic drugs and the effect of additives on clouding will allow better design of effective therapeutic agents. The critical micelle concentration (cmc) of PMT decreases with increasing KCl concentration and increases with increasing temperature. The thermodynamic parameters have been evaluated, and they indicate greater stability of the PMT solution in the presence of KCl. The PMT shows phase separation also. The cloud point (CP) of PMT decreases with increasing pH because of deprotonation of the drug molecules. The CP values increase with increasing KCl and PMT concentrations, leading to micellar growth.

ASSOCIATED CONTENT

Supporting Information. Specific conductivity data at various temperatures. This material is available free of charge via the Internet at http://pubs.acs.org.

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