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Influence of electrolytes/non-electrolytes on the cloud point phenomenon of the aqueous promethazine hydrochloride drug solution

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Abstract

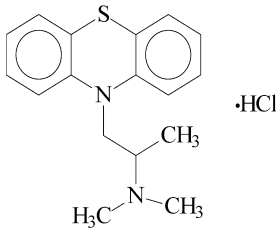
We have studied the clouding phenomena in promethazine hydrochloride (PMT) aqueous solutions in presence of electrolytes and non-electrolytes. PMT, a tranquillizer, shows phase separation. The cloud point (CP) decreases with increase in pH due to deprotonation of drug molecules. At constant pH, increasing salt addition causes an increase in CP, which is explained on the basis of their position in Hofmeister series and their hydrated radii. With quaternary salts CP increases due to adsorption/mixed micelle formation. Ureas decrease the CP and the behavior is explained on the basis of removal of water from the headgroup region.

Keywords: Phenothiazine drug; Promethazine hydrochloride; Cloud point; Hofmeister series; Mixed micelles

1. Introduction

Many drug molecules, though surface active, are complex aromatic or heterocyclic molecules and thus do not fit into the general picture of a surfactant monomer [1]. However, their amphiphilic character makes them aggregate in aqueous solution in a way the surfactants do. This behavior of drugs leads to different phases under different conditions. Promethazine hydrochloride, PMT, a phenothiazine drug (Scheme 1), contains a hydrophobic (rigid planar tricyclic) and a hydrophilic (tertiary amine) portion and, therefore, its aggregation also follows same principles as surfactants [2]. Like surfactants, aggregation of these amphiphilic drugs depends on the solution conditions of pH, ionic strength, additive concentration, temperature, etc. [3,4].

A fascinating phase behavior shown by non-ionic surfactants in aqueous solution is clouding [5–7]. Clouding results from a phase separation into a "cloudy" surfactant rich phase and a clear solution having surfactant concentration close to critical micelle concentration, cmc. This clouding occurs as the temperature is raised and the so-called lower consolute temperature is passed. The mechanism of lower consolute behavior in non-ionic surfactants has not been exactly known. However, ionic surfactant solutions are complex. Since the micelles are charged, there must be an electrostatic repulsion between the micelles in addition to the van der Waals attraction force. Occurrence of CP in ionic surfactant solutions under special conditions, e.g., high salt concentration [8], salt free aqueous solutions of certain surfactants with large headgroups [9,10] or large counterions [11,12] and some mixed cationic and anionic surfactant solutions [13,14] has been reported. The CP appearance in these systems is explained in terms of increased hydrophobic interactions, dehydration of hydrophilic group [15] and formation of large aggregates/clusters [16,17].



Scheme 1. Molecular structure of promethazine hydrochloride (PMT).

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Mouritsen and Jorgensen [18] have shown that drugs insert into membranes and affect the organization of lipids. Computer simulations indicated that partitioned drugs accumulate heterogeneously in the membrane. This accumulation may cause a localized high concentration. As clouding is concentration, pH and temperature dependent, it is essential to have a knowledge of clouding behavior of drugs under varying conditions. Promethazine hydrochloride is a phenothiazine-tranquillizing drug whose pure aqueous solutions do not show clouding from concentration level 0.125–200 mM. In 10 mM sodium phosphate (SP) buffer, however, clouding occurs without additives. To find an explanation at the molecular level, the present work focuses on the effect of pH and electrolyte as well as non-electrolyte additions on the CP of PMT in aqueous buffer solutions. The pK_a value of PMT is 9.1 [19]. At low pH values, the tertiary nitrogen atom acquires a positive charge (i.e., PMT exists in cationic form) while it becomes neutral at high pH values (Scheme 1).

2. Experimental

2.1. Materials

PMT hydrochloride (⩾95.0%, Sigma) was used as received. The electrolytes, lithium bromide, LiBr (⩾99.4%, Riedel-de Haen), sodium fluoride, NaF (⩾97%, BDH), sodium chloride, NaCl (⩾99.9%, BDH), sodium bromide, NaBr (⩾99%, LOBA Chemie), potassium bromide, KBr (⩾99%, Merck), ammonium bromide (⩾99%, LOBA Chemie), and quaternary ammonium bromides (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) were used as received. Trisodium phosphate dodecahydrate, TSP, and sodium dihydrogen phosphate monohydrate, SDP, were of reagent grade obtained from Merck.

The water used was doubly-distilled and deionized (sp. cond. = 1–2 × 10^{-6} S/cm). 10 mM SP buffer solutions were used throughout as solvent [20]. The pH of the PMT solutions was measured with an ELICO pH meter (model LI 120) using combined electrode.

2.2. Method

All CPs were obtained by placing Pyrex glass tubes (containing the drug solution) into a temperature controlled bath, the temperature was ramped at the rate of 0.1 °C/min near the CP and onset of clouding was noted by visual inspection. The temperature as the clouding commences was taken as CP [7,11,12]. However, the temperature was oscillated slowly through the CP until reproducible (±0.1 °C).

3. Results

Critical micelle concentration of PMT was determined by ring method and was found to be 47 mM which is in close agreement with the literature value (44 mM) [1]. Fig. 1 shows the effect of pH on the CP of PMT in presence of fixed concentration of electrolytes. CP decreases with the increase in pH from 6.0 to 6.7 in the absence of any salt. The same CP decreasing trend follows in the presence of salts. Effect of inorganic counterions (NaF, NaCl and NaBr) on the CP of PMT solutions is shown in Fig. 2. CP increase follows the order: NaBr > NaCl > NaF. Fig. 3 depicts the variation of CP of PMT solution in presence of inorganic co-ions (LiBr, NaBr, KBr and

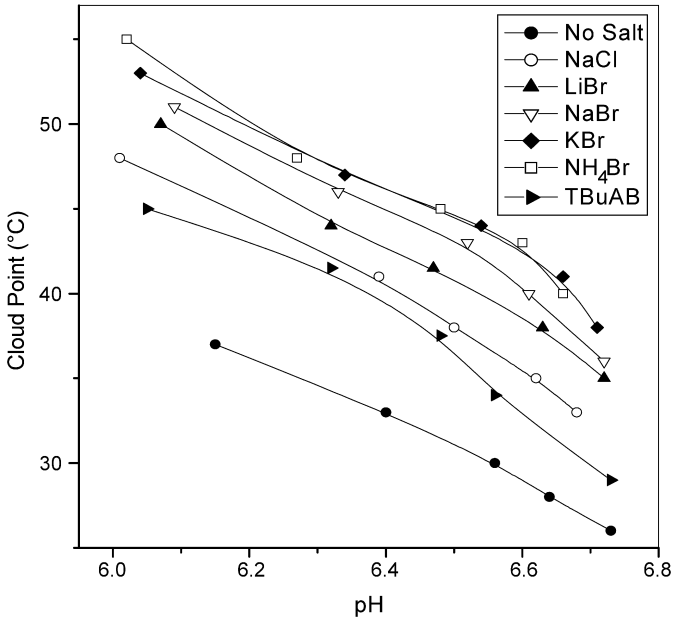

Fig. 1. Effect of pH on the CP of 50 mM PMT solution, prepared in 10 mM sodium phosphate buffer, containing no or a fixed salt concentration (50 mM).

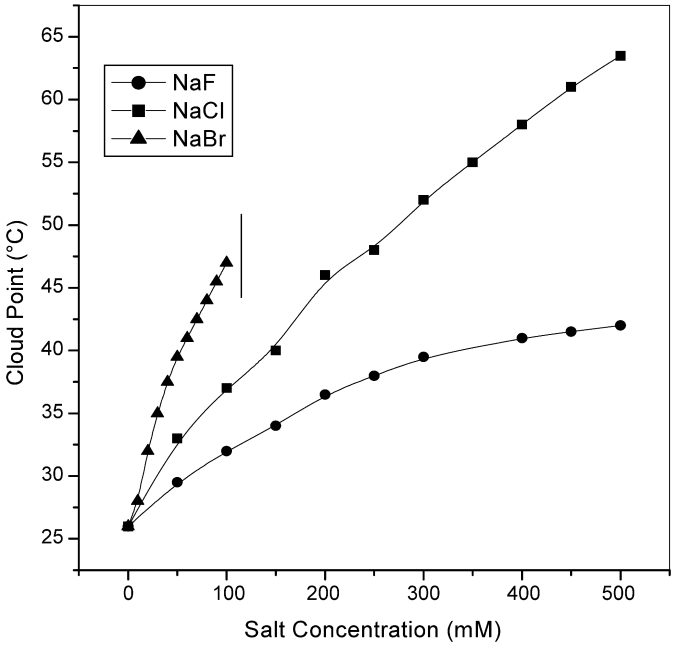

Fig. 2. Effect of anionic counterions on the CP of 50 mM PMT solution, prepared in 10 mM sodium phosphate buffer (pH = 6.7), | indicates precipitation occurring beyond [NaBr] > 100 mM at room temperature (which could be due to formation of nonmicellar phases).