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Mixed micellization between amphiphilic drug promethazine hydrochloride and cationic surfactant (conventional as well as gemini)

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ABSTRACT

The micellization behavior of an amphiphilic drug (promethazine hydrochloride (PMT)) in the presence of cationic surfactants (conventional as well as gemini) has been investigated conductometrically at different concentrations and temperatures. The micellar mole fractions of the surfactant (X_1^{Rub}, X_1^{M}, X_1^{Rod}, and X_1^{id}), calculated by different proposed models, show greater contribution of surfactant in mixed micelle and increases with the increase in concentration of the surfactant. Although α_1 (mole fraction of surfactant) is higher for DTAB than that of 12-4-12, the contribution of 12-4-12 is almost equal to that of DTAB. The interaction parameter (β) is negative at all temperatures and at all compositions indicating attractive interactions. Activity coefficients (f_1 and f_2) are always less than unity suggesting nonideality in the systems. Thermodynamic parameters suggest dehydration of the hydrophobic part of the drug at or above a certain temperature.

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1. Introduction

In an aqueous medium, amphiphiles in pure and mixed states self-assemble to form micelles. The threshold concentration of micellization, called the critical micellar concentration (*cmc*), is an important criterion for understanding the fundamentals of the self-organizing process. When two (or more) types of amphiphiles are in solution, a complex balance of intermolecular forces is responsible for the formation of mixed micelles as opposed to the formation of micelles by one type of amphiphile [1] and their properties are more interesting than of pure amphiphiles, from both physicochemical and application points of view. By virtue of the better performances in solubilization, transportation, and so forth, mixed surfactants have gained importance in the industrial, pharmaceutical, and biological fields [2].

In the past few decades, considerable attention has been focused on the development of new drug delivery systems which should ideally fulfill two prerequisites: (i) it should deliver the drug at a rate directed by the needs of the body, over a period of treatment, and (ii) it should channel the active entity to the site of action. Poor solubility and hydrophobicity of drugs limit their possible applications in drug formulation and delivery development [3].

In this context, the use of surfactants as a vector presents advantages in comparison to other alternatives. With drugs, the surfactants can form mixed micelles thereby decreasing the *cmc* of the surfactant. This is important from a pharmacological point of view as, upon intravenous administration, these drug–carrier systems undergo large dilution and micellar systems with very low *cmc* values will remain stable, while systems with high *cmc* values may disintegrate and their content may precipitate in the blood.

Gemini surfactants are a new class of dimer-like surfactants, consisting of two amphiphilic moieties connected at the level of the head groups by a spacer group of varied nature [4]. These surfactants have *cmc* values 10–100 times lower and higher surface activity than conventional ones. The lower *cmc* can be directly attributed to two tails in a single molecule which are more disruptive than individual chains in conventional surfactants. Cationic gemini surfactants, besides their surface activity, also show antibacterial properties [5,6]. Moreover, gemini surfactants can be used in small quantities as compared to conventional surfactants. The prospective applications of gemini surfactants are multi-fold. These include their potential use in cleaning agents and detergents; cosmetics and personal care products; preparative chemistry; pharmaceutical and biological applications; enhanced oil recovery, etc. [7]. One particular mode of application that is currently in vogue is the use of gemini surfactants in drug delivery.

Therefore, it is important to have knowledge of the effect of surfactants on the micellization tendency of drugs as surfactants form mixed micelles with drugs. Keeping the above points in mind, we have studied the effect of cationic surfactants (conventional as well as gemini) on the micellization behavior of the amphiphilic drug promethazine hydrochloride (PMT) at surfactant concentrations as low as possible in order to

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avoid formation of surfactant micelles. Also, the effect of temperature is seen on the process of micellization and different thermodynamic parameters are calculated. Analysis of thermodynamic parameters, combined with the study of physicochemical properties of the phenomena, allows an understanding of how the two molecules interact, and why they do so.

2. Materials and methods

2.1. Materials

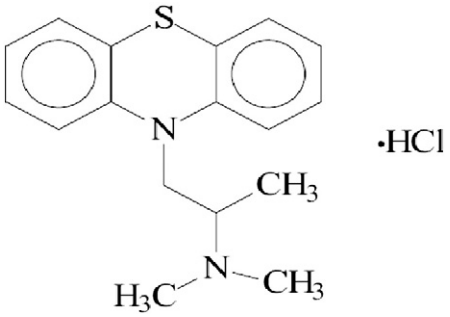
The amphiphilic drug promethazine hydrochloride, PMT (10-[2-(dimethylamino)propyl] phenothiazine hydrochloride) (≥98%, CAS Registry No. 58-33-3, Sigma, USA), and cationic conventional surfactant dodecyltrimethylammonium bromide, DTAB (≥98%, TCI, Japan) were used as received. Cationic gemini surfactant 1,4-bis(*N*-dodecyl-*N*,*N*-dimethylammonium)butane bromide (12-4-12) was synthesized by refluxing α,ω-dibromobutane with an excess of *N*,*N*-dimethyldodecylamine in dry ethanol for 2–3 days followed by more than four recrystallizations using a mixture of ethanol and ethyl acetate [8]. ^{1}H NMR, IR and mass spectra of the compound had satisfactory results.

2.2. Conductivity measurements

An ELICO conductivity meter (model CM 180) was used to perform the experiments. 12 ml water (double-distilled) was taken in a cell dipped in a thermostatic water bath. A dip-type conductivity cell of cell constant 1.026 cm^{-1} was inserted into the water. The temperature control was achieved by means of circulating water through a jacketed cell holding the solution under study. The experimental error in temperature was minimized to 0.2 K. The stock solutions of the PMT (with or without surfactant) were prepared in double-distilled water. A known volume of the stock solution was then added to water (in case of no additive) or water containing a fixed concentration of the additive with a pipette and thoroughly mixed, followed by measurement of conductance. This process was repeated after every addition. The conductance increases linearly with the concentration of the drug. The specific conductance was then plotted against drug concentration. The plots showed a change in slope above a certain concentration. The break in the plot, i.e., the point at which the slope changes, is considered as the *cmc* of the solution.

3. Results and discussion

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 [9]. It consists of a rigid, almost planar tricyclic ring system and a short hydrocarbon chain carrying a terminal nitrogen atom (Scheme 1). The nitrogen atom is positively charged/neutral at low/high pHs. It forms small aggregates of 6–12 drug molecules [10]. PMT is also used for the treatment of allergic symptoms. Drug hypersensitivity reactions have also been treated with PMT. It is usually given orally but can also be given by deep intramuscular or slow intravenous injections.



Scheme 1. Molecular structure of PMT.

3.1. Experimental and ideal critical micelle concentrations (cmc and cmc^{id})

The *cmc* values of individual components (on the basis of plots represented in Fig. 1) along with the degree of counterion dissociation (*g*) and thermodynamic parameters (i.e., ΔG^o_m, ΔH^o_m and ΔS^o_m) at different temperatures and compositions are presented in Table 1. The *cmc* values of pure components agree well with the literature values [10,11]. As the hydrophobic parts of the drugs are short, their *cmc* values are higher than most of the conventional surfactants. For surfactants, two hydrophobic chains of gemini 12-4-12 break more water structure and increase the tendency to form micelles. Hence, the *cmc* of 12-4-12 is lower than that of DTAB. Moreover, in the gemini, the presence of a spacer also contributes in *cmc* variation and hence a change in tail length shows a less prominent trend as compared to conventional ones. This is what we have observed in our results: the *cmc* values of DTAB at all temperatures are in line with CTAB and TTAB values whereas in the case of 12-4-12 the values are not so close to the predicted value [12].

Fig. 2 depicts the variation of *cmc* of the drug–surfactant mixed systems with the increase in mole fraction of surfactant (α_1) at different temperatures. The *cmc* values decrease when increasing the α_1. Drugs are known to form mixed micelles with the surfactants [12,13]. As the amount of surfactants added is always lower than their *cmc* values, their mole fraction in solution is lower and hence the *cmc* of the mixed systems remains close to the *cmc* value of the drug.

To get an idea about the nature of interactions among the components, Clint's phase separation model [14] is used. The model relates, through Eq. (1), the ideal mixed *cmc* (cmc^{id}) with the mole fraction (α_i) and *cmc* (cmc_i) values of the individual components

$$\frac{1}{cmc^{id}} = \sum_{i=1}^{n} \frac{\alpha_i}{cmc_i}. \quad (1)$$

The difference in cmc^{id} and experimentally obtained *cmc* gives an idea about ideality in mixed systems. A lower *cmc* value than cmc^{id}

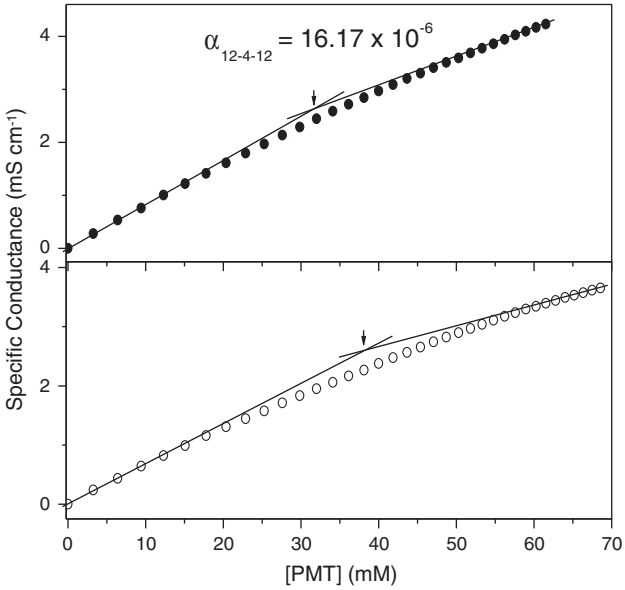


Fig. 1. Representative plots of specific conductance versus concentration of drug with (●) and without (○) surfactant (12-4-12) at 298.15 K.

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