# Amphiphilic Drug Promethazine Hydrochloride−Additive Systems: Evaluation of Thermodynamic Parameters at Cloud Point†

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At the cloud point (CP, where phase separation occurs), the thermodynamic properties of aqueous buffer solution of the amphiphilic phenothiazine drug promethazine hydrochloride (PMT) are calculated in the presence of various additives (viz., alcohols, surfactants, and polymers). PMT undergoes clouding phenomena, which depend upon the physicochemical conditions (e.g., concentration, pH, temperature, etc.). As the clouding components release their solvated water, they separate out from the solution. Therefore, the CP of an amphiphile can be considered the limit of its solubility. Herein, we report the thermodynamics of clouding in PMT in the presence of additives. The standard Gibbs energy change of solubilization ($\Delta_s G^0$) for all of the additives is found to be positive. However, the standard enthalpy change ($\Delta_s H^0$) and the product of temperature and the standard entropy change ($T\Delta_s S^0$) values are negative as well as positive depending upon the type and nature of the additive. The results are discussed on the basis of these factors.

## Introduction

Amphiphilic molecules (viz., surfactants, drugs, polymers, etc.), in an aqueous environment, can form micelles, a kind of self-organized molecular assembly above their critical micelle concentrations (cmc).[1−12] 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 and acceptor, and metal−ligand coordination networks.[13] 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 they can solubilize water-insoluble substances (including certain medicines/drugs) in their hydrophobic cores.[14]

A large number of drug molecules are amphiphilic and, like surfactants, self-associate in aqueous environment to form small aggregates.[15−20] 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.[15] In pharmacy, the interaction of small molecules with drugs is one of the most extensively studied. In this respect, many drugs, particularly those with local anesthetic, tranquillizer, antidepressant, and antibiotic actions, exert their activity by interaction with biological membranes, which can be considered as a complex form of amphiphilic bilayers. Therefore, a full knowledge of the mechanism of the interactions of drugs with other foreign materials is required before the 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).

One of the most important properties of nonionic surfactants is the clouding phenomenon, which can be induced by changing the temperature of the solution. The temperature at which a clear, single phase becomes cloudy and phase separation occurs upon heating is known as the cloud point (CP).[21] The mechanism of clouding in nonionic surfactants, however, is not yet very clear and continues to be a source of controversy among different research groups. However, the occurrence of CP in charged micellar (i.e., ionic surfactants) solutions is not usual except under special conditions, for example, high salt concentration,[22−26] salt-free aqueous solutions of certain surfactants with large headgroups[23,26] or large counterions,[23,25] and some mixed cationic and anionic surfactant solutions.[27] The CP appearance in these systems is explained in terms of increased hydrophobic interactions, dehydration of a hydrophilic group,[25] and formation of large aggregates/clusters.[26]

Like ionic surfactants, some amphiphilic drugs undergo pH-, concentration-, and temperature-dependent phase separation.[28−40] It was observed that their CPs can vary with additives.

Promethazine hydrochloride (PMT) is an amphiphilic drug. It is a phenothiazine with neuroleptic activity, showing a large capacity to interact with biological membranes, and sometimes is used as a local anesthetic.[41] 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). Also, the p$K_a$ value of this drug is 9.1.[42] PMT is often regarded as a model drug for the investigation of interactions between drugs and biological or model membranes.[16] Phenothiazine drugs aggregate in a micelle-like manner with the value of $N_{agg}$ (aggregation number) of the order of 6 to 15.[15,16] As clouding is concentration-, pH-, and temperature-dependent, it is essential to have a knowledge of clouding behavior of the drug under varying conditions.

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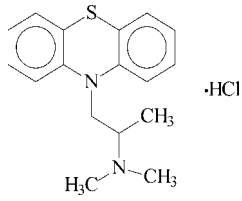
**Scheme 1. Molecular Structure of the Amphiphilic Phenothiazine Drug Promethazine Hydrochloride (PMT) Used in the Present Study**




In our previous studies,[32,33,35,37] we examined the clouding behavior of PMT in aqueous buffer solution (10 mM sodium phosphate buffer) in the presence and absence of additives.[32,33,35,37] In the present paper, we report the thermodynamics of phase separation of the amphiphilic drug PMT (the CP data were taken from literature[33,35]) in the presence and absence of additives. The results have relevance in drug delivery and model drug delivery.

## Materials and Methods

***Materials. Drug.*** 10-[2-(Dimethylamino)propyl]phenothiazine hydrochloride (PMT; ≥ 98 %, Sigma, U.S.A.) was used as received.

***Surfactants.*** Anionic surfactants were sodium dodecyl sulfate, SDS (≥ 99 %, Sigma, U.S.A.), and sodium dodecylbenzene sulfonate, SDBS (≥ 99 %, TCI, Japan). Cationic surfactants were cetyltrimethylammonium bromide, CTAB (≥ 99 %, BDH, England); tetradecyltrimethyl ammonium bromide, TTAB (99 %, Sigma, U.S.A.); cetylpyridinium chloride, CPC (≥ 98 %, BDH, England); and cetylpyridinium bromide, CPB (≥ 99 %, E. Merck, Germany). Nonionic surfactants were *t*-octylphenoxypolyethoxyethanol, TX-100 (≥ 99 %, Fluka, Switzerland); polyethylene glycol dodecylether, Brij 35 (BDH, England); polyoxyethylenesorbitan monolaurate, Tween 20 (LOBA Chemie, India); polyoxyethylenesorbitan monopalmitate, Tween 40 (Koch-Light, England); polyoxyethylenesorbitan monostearate, Tween 60 (LOBA Chemie, India); and polyoxyethylenesorbitan monooleate, Tween 80 (LOBA Chemie, India). All were used as received. The gemini surfactants, 1, 4-butanediyl-α,ω-bis(*N*-hexadecyl-*N*,*N*-dimethylammonium bromide) (16-4-16), 1,5-pentanediyl-α,ω-bis(*N*-hexadecyl-*N*,*N*-dimethylammonium bromide) (16-5-16), and 1,6-hexanediyl-α,ω-bis(*N*-hexadecyl-*N*,*N*-dimethylammonium bromide) (16-6-16) were prepared and characterized by the method reported elsewhere.[43]

***Alcohols.*** 1-Pentanol, $C_5OH$ (> 99 %, Fluka, Switzerland), hexan-1-ol, $C_6OH$ (> 99 %, BDH, England), heptan-1-ol, $C_7OH$ (> 99 %, BDH, England), 1-octanol, $C_8OH$ (> 97 %, Fluka, Switzerland), allyl alcohol (> 95 %, Duchem Lab, India), cyclopentanol (≥ 98 %, Fluka, Switzerland), and cyclohexanol (> 98 %, BDH, India) were used as received.

All polymers [polyvinyl pyrrolidones, PVP's (PVP 15, PVP 25, PVP 30, PVP 60, and PVP 90)] were obtained from Fluka, Switzerland.

Trisodium phosphate dodecahydrate (TSP) and sodium dihydrogen phosphate monohydrate (SDP) were of reagent grade obtained from Merck, India. All of the solutions were prepared in doubly distilled deionized water (steam-distilled water, first time over $KMnO_4$: specific conductivity of (1 to 2) $\mu S \cdot cm^{-1}$).

***Methods.*** The critical aggregation concentration (cac) of PMT in pure water was determined by measuring the surface tension of pure drug solutions of various concentrations at 30 ± 0.5 °C. The drug cac was obtained by plotting surface tension ($\gamma$) against log*C* (*C* is the concentration of PMT (M)). The constancy in $\gamma$ versus log *C* plot was taken as the cac of PMT. The uncertainty in the measured cac was 1 to $2 \cdot 10^5$ M.

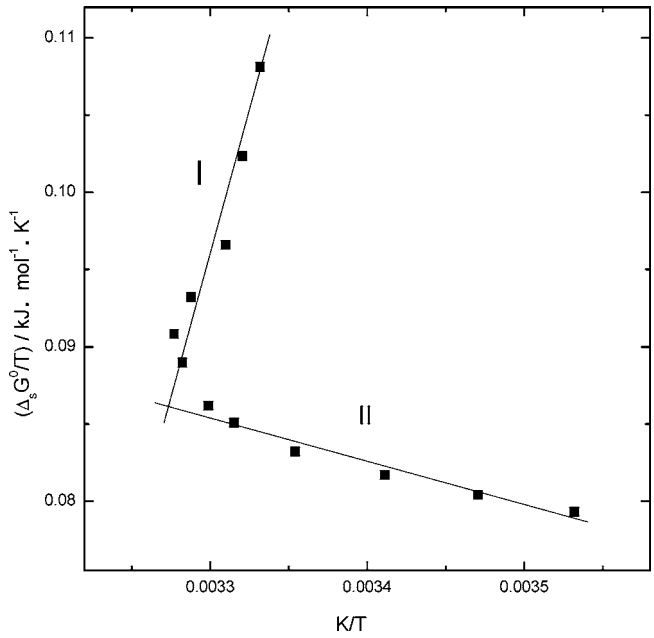



**Figure 1.** $\Delta_s G^0/T$ vs $1/T$ plot of PMT−SDBS system to derive the enthalpy change of clouding ($\Delta_s H^0$). The stages are denoted by I and II.

The experimental method of CP measurements is reported elsewhere.[33] The uncertainty in the measured CP was ± 0.5 °C.

The CP value of a clouding agent (amphiphile) may be treated as the temperature at which the phase separation occurs. The clouding components release their solvated water and separate out from the solution. Assuming that the species attains maximum solubility at the CP, the standard Gibbs free energy change of solubilization ($\Delta_s G^0$) associated with the phase separation from a homogeneous phase to a heterogeneous phase containing pure amphiphile may be calculated from the following relation:

$$\Delta_s G^0 = -RT \ln \chi_s \tag{1}$$

where $\chi_s$ is the mole fraction concentration of additive at CP, *R* is the gas constant, and *T* is the clouding temperature in Kelvin scale. The hypothetical state of ideal solution of unit mole fraction is taken as the standard state.

The standard enthalpy of clouding ($\Delta_s H^0$) was evaluated employing the following equation:

$$\Delta_s H^0 = \frac{\partial(\Delta_s G^0/T)}{\partial(1/T)} \tag{2}$$

Using the Gibbs−Helmoltz equation, the standard entropy of clouding ($\Delta_s S^0$) was obtained:

$$T\Delta_s S^0 = \Delta_s H^0 - \Delta_s G^0 \tag{3}$$

The thermodynamic parameters were calculated using eqs 1 to 3. $\Delta G^0_s/T$ versus $1/T$ curves have two stages (a representative plot is shown in Figure 1): the first stage is enthalpy-controlled, that is, $\Delta_s H^0 > T\Delta_s S^0$, whereas the second stage is controlled by both enthalpy and entropy, that is, $\Delta_s H^0 \approx T\Delta_s S^0$.

## Results and Discussion

The thermodynamic quantities of clouding data for the drug PMT in the presence of additives are evaluated (see Supporting

Information (SI), Tables 1 to 5). These thermodynamic parameters reveal that for all additives $\Delta_s G^0$ is positive. However, $\Delta_s H^0$ and $T\Delta_s S^0$ values are negative or positive depending upon the type and nature of the additives.

***A. Effect of Alcohols.*** The values of the $\Delta_s H^0$ and $T\Delta_s S^0$ were found to be large and negative for all alcohols (see SI, Table 1). At standard conditions, the dissolution of 1 mol of drug in the presence of additives releases heat with an overall ordering of the drug−additive system. These additives (e.g., long chain alcohols, allylalcohol, and cycloalcohols) are only partially soluble in water and, hence, solubilize more in micelles with their head groups toward the surface and alkyl chains penetrating into the micelles. This results in the formation of larger aggregates that ends up with the release of heat with overall ordering in the system.

***B. Effect of Surfactants. i. Anionic Surfactants.*** In the presence of anionic surfactants (both SDS and SDBS), the values of thermodynamics parameters ($\Delta_s H^0$ and $T\Delta_s S^0$) change sign from positive to negative in the concentration range used (see SI, Table 2). Before reaching a certain concentration (cmc), they have the positive $\Delta_s H^0$ and $T\Delta_s S^0$ values, and then after the values of $\Delta_s H^0$ and $T\Delta S^0{}_s$ become negative. At a low concentration of these surfactants (anionic), $\Delta_s H^0$ and $T\Delta_s S^0$ come out to be positive, and $\Delta_s H^0 > T\Delta_s S^0$. At low concentrations, these surfactants hinder micelle formation, and the overall system is in disordered state. As the concentration of surfactant increases, micellar growth increases, and large aggregates form; $\Delta_s H^0$ and $T\Delta_s S^0$ become positive with $\Delta_s H^0 \approx T\Delta_s S^0$.

***ii. Cationic Surfactants. a. Conventional Surfactants.*** At all mole fractions of conventional cationic surfactants, the thermodynamic parameters, both $\Delta_s H^0$ and $T\Delta_s S^0$, are positive (see SI, Table 3). The added cationic surfactants exist in the solution as monomers, micelles, or mixed micelles,[18] which increase the interaggregate repulsion. As the alkyl chain of the cationic surfactant becomes longer, the values of $\Delta_s H^0$ and $T\Delta_s S^0$ decrease. It can be seen (from SI, Table 3) that the addition of bromide surfactants increases the CP more than chloride surfactants and decreases $\Delta H^0{}_s$. The presence of counterion ($Cl^-$/$Br^-$) is responsible for the decrease in surface area occupied per headgroup ($a_o$) with the increase in Mitchell−Ninham parameter, the $R_p$ ($= V_c/a_o l_c$ where $V_c$ is the volume of alkyl part of the drug) value. The degree of counterion binding has an effect on the size and shape of micelles. As the $Br^-$ ion has a stronger binding effect than $Cl^-$, the addition of $Br^-$ causes an increase in $R_p$ and therefore produces lower $\Delta_s H^0$ than $Cl^-$ ions.

***b. Gemini Surfactants.*** Like conventional cationic surfactants, in the presence of cationic gemini surfactants also have positive thermodynamic parameters at all mole fractions (SI, Table 3). Cationic (conventional and gemini) surfactants form mixed micelles with drugs.[18] Above the cmc values of gemini surfactants, the gemini micelles could be present in the solution along with the drug micelles. This would increase the intermicellar repulsions, which causes both $\Delta_s H^0$ and $T\Delta_s S^0$ to be positive (see SI, Table 3). A large effective charge is expected for a spheroidal micelles and a small effective charge for an ellipsoidal morphology.[44] Gemini surfactants with short spacers show a strong tendency for micellar growth and formation of micelles of low curvature, and this ability decreases with the increase in spacer chain length.[45] A surfactant with spacer 4 forms larger micelles than of spacer 6. Therefore, micelles with spacer 4 carry a less effective charge and would create less repulsion, producing lower $T\Delta_s S^0$ values.

***iii. Nonionic Surfactants.*** For nonionic surfactants the $\Delta_s H^0$ values are positive, whether the $T\Delta_s S^0$ values are positive or negative (see SI, Table 4). These surfactants possess hydrophilic oxyethylene chains and form mixed micelles of drug−surfactants[18] which would be highly hydrated. The CP increase with the addition of nonionic surfactants is obviously due to this headgroup hydration, where the randomness of the systems increases (i.e., $T\Delta_s S^0$).

***C. Effect of Polymers.*** The polymers in the present study that we used are the series of PVPs. PVP is biocompatible and a prospective material for use as a serum for artificial blood preparation. Because of the presence of the amide functions in the PVP molecule, it has similarities with protein molecules. In aqueous solution, it remains well-hydrated and does not manifest clouding on heating. It can form a strong purple-colored complex with $I_3^-$ and can be used for deiodification purpose.[46] The desolvation of PVP by heating at temperatures below 100 °C at atmospheric pressure is not sufficient enough to produce insolubility (or clouding) of the material in water.

Like anionic surfactants, in the presence of PVPs, the values of $\Delta_s H^0$ change sign, but they follow the opposite trend [from negative to positive (see SI, Table 5)]. First, they have negative $\Delta_s H^0$ and $T\Delta_s S^0$, and then after a certain concentration (different for different PVPs), the values of $\Delta_s H^0$ become positive. But for all cases, the values of $T\Delta_s S^0$ are negative. Polymers with lower molecular weights have a larger value of $T\Delta_s S^0$ compared to the higher molecular weight polymers. The $T\Delta_s S^0$ value is highest for the lowest molecular weight polymer (PVP 15), whereas the value is lowest for the polymer with highest molecular weight (PVP 90). Here, it is clear that the polymer size have a role to play in changing the thermodynamic parameters. Polymers interact with PMT micelles and vary the water of hydration to a different extent.

The exothermicity of the clouding phenomenon, no doubt, is due to the aggregation of weakly solvated amphiphile molecules and their phasing out into the condensed phase. This is a simplified explanation; otherwise, various environmental and structural factors and their combinations (like desolvation, solvent modification, micellar growth, morphological transition, intermicellar interactions, etc.) have their due share on the energetics of clouding.

## 4. Conclusions

PMT, an amphiphilic phenothiazine drug, undergoes clouding phenomena in the presence and absence of additives. Additives which increase the micelle size decrease the randomness of the system, and hence the $T\Delta_s S^0$ value becomes negative. On the other hand, additives which cause the breakdown of micelles and are water structure breakers give positive $\Delta_s H^0$ and $T\Delta_s S^0$ values. The above two points have clearly been demonstrated by studying the CP of the drug PMT in the presence of various additives.

**Supporting Information Available:**

Tables 1 to 5 which contain the CP and energetic parameters for clouding in 50 mM PMT prepared in 10 mM sodium phosphate buffer solutions (pH = 6.7) in the presence of different additives (viz., alcohols, anionic surfactants, cationic surfactants, nonionic surfactants, and polymers). This material is available free of charge via the Internet at http://pubs.acs.org.

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