Cloud-Point Modulation of an Amphiphilic Drug with Pharmaceutical Excipients

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The purpose of this study was to determine the cloud point of an amphiphilic drug and to search for means to boost or suppress the cloud point, used in pharmaceutical formulations. Organic compounds (amino acids, saccharides, alcohols, surfactants, and polymers), which are used as pharmaceutical excipients, were tested to demonstrate their effect on the cloud point of the amphilphilic drug promethazine hydrochloride (PMT). A number of compounds raised the cloud point of the drug. These excipients can be classified as ionic and nonionic cloud-point boosters (CPBs). The nonionic CPBs include high molecular weight poly(ethylene glycols), poly(oxyethylene cetyl ethers), whereas ionic CPBs are cetylpyridinium chloride (CPC), cetylpyridinium bromide (CPB), cetyltrimethylammonium bromide (CTAB), tetradecyltrimethylammonium bromide (TTAB), dodecyltrimethylammonium bromide (DTAB), 14-*s*-14 ($s = 4, 5, 6$), and 16-*s*-16 ($s = 4, 6$). The cloud-point suppressers include saccharides (sugars), amino acids, and alcohols. The extent of cloud-point (T_{CP}) variation by different excipients is different (dependent on the nature and structure). The thermodynamic parameters are evaluated: whereas ΔG_c° is found to be negative, ΔH_c° and $T\Delta S_c^\circ$ values are negative as well as positive (depending upon the type and nature of the additive).

Introduction

The different types of amphiphilic drugs, such as phenothiazines, tranquillizers, analgesics, peptides, antibiotics, tricyclic antidepressants, and so forth, have various clinical uses.[1−5] Many of the amphiphilic drugs contain one or more (condensed or not) aromatic rings, while others are of peptide nature which may undergo different kinds of associations such as micelles, bilayers, monolayers, and so forth. The spatial separation between the polar and the nonpolar moieties, as well as the shape[6] and hydrophilic−hydrophobic balance,[7] determines their tendency to form different structures which are a function of pH, temperature, ionic strength, concentration, and so forth. An understanding of the self-aggregation mechanism of amphiphilic drugs and their solubilization by surfactants is crucial in the development of effective drug delivery systems. The incorporation of an amphiphilic drug into an aggregate, either upon self-association or by intercalation into other micelles, will affect its physicochemical properties such as the degree of ionization and reaction rates.[8] One such property of amphiphilic drugs as well as that of surfactants which gets affected is clouding or phase separation, the phenomenon generally observed with nonionic surfactant micellar solutions when the temperature is raised to a certain value.[9−11] The phase separation occurs within a narrow temperature range into the micelle-rich phase and micelle-free phase, because of the density difference due to a sharp increase in the aggregation number of the micelles and the decrease in intermicellar repulsion. The observation of T_{CP} in anionic surfactant sodium dodecyl sulfate solutions with symmetrical quaternary (R_4N^+) bromides with $R \geq 4$ is one such example (as already mentioned; whereas the phenomenon is general with nonionic surfactants, it is rare with ionic surfactants).[12−15] Various authors have studied the effect of various additives on the T_{CP} of amphiphilic drugs. Shah et al.[16−19] studied the effect of electrolytes, alcohols, and surfactants on the T_{CP} of AMT, and our own group has been involved in studying the effect of various additives on the T_{CP} of amphiphilic drugs promethazine hydrochloride (PMT), amitriptyline hydrochloride (AMT), imipramine hydrochloride (IMP), and so forth.[20−22]

Amphiphilic drugs solubilize in body fluids and interact with membranes in an organism before they reach their final targets. An understanding of the self-aggregation mechanism of amphiphilic drugs at the molecular level and their solubilization by the surfactant and polymeric micelles is crucial in the rational design of more effective drug delivery systems. As indicated by computer simulations that partitioned drugs accumulate heterogeneously in the membrane, local concentrations may be much higher than in the bulk aqueous phase or even in the other regions in the lipid bilayer.[23,24] Since clouding phenomenon produces a concentration difference, it is essential to have a proper knowledge of clouding behavior of PMT drug under the influence of various additives such as alcohols, saccharides, amino acids, surfactants, and polymers which are present in the living systems. In this work, the tricyclic PMT (used as tranquilizer) was employed as a model amphiphilic drug to study the effect of various excipients mentioned above. The tricyclic portion of the PMT molecule is hydrophobic, and the tertiary amine portion is hydrophilic which becomes protonated (cationic) at low pHs and deprotonated (neutral) at high pHs. The drug solutions were prepared in pentane-1,5-bis(dimethylcetylammonium bromide) (16-5-16, a gemini surfactant) and sodium phosphate buffer (pH = 6.7). The gemini surfactant 16-5-16 has been found to be a better surfactant that can prevent clouding under physiological conditions. It can thus be used as a drug carrier system that increases the storage stability. As the purpose was to find the effect of various excipients on the enhanced stability of the drug and to search the means which can boost or suppress the T_{CP}, the cloud points were determined for the chosen mixture (i.e., PMT + 16-5-16). This study will give further insight about the behavior of the PMT drug, and the experimental results of the present study may be of use to the

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understanding and prediction of the applicability of the drugs under varied physiological conditions.

Materials and Methods

The chemicals, which were used as received, are given as follows: PMT hydrochloride (≥ 0.98 in mass fraction, CAS Registry No. 58-33-3, Sigma, USA), methanol, C_1OH (≥ 0.998 in mass fraction, Ranbaxy, India), ethanol, C_2OH (≥ 0.98 in mass fraction, Merck, Germany), propanol, C_3OH (≥ 0.999 in mass fraction, BDH, India), butanol, C_4OH (≥ 0.999 in mass fraction, Sarabhai, India), pentanol, C_5OH (≥ 0.99 in mass fraction, Fluka, Switzerland), hexanol, C_6OH (≥ 0.99 in mass fraction, BDH, England), heptanol, C_7OH (≥ 0.99 in mass fraction, Merck, Germany), octanol, C_8OH (≥ 0.97 in mass fraction, Fluka, Switzerland), allyl alcohol (Pfizer, USA), ethanediol (≥ 0.99 in mass fraction, BDH, India), propane-diol (≥ 0.98 in mass fraction, BDH, India), cylcopentanol (≥ 0.98 in mass fraction, Fluka, Switzerland), dextrose (≥ 0.99 in mass fraction, Merck, India), fructose (≥ 0.99 in mass fraction, Merck, India), mannose (0.99 in mass fraction, SD fine, India), sorbose (≥ 0.98 in mass fraction, Fluka, Switzerland), arabinose (0.99 in mass fraction, Fluka, Switzerland), aspartic acid (≥ 0.99 in mass fraction), glutamic acid (≥ 0.99 in mass fraction), glycine (≥ 0.995 in mass fraction), phenylalanine (≥ 0.99 in mass fraction), alanine (≥ 0.99 in mass fraction), (all SISCO, India), leucine (≥ 0.999 in mass fraction, E. Merck, Germany), asparagine (≥ 0.99 in mass fraction, Reanal, Hungary), threonine (≥ 0.985 in mass fraction, BDH, England), lysine (≥ 0.98 in mass fraction), arginine (≥ 0.995 in mass fraction) (all Fluka, Switzerland), histidine (0.99 in mass fraction, Loba Chemie, India), lysine monohydrochloride (≥ 0.99 in mass fraction, SD fine, India), arginine monohydrochloride (0.99 in mass fraction, Loba Chemie, India), sodium dodecyl sulfate, SDS (≥ 0.99 in mass fraction, Sigma, USA), sodium dodecylbenzene sulfonate, SDBS (≥ 0.99 in mass fraction, TCI, Japan), cetyltrimethylammonium bromide, CTAB (≥ 0.99 in mass fraction, BDH, England), tetradecyltrimethylammonium bromide, TTAB (0.99 in mass fraction, Sigma, USA), dodecyltrimethylammonium bromide, DTAB (≥ 0.99 in mass fraction, TCI, Japan), cetylpyridinium chloride, CPC (≥ 0.98 in mass fraction, BDH, England), cetylpyridinium bromide, CPB (≥ 0.99 in mass fraction, Merck, Germany), *t*-octylphenoxypolyethoxyethanol, TX-100 (Fluka, Switzerland), polyethoxyglycol *t*-octylphenyl ether, TX-114 (Fluka, Switzerland), polyethylene glycol dodecylether, Brij-35 (BDH, England), polyethylene (10) cetyl ether, Brij-56 (BDH, England), polyethylene (20) cetyl ether, Brij-58 (Merck, Germany), polyoxyethylenesorbitan monolaurate, Tween-20 (LOBA Chemie, India), polyoxyethylenesorbitan monopalmitate, Tween-40 (Koch-Light, England), polyoxyethylenesorbitan monostearate, Tween-60 (LOBA Chemie, India), polyoxyethylenesorbitan monooleate, Tween-80 (LOBA Chemie, India), polyethylene glycols (PEG): PEG-200, PEG-300, PEG-400, PEG-600, PEG-1000 (Fluka, Switzerland), trisodium phosphate dodecahydrate (TSP), and sodium dihydrogen phosphate monohydrate (SDP) (both Merck, India). The gemini surfactants, namely, hexanediyl-α,ω-bis(dimethylcetylammonium bromide) (16-6-16), pentanediyl-α,ω-bis(dimethylcetylammonium bromide) (16-5-16), butanediyl-α,ω-bis(dimethylcetylammonium bromide) (16-4-16), hexanediyl-α,ω-bis(dimethyltetradecylammonium bromide) (14-6-14), pentanediyl-α,ω-bis(dimethyltetradecylammonium bromide) (14-5-14), and butanediyl-α,ω-bis(dimethyltetradecylammonium bromide) (14-4-14) were synthesized according to the protocol

$$\mathrm{Br(CH_2)_mBr} \xrightarrow[\text{reflux}]{a} \mathrm{C_nH_{2n+1}(Me)_2N^+ - (CH_2)_m - {}^+N(Me)_2C_nH_{2n+1}, 2Br^-}$$

$(n = 14,\ 16,\ m = 4 - 6),\ a = \mathrm{C_nH_{2n+1}N(Me)_2}$ (3.0 equiv)

They were characterized by ^{1}H NMR.[25] The purity of the gemini surfactants (≥ 0.99 in mass fraction) was checked by C, H, and N elemental analyses. Mixtures of TSP and SDP were used to fix the pH of the sample solutions.[26] Throughout, double-distilled deionized water (with a specific conductivity of (1 to 2)·10^{-6} S·cm^{-1} was used. Cloud points (T_{CP}) were obtained by placing Pyrex glass tubes (containing the sample solutions) into a temperature-controlled bath, the temperature of which was ramped at the rate of 0.1 K·min^{-1} near the T_{CP}. The temperature at the onset of turbidity in the solution (on heating) was noted. The heating was continued well above this temperature and then discontinued until the solution became clear: this temperature was also noted. The values of the two steps agreed within 0.5 K. The temperature was cycled twice in this way, and the quoted T_{CP} values are the average of two such determinations. The uncertainty in the measured T_{CP} was ± 0.5 K. Unless mentioned otherwise, the pH and drug concentration of the solutions were fixed at 6.7 and 50 mmol·L^{-1}, respectively. An ELICO pH meter (model LI 120, India) with a combination electrode (CL 51 B) was used for the pH measurements.

Results and Discussion

The pK_a value for PMT, whose molecular structure is shown in Figure 1, is 9.1.[27] The critical micelle concentration (cmc) of aqueous PMT solution was determined by the conductivity method and was found to be 38.31 mmol·L^{-1}, which is close to the reported value (44 mmol·L^{-1}).[28] The cloud point (T_{CP}) of pure drug (50 mmol·L^{-1}) in 10 mmol·L^{-1} SP buffer (pH = 6.7) solution was found to be 299 K; on the addition of 2.5 mmol·L^{-1} 16-5-16 gemini surfactant to the drug solution, the T_{CP} increased to 313 K because of electrostatic repulsion within micelles. The concentration of the drug (50 mmol·L^{-1}) used in this study is above the cmc. The T_{CP} decreased with the increase in pH also. As the pH increases, more drug molecules become deprotonated, and hence repulsion due to charge on headgroup decreases. This increases the compactness of micelles and decreases the T_{CP}.

A large number of excipients of different nature and properties were tested at different concentrations to check the stability or phase separation (clouding) of PMT drug by the variation of temperature. The excipients used were alcohols, saccharides, amino acids, surfactants, and polymers. The effect of these excipients is mentioned in detail below.

Effect of Alcohols. The cloud point (T_{CP}) variation of PMT with alcohols depends on the chain length of the alcohol. All of the alcohols decreased the T_{CP}. The T_{CP} variation by methanol to propanol (C_1−OH-C_3−OH) is almost similar; no marked effect is observed by the same alcohol concentration, but butanol (C_4−OH) onward show a obvious decrease in T_{CP} (Figure 2) due to the progressive partitioning of the long-chain alcohols into PMT micelles. Long-chain alcohols usually partition in the headgroup, with the alkyl chain penetrating into the micellar core,[12−14,29,30] which replaces more water near the headgroup region as compared to smaller chain alcohols; thus a lower temperature is required to obtain clouding. Whereas smaller-chain alcohols have the least capacity to micellize (so their tendency to affect T_{CP} is also very small), higher-chain alcohols are effective T_{CP} suppressers. The steric hindrance at the hydrophilic headgroup of PMT leaves only the option of partitioning into micelles, thus reducing the chance of hydro-

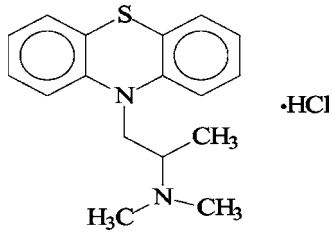


Figure 1. Molecular structure of the amphiphilic drug promethazine hydrochloride (PMT).

philic interactions. Added allyl alcohol molecules are placed outside of the PMT micelles, which hinder the micellar aggregation, resulting in an increase in T_{CP}. Short-chain alcohols are hydrophilic molecules which decrease the polar character of the solution medium. These molecules adsorb preferentially at the micelle−water interface.[17,31,32]

Effect of Saccharides (Sugars). Carbohydrates are structural components of the cell walls and exist as polyhydroxyaldehydes or polyhydroxyketones. The T_{CP} variation by saccharides follows the similar trends (Figure 3) as that of alcohols, that is, they also lower the clouding temperature (T_{CP} suppressers). Carbohydrates are water structure makers;[33] therefore, hydrophobic interactions increase with their addition by removing water molecules surrounding the micelles, which affect the T_{CP} by two ways: (a) a decrease of hydration and (b) making an easy approach of micelles to each other, leading to the formation of large micelles. Arabinose is the most effective in reducing the T_{CP} as compared to other sugars. Arabinose is an aldopentose, a monosaccharide containing five carbon atoms, with three chiral centers and including an aldehyde (CHO) group. The presence of an aldehyde function in the open chain form makes aldose (arabinose) active, thereby removing more water molecules surrounding the micelles as compared to other sugars. The other sugars, though having the same functional group and same number of carbon atoms, differ only in the configuration of the stereogenic (chiral) carbon atom, nearest the aldehyde functional group.

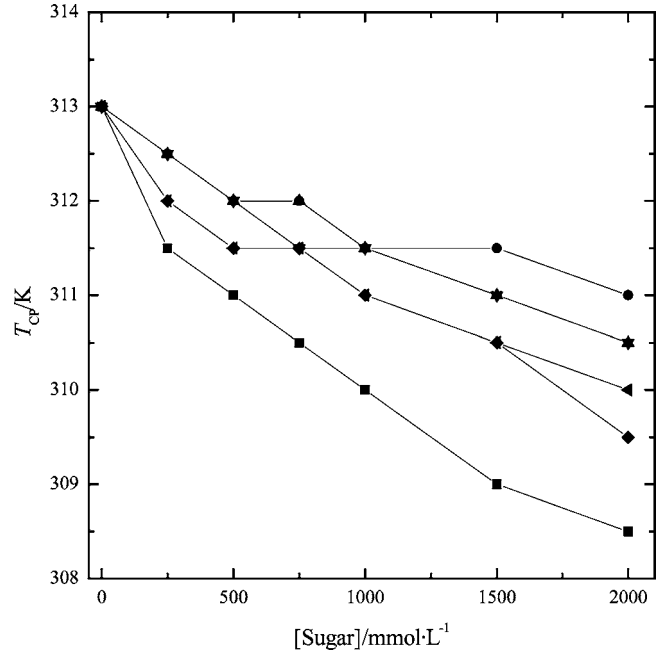
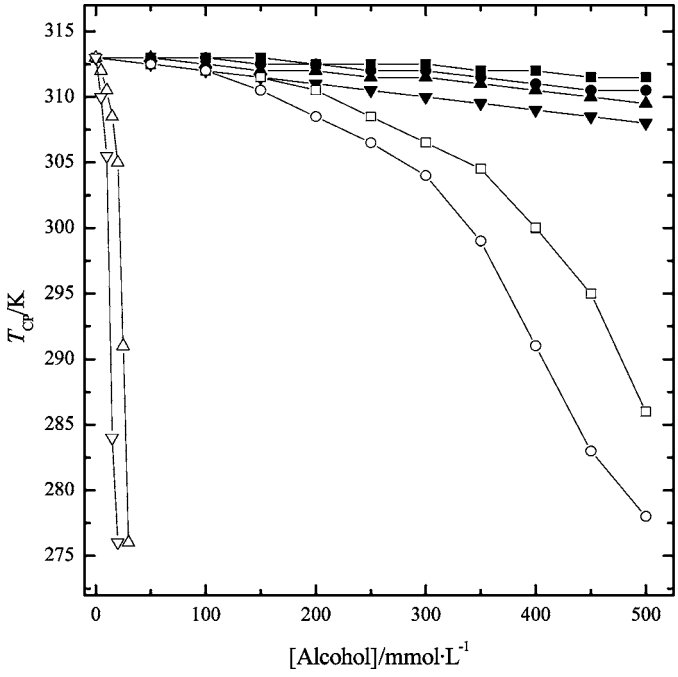


Figure 3. Effect of the addition of saccharides (sugars) on the cloud point of 50 mmol·L^{-1} PMT + 2.5 mmol·L^{-1} 16-5-16 solutions in 10 mmol·L^{-1} sodium phosphate buffer (pH = 6.7): ■, arabinose; ●, dextrose; ▲, fructose; ▼, xylose; ◆, mannose; solid left-pointing triangle, sorbose. Solid lines are for visual purposes.

Effect of Amino Acids. Amino acids are carboxylic acids that contain an amine function. The most important aspect of amino acids that occurs in proteins shares the common feature of being α-amino acids, and the differences among them are in their side chains. Peptide bonds characterize the structure of proteins, but it is the side chain that is mainly responsible for their properties. The major differences between amino acid side chains concern: (a) the size and shape and (b) electronic characteristics and their effects on the ability of side chains to engage in ionic bonding, covalent bonding, hydrogen bonding,



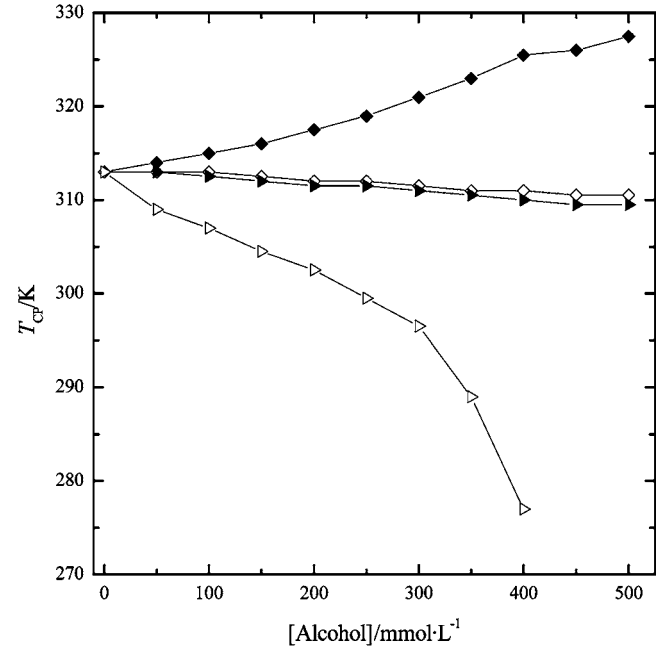


Figure 2. Effect of the addition of alcohols on the cloud point of 50 mmol·L^{-1} PMT + 2.5 mmol·L^{-1} 16-5-16 solutions in 10 mmol·L^{-1} sodium phosphate buffer (pH = 6.7): ■, methanol; ●, ethanol; ▲, propanol; ▼, butanol; □, pentanol; ○, hexanol; △, heptanol; ▽, octanol; ◆, allyl alcohol; ◇, ethane-diol; solid right-pointing triangle, propane-diol; open right-pointing triangle, cyclopentanol. Solid lines are for visual purposes.

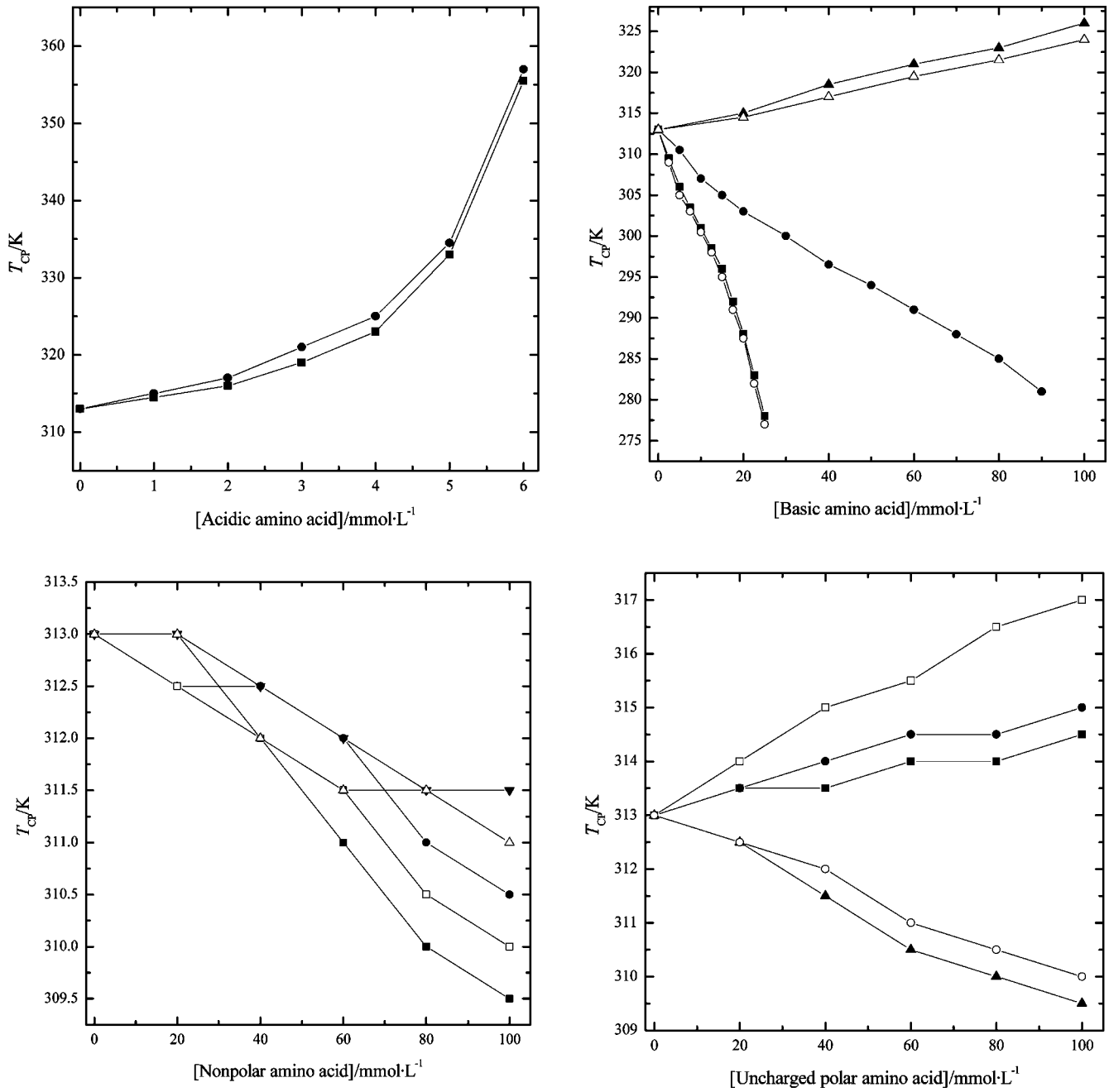


Figure 4. Effect of the addition of amino acids on the cloud point of 50 mmol·L^{-1} PMT + 2.5 mmol·L^{-1} 16-5-16 solutions in 10 mmol·L^{-1} sodium phosphate buffer (pH = 6.7). Acidic amino acids: ■, glutamic acid; ●, aspartic acid. Basic amino acids: ■, arginine; ●, histidine; ○, lysine; ▲, arginine HCl; △, lysine HCl. Nonpolar amino acids: ■, alanine; ●, leucine; ▲, methionine; ▼, valine; □, isoleucine; △, phenylalanine. Uncharged polar amino acids: ■, glutamine; ●, threonine; ▲, serine; □, asparagine; ○, glycine. Solid lines are for visual purposes.

van der Waals forces, and acid−base chemistry. Therefore, the effect of amino acids on the T_{CP} variation will be mainly guided by polar or nonpolar nature of the side chains and also by their acidic or basic nature. Acidic amino acids, having negatively charged side chains and also hydrochloride salts of basic amino acids, interact with the amine group of the PMT molecule at pH = 6.7, enhancing the hydrophilic nature of the headgroup; hence, more hydration leads to an increase in T_{CP}, whereas nonpolar and uncharged polar amino acids partition in the micellar interior, thus reducing the headgroup hydration. As a result, a decrease in T_{CP} is observed. Basic amino acids behave in a manner opposite to that of acidic ones. They prefer a polar environment and would intercalate between monomer head groups. This would replace water from the headgroup region, resulting in the dehydration of micelles, and hence a decrease in T_{CP} is observed (Figure 4). The above discussions on micellar interactions and micellar growth are qualitative explanations. Further studies employing light scattering and fluorescence techniques are needed to make a thorough interpretation of the data, which is the next step of our study.

Effect of Surfactants. Surfactant micelles are of interest to both chemists (because of their unusual catalysis of organic reactions) and biochemists (because of the similarity to biological membranes and globular proteins which can be used as models). Figure 5 shows the effect of surfactants on the clouding behavior of PMT micellar solution.

i. Anionic Surfactants. One can see that the addition of anionic SDS or SDBS to the PMT micellar solutions increases the T_{CP} up to a certain surfactant concentration followed by a decrease. The electrostatic interaction between the anionic

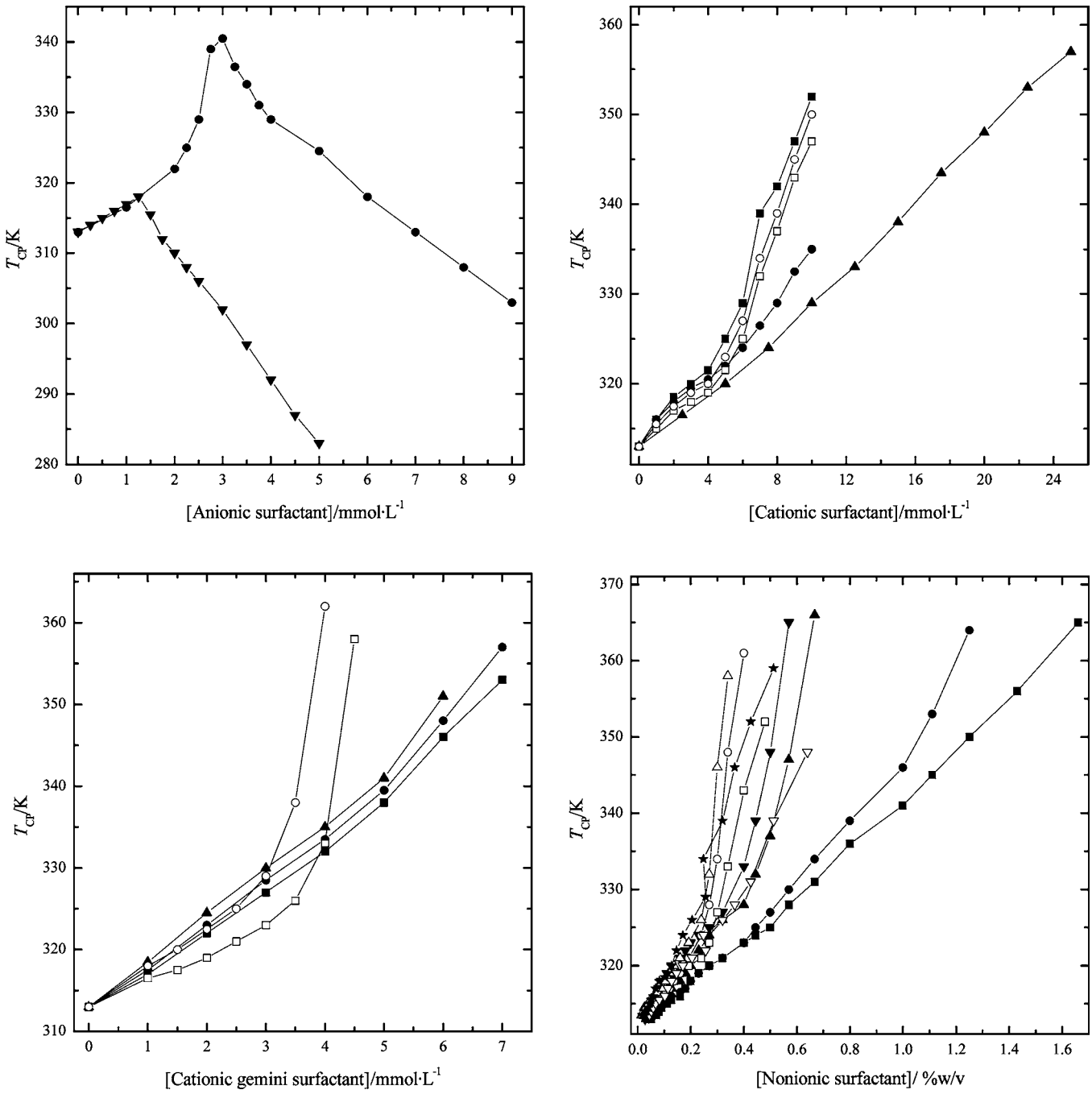


Figure 5. Effect of the addition of surfactants on the cloud point of 50 mmol·L^{-1} PMT + 2.5 mmol·L^{-1} 16-5-16 solutions in 10 mmol·L^{-1} sodium phosphate buffer (pH = 6.7). Anionic surfactants: ●, SDS; ▲, SDBS. Cationic surfactants: ■, CTAB; ●, TTAB; ▲, DTAB; □, CPC; ○, CPB. Cationic gemini surfactants: ■, 14-4-14; ●, 14-5-14; ▲, 14-6-14; □, 16-4-16; ○, 16-6-16. Nonionic surfactants: ■, Tween-20; ●, Tween-40; ▲, Tween-60; ▼, Tween-80; □, Brij-35; ○, Brij-56; △, Brij-58; ▽, TX-100; ★, TX-114. Solid lines are for visual purposes.

surfactant and the PMT hinders the micellar aggregation as reflected by an increase in T_{CP} (i.e., molecules or micelles of the added anionic surfactants are adsorbed on the PMT micellar surface making the PMT micelles difficult to associate), whereas at higher concentrations, alkyl chains (dodecyl) penetrate into the micelle, with polar groups (sulfate anion) remaining in the headgroup region, resulting in the micellar growth, and hence a reduction in T_{CP} is observed. CP variation by SDS is an interesting physicochemically modified process. At low [SDS], it binds with N^+ of the drug with the release of solvated water from the attached centers, increasing the surface charge of micelles, while at a higher concentration range, the surfactant plays the role of salt, and the salt-out effect exists, resulting in the T_{CP} reduction.[34]

ii. Cationic Surfactants. All of the cationic surfactants (CPC, CPB, CTAB, TTAB, DTAB, and their gemini homologues 14-*s*-14 (s = 4, 5, 6) and 16-*s*-16 (s = 4, 6)) boost the T_{CP}. Two structural features of these ionic cloud-point boosters (CPBs) are: (i) a hydrophobic group to allow association with drug molecule and (ii) a net charge to impart electrostatic repulsion to the drug molecules. Long-chain surfactants boost the T_{CP} more than short-chain surfactants showing dependence of the T_{CP} phenomenon on the hydrophobicity of the amphiphile as well as on the nature and charge of headgroup. This is further supported by gemini surfactants, as they are more effective CPBs in comparison to their conventional counterparts, the increase being greater with an increase both in chain and spacer length.

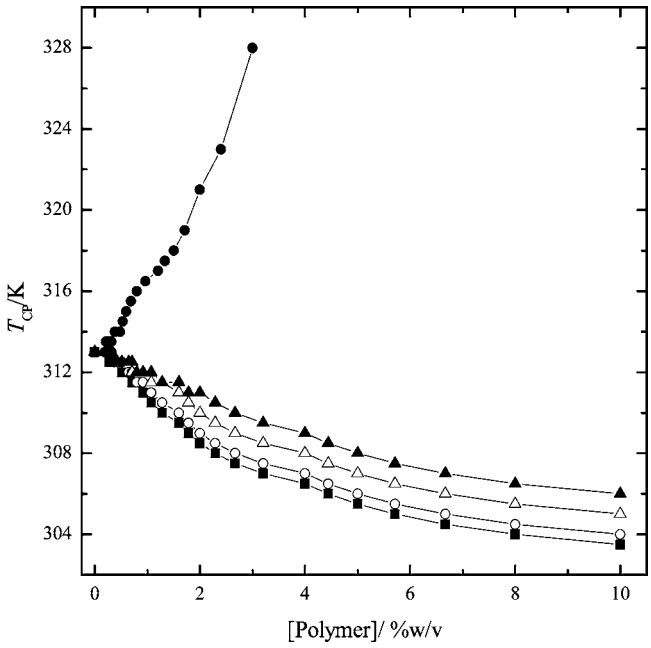


Figure 6. Effect of the addition of polyethylene glycols (PEGs) on the cloud point of 50 mmol·L^{-1} PMT + 2.5 mmol·L^{-1} 16-5-16 solutions in a 10 mmol·L^{-1} sodium phosphate buffer (pH = 6.7): ■, PEG-200; ○, PEG-300; △, PEG-400; ▲, PEG-600; ●, PEG-1000. Solid lines are for visual purposes.

iii. Nonionic Surfactants. The nonionic surfactants with a poly(oxyethylene) headgroup have a large number of oxygen atoms with lone pair of electrons and will have a tendency to interact with the tertiary amine cationic hydrophilic headgroup of the drug-forming complex structures, making it difficult for the PMT micelles to associate; this enhances the T_{CP}. Thus, nonionic CPBs weaken the hydrophilic interactions between the headgroups of the drug molecules. Further details about the mechanism are given in the polymer section.

Effect of Polymers. The phase separation in the presence of polymers finds use in chemical and pharmaceutical processes in solution in combination with other components in salt environments under varied thermal conditions. There has been particular interest in self-assembled micelles with polyethylene glycol (PEG) as the corona-forming block because of its excellent biocompatibility, long blood circulation, and nontoxicity.[33] The plots (Figure 6) show that polymer size seemingly has a role to play in varying the T_{CP} of PMT. Polymers interact with PMT micelles and cause a variation in hydration to a different extent. Low molecular weight polymers suppress the cloud point because of partitioning into PMT micelles, whereas PEG-1000 hinders the micellar aggregation as reflected by sharp increase in T_{CP}. Apart from weakening of the hydrophilic interactions between the headgroups of an amphiphile, a more clear and quantitative approach for understanding the effect of nonionic CPBs is through preferential interaction, which lowers the chemical potential and enhances the solubility of the amphiphile.[35] The effectiveness of PEGs as T_{CP} suppressers measured by the change in cloud point per unit concentration of PEG decreased with increasing molecular weight. In addition to the commonly known interacting forces between the small molecules, one expects the excluded volume (i.e., two molecules cannot occupy the same space at the same time) to come into play in the interaction between the PEG and th eamphiphile.[36] This steric exclusion effect favors the phase separation of the amphiphile and lowers the T_{CP}.

Thermodynamics of Clouding Phenomenon. The appearance of turbidity in the aqueous solution and its separation into two phases has resulted in investigations to determine the effect of solubilization on the temperature at which clouding appears. The clouding components release their solvated water and separate out from the solution and can be considered as the limit of solubility. Assuming that species attain maximum solubility at the T_{CP}, the standard free energy change of clouding (ΔG_c°) associated with phase separation from a homogeneous phase to a heterogeneous phase and hence the standard free energy of clouding (ΔG_c°) of the amphiphile can be evaluated from the relation

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

where X_c is the mole fraction solubility at T_{CP}, R is the gas constant, and T is the clouding temperature in Kelvin scale. The standard enthalpy of clouding, ΔH_c°, and the standard entropy of clouding, $T\Delta S_c^\circ$, can then be evaluated using eqs 2 and 3

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

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

These thermodynamic parameters reveal that for all additives ΔG_c° is negative (Table 1); however, ΔH_c° and $T\Delta S_c^\circ$ values are negative or positive depending upon the type and nature of the additive (the thermodynamic parameters were calculated only for the species which phase-separate with the drug because of either their little solubility or/and the formation of mixed micelles).

Negative Values of ΔH_c° and $T\Delta S_c^\circ$. Cationic (conventional and their gemini homologues) and nonionic surfactants (which boost the T_{CP}) form mixed micelles with the drug, which decrease the overall entropy of the system. At low concentrations for anionic surfactants, values of ΔH_c° and $T\Delta S_c^\circ$ come out to be negative which hinders the micellar aggregation, whereas at higher concentrations, micellar growth occurs, resulting in large aggregates, and values of ΔH_c° and $T\Delta S_c^\circ$ become positive with $T\Delta S_c^\circ > \Delta H_c^\circ$. In cationic (conventional and their gemini homologues) surfactants, values of ΔH_c° and $T\Delta S_c^\circ$ are negative because of an increase in the intermicellar repulsion. The values of ΔH_c° and $T\Delta S_c^\circ$ increase with the increase in chain and spacer length, as short spacer geminis form larger micelles and a less effective charge would create less repulsion, producing lower values of $T\Delta S_c^\circ$. The solubilization of these excipients into the micelles results into the formation of larger aggregates that ends up with the release of heat with overall ordering in the system. The driving force for the overall process is enthalpy-driven as shown by large negative values of ΔH_c°. The difference between the negative values of ΔH_c° and $T\Delta S_c^\circ$ narrows down with the increase in additive concentration with consistent increases in $T\Delta S_c^\circ$; that is, the entropy factor starts to prevail, but the overall process is a compromise of both with a major contribution from the enthalpy factor.

Positive Values of ΔH_c° and $T\Delta S_c^\circ$. The values of ΔH_c° and $T\Delta S_c^\circ$ were found to be positive for all alcohols (C_5-C_8), polymers (except high molecular weight PEG-1000), and a few surfactants (mostly anionic), all of which are cloud-point suppressers. For anionic surfactants SDS and SDBS, the values change sign in the concentration range used (Table 1). The large

Table 1. Energetic Parameters (Standard Free Energy (ΔG_c°), Enthalpy (ΔH_c°), and Entropy ($T\Delta S_c^\circ$)) for Clouding in 50 mmol·L^{-1} PMT + 2.5 mmol·L^{-1} 16-5-16 Prepared in 10 mmol·L^{-1} Sodium Phosphate Buffer Solutions (pH = 6.7) in the Presence of Additives (Alcohols (A), Sufactants (B), and Polymers (C))

mole fraction of additive	ΔG_c° / kJ·mol^{-1}	ΔH_c° / kJ·mol^{-1}	$T\,\Delta S_c^\circ$ / kJ·mol^{-1}	mole fraction of additive	ΔG_c° / kJ·mol^{-1}	ΔH_c° / kJ·mol^{-1}	$T\,\Delta S_c^\circ$ / kJ·mol^{-1}
			(A) Alcohols				
	Pentanol				Hexanol		
$0.90\cdot10^{-3}$[a]	−18.2	19.6	37.8	$0.90\cdot10^{-3}$	−18.2	11.4	29.7
1.80	−16.4		35.9	1.80	−16.4		27.8
2.69	−15.3		34.9	2.69	−15.3		26.7
3.59	−14.5		34.1	3.59	−14.5		25.9
4.48	−13.9		33.5	4.48	−13.8		25.2
5.37	−13.3		32.9	5.37	−13.2		24.6
6.26	−12.9		32.4	6.26	−12.6		24.1
7.15	−12.3		31.9	7.15	−12.0		23.4
8.03	−11.8		31.4	8.03	−11.3		22.8
8.91	−11.2		30.8	8.91	−10.9		22.3
	Heptanol				Octanol		
$0.90\cdot10^{-4}$	−24.2	9.7	33.9	$0.90\cdot10^{-4}$	−24.0	16.0	40.0
1.80	−22.3		32.0	1.80	−21.9		37.9
2.70	−21.1		30.8	2.70	−19.4		35.4
3.60	−20.1		29.9	3.60	−18.2		34.2
4.50	−18.7		28.4				
5.40	−17.3		27.0				
	Cyclopentanol						
$0.45\cdot10^{-3}$	−19.8	50.3	70.1				
0.90	−17.9		68.2				
1.35	−16.7		67.1				
1.80	−15.9		66.2				
2.25	−15.2		65.5				
2.69	−14.6		64.9				
3.14	−13.9		64.2				
3.59	−13.0		63.3				
			(B) Surfactants				
	SDS				SDBS		
$1.80\cdot10^{-5}$	−28.8	−40.7	−11.9	$0.45\cdot10^{-5}$	−32.2	−213.6	−181.5
3.60	−27.4		−13.2	0.90	−30.4		−183.2
4.05	−27.3		−13.3	1.35	−29.5		−184.1
4.50	−27.4		−13.3	1.80	−28.8		−184.8
4.95	−28.0		−12.7	2.25	−28.3		−185.3
5.40	−27.8		−12.8	2.70	−27.6	39.1	66.7
5.85	−27.3	29.8	57.0	3.15	−26.9		66.0
6.30	−26.9		56.6	3.60	−26.4		65.5
6.75	−26.8		56.2	4.05	−25.9		65.0
7.20	−26.1		55.9	4.50	−25.5		64.6
8.99	−25.1		54.9	5.40	−24.7		63.8
10.80	−24.2		53.9	6.30	−23.9		63.0
12.60	−23.3		53.1	7.20	−23.2		62.3
14.40	−22.7		52.4	8.10	−22.5		61.3
16.20	−22.0		51.8	8.99	−21.9		61.0
	CPC				CPB		
$1.80\cdot10^{-5}$	−28.6	−57.5	−28.9	$1.80\cdot10^{-5}$	−28.7	−49.9	−21.2
3.60	−27.0		−30.5	3.60	−27.0		−22.9
5.40	−26.0		−31.5	5.40	−26.1		−23.8
7.20	−25.3		−32.2	7.20	−25.4		−24.5
8.99	−24.9		−32.6	8.99	−25.0		−24.9
10.80	−24.6		−32.8	10.80	−24.8		−25.1
12.60	−24.8		−32.7	12.60	−24.9		−25.0
14.40	−24.8		−32.7	14.40	−24.9		−25.0
16.20	−24.9		−32.7	16.20	−25.0		−24.9
17.99	−24.9		−32.6	18.0	−25.1		−24.8
			−32.6				
	CTAB				TTAB		
$1.80\cdot10^{-5}$	−28.7	−196.9	−168.2	$1.80\cdot10^{-5}$	−28.7	−99.0	−70.3
3.60	−27.1		−169.8	3.60	−27.1		−71.9
5.40	−26.2		−170.8	5.40	−26.1		−72.9
7.20	−25.5		−171.4	7.20	−25.4		−73.6
8.99	−25.2		−171.7	8.99	−25.0		−74.1
10.80	−25.0		−171.9	10.80	−24.6		−74.4
12.60	−25.3		−171.6	12.60	−24.4		−74.6
14.40	−25.2		−171.8	14.40	−24.2		−74.8
16.20	−25.2		−171.7	16.20	−24.1		−74.9
17.99	−25.2		−171.7	17.99	−24.0		−75.0

Table 1. Continued

mole fraction of additive	ΔG_c° / kJ·mol^{-1}	ΔH_c° / kJ·mol^{-1}	$T\,\Delta S_c^\circ$ / kJ·mol^{-1}	mole fraction of additive	ΔG_c° / kJ·mol^{-1}	ΔH_c° / kJ·mol^{-1}	$T\,\Delta S_c^\circ$ / kJ·mol^{-1}
	DTAB				14-4-14		
$0.45\cdot10^{-4}$	−26.4	−45.6	−19.2	$1.80\cdot10^{-5}$	−28.8	−42.5	−13.7
0.90	−24.8		−20.8	3.60	−27.4		−15.1
1.35	−24.0		−21.6	5.40	−26.7		−15.8
1.80	−23.6		−22.0	7.20	−26.3		−16.2
2.25	−23.3		−22.3	8.99	−26.2		−16.3
2.70	−23.1		−22.5	10.80	−26.3		−16.2
3.15	−23.0		−22.6	12.60	−26.4		−16.1
3.60	−23.0		−22.6				
4.05	−22.9		−22.7				
4.50	−22.9		−22.7				
	14-5-14				14-6-14		
$1.80\cdot10^{-5}$	−28.9	−50.8	−21.9	$1.80\cdot10^{-5}$	−28.9	−59.8	−30.9
3.60	−27.5		−23.3	3.60	−27.6		−32.2
5.40	−26.9		−23.9	5.40	−27.0		−32.9
7.20	−26.5		−24.3	7.20	−26.6		−33.3
8.99	−26.3		−24.5	8.99	−26.4		−33.4
10.80	−26.4		−24.3	10.80	−26.7		−33.2
12.60	−26.7		−24.1				
	16-4-16				16-6-16		
$1.80\cdot10^{-5}$	−28.8	−86.9	−58.2	$1.80\cdot10^{-5}$	−28.9	−130.2	−101.3
2.70	−27.8		−59.2	2.70	−28.0		−102.2
3.60	−27.2		−59.8	3.60	−27.5		−102.8
4.50	−26.7		−60.2	4.50	−27.1		−103.2
5.40	−26.4		−60.5	5.40	−26.9		−103.3
6.30	−26.2		−60.7	6.30	−27.2		−103.0
7.20	−26.4		−60.5	7.20	−28.7		−101.5
8.10	−28.1		−58.9				
	Tween-20				Tween-40		
$0.82\cdot10^{-8}$	−48.5	−118.8	−70.3	$0.67\cdot10^{-8}$	−49.0	−122.8	−73.8
1.02	−48.0		−70.8	0.80	−48.6		−74.2
1.17	−48.0		−71.0	0.99	−48.0		−74.8
1.28	−47.5		−71.3	1.09	−47.9		−74.9
1.44	−47.2		−71.5	1.25	−47.6		−75.2
1.76	−46.8		−72.0	1.41	−47.4		−75.4
2.04	−46.5		−72.3	1.72	−46.9		−75.9
2.55	−46.0		−72.8	2.00	−46.6		−76.2
2.87	−45.8		−73.0	2.50	−46.1		−76.7
3.19	−45.7		−73.1	2.81	−45.8		−77.0
3.67	−45.4		−73.4	3.12	−45.7		−77.1
4.31	−45.1		−73.6	3.59	−45.5		−77.3
5.11	−44.8		−74.0	4.21	−45.2		−77.6
6.38	−44.5		−74.3	4.99	−44.9		−77.9
7.08	−44.4		−74.4	6.24	−44.6		−78.2
7.98	−44.2		−74.6	6.93	−44.6		−78.3
9.09	−44.2		−74.6	7.80	−44.5		−78.3
10.60	−44.2		−74.6	8.89	−44.6		−78.3
12.80	−44.4		−74.4	10.40	−44.7		−78.2
15.96	−44.4		−74.4	12.50	−44.8		−78.0
17.70	−44.6		−74.2	15.60	−45.1		−77.7
19.90	−44.9		−73.9	17.30	−45.7		−77.1
22.80	−45.3		−73.5	19.50	−46.8		−76.0
26.50	−46.0		−72.8				
	Tween-60				Tween-80		
$0.44\cdot10^{-8}$	−50.1	−189.6	−139.5	$0.39\cdot10^{-8}$	−50.4	−134.6	−84.2
0.51	−49.8		−139.8	0.44	−50.2		−84.4
0.59	−49.4		−140.1	0.51	−49.8		−84.8
0.70	−49.0		−140.6	0.59	−49.5		−85.1
0.88	−48.5		−141.1	0.70	−49.1		−85.5
0.96	−48.3		−141.3	0.88	−48.6		−86.0
1.10	−48.0		−141.5	0.92	−48.5		−86.1
1.23	−47.8		−141.8	1.10	−48.3		−86.3
1.51	−47.3		−142.2	1.24	−48.2		−86.4
1.76	−47.1		−142.5	1.51	−47.8		−86.8
2.19	−46.6		−142.9	1.76	−47.5		−87.1
2.47	−46.5		−143.1	2.20	−47.1		−87.5
2.74	−46.3		−143.2	2.47	−46.9		−87.7
3.16	−46.3		−143.3	2.75	−46.8		−87.8
3.70	−46.1		−143.4	3.16	−46.5		−88.1
4.39	−45.9		−143.6	3.71	−46.3		−88.4
5.49	−45.6		−143.9	4.40	−46.1		−88.5
6.09	−45.9		−143.7	5.50	−46.3		−88.3
6.86	−46.2		−143.3	6.10	−46.8		−87.8
7.82	−47.2		−142.3	6.87	−47.7		−86.8
9.15	−49.3		−140.2	7.83	−49.7		−84.9

Table 1. Continued

mole fraction of additive	ΔG_c° / kJ·mol^{-1}	ΔH_c° / kJ·mol^{-1}	$T\,\Delta S_c^\circ$ / kJ·mol^{-1}	mole fraction of additive	ΔG_c° / kJ·mol^{-1}	ΔH_c° / kJ·mol^{-1}	$T\,\Delta S_c^\circ$ / kJ·mol^{-1}
	TX-100				TX-114		
$1.44\cdot10^{-8}$	−47.1	−123.7	−76.6	$0.60\cdot10^{-8}$	−49.4	−185.3	−135.9
1.60	−46.8		−76.9	0.69	−49.0		−136.3
1.80	−46.6		−77.1	0.77	−48.7		−136.6
2.06	−46.3		−77.4	0.91	−48.4		−136.9
2.40	−46.0		−77.7	1.11	−47.9		−137.4
2.88	−45.6		−78.1	1.37	−47.4		−137.9
3.60	−45.1		−78.7	1.52	−47.2		−138.1
4.01	−44.9		−78.8	1.72	−46.9		−138.3
4.50	−44.7		−79.0	1.96	−46.7		−138.6
5.14	−44.5		−79.2	2.29	−46.4		−138.9
6.02	−44.3		−79.4	2.74	−46.0		−139.2
7.20	−43.9		−79.8	3.43	−45.5		−139.7
9.01	−43.5	−56.1	−12.6	3.82	−45.3		−139.9
9.99	−43.4		−12.6	4.29	−45.2	−68.0	−22.9
11.30	−43.4		−12.7	4.89	−45.0		−23.0
12.90	−43.3		−12.8	5.73	−44.9		−23.1
15.00	−43.3		−12.8	6.86	−44.7		−23.3
18.00	−43.8		−12.3	8.58	−44.5		−23.5
22.50	−44.3		−11.8	9.52	−44.9		−23.1
				10.70	−45.3		−22.8
				12.30	−45.8		−22.2
				14.30	−46.1		−21.9
				17.20	−46.5		−21.5
	Brij-35				Brij-56		
$0.39\cdot10^{-8}$	−50.5	−277	−226.5	$0.58\cdot10^{-8}$	−49.5	−264.1	−214.7
0.46	−50.1		−227.0	0.68	−49.1		−215.1
0.58	−49.5		−227.5	0.81	−48.6		−215.5
0.63	−49.3		−227.7	1.01	−48.1		−216.1
0.72	−48.3		−228.0	1.11	−47.9		−216.2
0.83	−48.7		−228.3	1.26	−47.6		−216.6
0.96	−48.4		−228.6	1.45	−47.3		−216.8
1.15	−48.0		−229.0	1.69	−46.9		−217.2
1.44	−47.5		−229.5	2.02	−46.5		−217.6
1.61	−47.3		−229.8	2.53	−46.0		−218.1
1.80	−47.0		−230.0	2.82	−45.8		−218.4
2.06	−46.8		−230.2	3.16	−45.5		−218.6
2.40	−46.6		−230.5	3.61	−45.3		−218.8
2.88	−46.2		−230.8	4.22	−45.1		−219.1
3.61	−45.8		−231.2	5.06	−44.9		−219.3
4.06	−45.7		−231.3	6.32	−44.7		−219.5
4.51	−46.0		−231.0	7.11	−44.9		−219.2
5.11	−46.5		−230.5	7.91	−45.4		−218.7
6.01	−47.4		−229.6	8.96	−47.0		−217.2
7.21	−48.1		−228.9	10.50	−48.2		−215.9
	Brij-58						
$0.25\cdot10^{-8}$	−51.7	−371.3	−319.6				
0.27	−51.4		−319.9				
0.31	−51.1		−320.2				
0.35	−50.9		−320.4				
0.41	−50.5		−320.7				
0.49	−50.0		−321.2				
0.62	−49.5		−321.7				
0.67	−49.3		−322.0				
0.77	−49.0		−322.2				
0.89	−48.7		−322.6				
1.02	−48.4		−322.9				
1.23	−48.0		−323.3				
1.54	−47.4		−323.8				
1.71	−47.3		−324.0				
1.92	−47.1		−324.1				
2.19	−46.9		−324.3				
2.56	−46.7		−324.6				
3.07	−46.5		−324.8				
3.48	−46.3		−325.0				
4.32	−46.8		−324.4				
4.80	−48.5		−322.8				
5.44	−49.8		−321.5				

Table 1. Continued

mole fraction of additive	ΔG_c° / kJ·mol^{-1}	ΔH_c° / kJ·mol^{-1}	$T\,\Delta S_c^\circ$ / kJ·mol^{-1}	mole fraction of additive	ΔG_c° / kJ·mol^{-1}	ΔH_c° / kJ·mol^{-1}	$T\,\Delta S_c^\circ$ / kJ·mol^{-1}
			(C) Polymers				
	PEG-200				PEG-300		
$2.30\cdot10^{-7}$	−39.8	247.8	287.6	$1.54\cdot10^{-7}$	−40.9	261.0	301.8
2.52	−39.5		287.3	1.68	−40.6		301.6
2.88	−39.1		287.0	1.92	−40.3		301.2
3.33	−38.8		286.6	2.22	−39.8		300.8
3.87	−38.4		286.2	2.58	−39.4		300.4
4.61	−37.9		285.7	3.07	−39.0		299.9
5.76	−37.3		285.1	3.84	−38.3		299.3
6.39	−37.0		284.8	4.30	−38.1		299.0
7.20	−36.7		284.5	4.80	−37.7		298.7
8.22	−36.2		284.1	5.48	−37.4		298.3
9.63	−35.8		283.6	6.42	−36.9		297.9
11.52	−35.3		283.1	7.68	−36.4		297.3
14.44	−34.6		282.4	9.60	−35.7		296.7
16.02	−34.3		282.1	10.60	−35.4		296.4
18.00	−33.9		281.8	12.00	−35.0		296.0
20.61	−33.5		281.4	13.74	−34.6		295.6
24.03	−33.1		280.9	16.02	−34.2		295.2
28.80	−32.6		280.4	19.20	−33.7		294.6
36.00	−32.0		279.8	24.00	−33.0		294.0
39.95	−31.6		279.5	26.64	−32.7		293.7
45.00	−31.3		279.1	29.99	−32.4		293.3
51.38	−30.9		278.7	34.26	−32.0		292.9
60.02	−30.5		278.3	40.01	−31.5		292.5
71.99	−29.9		277.8	47.99	−31.0		292.0
89.99	−29.3		277.2	59.99	−30.4		291.4
	PEG-400				PEG-600		
$1.52\cdot10^{-7}$	−41.6	240.8	282.3	$0.77\cdot10^{-7}$	−42.7	242.3	285.0
1.26	−41.4		282.1	0.84	−42.4		284.7
1.44	−41.0		281.8	0.96	−42.1		284.4
1.66	−40.6		281.3	1.11	−41.6		283.9
1.93	−40.2		280.9	1.29	−41.2		283.6
2.30	−39.7		280.5	1.54	−40.8		283.1
2.88	−39.2		279.9	1.92	−40.2		282.5
3.20	−38.8		279.6	2.13	−39.9		282.3
3.60	−38.5		279.3	2.40	−39.6		281.9
4.11	−38.2		278.9	2.74	−39.2		281.5
4.81	−37.7		278.4	3.20	−38.8		281.1
5.76	−37.2		278.0	3.84	−38.3		280.6
7.20	−36.6		277.3	4.79	−37.7		280.0
8.01	−36.3		277.0	5.34	−37.1		279.7
8.99	−35.9		276.6	5.99	−37.1		279.4
10.30	−35.5		276.2	6.87	−36.7		279.0
12.01	−35.0		275.8	8.01	−36.2		278.5
14.40	−34.5		275.3	9.60	−35.7		278.0
18.00	−33.9		274.6	12.00	−35.0		277.4
20.00	−33.6		274.3	13.32	−34.7		277.0
22.50	−33.2		274.0	15.00	−34.4		276.7
25.69	−32.8		273.6	17.13	−34.0		276.3
30.01	−32.4		273.1	20.00	−33.5		275.8
35.99	−31.9		272.6	24.00	−33.0		275.3
44.99	−31.2		272.0	30.00	−32.4		274.7
	PEG-1000						
$3.46\cdot10^{-7}$	−38.7	−259.7	−220.9				
3.78	−38.6		−221.1				
4.32	−38.2		−221.5				
4.86	−37.9		−221.8				
5.76	−37.5		−222.2				
6.91	−37.1		−222.6				
8.64	−36.5		−223.4				
9.54	−36.3		−223.7				
10.80	−36.0		−224.0				
12.40	−35.7		−224.3				
14.40	−35.4		−224.7				
17.30	−34.9		−225.3				
21.60	−34.4		−225.5				
23.94	−34.2		−225.8				
27.00	−33.9		−226.0				
30.78	−33.7		−226.2				
36.00	−33.5		−226.2				
43.19	−33.2		−226.5				
53.99	−33.1		−226.6				

[a] All successive mole fraction values are multiplied by the 10^{-x} indicated with the first mole fraction values.

positive values of entropy suggest a highly endothermic process as confirmed by large positive values of ΔH_c°. Positive ΔS_c° values manifest parallelism with micelle formation. The overall system is in a disordered state at the cloud point.

In summary, a number of compounds increased the cloud point of the drug. These excipients can be classified as ionic and nonionic CPBs. The nonionic CPBs include high molecular weight poly(ethylene glycols) and poly(oxyethylene cetyl ethers), whereas ionic CPBs are CPC, CPB, CTAB, TTAB, DTAB, 14-*s*-14 ($s = 4, 5, 6$), and 16-*s*-16 ($s = 4, 6$). The cloud-point suppressers include saccharides, amino acids, and alcohols. The extent of cloud-point variation by different excipients is different depending on their nature and structure.

Conclusions

The cloud point of PMT can be modulated through the proper choice of excipients. The structural features of the ionic CPBs are a hydrophobic group (to allow association with the drug molecule) and a net charge (to impart electrostatic repulsion to the resulting drug−surfactant aggregate). Nonionic CPBs weaken the hydrophilic interactions between the headgroups of the amphiphile. For the excipients which are cloud-point suppressers, the values of ΔH_c° and $T\Delta S_c^\circ$ were found to be positive, whereas for CPBs, the values are negative.

Supporting Information Available:

Cloud point (T_{CP}) data for systems 50 mmol·L^{-1} PMT + 2.5 mmol·L^{-1} 16-5-16 prepared in 10 mmol·L^{-1} sodium phosphate buffer (pH = 6.7) solution for all additives. This material is available free of charge via the Internet at http://pubs.acs.org.

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