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Electrolytes and Polymers Affect the Clouding Behavior of Phenothiazine Drug Promethazine Hydrochloride Solution

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ABSTRACT: Herein we report the clouding behavior of promethazine hydrochloride (PMT) in the absence and presence of electrolytes and polymers. At constant pH, increasing salt additions caused the cloud point (CP; of PMT containing a fixed concentration of a gemini surfactant) to increase, which is explained on the basis of their position in Hofmeister series and the hydrated radii. With quaternary ammonium salts, CP increased due to adsorption/mixed micelle formation. However, the effect of polymer on CP was found to be dependent upon the number of units present in a particular polymer of poly(vinylpyrrolidone) (PVP) category. Thus, the extent of CP variation by different additives is different (dependent on the nature and structure).

INTRODUCTION

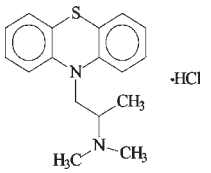
Like surfactants in aqueous solution, amphiphilic drugs (ionic or nonionic) tend to self-aggregate as micelles.[1−3] The drug structure as well as the physicochemical conditions, such as temperature, pH, and electrolyte concentration, have their due share toward aggregation.[1,4,5] This is the reason that micellar properties of the amphiphilic drugs have been investigated under varied conditions. Among many conventional drug delivery systems, designed to modulate the release of a drug over an extended period of time,[6] surfactant micelles, mixed micelles, and polymeric micelles, because of the ease of their preparation and their long shelf life,[7] have been extensively used as drug solubilizing agents as well as drug delivery vehicles. Polymers too are important in a variety of pharmaceutical applications. Polymer conjugated drugs have a prolonged half-life, higher stability and water solubility, and lower immunogenicity and antigenicity.[8−10]

Essentially, the concentration of a drug should be high enough at the targeted site to facilitate the therapeutic effect, but simultaneously, it should not be too high, because this may result in unfavorable side effects. Drugs solubilize in body fluids and interact with membranes before they reach their final targets. Various factors such as physicochemical properties of the drug, presence of excipients, physiological factors such as presence or absence of food, pH, and so on affect the rate and extent of drug absorption from formulations.[11]

Along with many advantages, one disadvantage of surfactants and polymers is their tendency to separate out from the aqueous medium at elevated temperatures. When the temperature is raised to a particular value, the so-called clouding phenomenon is observed, and phase separation occurs, forming the micellar-rich phase, or coacervate, and the micellar-dilute phase. The phenomenon has been found highly dependent on the presence of additives.[12−16] Whereas the occurrence of the clouding in nonionic surfactant solutions is general,[17] in ionic surfactant solutions it is not usual except under special conditions.[18−22] The CP (cloud point) appearance in the latter case is explained in terms of increased hydrophobic interactions, the dehydration of the hydrophilic group[19] and the formation of large aggregates or clusters.[20,21]

Since association behavior of promethazine hydrochloride (PMT), an amphiphilic phenothiazine tranquillizer, is similar to that of surfactants, we explored clouding phenomenon in this drug. PMT possesses a rigid hydrophobic ring system and a hydrophilic amine portion (Scheme 1), which becomes cationic at low pH values and neutral at high pH values ($pK_a = 9.1$[23]). As clouding is concentration-, pH-, and temperature-dependent, it is essential to have knowledge of clouding behavior of the drug under varying conditions.

Scheme 1. Molecular Structure of Amphiphilic Drug Promethazine Hydrochloride (PMT)



In this study we have examined the CP behavior of PMT solutions containing a fixed concentration of a gemini surfactant pentanediyl-α,ω-bis(dimethylcetylammonium bromide) (16-5-16) with and without additives (electrolytes and polymers). The gemini has been found 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 additives on the enhanced stability of the drug and to search the means which can boost/suppress the CP, the cloud points were determined for the chosen mixtures (i.e., PMT + 16-5-16) with electrolytes or polymers as additives.

MATERIALS AND METHODS

PMT (≥ 0.98 in mass fraction, CAS Registry No. 58-33-3, Sigma, USA), inorganic salts, lithium chloride, LiCl (0.98 in mass fraction, Loba Chemie, India), lithium bromide, LiBr (0.994 in mass fraction, Riedel-de Haen, Germany), sodium fluoride, NaF (0.97 in mass fraction, BDH, England), sodium chloride, NaCl (0.999 in

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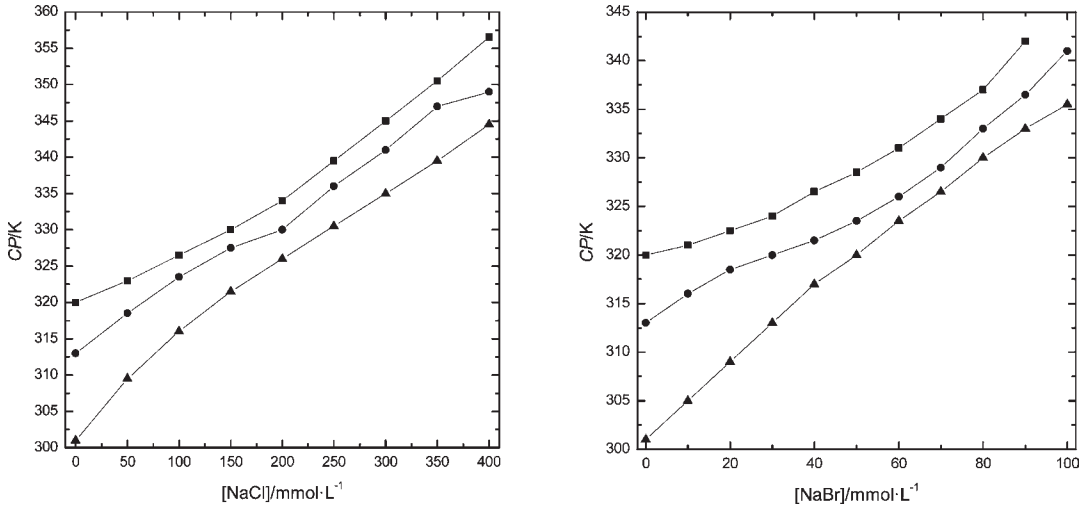

Figure 1. Effect of NaCl and NaBr concentration on the CP of 50 mmol·L^{-1} PMT solutions, prepared in 2.5 mmol·L^{-1} 16-5-16 + 10 mmol·L^{-1} sodium phosphate buffer of different pH values: ■, 6.5; ●, 6.7; ▲, 6.9. Solid lines are for visual purposes.

Table 1. Cloud Point (CP) Data for 50 mmol·L^{-1} PMT + 2.5 mmol·L^{-1} 16-5-16 Prepared in 10 mmol·L^{-1} Sodium Phosphate Buffer Solutions of Different pH Values with Added NaCl and NaBr

	pH = 6.5	pH = 6.7	pH = 6.9		pH = 6.5	pH = 6.7	pH = 6.9
NaCl	CP	CP	CP	NaBr	CP	CP	CP
mmol·L^{-1}	K	K	K	mmol·L^{-1}	K	K	K
0	320	313	301	0	320	313	301
50	323	318.5	309.5	10	321	316	305
100	326.5	323.5	316	20	322.5	318.5	309
150	330	327.5	321.5	30	324	320	313
200	334	330	326	40	326.5	321.5	317
250	339.5	336	330.5	50	328.5	323.5	320
300	345	341	335	60	331	326	323.5
350	350.5	347	339.5	70	334	329	326.5
400	356.5	349	344.5	80	337	333	330
				90	342	336.5	333
				100		341	335.5

mass fraction, BDH, England), potassium chloride, KCl (0.998 in mass fraction, BDH, India), sodium bromide, NaBr (0.998 in mass fraction, Loba Chemie, India), potassium bromide, KBr (0.99 in mass fraction, Merck, India), ammonium chloride, NH_4Cl (0.99 in mass fraction, Merck, India), and ammonium bromide NH_4Br (0.99 in mass fraction, Loba Chemie, India) were used as received. Polymers poly(vinylpyrrolidones) (PVP's: PVP-15, $M_W \sim 10\,000$; PVP-25, $M_W \sim 24\,000$; PVP-30, $M_W \sim 40\,000$; PVP-60, $M_W \sim 160\,000$; PVP-90, $M_W \sim 360\,000$) were obtained from Fluka, Switzerland. The gemini surfactant, pentanediyl-α,ω-bis(dimethylcetylammonium bromide) (16-5-16), was synthesized according to the literature method.[24] Trisodium phosphate dodecahydrate (TSP) and sodium dihydrogen phosphate monohydrate (SDP) were of reagent grade and obtained from Merck (Mumbai, India).

All of the solutions were prepared in double-distilled water with a specific conductivity of (1 to 2)·10^{-6} S·cm^{-1}. Mixtures

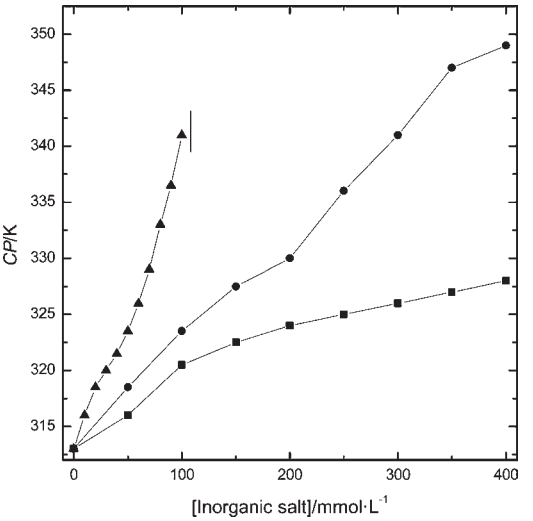

Figure 2. Effect of inorganic salt concentration on the CP of 50 mmol·L^{-1} PMT solutions, prepared in 2.5 mmol·L^{-1} 16-5-16 + 10 mmol·L^{-1} sodium phosphate buffer (pH = 6.7): ■, NaF; ●, NaCl; ▲, NaBr. Solid lines are for visual purposes.

of TSP and SDP were used to fix the pH of the sample solutions.[25] The drug solutions were prepared in sodium phosphate (SP) buffer solutions containing the required concentration of the 16-5-16 gemini.

For determining the cloud point, 2 mL of sample solution was taken in a stoppered Pyrex glass tube (15 mL capacity), which was then placed in a controlled heating apparatus. The temperature was raised slowly, at the rate of 0.5 K·min^{-1} near the CP, and the onset of sudden clouding in the solution was taken as the CP. The reproducibility of the results was ± 0.5 K. An ELICO pH meter (model LI 120, India) with a combination electrode (CL 51B) was used for pH measurements.

■ RESULTS AND DISCUSSION

The critical micelle concentration (cmc) of aqueous PMT solution was determined by a conductivity method and was found

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Table 2. CP Data for 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) with Added Electrolytes (Inorganic Salts)

NaF	CP	NaCl	CP	NaBr	CP	LiCl	CP
mmol·L^{-1}	K	mmol·L^{-1}	K	mmol·L^{-1}	K	mmol·L^{-1}	K
0	313	0	313	0	313	0	313
50	316	50	318.5	50	316	50	316
100	320.5	100	323.5	100	318.5	100	319
150	322.5	150	327.5	150	320	150	322
200	324	200	330	200	321.5	200	326
250	325	250	336	250	323.5	250	331.5
300	326	300	341	300	326	300	336
350	327	350	347	350	329	350	340
400	328	400	349	400	333	400	346

KCl	CP	NH_4Cl	CP	LiBr	CP	NaBr	CP
mmol·L^{-1}	K	mmol·L^{-1}	K	mmol·L^{-1}	K	mmol·L^{-1}	K
0	313	0	313	0	313	0	313
50	319.5	50	320	10	315	10	316
100	324.5	100	326	20	317	20	318.5
150	329.5	150	331	30	319.5	30	320
200	333.5	200	335	40	321	40	321.5
250	338.5	250	340	50	323	50	323.5
300	343	300	346	60	325	60	326
350	349	350	354	70	328	70	329
400	352			80	331	80	333
				90	333.5	90	336.5
				100	337	100	341

KBr	CP	NH_4Br	CP
mmol·L^{-1}	K	mmol·L^{-1}	K
0	313	0	313
10	317	10	317.5
20	319.5	20	320
30	321.5	30	323
40	323.5	40	326
50	326	50	329
60	328.5	60	332
70	331.5	70	335
80	335	80	338
90	338.5	90	341
100	342.5	100	345

to be 38.31 mmol·L^{-1}, which is in agreement with the litreture value (44 mmol·L^{-1}).[2] Therefore, the concentration of the drug was fixed at 50 mmol·L^{-1}, and the solution was prepared in 10 mmol·L^{-1} SP buffer of pH = 6.7. The CP of this solution was found to be 299 K, which increased to 313 K on the addition of 2.5 mmol·L^{-1} 16-5-16 gemini surfactant to this solution. The gemini surfactant concentration (2.5 mmol·L^{-1}) is above its cmc (cmc of 16-5-16 at 298 K = 0.031 mmol·L^{-1}), and the surfactant makes mixed micelles with the drug.[26] Both of the constituent moieties are positively charged, and hence the mixed micelles possess a net positive charge. Therefore, because of increased electrostatic repulsion among the head groups, the CP is increased, and clouding occurs at a much higher temperature.

The stability of the PMT drug by the variation of temperature was checked under different conditions, and the results are detailed below.

a. Effect of pH. As can be seen (Figure 1 and Table 1), the CP of the PMT solutions has been found highly sensitive to the solution pH. The experiments on drug solutions with NaCl/NaBr addition at different fixed pH values show that the CP decreases with increasing pH, at all salt concentrations. As mentioned before, the tricyclic part of PMT molecule (Scheme 1) is hydrophobic, and the *t*-amine portion is hydrophilic. Protonation of the hydrophilic part is highly dependent upon the solution pH: at low pH, the *t*-amine becomes protonated (i.e., cationic), while at high pH, it becomes deprotonated

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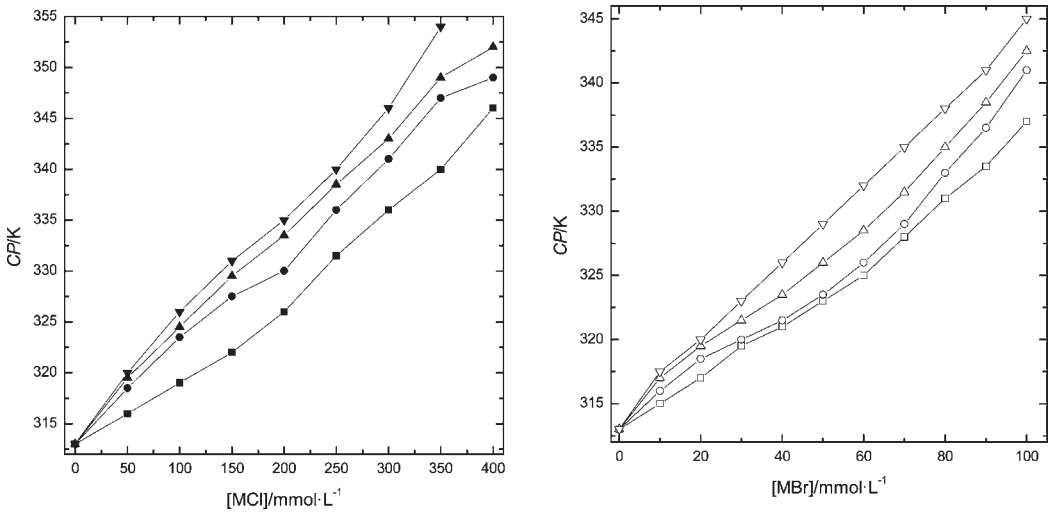

Figure 3. Effect of cationic co-ions: MCl (■, LiCl; ●, NaCl; ▲, KCl; ▼, NH_4Cl) and MBr (□, LiBr; ○, NaBr; △, KBr; ▽, NH_4Br) on the CP of 50 mmol·L^{-1} PMT solutions, prepared in 2.5 mmol·L^{-1} 16-5-16 + 10 mmol·L^{-1} sodium phosphate buffer (pH = 6.7). Solid lines are for visual purposes.

(i.e., neutral). The increase in solution pH, which increases the number of unionized (deprotonated) PMT molecules in micelles and, therefore, reduces the head−head repulsions, causes intermicellar compactness, leading to an increase in micellar aggregation and a decrease in CP.[27,28] Increasing the amount of NaCl/NaBr would, therefore, cause the micellar size to increase progressively[29] with the concomitant increase in CP.

b. Effect of Electrolytes. Figure 2 and Table 2 show the variation of CP of drug solutions as a function of the concentration of added inorganic salts. The order of increase in CP is NaF < NaCl < NaBr (the drug solution with NaBr as additive showed precipitation above 100 mmol·L^{-1} which barred further study). The micelles bear a positive charge, so the halide ions interact electrostatically with them. The degree of binding of halide ions to oppositely charged micelles are known to affect the size and shape of micelles.[2,30] Bromide ions bind strongly to the micelles and increase the size of micelles because it has a large size and small hydrated radius (3.30 Å) as compared to Cl^- and F^-. However, its closer approach to the drug head groups increases the water content of the headgroup region. Fluoride ions, due to large hydrated radius (3.52 Å), bind weakly with the drug head groups and therefore, with NaF addition micelle size/shape changes slowly with the result that CP increase is slow. The size of chloride ion (hydrated radius 3.32 Å) is in between F^- and Br^-; hence the CP increase is intermediate to the two ions. The CP increase with micellar growth has been proposed by Kim and Shah.[27] They observed a larger increase in CP as well as in UV−vis intensity of Sudan III dye solubilized in AMT drug solutions with the addition of NaBr as compared to NaF addition.

The CP increasing trend was found with MBr/MCl (M = Li, Na, K, or NH_4) addition too (Figure 3 and Table 2). The order of effectiveness of CP increase is Li^+ < Na^+ < K^+ < NH_4^+. According to their hydrated radius and salting-out strength, ions are classified into the Hofmeister series.[31] Salts on the left-hand side of this series are water structure-makers and decrease the solute solubility, while salts on the right-hand side are considered as water-structure breakers and increase the solute solubility in water.[32] Also, ions can be classified according to their

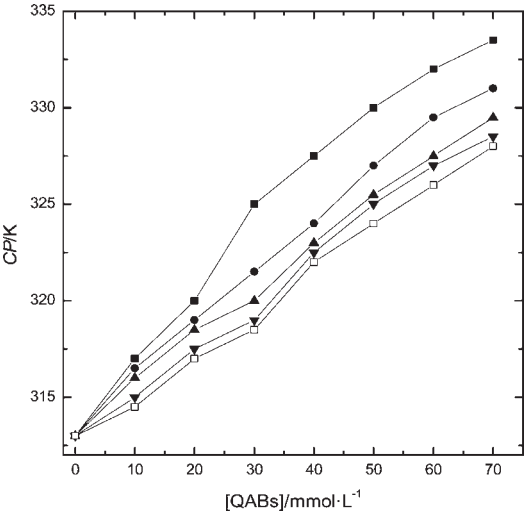

Figure 4. Effect of quaternary ammonium bromide salt (QAB) concentration on the CP of 50 mmol·L^{-1} PMT solutions, prepared in 2.5 mmol·L^{-1} 16-5-16 + 10 mmol·L^{-1} sodium phosphate buffer (pH = 6.7): ■, TMeAB; ●, TEtAB; ▲, TPrAB; ▼, TBuAB; □, TPeAB. Solid lines are for visual purposes.

salting-in/out property which is directly related to adsorption/desorption of the ion.[33] In the series of MCl/MBr salts, Li^+ is highly hydrated (r_h = 3.82 Å) and would act as a water-structure promoter, thereby decreasing the availability of water to the micelles which results in a slow increase in CP. K^+ or NH_4^+ (r_h = 3.31 Å) are comparatively less hydrated than Li^+; therefore, to remove water from micelles, they need much energy which leads the CP to increase sharply. The intermediate effect of Na^+ ion falls in line as expected (the r_h = 3.58 Å of Na^+ lies in between Li^+ and K^+), and comparatively less energy is required to remove water from the micelles in its presence than K^+ or NH_4^+ but more than Li^+.

c. Effect of Quaternary Ammonium Bromides. Figure 4 and Table 3 illustrate the variation of CP with the addition of quaternary ammonium bromides (QABs). The QAB salts increase the CP with the order being: TMeAB > TEtAB > TPrAB >

Table 3. CP Data for 50 mmol·L^{-1} PMT + 2.5 mmol·L^{-1} 16-5-16 Prepared in 10 mmol·L^{-1} Sodium Phosphate Buffer Solution (pH = 6.7) with Added Quaternary Ammonium Bromides (QABs)

TMeAB	CP	TEtAB	CP	TPrAB	CP	TBuAB	CP	TPeAB	CP
mmol·L^{-1}	K	mmol·L^{-1}	K	mmol·L^{-1}	K	mmol·L^{-1}	K	mmol·L^{-1}	K
0	313	0	313	0	313	0	313	0	313
10	317	10	316.5	10	316	10	315	10	314.5
20	320	20	319	20	318.5	20	317.5	20	317
30	325	30	321.5	30	320	30	319	30	318.5
40	327.5	40	324	40	323	40	322.5	40	322
50	330	50	327	50	325.5	50	325	50	324
60	332	60	329.5	60	327.5	60	327	60	326
70	333.5	70	331	70	329.5	70	328.5	70	328

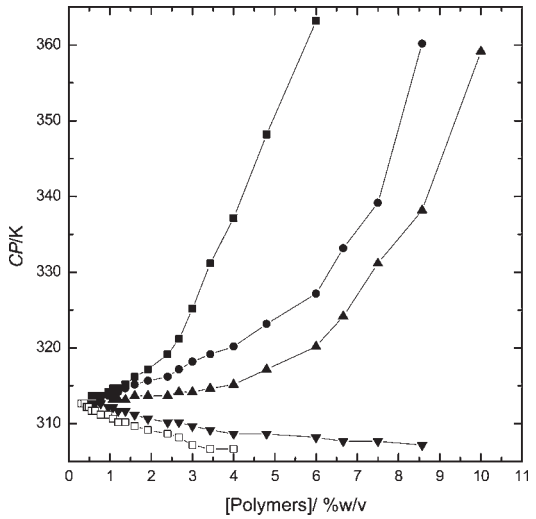

Figure 5. Effect of PVP concentration on the CP of 50 mmol·L^{-1} PMT solutions, prepared in 2.5 mmol·L^{-1} 16-5-16 + 10 mmol·L^{-1} sodium phosphate buffer (pH = 6.7): ■, PVP-15; ●, PVP-25; ▲, PVP-30; ▼, PVP-60; □, PVP-90. Solid lines are for visual purposes.

TBuAB > TPeAB. The tetraalkylammonium ions are well-known water-structure formers; therefore, the CP should increase with the increase in alkyl chain length of QAB. Actually, the CP rise is due to the adsorption/mixed micelle formation factor that dominates over water-structure formation.[34] QAB salts are less hydrated than the inorganic salts and are hydrophobic in nature. In such cases, mixed micelles are formed which would experience greater intermicellar repulsions and consequently higher CP. This indeed has been observed experimentally.

d. Effect of Polymers. PVPs are synthetic polymers, essentially consisting of linear 1-vinyl-2-pyrrolidone groups. These carbon chain polymers containing the amide group as the side substituent have a poly-*N*-vinylamide structure. Due to their water-soluble, nonionic, nontoxic, and biocompatible nature, PVPs are of substantial interest for biomedical applications (even as a serum for artificial blood preparation[35]). PVPs are capable of binding to various drugs, dyes, and toxins and, thus, act as a carrier for various substances in the blood and can be used in controlled delivery of drugs and in eliminating the toxins. In aqueous solution, they remain so well-hydrated that heating at temperatures below 373 K at atmospheric pressure is not sufficient enough to produce insolubility (or clouding) of the material in water.

Table 4. CP Data for 50 mmol·L^{-1} PMT + 2.5 mmol·L^{-1} 16-5-16 Prepared in 10 mmol·L^{-1} Sodium Phosphate Buffer Solution (pH = 6.7) with Added Polymers

PVP-15	CP	PVP-25	CP	PVP-30	CP	PVP-60	CP	PVP-90	CP
% w/v	K	% w/v	K	% w/v	K	% w/v	K	% w/v	K
0	313	0	313	0	313	0	313	0	313
0.55	313.5	0.77	313	1.07	313	0.48	313	0.31	313
0.64	313.5	0.96	313.5	1.20	313	0.55	312.5	0.38	312.5
0.77	313.5	1.07	313.5	1.37	313	0.64	312.5	0.43	312.5
0.96	314	1.20	314	1.60	313.5	0.77	312.5	0.48	312
1.07	314.5	1.37	314.5	1.92	313.5	0.96	312.5	0.55	312
1.20	314.5	1.60	315	2.40	313.5	1.07	312	0.64	311.5
1.37	315	1.92	315.5	2.67	314	1.20	312	0.77	311.5
1.60	316	2.40	316	3.00	314	1.37	311.5	0.96	311
1.92	317	2.67	317	3.43	314.5	1.60	311.5	1.07	311
2.40	319	3.00	318	4.00	315	1.92	311	1.20	310.5
2.67	321	3.43	319	4.80	317	2.40	310.5	1.37	310
3.00	325	4.00	320	6.00	320	2.67	310	1.60	310
3.43	331	4.80	323	6.66	324	3.00	310	1.92	309.5
4.00	337	6.00	327	7.50	331	3.43	309.5	2.40	309
4.80	348	6.66	333	8.57	338	4.00	309	2.67	308.5
6.00	363	7.50	339	10.00	313	4.80	308.5	3.00	308
		8.57	313		313	6.00	308.5	3.43	307
						6.66	308	4.00	306.5
						7.50	307.5		
						8.57	307.5		

The effect of addition of the PVP polymers on the CP of PMT solutions is illustrated in Figure 5 (see Table 4 also). One can see that the lowest molecular weight polymer first increases the CP slowly, and then a rapid increase follows, whereas the polymer with the highest molecular weight produces a decrease, that too, only marginally. Seemingly, the polymer size has a role to play in changing the CP. The PVP polymers interact with PMT micelles and, depending on the size, vary the water of hydration to different extent.

e. Effect of Drug Concentration. Figure 6 and Table 5 present a comparison of the effect of NaCl and NaBr addition

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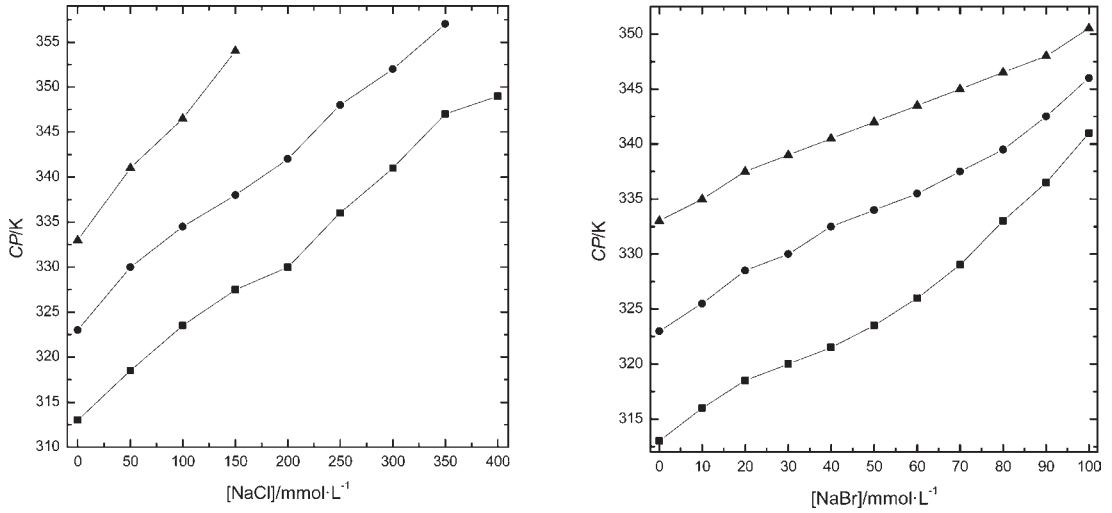

Figure 6. Effect of NaCl and NaBr concentration on the CP of PMT solutions of different fixed concentrations, prepared in 2.5 mmol·L^{-1} 16-5-16 + 10 mmol·L^{-1} sodium phosphate buffer (pH = 6.7): ■, 50 mmol·L^{-1}; ●, 75 mmol·L^{-1}; ▲, 100 mmol·L^{-1}. Solid lines are for visual purposes.

Table 5. CP Data for PMT + 2.5 mmol·L^{-1} 16-5-16 Prepared in 10 mmol·L^{-1} Sodium Phosphate Buffer Solution (pH = 6.7) with Added NaCl and NaBr at Different Fixed Drug Concentrations

	PMT = 50 mmol·L^{-1}	PMT = 75 mmol·L^{-1}	PMT = 100 mmol·L^{-1}		PMT = 50 mmol·L^{-1}	PMT = 75 mmol·L^{-1}	PMT = 100 mmol·L^{-1}
NaCl	CP	CP	CP	NaBr	CP	CP	CP
mmol·L^{-1}	K	K	K	mmol·L^{-1}	K	K	K
0	313	323	333	0	313	323	333
50	318.5	330	341	10	316	325.5	335
100	323.5	334.5	346.5	20	318.5	328.5	337.5
150	327.5	338	354	30	320	330	339
200	330	342		40	321.5	332.5	340.5
250	336	348		50	323.5	334	342
300	341	352		60	326	335.5	343.5
350	347	357		70	329	337.5	345
400	349			80	333	339.5	346.5
				90	336.5	342.5	348
				100	341	346	350.5

on the CP of PMT drug solutions of three different concentrations. As seen earlier, Br^- causes substantial growth; therefore, the observed behavior of it being more effective than Cl^- at each concentration is understandable in the light of enhanced electrical repulsion between the larger cationic micelles. The values of CP are higher for higher drug concentration, but the behavior is similar for all of the PMT concentrations. At any fixed NaCl/NaBr concentration, the increase in drug concentration (50 to 100 mmol·L^{-1}) increases the number, size, and charge of micelles that increases both inter- and intramicellar repulsions, causing an increase in CP.

■ CONCLUSIONS

Knowledge of clouding behavior of amphiphilic drugs and effect of additives on clouding will allow the better designing of effective therapeutic agents. We have performed the CP measurements to investigate the influence of electrolytes and polymers on the micellar behavior of PMT. The addition of electrolytes increased the micellar growth resulting in electrical repulsion and increase in CP. The binding effect for anions and cations was in the order: $Br^- > Cl^- > F^-$ and $Li^+ < Na^+ < K^+$. The trend of increasing CP with addition of increasing amounts of quaternary bromides was found to be dependent upon the alkyl chain length of the particular salt. The effect of addition of PVP polymers was found to be dependent on the polymer size.

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