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Micellization thermodynamics of Cetyltrimethylammonium bromide in presence of Promethazine and Ondansetron hydrochloride drugs at (298.15 K – 318.15 K)

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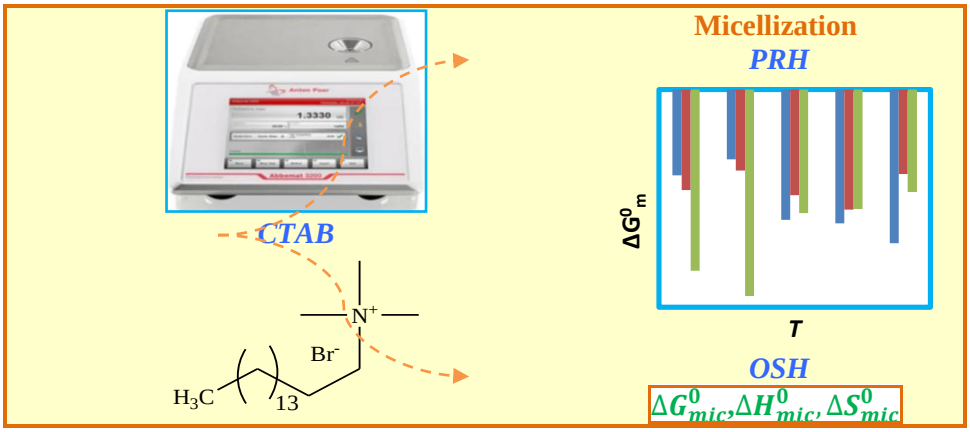
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Abstract
The critical micelle concentration (cmc) of cationic cetyltrimethylammonium bromide (CTAB) surfactant has been determined in presence and absence of antiemetic drugs namely promethazine (PRH) and ondansetron hydrochloride (OSH) at (298.15 K – 318.15 K) and 0.1 MPa by measurement of refractive indices (n) using Anton PaarAbbemat 3200 refractometer. The cmc values along with pre-micellar and post-micellar slopes ($\propto = \boldsymbol{S2/S1}$) of the plots of refractive indices versus concentration of surfactant (0.3 – 2.0 mM) were used to calculate thermodynamic parameters of micellization ($\Delta\boldsymbol{G^0_{mic}}$,$\Delta\boldsymbol{H^0_{mic}}$, $\boldsymbol{and}\Delta\boldsymbol{S^0_{mic}}$).The temperature dependence of cmc,$\Delta\boldsymbol{G^0_{mic}}$,$\Delta\boldsymbol{H^0_{mic}}$, $\boldsymbol{and}\Delta\boldsymbol{S^0_{mic}}$ and enthalpy ($\Delta\boldsymbol{H^0_{mic}}$) – entropy ($\Delta\boldsymbol{S^0_{mic}}$) relationships were studied. Significant effect of temperature has been found on cmc of surfactant.Ondansetron hydrochloride showed negligible effect on cmc and micellization of surfactant. The cmc of surfactant reduced, micellization and micellization thermodynamics has been found to be perturbed in presence of promethazine hydrochloride drug. Strong ion-pair and hydrophobic interactions were observed between amphiphilic promethazine hydrochloride and surfactant. The micellization process has been found to be spontaneous and entropy driven in all the studied systems.
Keywords: *Micelle · CTAB · Antiemetic drugs · CMC · Micellization thermodynamics*

Introduction

Cetyltrimethylammonium bromide (CTAB) is cationic surfactant and it is used to stabilize suspension and emulsions and it has applications in pharmaceutical and biotechnological processes [1].In pharmaceuticals, Cetyltrimethylammonium bromide (CTAB) is used as a solubilizing agent in DNA extraction via protein electrophoresis, where its cation (hexadecyltrimethylammonium) plays a crucial role in binding and precipitating nucleic acids.CTA^+ ($CTAB = CTA^+ + Br^-$) as an antiseptic agent [2-3]. After certain concentration of CTAB its hydrophobic parts minimise the exposure to the solvent and form aggregates which are called as micelles [2, 4].The aggregation number, cmc, physicochemical properties and thermodynamics of micellization of surfactants are affected by structure of surfactant, concentration, presence of additives, temperature, solvent composition and drug co-solutes in aqueous systems [2]. Temperature dependence of selected physical properties enables to determine the thermodynamic parameters for micellization of surfactants in presence of co-solutes. Our earlier work reports the effect of metformin drug on cmc and thermodynamics of micellization of CTAB at different temperatures [1]. Present work reports accurate determination of cmc of CTAB in water and in aqueous-promethazine/ondansetron hydrochloride drugs at different temperatures by the measurement of refractive indices of solutions.In surface chemistry, the micellization is important phenomena which have applications in number of pharmaceutical, industrial processes, petroleum industries, food industries, biological systems, and everyday applications [2-11].



Scheme 1. Schematic presentation of CTAB-PRH/OSH Gibbs free energy and instrumentation

Materials And Methods

The physicochemical properties of the cationic surfactant *cetyltrimethylammonium bromide* (CTAB) and the antiemetic drugs *promethazine* and *ondansetron* employed in the present study are summarized in Table 1. Aqueous solutions of CTAB and its mixtures with the drugs (0.02 mol · kg^{-1}) were prepared by accurately weighing the required quantities of solutes and co-solutes using a single-pan electronic balance (precision ± 0.00001 g). The weighed materials were dissolved in deionized, double-distilled water to obtain the desired concentration range of 0.3 – 2.0 mM. All solutions were prepared gravimetrically and stored in airtight, glass-stoppered bottles to prevent contamination and evaporation.

Refractive indices of the prepared solutions were measured using an Anton Paar compact digital refractometer (Abbemat 3200) with a precision of ± 0.00001. The instrument's internal temperature probe ensured accurate thermal control (± 0.05 K) during measurements. This high-precision setup allowed reliable determination of micellization parameters and thermodynamic quantities under strictly controlled conditions.

Table 1. Details of cationic surfactant (cetyltrimethylammonium)and antiemetic drugs (promethazine and ondansetron)used in the present work

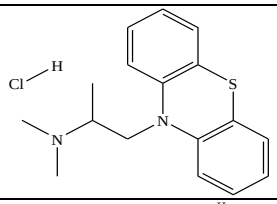
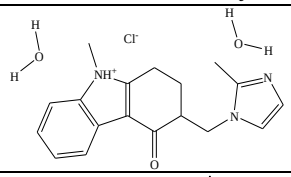
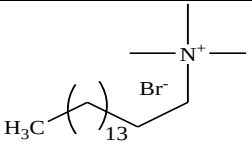
Name of chemical	Chemical formula	Molar mass, ($g \cdot mol^{-1}$)	Structure	Source	CAS number	Mass fraction purity (%)
Promethazine hydrochloride (PRH)	$C_{17}H_{21}N_2SCl$	320.88		Wockhardt Pharm, Aurangabad INDIA	58-33-3	>99.0 %
Ondansetron hydrochloride dihydrate (OSD)	$C_{18}H_{24}ClN_3O_3$	365.86		Cipla Pharma, Mumbai INDIA	103639-04-9	>99.0 %
Cetyltrimethylammonium bromide (CTAB)	$C_{19}H_{42}BrN$	364.46		Hi-Media INDIA	57-09-0	99.0 %

Table 2. Refractive indices of aq.-CTAB, OSH + aqueous-CTAB and PRH + aqueous-CTAB solutions at (298.15 K – 318.15 K) and 0.1 MPa

c/mM	298.15K	303.15K	308.15K	313.15K	318.15K	298.15K	303.15K	308.15K	313.15K	318.15K	298.15K	303.15K	308.15K	313.15K	318.15K
	Aq.-CTAB					*Aq.-CTAB + 0.02 m OSH*					*Aq.-CTAB + 0.02 m PRH*				
0.30	1.33280	1.33230	1.33161	1.33095	1.33011	1.33442	1.33391	1.33325	1.33251	1.33177	1.33448	1.33390	1.33326	1.33250	1.33175
0.50	1.33287	1.33236	1.33171	1.33101	1.33015	1.33448	1.33395	1.33330	1.33255	1.33178	1.33453	1.33395	1.33330	1.33254	1.33177
0.70	1.33296	1.33244	1.33178	1.33107	1.33023	1.33454	1.33399	1.33334	1.33259	1.33181	1.33456	1.33400	1.33332	1.33257	1.33180
0.80	1.33301	1.33249	1.33184	1.33111	1.33027	1.33459	1.33401	1.33337	1.33261	1.33182	1.33457	1.33402	1.33333	1.33258	1.33181
0.90	1.33306	1.33253	1.33187	1.33114	1.33031	1.33462	1.33404	1.33338	1.33263	1.33183	1.33457	1.33404	1.33334	1.33260	1.33182
1.00	1.33307	1.33256	1.33189	1.33117	1.33034	1.33462	1.33406	1.33339	1.33264	1.33185	1.33457	1.33404	1.33336	1.33261	1.33183
1.10	1.33307	1.33256	1.33191	1.33121	1.33037	1.33462	1.33406	1.33340	1.33266	1.33186	1.33457	1.33404	1.33337	1.33262	1.33184
1.20	1.33308	1.33257	1.33193	1.33124	1.33042	1.33463	1.33406	1.33340	1.33267	1.33187	1.33457	1.33404	1.33337	1.33263	1.33186
1.30	1.33308	1.33258	1.33193	1.33127	1.33045	1.33463	1.33407	1.33340	1.33268	1.33188	1.33457	1.33405	1.33337	1.33263	1.33187
1.40	1.33308	1.33258	1.33193	1.33127	1.33048	1.33463	1.33407	1.33340	1.33268	1.33189	1.33457	1.33405	1.33337	1.33263	1.33187
1.50	1.33309	1.33259	1.33194	1.33128	1.33049	1.33464	1.33407	1.33340	1.33268	1.33189	1.33458	1.33405	1.33337	1.33263	1.33187
1.60	1.33309	1.33260	1.33194	1.33128	1.33049	1.33464	1.33408	1.33341	1.33268	1.33189	1.33458	1.33405	1.33337	1.33264	1.33187
1.70	1.33310	1.33260	1.33194	1.33128	1.33050	1.33464	1.33408	1.33341	1.33269	1.33189	1.33458	1.33405	1.33338	1.33264	1.33188
2.00	1.33311	1.33260	1.33195	1.33129	1.33050	1.33465	1.33408	1.33341	1.33269	1.33190	1.33458	1.33405	1.33338	1.33264	1.33188

Results And Discussion

The measured refractive indices of binary aqueous-CTAB and ternary OSH + aqueous-CTAB and PRH + aqueous-CTAB solutions at (298.15 K – 318.15 K) and 0.1 MPa are given in Table 2.

Firstly, the refractive indices are found to be decreasing with rise in the temperature for all the binary and ternary studied systems. The refractive index values are higher in ternary systems compared to binary systems at given temperature which suggests increase in the compactness of solution due to drug-water/surfactant interactions.Variation in the refractive indices with concentration of CTAB in CTAB-water, OSH + CTAB and PRH + CTAB solutions is presented in Figure 1-3.

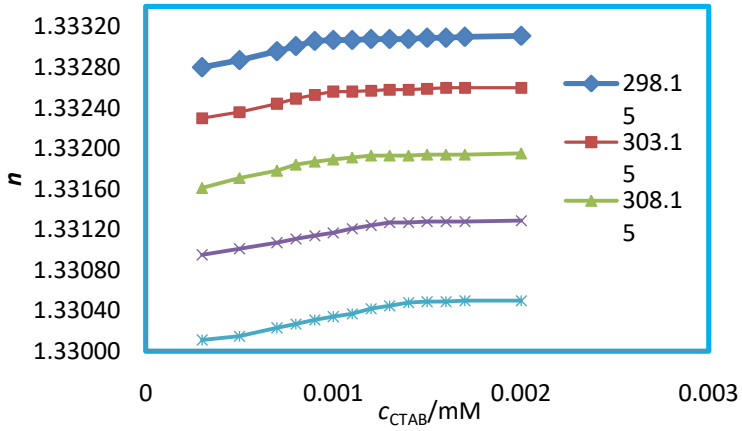


Fig. 1. Plots of refractive index versus concentration of CTAB in water

Effect of presence of drugs on micellization of CTAB

The cmc of CTAB in presence and absence of drugs has been determined form the inflection points in the plots of refractive indices against concentration of CTAB at different temperatures (Figure 1-3)and are given in Table 3. The variation of cmc of CTAB with temperature for different systems is presented in Figure 4. It is observed that the cmc of CTAB increase with rise in the temperature for all the systems. Form Figure 1 it is observed that OSH does not affect the cmc but PRH decrease the cmc of CTAB at all the temperatures. this indicates that in presence of PRH drug, the formation of micelle of CTAB are more favorable which may be due to interactions of ionic hydrophilic head of CTAB with protonated secondary amine group of PRH and hydrophobic tails of CTAB with hydrophobic part of PRH.

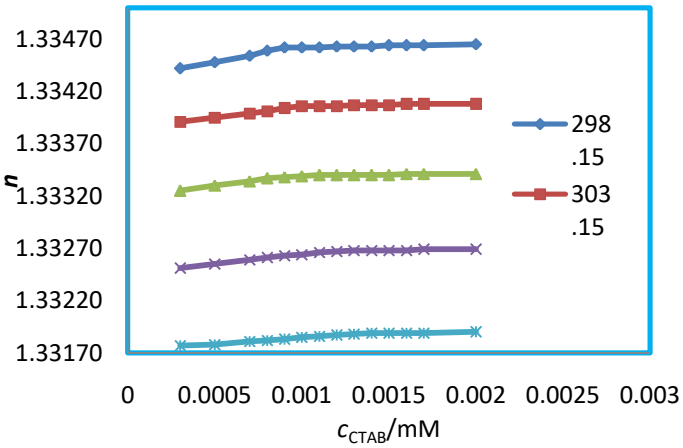


Fig. 2. Plots of refractive index versus concentration of OSH + aqueous-CTAB in solutions

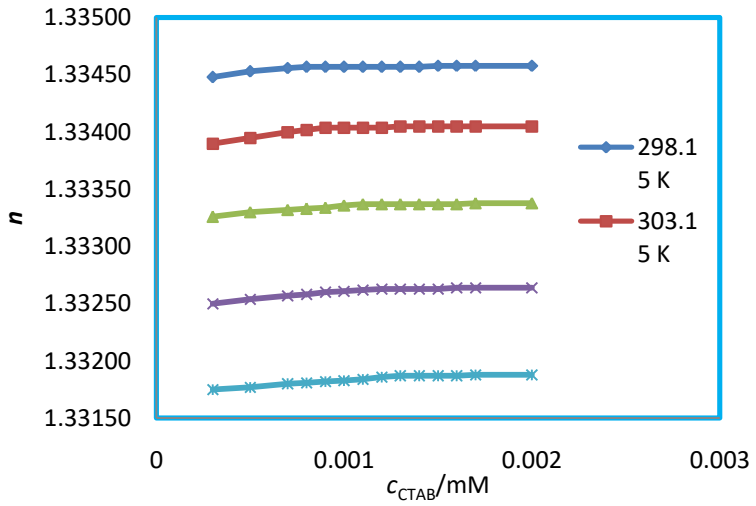


Fig. 3. Plots of refractive index versus concentration of PRH + aqueous-CTAB in solutions

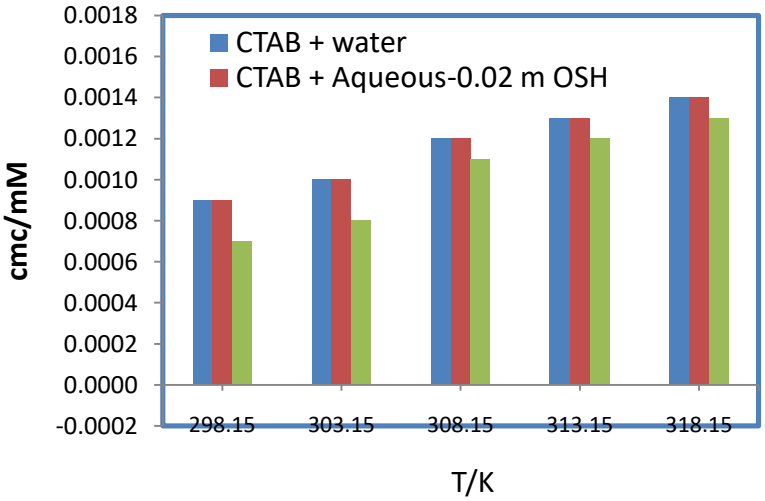


Fig. 4. Variation of cmc of CTAB with temperature for PRH/OSH + aqueous-CTAB solutions

Thermodynamic properties of micellization

The degree of counterion dissociation (β) were computed using per-micellar (S_1) and post-micellar (S_2) slopes of the plots of refractive indices versus concentration of CTAB using following relations [12-17].

$\beta = 1 - \alpha = 1 - S_2/S_1 \ldots (1)$

Where, $\alpha = S_2/S_1$ and S_2 is post micellar slope and S_1 is pre-micellar slope.

The standard Gibb's free energy (ΔG^0_{mic}), enthalpy (ΔH^0_{mic}) and entropy (ΔS^0_{mic}) of micellization of CTAB were calculated using following equations (2-4) [2, 18-21].

$$\Delta G^0_{mic} = (1+\beta)RTln\chi_{cmc} = (2-\alpha)RTln\chi_{cmc} \ldots (2)$$

$$\Delta H^0_{mic} = -(1+\beta)RT^2\left(\frac{dln\chi_{cmc}}{dT}\right)p = -(2-\alpha)RT^2\left(\frac{dln\chi_{cmc}}{dT}\right)p \ldots (3)$$

$$T\Delta S^0_{mic} = \Delta H^0_{mic} - \Delta G^0_{mic} \ldots (4)$$

Where, α is degree of counterion dissociation, β is degree of counterion binding, R is gas constant, T is temperature and χ_{cmc} is mole fraction cmc value of surfactant. The values of ΔG^0_{mic}, ΔH^0_{mic} and ΔS^0_{mic} are presented in Table 3 and evaluation of these properties with temperature is illustrated in Fig. 5-7.

The ΔG^0_{mic} values are negative at all temperatures indicating that the micellization is spontaneous [2, 22-23]. These values are not changing regularly with temperature due to the interactions of CTAB with drugs.The ΔH^0_{mic} values are negative in binary as well as ternary

systems at all the temperatures which indicates the process of micellization is exothermic. These values are nearly same in aqueous-CTAB and OSH + aqueous-CTAB solutions but are appreciably large negative in PRH + aqueous-CTAB solutions. This suggests that the micellization is more exothermic and favorable in presence of PRH. The ΔS^0_{mic} values are positive in all the studied systems at all the temperatures indicating increase in the systems randomness. But these values are relatively very small positive at all the temperatures in the presence of PRH drug. This suggests the ordered structure of PRH-water-CTAB system as compare to CTAB-water or OSH-water-CTAB system.

Therefore, from the comparisonof ΔG^0_{mic} , ΔH^0_{mic} and ΔS^0_{mic} values of all the three studied systems it can be confirmed that the micellization is more favorable and drug-CTAB interactions are present in PRH-water-CTAB systems.

The effect of drug on aggregation can be studied using following relation:

$$\Delta G^0_{trans} = (\Delta G^0_{mic})_{\text{drug + water}} - (\Delta G^0_{mic})_{\text{water}} \ldots (5)$$

Further, the relation between ΔS^0_{mic} and ΔH^0_{mic} is studied with the help of relation (6).

$$\Delta S^0_{mic} = \frac{1}{T_c}\Delta H^0_{mic} + \sigma \ldots (6)$$

From this linear relation, the graph is plotted between ΔS^0_{mic} and ΔH^0_{mic}, where $1/T_c$is slope and is an intercept. The is measure of solute-solvent interaction parameter.

Following relation (7) is a temperature dependence of ΔH^0_{mic} gives$\Delta_m C^0_p$, which is temperature dependent hydrophobic impact.

$$\Delta_m C^0_p = \frac{\partial \Delta H^0_{mic}}{\partial T} \ldots (7)$$

The $\Delta_m C^0_p$ is determined as a slope of ΔH^0_{mic} versus temperature graph.

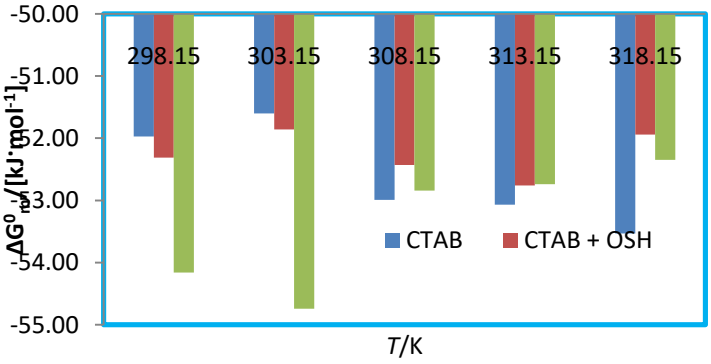


Fig. 5. Plots of Gibb's free energy change for micellization, (ΔG^0_m) versus temperature for PRH/OSH + aqueous-CTAB in solutions

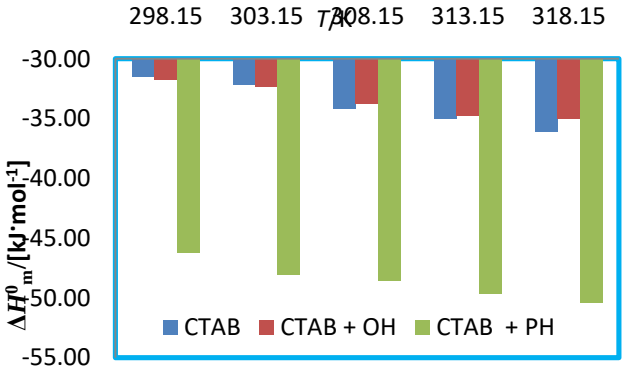


Fig. 6. Plots of enthalpy change for micellization, ΔH^0_m versus temperatureforPRH/OSH + aqueous-CTAB in solutions

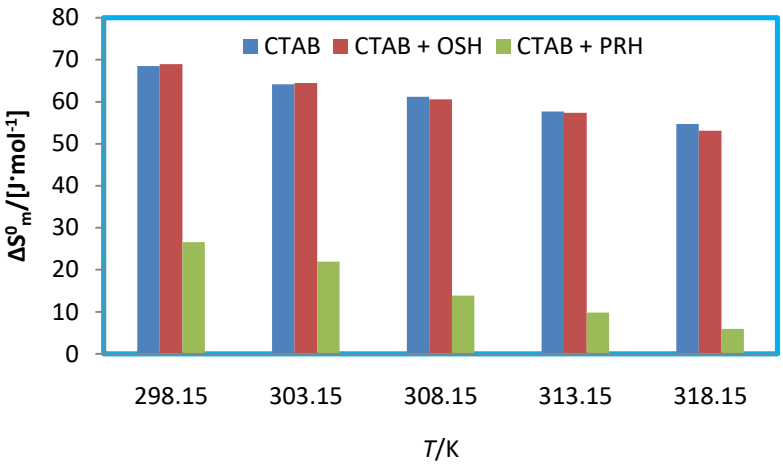


Fig. 7. Plots of enthalpy change for micellization, (ΔS_m^0) versus temperature for PRH/OSH + aqueous-CTAB in solutions

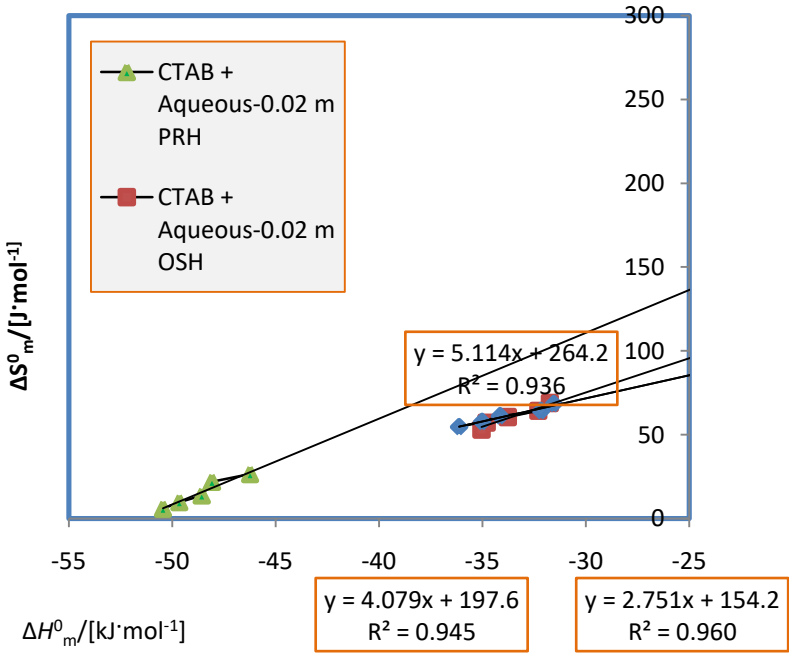


Fig. 8. Plots of ΔH_m^0 versus ΔS_m^0 for PRH/OSH + aqueous-CTAB in solutions

Table 3. The CMC, pre-micellar and post-micellar slopes and related □ and □and thermodynamic parameters of micellization of aqueous-CTAB solutions in presence and absence of OSH/PRH at different temperatures and 0.10 MPa

T/K	CMC [M]	S_1	S_2	X_{cmc}	ΔG^0_m [kJ·mol^{-1}]	ΔH^0_m [kJ·mol^{-1}]	ΔS^0_m [J·mol^{-1}]	ΔG^0_{trans} [kJ·mol^{-1}]	$\Delta_m C^0_p$ [kJ·mol^{-1}K^{-1}]	T_c/K	□ [J·mol^{-1}]
CTAB + water											
298.15	0.0009	0.435	0.043	1.62	-51.97	-31.55	68.48				
303.15	0.0010	0.385	0.048	1.80	-51.60	-32.16	64.13				
308.15	0.0012	0.358	0.027	2.16	-52.99	-34.14	61.17	-	-239.84	363.50	154.2
313.15	0.0013	0.324	0.029	2.34	-53.07	-35.01	57.67				
318.15	0.0014	0.352	0.031	2.52	-53.53	-36.13	54.70				
CTAB + Aq.-0.02 m OSH											
298.15	0.0009	0.336	0.029	1.62	-52.31	-31.75	68.96	-0.34			
303.15	0.0010	0.215	0.025	1.80	-51.86	-32.31	64.48	-0.26			
308.15	0.0012	0.172	0.016	2.15	-52.43	-33.77	60.55	0.57	-181.37	245.16	197.6
313.15	0.0013	0.173	0.017	2.33	-52.76	-34.79	57.37	0.31			
318.15	0.0014	0.116	0.017	2.51	-51.94	-35.04	53.11	1.59			
CTAB + Aq.-0.02 m PRH											
298.15	0.0007	0.180	0.011	1.26	-54.16	-46.24	26.58	-2.19			
303.15	0.0008	0.235	0.012	1.44	-54.74	-48.08	21.96	-3.14			
308.15	0.0011	0.131	0.013	1.97	-52.84	-48.57	13.87	0.15	-200.04	195.69	264.2
313.15	0.0012	0.143	0.016	2.15	-52.74	-49.66	9.84	0.33			
318.15	0.0013	0.120	0.017	2.33	-52.35	-50.45	5.95	1.18			

Conclusion

The *critical micelle concentration* (CMC) of the cationic surfactant cetyltrimethylammonium bromide (CTAB) was found to be strongly dependent on temperature in both aqueous and aqueous drug solutions. The presence of ondansetron hydrochloride (OSH) exhibited negligible influence on the CMC, whereas promethazine hydrochloride (PRH) significantly reduced the CMC of CTAB, indicating enhanced micellization. The thermodynamics of micellization—represented by the parameters ΔGmic0, ΔHmic0, and ΔSmic0—were markedly affected by the presence of both drugs.The micellization process of CTAB was found to be more spontaneous in the presence of PRH, as evidenced by the higher negative values of Gibbs free energy of micellization. Comparative analysis of the two drug systems revealed that PRH forms stronger lateral ion-pair interactions and hydrophobic associations within the CTAB micelle than OSH. These interactions contribute to enhanced micellar stability and lower CMC values. Overall, the study provides valuable insight into the drug–surfactant interaction mechanisms, suggesting that the presence of promethazine hydrochloride significantly modifies the micellization behavior of CTAB. Such findings have potential implications for the design of advanced pharmaceutical formulations and controlled-release systems involving cationic surfactants.

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Conflict Of Interest
The authors of this work declare that they have no conflicts of interest.

References
1. S.D. Deosarkar, A.D. Arsule, T.M. Kalyankar, Effect of antidiabetic metformin hydrochloride on physicochemical properties of cationic surfactant cetyltrimethylammonium bromide in aqueous solutions, Colloids and Surfaces A: Physicochemical and Engineering Aspects 613(2021)126052.
2. Md. Sayem Alam a a,b,* , Krishna Kanangattil a , Athulya Panthakkal a , Aswini Annadurai a,b , Effect of solvent and temperature on the micellization and thermophysical properties of cetyltrimethylammonium bromide , Journal of Molecular Liquids 414 (2024) 126247.
3. A Laemmli, Ulrich K., Cleavage of Structural Proteins during the Assembly of the Head of Bacteriophage T4, %J Nature, 227, 680-685, 1970
4. C. Carnero Ruiz, Thermodynamics of micellization of tetradecyltrimethylammonium bromide in ethylene glycol–water binary mixtures, ColloidPolym.Sci.277(1999)701–707.
5. Z.U. Haq, N. Rehman, F. Ali, N.M. Khan, H. Ullah, Physico-chemical properties of cationic surfactant cetyltrimethylammonium bromide in the presence of electrolyte, J. Mater. Environ. Sci. 8 (2017) 1029–1038.
6. S.M. Shaban, J. Kang, D.-H. Kim, Surfactants: recent advances and their applications, Compos. Commun. 22 (2020) 100537.
7. T.F. Tadros, Applied Surfactants: Principles and Applications, John Wiley & Sons, 2006.
8. T. Wang, D. Chang, D. Huang, Z. Liu, Y. Wu, H. Liu, H. Yuan, Y. Jiang, Application of surfactants in papermaking industry and future development trend of green surfactants, Appl. Microbiol. Biotechnol. (2021) 1–16.
9. Y.-Y. Luk, N.L. Abbott, Applications of functional surfactants, Curr. Opin. Colloid Interface Sci. 7 (2002) 267–275.
10. A.V. Dos Santos, G. Simonelli, L.C.L. Dos Santos, Review of the application of surfactants in microemulsion systems for remediation of petroleum contaminated soil and sediments, Environ. Sci. Pollut. Res. 30 (2023) 32168–32183.
11. M.K. Sah, K. Edbey, Z.O. Ettarhouni, A. Bhattarai, D. Kumar, Conductometric and spectral analyses of dye-surfactant interactions between indigo carmine and N alkyltrimethylammonium chloride, J. Mol. Liq. 399 (2024) 124413
12. J. Aguiar, J. Molina-Bolıvar, J. Peula-Garcıa, C.C. Ruiz, Thermodynamics and micellar properties of tetradecyltrimethylammonium bromide in formamide–water mixtures, J. Colloid Interface Sci. 255 (2002) 382–390.
13. A. Pal, S. Chaudhary, Thermodynamic and aggregation behavior of aqueous tetradecyltrimethylammonium bromide in the presence of the hydrophobic ionic liquid 3-methyl-1-pentylimidazolium hexafluorophosphate, J. Mol. Liq. 207 (2015) 67–72.
14. Md.S. Alam, S.K. Rajendran, J.H. Mondal, E. Linda, A.M. Siddiq, The micellar and thermophysical studies of a surfactant, sodium dodecyl sulfate with a hydrotrope, 3-Nitrobenzene sulfonic acid sodium salt, J. Mol. Liq. 315 (2020) 113815.
15. Md.S. Alam, A.B. Mandal, The clouding phenomena of mixed surfactant (non-ionic Triton X-114+ cationic gemini 16-5-16) solutions: influence of inorganic and organic additives on the cloud point, J. Mol. Liq. 212 (2015) 237–244.
16. T. Gil´anyi, On the counterion dissociation of colloid electrolytes, J. Colloid Interface Sci. 125 (1988) 641–648.
17. R. De, A. Banerjee, S. Santra, B. Das, Counterion dissociation in mixtures of sodium polystyrenesulfonate with different molar masses in aquo-organic media, New J. Chem. 46 (2022) 23245–23253.
18. R. Zana, Critical micellization concentration of surfactants in aqueous solution and free energy of micellization, Langmuir 12 (1996) 1208–1211.

19. L.K. Tiwary, A. Mandal, Md.S. Alam, S. Thennarasu, A.B. Mandal, Thermodynamics studies on tyrosine-hydantoin drug–cetyltrimethylammonium bromide mixed micellar system, Colloids Surf. B Biointerfaces 82 (2011) 126–133.
20. Md.S. Alam, A.B. Mandal, Thermodynamics at the cloud point of phenothiazine drug chlorpromazine hydrochloride additive systems, J. Chem. Eng. Data 55 (2010) 1693–1699.
21. Md.S. Alam, R. Ragupathy, A.B. Mandal, The self-association and mixed micellization of an anionic surfactant, sodium dodecyl sulfate, and a cationic surfactant, cetyltrimethylammonium bromide: conductometric, dye solubilization, and surface tension studies, J. Dispers. Sci. Technol. 37 (2016) 1645–1654.
22. Md.S. Alam, A.M. Siddiq, Density, dynamic viscosity, and kinematic viscosity studies of aqueous solution of a cationic gemini surfactant, hexanediyl-1, 6-bis (dimethylcetylammonium bromide (16-6-16): influence of electrolytes and temperature, J. Mol. Liq. 242 (2017) 1075–1084.
23. W. Li, Y.-C. Han, J.-L. Zhang, L.-X. Wang, J. Song, Thermodynamic modeling of CTAB aggregation in water-ethanol mixed solvents, Colloid J. 68 (2006) 304–310.