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Interaction of cephradine monohydrate with Cetyldimethylethylammonium Bromide

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ABSTRACT

Interaction of cephradine monohydrate (CDM) with Cetyldimethylethylammonium Bromide (CDMEAB) has been studied by conductance measurements in pure form and in the presence of salts like potassium chloride (KCl) and potassium sulphate (K_2SO_4) over the temperature range of (298.15 to 318.15) K. From conductivity *vs.* surfactant concentration plots, two critical micelle concentrations like c_1^* and c_1^* were obtained for (CDM + CDMEAB) systems. The variation of c^* values of CDMEAB in the presence of CDM is the indication of the interaction between CDM and CDMEAB. For the (CDM + CDMEAB) system, the values of c^* values are higher in magnitude in contrast to that of pure CDMEAB in water over the range in temperature studied. In aqueous solutions of KCl and K_2SO_4, the c^* values are changed with the increase of the concentration of salts and hence the micellization is dependent on salt concentration. The ΔG_m^0 values were negative and the spontaneity of micellization process is found to be increased with increase of temperature. The values of $\Delta H_{1,m}^0$ and $\Delta S_{1,m}^0$ indicated that the drug mediated CDMEAB aggregation in water was controlled at lower temperatures while at higher temperatures the aggregation was both enthalpy and entropy controlled. The $\Delta H_{2,m}^0$ and $\Delta S_{2,m}^0$ values revealed that the micellization in water was both enthalpy and entropy controlled at lower and higher temperatures though the effect of entropy at middle temperature was dominant. The results indicated that binding interactions between CDM and CDMEAB are both electrostatic and hydrophobic in nature while the contribution of hydrophobic interaction is dominant at lower temperatures. In aqueous solution of KCl, The ΔH_m^0 and ΔS_m^0 values indicated that the micellization was both enthalpy and entropy controlled at lower temperature while the process was entirely entropy driven at higher temperatures. In case of aqueous K_2SO_4 solution, the micellization was mostly entropy driven over the range of temperatures studied.

The negative molar heat capacity change ($\Delta_m C_p^0$) for micelle formation shows that ΔH_m^0 comes to be more negative as the temperature rises. The small $\Delta_m C_p^0$ and the overall positive binding entropy indicate slight structural rearrangement of CDMEAB micelle in the course of binding with CDM. The presence of linear correlation between ΔH_m^0 and ΔS_m^0 values was perceived in all cases.

1. Introduction

Surfactants are used extensively in pharmaceutical formulations to facilitate the preparation, patient tolerability, effective dosage form and also be used as diluents, disintegrating agents, suspending agents, solubilizing agents and emulsifying agents [1–4]. Thus surfactants become imperative constituent in both biological and applied systems. Surfactant micelles have been extensively utilized as an approach to enhance the water solubility of many pharmaceutical ingredients that stands for an arduous problem in formulation of an acceptable dosage form [5–9]. The physico-chemical interaction of drugs with surfactant micelles can be imagined as an approximation for their interactions with biological surfaces. This provides an understanding into more complex biological processes, such as the passage of more complicated biological and prototype drugs through the cell membranes as well as encapsulates to counteract the side effect of drugs. Surfactants have versatile applications as physical models anticipated to simplified model of biomembranes [10]. For this, the feedback of interactions between surfactants and drugs has been a topic of central and pragmatic research in the preceding decades [2,11].

Cephradine monohydrate (scheme I) is an orally administrated broad-spectrum first-generation antibiotic which is used in the remedial of bacterial infections to wit streptococcal tonsillitis, skin infections, urinary tract and reproductive tract. The various physicochemical interactions in the body are always taking place in biological fluids where potassium salts of different forms are present and may influence the interactions of biological systems. Although a number of studies on the interaction of surfactants with drug

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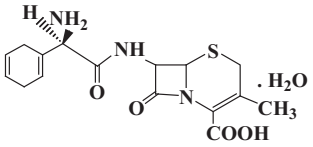
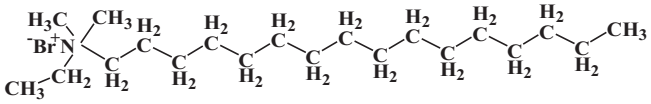


SCHEME I. Cephradine monohydrate (CDM).



SCHEME II. Cetyldimethylethylammonium Bromide (CDMEAB).

molecules are reported in the literature [4,12,13], to the best of our knowledge very little is known about the interaction of cephalosporin drugs with ionic surfactants. In our earlier paper, interaction of cephalosporin drugs with ionic surfactants in pure water and in presence of salt was reported [12,14,15]. In continuation of the study, the interaction of cephalosporin drug such as CDM with a model cationic surfactant CDMEAB (scheme II) in pure water as well as in the presence of salts like KCl and K_2SO_4 was carried out using conductometric technique. To illustrate the CDM–CDMEAB interactions, the values of critical micelle concentration (c^*), fraction of counter ion binding (β) and thermodynamic parameters such as ΔG_m^0, ΔH_m^0, ΔS_m^0 and $\Delta_m C_p^0$ associated with the CDM mediated CDMEAB micellization in pure water as well as in KCl and K_2SO_4 solutions have been evaluated.

2. Materials and method

CDMEAB (Acros Organics, USA), CDM (USP standard sample), KCl (BDH, England) and K_2SO_4 (Merck, Mumbai) were used in this study without any further treatment and their purity in mass fraction unit were 0, 99, 0.98, 0.995 and 0.99 respectively. Distilled–deionized water of specific conductance 1.5–2.0 $\mu S \cdot cm^{-1}$ was used in all preparations. A summary of the provenance and purity of the studied materials is given in table 1a.

The specific conductances of the (CDM + CDMEAB) systems both in water and in aqueous salts solution were measured using a 4510 conductivity meter (Jenway, UK) with a temperature-compensated cell (cell constant provided by manufacture is 0.97 cm^{-1}) using the procedure reported in the literatures [12,14–18]. The accuracy of the measured conductances was within ±0.5%. The concentrated CDMEAB (50 mM) solution was progressively added to the CDM solution (0.5258 mM) taken in a test tube and then the conductances were measured after thorough mixing as well as allowing time for temperature equilibration. The concentration of CDM was kept constant as 0.5258 mM to study the effect of temperature both in water and aqueous solution of salts studied whereas the concentration of CDM was varied in the case of studying the effect of the concentration of drug on the micellization of pure CDMEAB. The desired constant temperature was maintained using RM6 Lauda circulating water thermostated bath with precision of ±0.1 K. To examine the effect of salts such as KCl and K_2SO_4 on the interaction of CDM with CDMEAB, both the CDM and CDMEAB solutions were prepared in such a way that both solutions contain the identical concentration of salt.

3. Results and discussion

The specific conductance of drug solution is found to be changed with the addition of CDMEAB surfactant in pure water and in the presence of salts. The values of (CDM + CDMEAB) system in water at temperature 303.15 K for the gradual addition of CDMEAB to CDM solution are presented in table 1b. Figure 1 is a distinctive plot of specific conductivity (κ) *vs.* concentration of CDMEAB for pure CDMEAB and (CDM + CDMEAB) system in water and/or in aqueous solution of salt at 303.15 K. The sudden changes in conductivity (κ) at certain concentration of surfactant produces sharp break point in the plots and the concentration corresponding to the break points are taken as the critical micelle concentration [12,14–20]. Two such break points are observed for both pure CDMEAB and (CDM + CDMEAB) systems both in pure water and in aqueous solutions of salts. These critical micelle concentrations are labeled as c_1^* and c_2^* in this study. Such more than one c^* value is also reported in the literature by others and us [14–20]. For pure CDMEAB, c_1^* value indicates the formation of free micelle and the c_2^* value refer to the structural micellar change in solution from one shape to other [21]. For the (CDM + CDMEAB) systems, the c_1^* value is also the critical micelle concentration of CDMEAB which depends on the drug concentration. The c_2^* values can also indicate the transition of the formed CDMEAB micelle to a other shape. The degree of ionization of micelles (α) was determined from the quotient of the slopes of the two intersecting straight lines corresponding to the upstairs and beneath c^* [14–16,22–24]. By deducting the value of α from unity, the fraction of counter ion binding, β at c^* was determined.

The values of c^* and β in water containing different concentrations of drugs at 303.15 K are presented in table 2. The values of c^* for pure CDMEAB in water is found to be changed with the addition of CDM and the c^* values for (CDM + CDMEAB) system are higher in magnitude compared to those of pure CDMEAB in water [14]. Also there is an alteration in the c^* values for (CDM + CDMEAB) system with the variation of the concentration of drug at 303.15 K which point out the interaction between drug and surfactant. The values of c^* and β for (CDM + CDMEAB) system at 303.15 K temperature in the presence KCl and K_2SO_4 is documented in table 3. The c_1^* values of (CDM + CDMEAB) system in salts solution are found to be lower in magnitude compared to the c_1^* values in water whereas the c_2^* values in salts solution are higher compared to those in water for pure surfactant. Also the c_1^* values are found to decrease with increase of the concentration of KCl whereas for K_2SO_4, the c_1^* values decrease firstly, then tend to increase with increase of the concentration of K_2SO_4. This reveals the increase of interaction between CDM and CDMEAB and the aggregation of CDM and CDMEAB starts at lower concentration in salts solution compared to that in water. A considerable decrease of c_1^* values reveal that drug–surfactant interaction is much favored in aqueous salts solution where the effect is much pronounced in K_2SO_4 solution compared to that in pure water. The decrease in the c^* value in these cases is observed mainly due to the decrease in depth of the ionic atmosphere surrounding the ionic head groups in the presence of the additional electrolyte and the resulting decrease of electrical repulsion in the middle of them in the micelle [9]. With addition of salt, a decrease of c^* values was reported for the micellization of pure ionic surfactants and also for (drug + surfactant) systems [14,17,25]. In the presence of K_2SO_4 for (CDM + CDMEAB) systems, c_2^* values are much higher in magnitude compared to those of the c_2^* values in both pure water and aqueous KCl solution. Also the c_2^* values increase with the increasing concentration of K_2SO_4 which reveal that the amount of bound surfactant to drug gradually increases with salt concentration and thus micellization takes place at higher surfactant concentration. The entire consequences of an electrolyte come into view to limit on the sum of its effects on the drug and surfactant molecule in associate with the aqueous phase. Hydrophilic groups of the surfactant molecules are in associate with the aqueous phase in mutually the monomeric and micellar forms of the