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Physico-chemical study of the interaction between levofloxacin hemihydrate Drug with Cetylpyridinium chloride in aqueous medium: Conductometric and spectrophotometric investigation

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Abstract
Herein, the interaction between levofloxacin hemihydrate (LFH), a fluoroquinolone antibiotic drug, and cetylpyridinium chloride (CPC), a cationic surfactant, has been studied by applying conductometric and spectrophotometric techniques at various temperatures. The binding constant of LFH to various types of micelles has also been calculated by means of the Benesi-Hildebrand Equation. (CPC+LFH) mixed system exhibits lower critical micelle concentration (*cmc*) values in magnitude compared to the pure CPC in aqueous solution at a particular temperature as confirmed by the conductometric measurements. The profound change in the *cmc* values of the (CPC+LFH) mixtures by varying the concentration of LFH signify the synergistic (attractive) interaction between CPC and LFH. In addition, The negative values of standard free energy demonstrate the stability of the (CPC+LFH) mixture. Furthermore, the other thermodynamic parameters such as the standard enthalpy and standard entropy data suggest the existence of hydrophobic interaction between LFH and surfactants.

Keywords: Levofloxacin hemihydrates, Cetylpyridinium chloride, conductivity, critical micelle concentration, hydrophobic interaction

1. Introduction
Surfactants (or surface-active agent) are amphiphilic substances in nature that have characteristic properties to reduce the surface tension (or interfacial tension) of the water and most of the solvent [1]. The presence of both hydrophobic and hydrophilic moieties of an individual surfactant molecule is accountable for their tendency to form aggregates in an aqueous /non-aqueous solution termed as micelles. The aggregation takes place beyond a particular surfactant concentration referred to as critical micelle concentration (*cmc*), which is perhaps the most crucial property of a surfactant. Surfactants (cationic/anionic/nonionic) have been considered to play a vital role in pharmaceutical and textile products: they are extensively used not only as fabric softeners, antimicrobial agents but also for their leniency to eyes, skin, and clothes along with their biodegradability [2]. Besides, amphiphilic compounds are largely used in both fundamental and applied science in the drug delivery system; therefore, the interaction between drugs and surfactants has been studied with considerable attention in recent years [1, 3].
Surfactant micelles are being widely used in pharmaceutical formulations e.g., solubility enhancer, emulsifier, diluents, stabilizer, drug delivery, and drug targeting systems as well as in more complicated biological and prototype drug delivery systems [3, 4]. Besides, surfactant micelles have also been considered as a pseudo model of simple bio-membranes. Based on the detected *cmc* values for pure surfactant and surfactant-additive mixed systems at various temperatures, the related thermodynamic parameters, e.g. enthalpy, entropy, free energy of micellization (ΔH_m^0 , ΔS_m^0 and ΔG_m^0) could be determined. For decades, intensive researches on the influence of different environmental factors such as temperature, salt, solvent, etc. on the *cmc*, binding constant, and thermodynamic quantities, ΔH_m^0 , ΔS_m^0 and ΔG_m^0 have been carried out to characterize the different modes of interaction between drug and surfactant [5, 8].

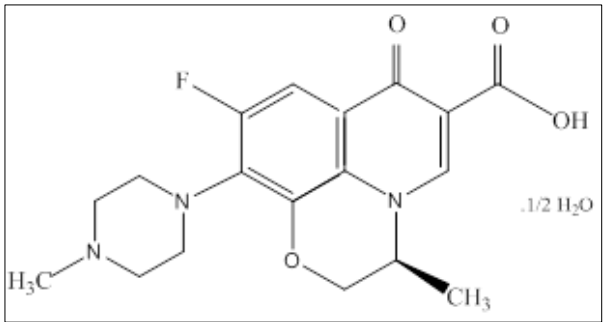
Moreover, surfactant micelles have lots of benefits as a drug carrier since they increase the bioavailability of the hydrophobic drug by enhancing the solubility in the micelle core [9]. For instance, they are capable of staying in the blood for an extended time and affording slow gathering in drug target sites. The size of micelles is expected to be moderately sufficient for their amassing in body areas with permeable vasculature [10], and also they can be simply prepared on a considerable amount.

A number of studies suggested that the physico-chemical properties such as degree of ionization, reaction rates, and clouding/phase separation are affected by the addition of various additives into aggregates of an amphiphile [11, 12]. In biological systems, the two most important metal ions such as sodium and potassium are present intra-extra cellular system. While sodium is the abundant positive ion in the outside of the cell, potassium is the leading ion in the inside of the cells. Sodium-Potassium (Na^+/K^+) pump, also plays a crucial role in transmitting nerve signals, maintains the variation of the concentration of these two ions between intra-extra cellular system and keeping the blood pressure constants in the human body [13]. Attendance of inorganic salts supports micelle growth by withdrawing the electrostatic interaction among the polar head groups. Salts might reduce the *cmc* consequently enhance the aggregation number (N_{agg}) of amphiphiles in the solvent [14]. Diminishing the electrostatic repulsion between the polar head groups at higher salt concentration changes the shape of spherical micelle to non-spherical and the micelle growth commences by the migration of the hydrophobic groups apart from the aqueous surroundings [15].

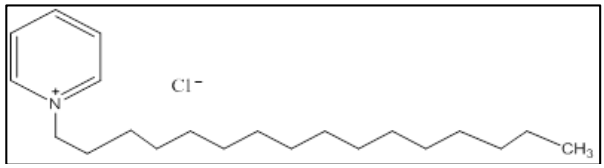
The *cmc* of tetracaine hydrochloride and sodium deoxycholate surfactant mixture was determined successfully by examining the interaction between the amphiphiles and found to have synergism (positive interaction) between the components, as reported by Srivastava *et al.* [16]. Meanwhile, Yang and his team [17] have studied the interaction of ciprofloxacin hydrochloride (CFH), a beta-lactum antibiotic drug**,** with different surfactants using the spectroscopic fluorescence method. The variation of fluorescence intensity is observed suggesting the presence of hydrophobic interaction between CFH and surfactants. Chauhan *et al*. [18] reported on the micellization of sodium dodecyl sulfate (SDS) in the attendance of furosemide (cardiovascular drug) and dimethylsulfoxide (DMSO)/salts at various temperatures. This group proposed that SDS's micellization behavior in aqueous electrolyte solutions in the presence of DMSO arose from counterion-/solvent (DMSO) and intermolecular interactions. The addition of DMSO has a profound influence on SDS's micellar properties and leads to the formation of a charged complex between DMSO and furosemide preferentially due to the solubilization of drugs micellar core.

Levofloxacin hemihydrate (LFH), Scheme I, is a broad-spectrum antibiotic drug suggested to use in the treatment of bacterial infections such as urinary tract infections, acute sinusitis. It is also used as uncomplicated cervical and inhalational anthrax, sinuses, skin, lungs, ears, bones, in addition to joints attributable to susceptible bacteria [19]. On the other hand, cetylpyridinium chloride (CPC), Scheme II, is a cationic surfactant with strong bactericidal properties and fungi resistance. Additionally, CPC has a wide variety of utilization in applied fields such as pharmaceuticals, cosmetics, toiletries and industrial use [20].

Although the extensive research works have been reported on drug-surfactant interactions and according to our best knowledge, the physico-chemical study of cationic surfactant CPC interaction with antibiotics drug LFH by spectrophotometric and conductometric technique was not studied yet. In our present investigation, the conductivity and the UV-Vis spectroscopy measuring tools have been utilized to estimate the *cmc*, fraction of counter ions, thermodynamic parameters e.g., free energy, enthalpy, entropy of micellization ($\Delta G_m^0, \Delta H_m^0, \Delta S_m^0$), and binding constants to illustrate the modes of interaction between drug and amphiphiles used.



Scheme 1: Levofloxacin hemihydrate (LFH) antibiotic drug



Scheme 2: Cetylpyridinium chloride (CPC) cationic surfactant

2. Materials and Methods

2.1 Materials

All the materials in this study such as CPC (Acros organic, USA), LFH (General Pharmaceuticals Ltd), NaCl (Merck, Germany) of analytical reagent grade were used as received from the source without any further purification. Drug sample such as LFH (USP standard sample of purity > 95%) was provided by General Pharmaceuticals Ltd, Bangladesh as a gift item. All the solutions were prepared using distilled deionized conductivity water.

2.2 Preparation of solutions

All the surfactant solutions were prepared in either water or aqueous solution of NaCl based on the requirements of the investigation procedure. At first, 20 mmol.kg^{-1} solution of the CPC was prepared in water (in case of no salt) with a view to determining the *cmc* values for individual surfactant, CPC. The specific conductivity value of an amount of 20 mL of the desired solvent stored in a test tube was measured and recorded first, and then 20 mmol.kg^{-1} CPC solution was gradually added to that solvent. To determine the *cmc* values of (CPC+LFH) mixed system, initially 20 mmol.kg^{-1} CPC solutions were prepared in aqueous LFH solutions of various concentrations with and without addition of NaCl so that the desired concentration of LFH in the resultant (CPC+LFH) mixture attained. A 0.05 mL of LFH solution was successively added to the 20 mL of solvent utilizing a high-performance micropipette (Glassco, UK) so that CPC concentration can vary with gradual addition, but the concentration of CPC along with salt concentration remain fixed. The resultant solution was allowed to stay for some time to attain temperature equilibrium and proper mixing after each addition. The solutions of both CPC and (CPC+LFH) mixed systems were prepared in the aqueous NaCl solution in order to study the salt effect on their *cmc* values i.e. on their

micelle formation. The desired temperature of the solution was reached via RM6 Lauda thermostated water bath with a precision of ±0.2 K. The procedure of preparing solutions of surfactant and/or drug-surfactant systems and their conductometric analyses described in the present study were adapted from the reports published elsewhere [21, 25].

2.3 Methods

2.3.1 Conductivity technique

The conductivity technique is being taken into consideration by so many different researchers to investigate surfactant-based system [21, 29]. The investigation associated with this paper also involves the implementation of conductivity technique with the utilization of a conductivity meter (model 4510, Jenway, UK), having a dip cell of cell constant 0.97 cm^{-1} (value provided by the manufacturer) and with alternating current (AC) voltage source at a frequency of 60 Hz to record and enlist the specific conductivity data of the resultant single/mixed surfactant solutions. Prior to each experiment, the conductivity meter was calibrated using a KCl solution having appropriate concentration of calibration. The specific conductivity values for the test solutions prepared by an addition of CPC solution of concentration 20 $mmol.kg^{-1}$ (with or without a fixed concentration of NaCl) to 20 mL of LFH solution of a particular concentration (with or without a fixed concentration of NaCl) at a constant temperature (see section 2.2) was evaluated by using the conductivity meter. Then, the specific conductivity is consequently plotted against the surfactant's concentration to obtain the *cmc* values in a systematic way. In this study, all the calculations and graphical representation were performed using Microsoft Excel and Origin Pro 8 software. The accuracies of the measurement precision was around ± 0.5%.

2.3.2. UV-visible spectroscopic method

Owing to understand the binding phenomena of LFH-CPC drug-surfactant system, UV-visible spectrometric investigation was carried out by utilizing a UV–visible spectrophotometer (1601, Shimadzu, Japan) having a temperature controller of a setting accuracy of ± 0.5° C. Firstly, a series of solutions of LFH and CPC were prepared followed by the baseline of the spectrophotometer was calibrated against the solvent. The absorbance data of the series of solutions of LFH, CPC, and (LFH+CPC) systems were recorded at the maximum wavelength of CPC-LFH molecules which leads us to evaluate an important parameter i.e. binding constant (K_b) of the (LFH+CPC) system.

3. Results and Discussion

3.1 Critical micelle concentration (cmc), fraction of counter ion binding (β) of pure CPC, (CPC+LFH) mixed system in water, and aqueous solution of NaCl

The *cmc* values of pure CPC and (CPC+LFH) mixtures in aqueous systems are determined from the abrupt change in drug-surfactant system conductivity with the gradual increase of surfactant, CPC concentration. The typical plots of variation of specific conductivity (κ) vs. concentration of surfactant ($c_{surfactant}$) of pure CPC solution and (CPC+LFH) mixture in water have been displayed in Figure 1 (a) and 1 (b), respectively. For both pure CPC and (CPC+LFH) mixture systems a sharp breakpoint is observed between the two straight lines due to an abrupt change in conductivity at a certain surfactant concentration which suggest the aggregation of surfactants. According to the previous reports, the $c_{surfactant}$ corresponding to such disdinct breakpoint obtained from plot of κ vs. $c_{surfactant}$ is regarded as the *cmc* value of the surfactant-based system [6, 15, 25, 30, 35].

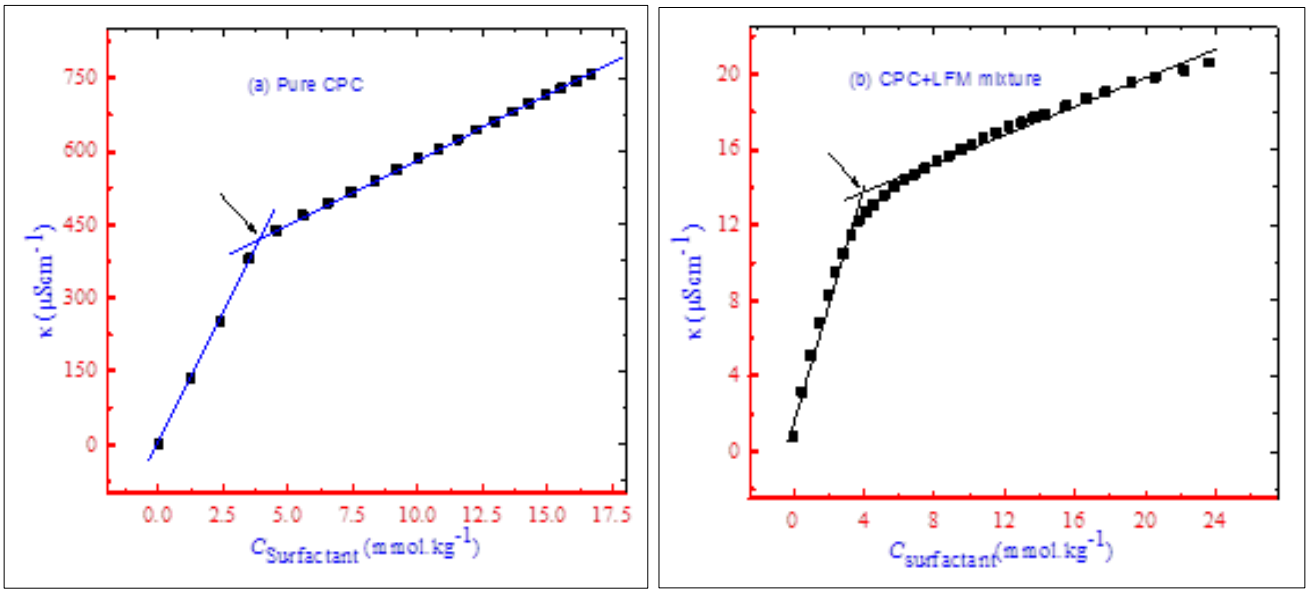


Fig 1: Plots of κ vs. $c_{surfactant}$ of (a) pure CPC and (b) (CPC+ 3.0 $mmol.kg^{-1}$ LFH) mixed system in water at 303.15 K.

The initial rise in κ values at low surfactant concentration (below the *cmc*) is ascribed due to the contributions from free CP^+ and Cl^- entities. Above the *cmc*, the incremental increase of κ values becomes lower because of the formation of CPC micelles and also due to the condensation of the Cl^- ions with CPC micelles to construct the Helmholtz layer, which stabilizes the self-aggregated surfactant system by way of surface charge neutralization and thereby lessening the intermolecular repulsion potential [35]. Thus the micelles have lower mobility in comparison to the free ions of CPC.

The degree of ionization of micelles, α, was estimated from the ratio of the slopes of the straight lines corresponding to above and below the *cmc* obtained in Figure 1 (a and b) [6, 15, 25]. Assuming S_1 and S_2 are the slopes of the above and below of *cmc*, respectively, the fraction of counter ion binding, β, at *cmc* was calculated by deducting the value of α from unity

i.e., $\beta = (1- \alpha)$. The *cmc* and the β values of pure CPC and (CPC+LFH) in water and aqueous solution of NaCl are tabulated in Tables 1 and 2. The obtained values of *cmc* for pure CPC in water over the range of temperature 303.15 K to 323.15 K are in good agreement with the previously reported values [1, 30, 39]. The *cmc* values of (CPC+LFH) mixed system in aqueous medium at 308.15 K (Table 2) are lower compared to the achieved *cmc* values of pure CPC (Table 1) which indicates the presence of synergistic (attractive) interaction between LFH and CPC. It also indicates that formation of micelle of CPC occur at the lower concentration of LFH in aqueous system. With the increase in the LFH concentration, the obtained *cmc* values are increased linearly at a constant temperature which reveals that lower concentration of drug solution provides a convenient environment for the micellization of CPC [25].

Table 1: The *cmc* and β values of pure CPC in aqueous solutions in the absence and presence of NaCl at various temperatures.

***T* (K)**	***cmc* (mmol.kg^{-1})**	***β***
	Pure CPC	
303.15	3.90	0.39
308.15	4.03	0.38
313.15	4.11	0.40
318.15	4.33	0.39
323.15	4.45	0.38
	(CPC+NaCl[a])	
303.15	3.63	0.46
308.15	3.70	0.47
313.15	3.90	0.40
318.15	4.03	0.43
323.15	4.41	0.42

[a]Ionic strength of NaCl, I_{NaCl} = 1.5024 mmol.kg^{-1}.

The effect of addition of salt, NaCl on the *cmc* and β values was also studied for pure CPC as well as (CPC+LFH) mixture system at several temperatures. Table 2 demonstrates that the collected *cmc* values of (CPC+LFH) mixed system in the attendence of NaCl solution are lower than those in aqueous medium. The *cmc* values in both cases also found to be decreased with an increase of NaCl concentration at a fixed temperature indicating the reduction of electrostatic repulsion among the polar head groups of amphiphiles and enhancement of hydrophobic interaction between the studied components' alkyl chains.

Table 2: The *cmc* and β values of (CPC+LFH) mixed system in water and aqueous NaCl solutions at various temperatures.

Medium	**c_{LFH} (mmol.kg^{-1})**	**I_{NaCl} (mmol.kg^{-1})**	***T* (K)**	***cmc* (mmol.kg^{-1})**	***β***
H_2O	0.057	0	308.15	2.36	0.45
	0.113			2.38	0.54
	0.199			2.46	0.43
	3.501			2.58	0.62
	4.059			2.64	0.66
	8.125			2.67	0.63
	9.873			2.72	0.62
H_2O	3.501	0	303.15	2.96	0.40
			308.15	2.90	0.42
			313.15	3.04	0.40
			318.15	3.16	0.43
			323.15	3.29	0.42
(H_2O+NaCl)	3.501	0.1021	308.15	3.35	0.52
		1.0345		3.24	0.48
		1.5024		3.17	0.49
		3.0054		2.98	0.45
		5.0032		2.73	0.5
(H_2O+NaCl)	3.501	1.5024	303.15	3.30	0.46
			308.15	3.17	0.47
			313.15	3.08	0.4
			318.15	3.26	0.43
			323.15	3.47	0.42

Addition of salt into the H_2O-surfactant system possibly offers a change in both intra and inter molecular interactions [40]. Reduction of *cmc* values of surfactant with the addition of NaCl was also reported in our previous works [25] which gives better support to these values of the present study. The inorganic salts presumably provide a suitable environment for a gathering of the monomers with the result in the decrease of *cmc* values by reducing the electrostatic repulsion among the charged head groups inside a micelle [1]. Hydrophilic hydration of the polar head groups is responsible for lowering electrostatic repulsion between polar head groups in the presence of inorganic salt. Therefore, surfactant monomers promote their closing approach for micellization and thus, the *cmc* values are decreased [41].

Moreover, the gradual decrease of *cmc* values with an increase of NaCl concentration at a fixed temperature indicates the increase of the convenient environment of micelle formation at a higher salt concentration. The effective area of per head groups of micelle is minimized due to decreased electrostatic repulsion; consequently, micelle growth enhanced.

This is evidenced by the lessened in *cmc* and/or enhancement of the micelle aggregation number. Augmenting the salt concentration tends to transfer the spherical aggregation into non-spherical ones by screening electrostatic repulsion among the polar head groups and movement of the hydrophobic alkyl chains away from the aqueous environment is attributed to micelle growth [1].

3.2 Effect of temperatures on the cmc and β values of pure CPC and (CPC+LFH) mixed system

From Table 1, the *cmc* values of CPC in water and aqueous NaCl solution are found to be increased gradually with increasing temperatures. For (CPC+LFH) mixed system in water, all the *cmc* values increased up to a certain temperature, attain maximum value and after that they tend to decrease with the further increase of temperature as seen from Table 2. On the other hand, for (CPC+LFH) mixed system in aqueous NaCl solution, the c*mc* values decreased up to a particular temperature, reach a minimum value followed by an increase with a further rise of temperature (Table 2). The temperature effect on the micellar parameters can be

explained with the change of hydration modes around the CPC/drug-mediated CPC micelles with a variety of temperatures. The monomeric form of surfactant can be experienced by hydrophilic and hydrophobic hydration, whereas hydrophilic hydration exerts its effect on the micellized CPC. However, both kinds of hydration are considered to decrease with the increase of temperature. Several reports [1, 15, 41] revealed that micellization becomes more favorable if hydrophilic hydration decreases with raising the temperature. Otherwise, it becomes disfavor in case of decrease of hydrophobic hydration with the rise of temperature. Thus, the magnitude of these two effects helps determining whether the *cmc* values increase or decrease over a certain temperature range.

The significant changes in *cmc* values of the drug-mediated (CPC+LFH) mixed system in an aqueous medium with rising temperatures indicate that the second factor dominates at lower temperatures while the first factor prevails at higher temperatures. Generally, the micellar phenomena of the surfactant don't exhibit any particular trend with changing temperature.

In the case of ionic surfactants, it is usually observed that the *cmc* against the temperature curve exhibit U-shaped nature [42, 43] and nonionic amphiphiles demonstrate a regular trend of reduction of the *cmc* with rising temperature. An increase or decrease of *cmc* values with ionic amphiphiles temperatures was also found in the literature [15].

3.3 Thermodynamics of pure CPC and (CPC+LFH) mixed system in aqueous medium

The thermodynamic state functions, the standard free energy change (ΔG^0_m), the enthalpy change (ΔH^0_m), and the entropy change (ΔS^0_m) during the process of micellization are important parameters for the basic understanding of the feasibility of the process and its inherent constraints' etc. For the ionic surfactants of the 1:1 electrolyte type, the standard free energy of micellization, ΔG^0_m, was calculated according to the following equation for drug- surfactant system [25]:

$$\Delta G^0_m = (1+\beta)\, RT \ln X_{cmc} \quad (1)$$

In which, β, the fraction of counterion binding values at various temperatures and X_{cmc} is the *cmc* values in mole fraction units. The standard enthalpy change, ΔH^0_m, of the processes will be calculated using the modified van't Hoff equation [25].

$$\Delta H^0_m = -(1+\beta)\, RT^2\, \partial \ln X_{cmc} / \partial T \quad (2)$$

The $\ln X_{cmc}$ vs. T plot is made to calculate ΔH^0_m. When $\ln X_{cmc}$ vs. T plots are nonlinear, a tangent is drawn through the required point i.e. at each temperature of the plot, and the slope of the tangent at each temperature is referred as $\partial \ln X_{cmc}/\partial T$ to calculate ΔH^0_m. When $\ln X_{cmc}$ vs. T plots are linear, the straight line slope will be taken as equal to $\partial \ln X_{cmc}/\partial T$. The values of standard entropy change, ΔS^0_m, of micellization will be calculated from the equation given below [44]:

$$\Delta S^0_m = (\Delta H^0_m - \Delta G^0_m)/T \quad (3)$$

The temperature dependence of mole fraction of *cmc* of the surfactant (X_{cmc}), can be expressed as a parabolic curve according to the equation as follows [25],

$$\ln X_{cmc} = A + BT + CT^2 \quad (4)$$

where the regression analysis of least squares determines the constants A, B, and C. Figure 2 represents a schematic second-order polynomial fitting curve for the plot of $\ln X_{cmc}$ vs. T for an aqueous solution of CPC with and without NaCl to determine ΔH^0_m of the micellization process. The constants A, B, and C are tabulated in Table S1 (supplementary materials). Finally, ΔH^0_m of micellization is determined by the equation as given below [45]:

$$\Delta H^0_m = -(1+\beta)\, RT^2\, [B+2CT] \quad (5)$$

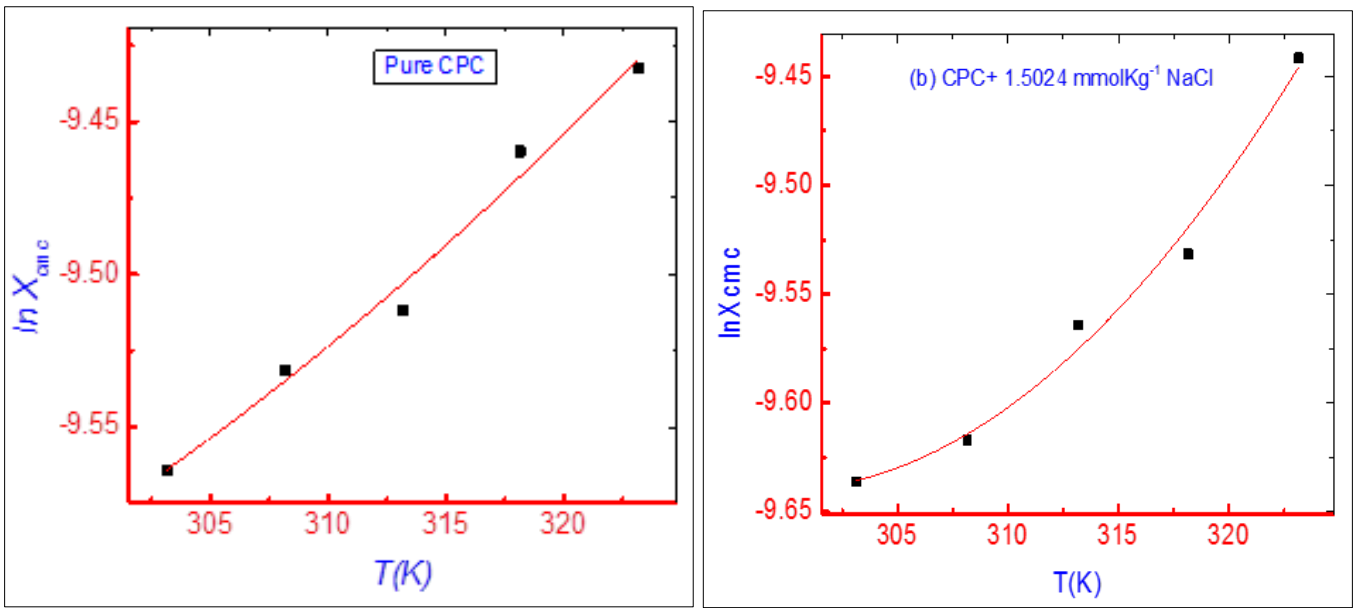


Fig 2: Representative plots of second order polynomial fitting curve of $\ln X_{cmc}$ vs. T for (a) pure CPC and (b) CPC+1.5024 mmol.kg^{-1} NaCl in water.

The values of various thermodynamics parameters for CPC and (CPC+LFH) mixed system with and without NaCl are listed in Table 3. The ΔG^0_m values were negative for pure CPC and (CPC+LFH) mixed systems in the absence and presence of salt as depicted in Table 3, signifying the formation of the micelles is spontaneous phenomena [25]. The

negative ΔG^0_m values for CPC and (CPC+LFH) mixed systems in NaCl solution are higher than those in the aqueous solution which declares the better spontaneity of mixed systems due to lessening of electrostatic repulsion among the polar head groups of current amphiphiles [46]. With the attendance of inorganic salt, NaCl, the negative ΔG^0_m values are achieved to be the additional negative signifying easy facilitation of the associated phenomena since the dynamic force for aggregation was considerably enhanced in attendance of salt.

Figure 3 displays the variation of ΔH^0_m for pure CPC and (CPC+LFH) mixed system in an aqueous medium with an increase in temperature. For pure CPC, the ΔH^0_m values were negative at all studied temperatures and tend to increases with temperatures as shown in Figure 3. The values of ΔS^0_m of pure CPC are positive and the positive values tend to decrease with raising the temperature (Table 3). Thus the CPC micellization process is observed to be entropy and enthalpy controlled over the range of temperatures 303.15–323.15 K. With the addition of NaCl the values of ΔS^0_m of the CPC micellization process are also found to be positive and tend to decrease with increasing temperatures. Thus the CPC micellization process in the presence of NaCl is entirely entropy directed over the range of temperatures studied.

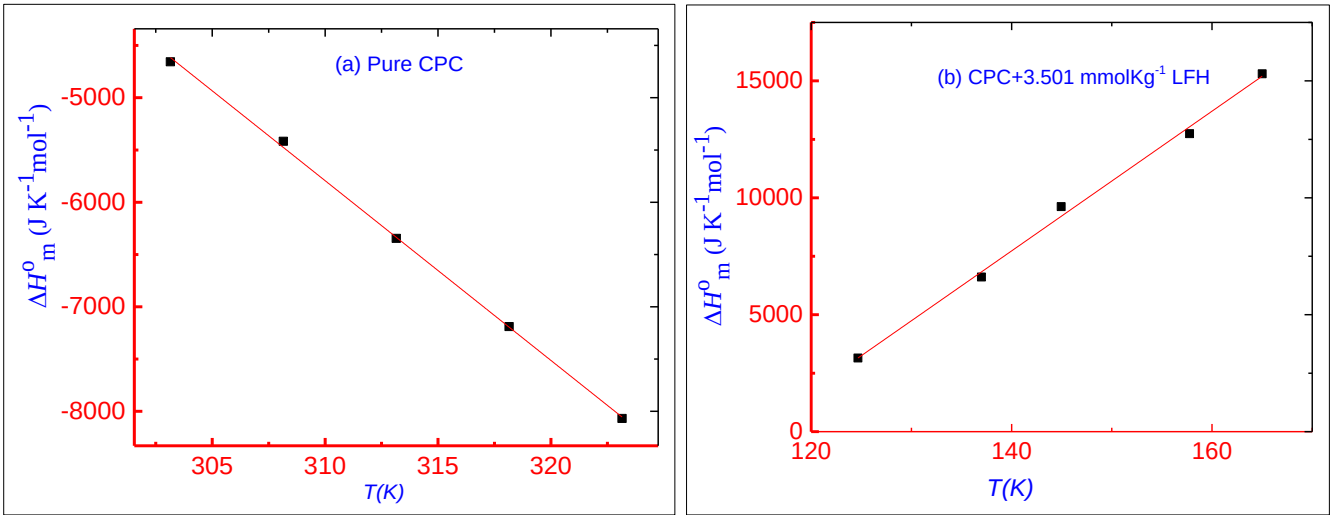


Fig 3: The plot of ΔH^0_m vs. T for (a) pure CPC, (b) CPC containing 3.501 mmol.kg^{-1} LFH in water.

In the case of (CPC+LFH) mixed system in water and NaCl solution, the ΔH^0_m values were positive over the studied temperature range; the positive values tend to decrease with the increase of temperatures. Thus the aggregation and phase transition processes for the (CPC+LFH) mixed system in water and NaCl solution are endothermic. The endothermic behavior is probably owing to the dehydration of the hydrophobic part of the CPC surfactant. The values of ΔS^0_m are positive, and the positive values are decreased with the increase in temperatures. The ΔH^0_m and ΔS^0_m values reveal that the interactions between CPC and LFH are mainly of hydrophobic origin. Over the temperature range of 303.15–323.15 K, the hydrophobic attraction is dominant on the interaction between LFH and CPC. In the presence of the aqueous solution of NaCl into (CPC+LFH) mixed system, the obtained higher positive values of ΔH^0_m indicate the enhanced hydrophobic interactions.

Table 3: Values of ΔG^0_m, ΔH^0_m, ΔS^0_m and $\Delta_m C^0_p$ of pure CPC and (CPC+3.501 mmol.kg^{-1} LFH) mixed system in water and aqueous NaCl solutions at various temperatures.

System	Medium	I_{NaCl} (mmol.kg^{-1})	T (K)	ΔG^0_m (kJmol^{-1})	ΔH^0_m (kJmol^{-1})	ΔS^0_m (Jmol^{-1}K^{-1})	$\Delta_m C^0_p$ (kJmol^{-1}K^{-1})
CPC	H_2O	0	303.15	–33.51	–4.66	95.17	–0.17
			308.15	–33.70	–5.42	91.78	
			314.15	–34.67	–6.35	90.45	
			318.15	–34.78	–7.19	86.72	
			323.15	–34.97	–8.07	83.25	
CPC	H_2O+NaCl	1.5024	303.15	–35.46	29.72	215.00	–0.57
			308.15	–36.22	27.51	206.80	
			314.15	–34.86	23.70	187.02	
			318.15	–36.05	21.46	180.86	
			323.15	–36.02	18.36	168.28	
CPC+LFH	H_2O	0	303.15	–34.72	15.30	165.01	–0.60
			308.15	–35.87	12.74	157.77	
			314.15	–35.77	9.62	144.95	
			318.15	–36.97	6.61	136.99	
			323.15	–37.14	3.15	124.67	
			303.15	–35.81	35.78	236.15	–1.75
			308.15	–36.80	28.13	210.72	
CPC+LFH	H_2O+NaCl	1.5024	314.15	–35.72	18.73	173.88	
			318.15	–36.85	10.32	148.28	
			323.15	–36.93	0.92	117.13	

Nusselder and Engberts have suggested that it is the London-dispersion forces responsible for the micellar process for negative enthalpy magnitudes [47]. The positive ΔH^0_m value indicates the destruction of structured (or hydrogen-bonded) water molecules around hydrophobic chains showing the importance of hydrophobic interactions in the micelle formation process. The positive and negative enthalpy values were also earlier obtained by Rub *et al.* for the single system [48]. A negative ΔH^0_m may occur when hydration of water molecule around the hydrophilic head group become more significant than that of the water structure around the hydrophobic alkyl chains of surfactant monomers. The positive values of ΔS^0_m for pure CPC and (CPC+LFH) mixtures micellization can be explained by bearing two factors. First one is the transfer of hydrophobic chains from a hydrated form in the aqueous medium to the non-polar interior micelle core rupturing iceberg structures and the second one is an enhancement of the rotational degree of freedom of hydrophobic chains in the micelle interior compared to the aqueous environment [49]. The negative values of ΔS^0_m may occur when forming the iceberg structure surrounding the LFH and CPC is much dominant than the above two effects.

The molar heat capacity changes ($\Delta_m C^0_p$) for micelle formation, is an important sign of protein structural changes in response to different ligands which is obtained from the slope of the plot of ΔH^0_m vs. T according to the following equation [41].

$$\Delta_m C^0_p = ((\partial \Delta H^0_m)/\partial T)_p \quad (6)$$

The change in heat capacity associated with LFH-surfactant binding is believed to be associated with motion restriction and is proportional to the burial of the molecular surface, which generally correlates with a change in the solvent-accessible surface area [50]. The $\Delta_m C^0_p$ for the micellization of pure CPC and (CPC+LFH) mixed system was determined from the slope of the plot of ΔH^0_m vs. T (Figure 3) utilizing equation 6 [41]. The $\Delta_m C^0_p$ values for pure CPC and the mixture of CPC and LFH both in water and salt solution were negative indicating alteration in the conformations of CPC micelles with the addition of LFH drug.

3.4 Determination of entropy−enthalpy compensation

The enthalpy−entropy compensation can be examined from a linear relationship between ΔH^0_m and ΔS^0_m. Figure 4 shows an excellent linear relationship between ΔH^0_m and ΔS^0_m for pure CPC and (CPC+LFH) mixture in water with R^2 value in the range of 0.985−1.00 in all cases, according to the regression equation 7 [25].

$$\Delta H^0_m = \Delta H^{0,*}_m + T_c \Delta S^0_m \quad (7)$$

The slope, T_c, is the compensation temperature that described the solvation part of the micellization process and assists as the basis of comparison for differing examples of compensation behavior. The y-intercept $\Delta H_m^{0,*}$, is the intrinsic enthalpy gain.

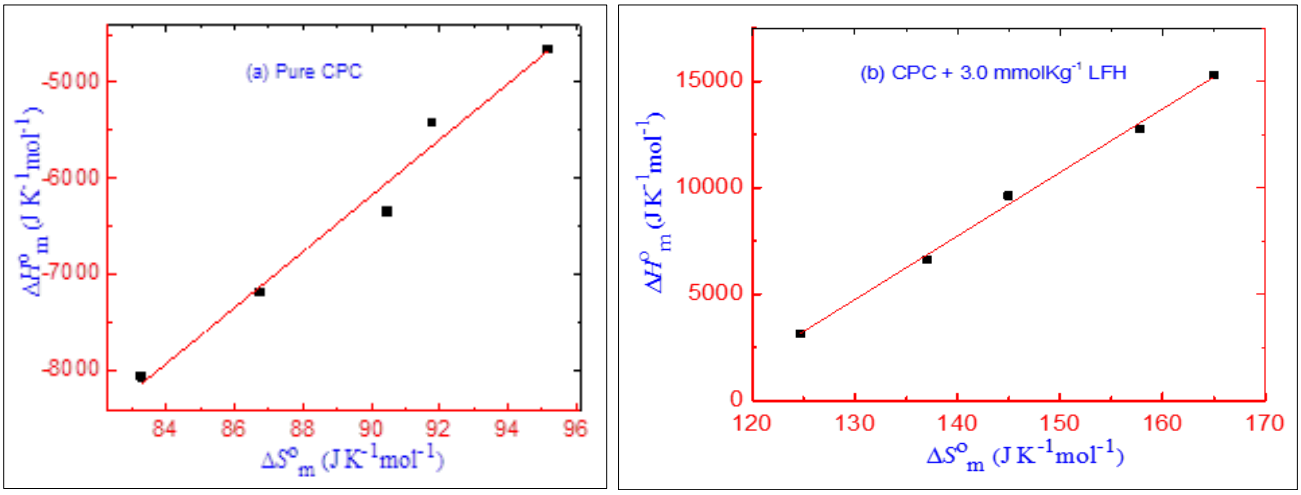


Fig 4: Representative plots for enthalpy-entropy compensation of (a) pure CPC and (b) (CPC + 3.501 mmol.kg^{-1}LFH) mixed system in water.

The values of T_c and $\Delta H^{0,*}_m$ of enthalpy-entropy compensation phenomenon for pure CPC and (CPC+LFH) mixtures in water and in the presence of aqueous NaCl are presented in Table 4. The higher negative $\Delta H^{0,*}_m$ value, signifies that the CPC and (CPC+LFH) mixtures' micellization is favored even at ΔS^0_m = 0. A raise in the negative $\Delta H^{0,*}_m$ values corresponds to the increase in the stability of the micelles [6]. The intercept $\Delta H^{0,*}_m$ exposes the solute-solute interaction and stands for an index of the hydrophobic moiety efficiency to contribute to the micelle development.

Table 4: Enthalpy-entropy compensation parameters for pure CPC and (CPC + 3.501 mmol.kg^{-1} LFH) mixed system in water and in aqueous solution of NaCl.

System	Medium	I_{NaCl} (mmol.kg^{-1})	$\Delta H^{0,*}_m$ (kJ mol^{-1})	T_c (K)	R^2
CPC	H_2O	0	–32.45	291.86	0.97166
CPC	H_2O+NaCl	1.5024	–21.43	237.95	0.99115
CPC+LFH	H_2O	0	–34.09	298.74	0.99547
CPC+LFH	H_2O+NaCl	1.5024	–32.77	290.85	0.99797

The T_c values are found to be between 237.95–298.74 K in this study. The T_c values obtained in the range of 270 − 300 K have been utilized as an indicative examination for water contribution in the protein solution [30]. Therefore the T_c

values for (CPC+LFH) are almost comparable to the biological fluid with a few exceptions. Such a compensation phenomenon was also obtained earlier by others to micellize ionic surfactants in aqueous solution [31].

3.5 Determination of the thermodynamic properties of transfer for (CPC+LFH) mixed system: The free energy of transfer ($\Delta G^0_{m.tr}$), enthalpy of transfer ($\Delta H^0_{m.tr}$) and entropy of transfer ($\Delta S^0_{m.tr}$) of micelles from water to the aqueous of additives can be achieved using the subsequent set of equations [25]:

$$\Delta G^0_{m.tr} = \Delta G^0_m \text{ (aq. additive)} - \Delta G^0_m \text{ (aq.)} \quad (8)$$

$$\Delta H^0_{m.tr} = \Delta H^0_m \text{ (aq. additive)} - \Delta H^0_m \text{ (aq.) and} \quad (9)$$

$$\Delta S^0_{m.tr} = \Delta S^0_m \text{ (aq. additive)} - \Delta S^0_m \text{(aq.)} \quad (10)$$

The values of $\Delta G^0_{m.tr}$ $\Delta H^0_{m.tr}$ and $\Delta S^0_{m.tr}$ for (CPC+LFH) mixtures in aqueous solution as well as in attendance of salt, NaCl are summarized in Table 5. The $\Delta G^0_{m.tr}$ for CPC micellization in NaCl solution and (CPC+LFH) mixtures in aqueous solution are obtained to be negative. On the other hand, the values for (CPC+LFH) mixtures in an aqueous solution of NaCl is negative at lower temperature, but positive at higher temperature. The $\Delta H^0_{m.tr}$ for the micellization of CPC in NaCl solution are positive. The $\Delta H^0_{m.tr}$ for the micellization of (CPC+LFH) mixtures in aqueous solution and in the attendance of NaCl were found to be positive. In the presence of inorganic salt and amino acids from aqueous solution to the urea solution, negative transfer enthalpies were observed earlier by other research group [40]. The positive transfer of enthalpies disclose that the transfer of hydrophobic groups from aqueous solution to the solution of LFH and LFH+salt mixtures are endothermic. The $\Delta S^0_{m.tr}$ of (CPC+LFH) mixed systems in water and salt medium are positive in almost all cases, indicating that the systems are not entropically controlled strongly.

Table 5: Transfer of thermodynamic parameters of micellization of pure CPC and (CPC + 3.0 mmol.kg^{-1} LFH) mixtures in aqueous solution (in absence and presence of NaCl of 1.50 mmol.kg^{-1}) at various temperatures.

System	Medium	I_{NaCl} (mmol.kg^{-1})	T (K)	$\Delta G^0_{m.tr}$ (kJmol^{-1})	$\Delta H^0_{m.tr}$ (kJmol^{-1})	$\Delta S^0_{m.tr}$ (Jmol^{-1}K^{-1})
aq. CPC to (CPC in NaCl Solution)						
CPC	H_2O+NaCl	1.5024	303.15	–1.95	34.37	119.83
			308.15	–2.52	32.92	115.02
			314.15	–0.19	30.05	96.56
			318.15	–1.27	28.65	94.04
			323.15	–1.05	26.43	85.02
From aq. CPC to aq. (CPC+LFH)						
CPC+LFH	H_2O	0	303.15	–1.21	19.96	69.84
			308.15	–2.17	18.16	65.98
			314.15	–1.10	15.97	54.50
			318.15	–2.19	13.80	50.27
			323.15	–2.17	11.22	41.42
aq. (CPC+LFH) to (CPC+LFH) in NaCl Solution						
CPC+LFH	H_2O+NaCl	1.5024	303.15	–1.09	20.48	71.14
			308.15	–0.93	15.39	52.95
			314.15	0.05	9.11	28.93
			318.15	0.12	3.71	11.30
			323.15	0.20	2.23	–7.54

3.6 Binding phenomena of LFH drug with CPC: UV-visible spectroscopic investigation

The UV-visible spectroscopic technique is generally used to study the interaction between different molecules because in this technique there might be a noticeable change in the one or both absorption band as well as the absorbance of the mixture due to interaction between the components. The binding constants for LFH-CPC interaction were estimated by utilizing UV-visible spectroscopic method as reported earlier [51, 53]. Assuming micelles and water as separate pseudo phases the equilibrium reaction for drug and micelle can be presented as follows:

$$D + M \underset{}{\overset{K_b}{\rightleftharpoons}} DM \quad (11)$$

in which D, M, DM, and K_b are the drug, micelle, drug-micelle associate, and binding constant, respectively. The fraction of micelle-bound drug to the total amount of drug, f, may be defined as: $f = DM/D_T$, where D_T is the total drug concentration. The fraction, f, can be estimated from the experimental results using the equation given below [51, 54]:

$$f = \frac{\Delta A}{D_T(\varepsilon_M - \varepsilon_0)l} \quad (12)$$

where $\Delta A = A - A_0$ in which A and A_0 are the absorbances of the drug in the presence and absence of surfactants, respectively. ε_M and ε_0 represent molar extinction coefficients of the drug fully bound to micelles determined in a large excess of the micelles and drug in the absence of surfactants, and l is the optical path length of the solution (l =1 cm). The Benesi-Hildebrand Equation, which is valid for high surfactant concentrations is widely used to determine the binding constant, K_b, for drug-micelle system [52, 54]. In this study the K_b value related to the drug-micelle interaction was calculated by the Benesi-Hildebrand formula represented by the following modified equation.

$$\frac{[D]}{A} = \frac{1}{\varepsilon[C]K_b} + \frac{1}{\varepsilon} \quad (13)$$

In this equation, the terms $[D]$ and $[C]$ represent the initial concentrations of drug and surfactant monomer in the drug + surfactant mixture, A is the absorbance and ε is the molar absorption coefficient of the drug-surfactant system, while K_b describes the binding constant (in L mol^{-1}) at a particular temperature.

The plot of $[D]/A$ against $1/[C]$ results a linear line with a slope equal to $1/\varepsilon K_b$ and the y-intercept of $1/\varepsilon$. The values of K_b corresponding to LFH-CPC assembly were evaluated from the intercept and the slope of $[D]/A$ vs. $1/[C]$ plot. A representative plot of $[D]/A$ vs. $1/[C]$ is provided in supplementary plot 1.

Figure 5 (a and b) shows absorbance band obtained for aqueous solutions of pure CPC and (CPC+LFH) mixed system and the effect of the addition of 0.10 mmol.L^{-1} CPC solution on the absorption spectra of LFH solutions of various concentrations at 298.15 K.

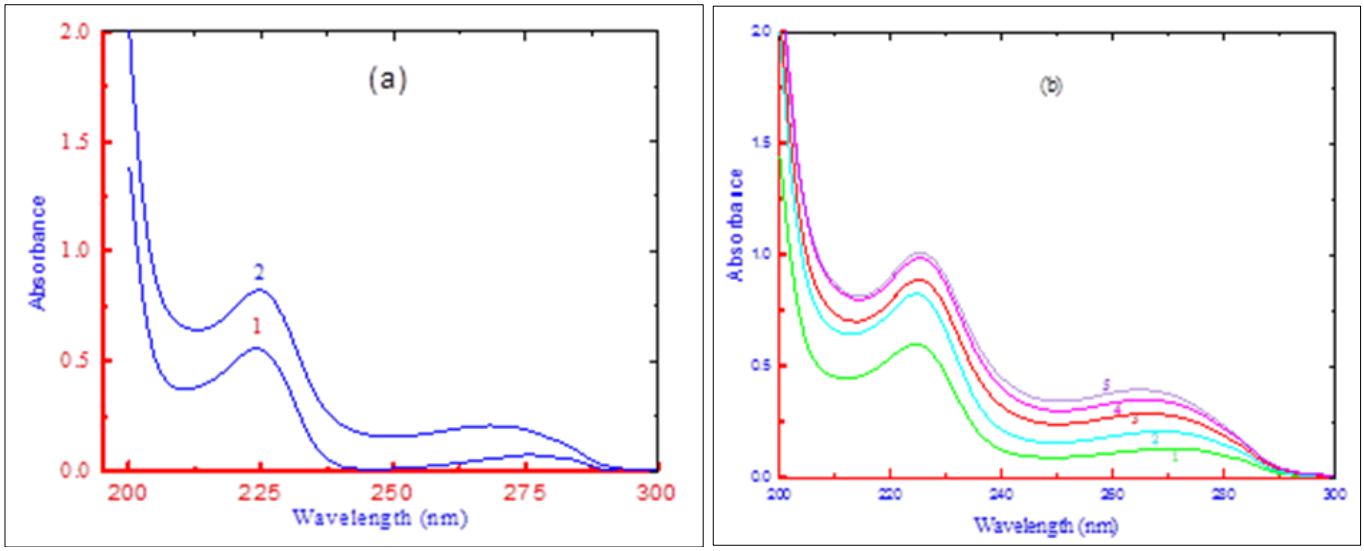


Fig 5: Absorption spectra for (a) pure CPC of 10.0mM aqueous solution (1) and (CPC+LFH) system containing 0.01 mmol.L^{-1} LFH (2); (b) (CPC+LFH) system at constant concentration of 0.10 mmol.L^{-1} CPC and having various concentrations of LFH such as 0.01 (1), 0.02 (2), 0.03 (3), 0.04 (4) and 0.05 mmol.L^{-1} (5) at 298.15 K.

From the absorption spectra recorded at 298.15 K for different solutions of LFH, having 0.10 mmol.L^{-1} of CPC, it is observed that the intensity of the absorption band was increased gradually with increasing LFH concentration. In addition, the maximum wavelength λ_{max} shows the hypsochromic shift or the blue shift. The shift of λ_{max} to the short-wavelength absorption band i.e., from 228 nm to 225 nm. is indicative of strong LFH-CPC interaction. At a particular wavelength, the values of K_b for the interaction of LFH-CPC assembly could be obtained by using equation [13].

The calculated values of K_b for case of CPC+LFH mixture with the variety of LFH concentrations over the range of 298.15–318.15 K are presented in Table 6. The Table confirms that there is a profound rise in K_b values as the concentration of LFH increases.

The change in K_b, with respect to the concentration of LFH, is an indication of the existence of strong LFH-CPC bond, which could be attributed as the dipole-dipole interactions or H-bond between the drug molecule and the polar head groups of surfactant monomer.

Table 6: The values of K_b of CPC system containing various concentrations of LFH at 224.2 nm λ_{max} at various temperatures.

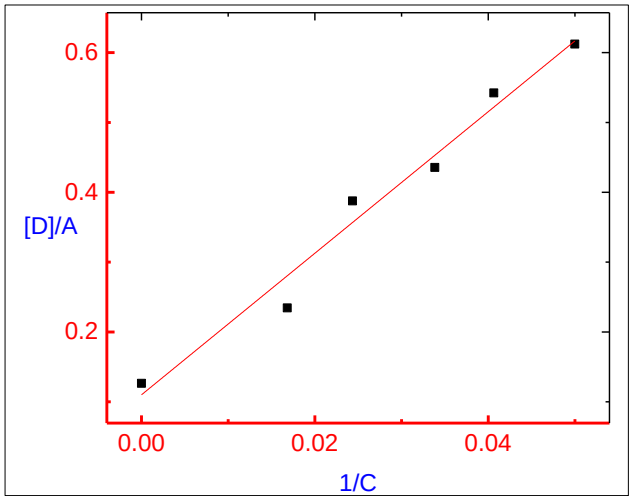
T (K)	c_{LFH} (mol L^{-1}×10^{-5})	$K_b \times 10^3$ (L mol^{-1})
298.15	1.001	2.128
298.15	2.012	3.129
298.15	3.0321	4.717
298.15	4.0921	5.356
298.15	5.5432	5.635
298.15	3.0321	3.717
303.15	3.0321	3.562
308.15	3.0321	3.038
313.15	3.0321	3.118
318.15	3.0321	3.364

The influence of temperature on the interaction of LFH-CPC was studied considering the experimental temperatures of our present observation in the range of 298.15–318.15 K. This temperature range fairly encompasses the ambient, as well as the body temperature of human adult. Table 6 shows that the K_b undergoes a decrease, at low temperature range, then drops down to the lowest point, and then experience an increase as the temperature goes up. A similar effect of temperature is also visible in the micellization process of cationic surfactants: the development of more hydrophobic and active binding sites accelerates to bind even a higher number of drug molecules [54].

Supplementary Table 1

T(K)	*cmc* mmol. Kg^{-1}	*cmc* mol.kg^{-1}	No. of Moles of Water	Total moles of water and CPC	X_{cmc} (*mol frac.*) $\times 10^{-5}$	Ln *cmc*	*B*	*C*
Pure CPC								
303.15	3.90	0.00390	55.56	55.56390	7.01	-9.56	-0.0319	6.0×10^{-5}
308.15	4.03	0.00403	55.56	55.56403	7.25	-9.53	-0.0319	6.0×10^{-5}
313.15	4.11	0.00411	55.56	55.56411	7.39	-9.51	-0.0319	6.0×10^{-5}
318.15	4.33	0.00433	55.56	55.56433	7.79	-9.46	-0.0319	6.0×10^{-5}
323.15	4.45	0.00445	55.56	55.56445	8.00	-9.43	-0.0319	6.0×10^{-5}
CPC+1.5024 mmol. Kg^{-1} NaCl								
303.15	3.63	0.00363	55.56	55.56363	6.53	-9.64	-0.2091	0.0003
308.15	3.70	0.00370	55.56	55.56370	6.65	-9.62	-0.2091	0.0003
313.15	3.90	0.00390	55.56	55.56390	7.01	-9.56	-0.2091	0.0003
318.15	4.03	0.00403	55.56	55.56403	7.25	-9.53	-0.2091	0.0003
323.15	4.41	0.00441	55.56	55.56441	7.93	-9.44	-0.2091	0.0003
CPC+3.501 mmol. Kg^{-1} LFH+0.0mm NaCl								
303.15	2.96	0.00296	55.56	55.56296	5.32	-9.84	-0.1965	0.0003
308.15	2.90	0.00290	55.56	55.56290	5.21	-9.86	-0.1965	0.0003
313.15	3.04	0.00304	55.56	55.56304	5.47	-9.81	-0.1965	0.0003
318.15	3.16	0.00316	55.56	55.56316	5.68	-9.77	-0.1965	0.0003
323.15	3.29	0.00329	55.56	55.56329	5.92	-9.73	-0.1965	0.0003
CPC+3.501 mmol. Kg^{-1} LFH+1.5024 mmol. Kg^{-1} NaCl								
303.15	3.30	0.00330	55.56	55.56330	5.93	-9.73	-0.5178	0.0008
308.15	3.17	0.00317	55.56	55.56317	5.70	-9.77	-0.5178	0.0008
313.15	3.08	0.00308	55.56	55.56308	5.54	-9.80	-0.5178	0.0008
318.15	3.26	0.00326	55.56	55.56326	5.86	-9.74	-0.5178	0.0008
323.15	3.47	0.00347	55.56	55.56347	6.24	-9.68	-0.5178	0.0008

Supplementary Plot 1



Supplementary Fig 1: Plot of [*D*]/*A* vs. 1/[*C*] for LFH-CPC having 0.01 mmol.L^{-1} drug at 298.15 K.

4. Conclusions

The current study successfully depicts and investigates the role of the variation of temperature and the concentration of drug, LFH on the micellization behavior of cationic surfactant CPC in the absence and presence of NaCl. A significant reduction in the *cmc* values of pure surfactant regardless of operating temperatures was observed by the addition of drug. The decrease in the *cmc* values of the mixture of CPC with the LFH in the presence of NaCl is also observed. The feasibility and spontaneity of the micellization phenomena of CPC and (CPC+LFH) mixed systems with the attendance of NaCl was confirmed from the thermodynamic parameters enumerated for the present systems. The various thermodynamic parameters disclose that both hydrophobic and exothermic interaction is the binding forces amid CPC molecules and between CPC and LFH. The negative values of $\Delta_m C^0_p$ reveal the modification in the conformations of CPC micelles in attendance of LFH at varying circumstances. Transfer of thermodynamic parameters ($\Delta G^0_{m.tr}$ $\Delta H^0_{m.tr}$ and $\Delta S^0_{m.tr}$) was also evaluated and illustrated. All these experimental analyses concluded the presence of attractive interactions between the studied components. The K_b values for the LFH-CPC binding process were found to be dependent on the LFH concentrations and variation of temperatures. The LFH-CPC binding process is spontaneous, and the binding interactions between LFH and CPC are hydrophobic.

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