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Energetics and Temperature Dependent Behaviour of Amitriptyline Hydrochloride with Conventional Surfactant in Aqueous Medium

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ABSTRACT

The use of surfactants for improved solubilization of hydrophobic drugs is of great pharmacological significant. This study investigates the interaction of a nitrogen-based surfactant, cetyltrimethylammonium bromide (CTABr) with varied concentrations of a tricyclic antidepressant drug, amitriptyline hydrochloride (AHCl), at different temperatures, 298.1 – 318.1 K with a view to determine the energetics of the system. The critical micelle concentration for the system (C^{SYS}) occurred far below that for CTABr at $6.65x10^{-4} - 9.01x10^{-4} moldm^{-3}$, indicating a favourable interaction. In addition, the change in Gibbs free energy ΔG_{SYS} ($kJmol^{-1}$) of the system was both temperature and concentration dependent and varied from -47.71 to -51.479. The results of enthalpy (ΔH_{SYS}) and entropy ΔS_{SYS}) of the system showed that the system was exothermic and entropy driven on the overall. The change in molar heat capacity ($\Delta_{sys}C_P$) for the system was also found to be negative and the micellization process of CTABr-AHCl was enthalpy-entropy compensated with the value of compensation temperature (T_c) of 325.65 K.The micelle-lipophilic drug system was found to be thermodynamic spontaneous and feasible at the investigated temperatures and concentrations.

Keywords: Antidepressant drug, Energetics, Molar heat capacity, Solubilization, Surfactant

INTRODUCTION

The molecular structure of an amphiphile which consists of lipophilic and hydrophilic groups confers on them important characteristic that make them an integral part of many research and technical operations as solubilizing, levelling, softening, and dispensing agents, (Aguirre-Ramírez *et al.*, 2021; Lu *et al*., 2021; Shah *et al*., 2013). Surfactant molecules in aqueous medium aggregate into micelles when a compromise between the attractive lipophilic and repulsive hydrophilic forces is attained, usually at a concentration known as the critical micelle concentration (CMC), (Di Michele *et al*., 2011). This characteristic of surfactant micelles at CMC has confirmed the crucial role played in biological events, (Alam and Mandal 2010; Lu *et al*., 2021), as carriers to solubilize water insoluble, or sparingly water soluble drugs, and also to protect drugs from degradation, and unwanted enzymatic action (Shelar *et al*., 2020**).** These various functions of surfactant micelles, to a large extent, however, are dependent on structural moiety, (Usman *et al*., 2013), temperature and other environmental conditions, (Osundiya *et al*., 2021). Drug solubilization is a key aspect of drug delivery, and bioavailability is a critical step in therapeutics, (Shelar *et al*., 2020), and in view of this, there has been a sustained interest on studies related to simplified models such as micelle as drug delivery vehicle, (Alam and Mandal 2010), for improved drug loading and prompt delivery to the target cell membranes, (Azum *et al*., 2021; Schreier *et al.*, 2000)**.**

A large number of pharmacological compounds such as antihistamines, tranquilizers, antidepressants (amitriptyline-HCl, butriptyline-HCl, clomipramime-HCl, and imipramine-HCl) are surface active, but form aggregates at a higher concentration (CMC), due to the short alkyl chain length occasioned by the fused benzene rings in the structure. The delay in the aggregation of these amphiphilic drugs is of great concern for economic consideration, and clinical success (bio-distribution), (Alam and Mandal 2010; Kumar *et al*., 2018; Schreier *et al*., 2000). However, the micellization process can be induced for therapeutic purpose with the aid of co-solute or co-solvent depending on the behaviour of the additives, (Ali and Ansari 2010). Amitriptyline hydrochloride (AHCl) is an amphiphilic drug with a short hydrophobic segment that contains fused aromatic rings and an amine group on the hydrophilic group (Figure 1). AHCl belongs to the tricyclic class (TCA) and it is used for the treatment of major depressive disorder and other conditions which include anxiety disorders, chronic

and neuropathic pain conditions, (Kumar *et al.*, 2018; Schreier *et al*., 2000).

Studies on hydrophobic and amphiphilic drugs with focus on the application of some conventional surfactants as solubilizers have been reported in the literature, (Schreier *et al*., 2000). Khan *et al*. (2015) studied the interaction of an amphiphilic drug and bis(2-ethylhexyl)sulfosuccinate at low concentrations in the absence and presence of sodium chloride, and the role of mixed micelles in drug delivery was also investigated, (Kapare and Metkar 2020). Furthermore, the interaction of chlorpromazine and trifluoperazine with anionic sodium dodecylsulfate (SDS) micelles has been reported (Caetano and Tabak2000). The interaction of cefadroxyl monohydrate with hexadecyltrimethylammonium bromide and sodium dodecyl sulfate was examined (Akhtar *et al*., 2008). However, to the best of our knowledge, study on the energetics of interaction of micellar-encapsulated drug from a single phase origin has not received the much needed attention. This study, therefore, employed conductometric technique to investigate the energy contributions of different solute-solute and solute-solvent interaction parameters to the formation of the CTABr-drug aggregate at different temperatures with a view to having insight into the thermodynamics status of the system. The structures of Cetyltrimethylammonium bromide (CTABr) and Amitriptyline hydrochloride(AHCl) are presented in Figure 1.

MATERIALS AND METHODS

The electrical conductivity method which has been the most frequently used technique for surface active agents with a net positive charge on the head segment of the molecule was used for this study, (Osundiya *et al*., 2021).

The cationic surfactant, Cetyltrimethylammonium bromide (CTABr) and Amitriptyline hydrochloride (AHCl) of mass purity of 0.99 were purchased from Sigma Aldrich, and were used without further purification. The study was conducted in re-distilled de-ionized water of specific conductance value of 1-4 μScm^{-1} (at room temperature) using Jenway 4510 conductivity meter. A standard solution of potassium chloride (0.01 M) of known conductivity value was used to calibrate the meter before the commencement of the experiment. Stock solutions of AHCl were prepared in aqueous medium and various concentrations of 0.1, 0.3, 0.5, 0.6 and 1 mM were obtained through serial dilution method.

These solutions of different concentrations were used as solvent to prepare 4.59 mM CTABr. A 10 ml of the solvent of a particular concentration was placed in the cuvette, and the conductivity was recorded, after which 0.2 ml of the surfactant-drug solution was progressively added with the conductivity values recorded after thorough mixing. This procedure continued until the desired concentration was achieved, which is the concentration at which micelles are formed (Olubunmi *et al*. 2020), and the solubilization of the drugs has occurred in the micellar core. This phenomenon was observed when the successive conductivity values became closer, to one another due to the binding of some of the counter-ions to the micellar surface as the experiment was progressing. The binding of some of these counter-ions forms the basis of (β) (Owoyomi *et al*., 2011). The above process was repeated for the other concentrations of the drug (AHCl,) with freshly prepared solutions at 298.1, 303.1, 308.1, 313.1, and 318.1 K. The experiments were carried out at 5 K interval under thermostated water-bath with precision of ±273.2 K.

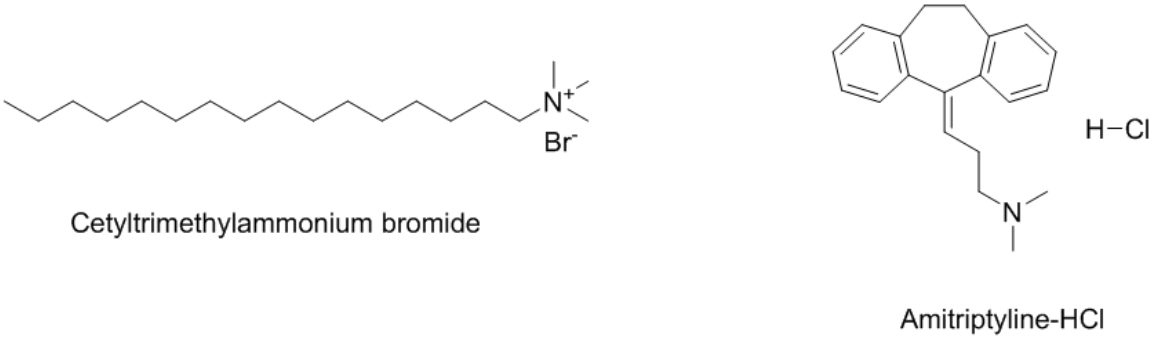

Figure 1: Structures of Cethyltrimethylammonium bromide and Amitriptyline-HCl

RESULTS AND DISCUSSION

Determination of the Critical Micelle Concentration (C^{SYS}) of CTABr+AHCl

The single break point obtained from the plot of conductivity against the concentration of the CTABr+AHCl system (conventional method) was not very sharp at higher temperatures as a result of gradual transition from monomers to micelle. This conventional method of determining the CMC has been controversial as many authors had taken the curvature in the region of surfactant saturation when the transition from monomers to micelle is not abrupt as the second critical micelle concentration (CMC), (Owoyomi *et al*., 2011). In

view of the above, the values of the critical micelle concentration (C^{SYS}) of the system were obtained using the method proposed by (Carpena *et al*., 2002; Olubunmi *et al*., 2020) which involves fitting of the conductivity data as a function of the concentration of CTABr+AHCl to the integral form of the Boltzmann-type sigmoidal equation as expressed in Equation 1.

$$\frac{\delta\kappa}{\delta c} = \frac{A_1 - A_2}{1 + exp^{(c-C^{SYS})/d}} + A_1 \qquad (1)$$

Where$\kappa$is the conductivity values, c is the concentration of CTABr-AHCl, $A_{1,}, A_2$, representthe values at the pre-micelle and post-micelle slopes, c^{SYS} is the centre of transition and d is the width of the transition. The degree of counter-ion binding (β) which is dependent on surface charge density of the aggregate was obtained by subtracting the ratio of the slopes (α) from unity ($\beta = 1 - \frac{A_2}{A_1}$);$\alpha$ is the degree of counter-ion dissociation.

Table 1 shows the results of the C^{SYS} in the absence of AHCl in aqueous medium and at different temperatures. The C^{SYS} values obtained increases as the temperature increases, and this trend was similar to earlier report in the literature, (Nabi *et al*., 2018).The values of the various thermodynamic parameters indicated that the CTABr system was spontaneous to a varying degree at all temperatures. In addition, the entropy of the system decreases as the temperature increases, while the system was endothermic and exothermic at low and high temperatures respectively.

Table 1: Critical micelle concentration (C^{SYS}), and Thermodynamic parameters of the micellization for CTABr with 0.0 mM AHCl in aqueous medium

System	Temperature (K)	C^{SYS} ($moldm^{-3}$)	$-\Delta G_{SYS}$ ($kJmol^{-1}$)	$-\Delta H_{SYS}$ ($kJmol^{-1}$)	ΔS_{SYS} ($Jmol^{-1}K^{-1}$
	298.1	$9.053x10^{-4}$	47.435	-13.724	205.162
	303.1	$8.957x10^{-4}$	48.079	-1.585	163.855
CTABr+AHCl	308.1	$9.062x10^{-4}$	47.045	10.124	119.835
(0.0) mM					
	313.1	$9.815x10^{-4}$	49.482	22.406	86.475
	318.1	$1.065x10^{-3}$	49.352	34.254	47.464

The conductivity value of surfactant changed drastically when AHCl was added and result of the Critical micelle concentration (C^{SYS}) for the system at different concentrations were summarized in Table 2. The system that contained 0.1, and 0.3 mM AHCl showed a linear increase in C^{SYS} as the temperature increases. Such trend has been reported as one of the characteristics of charged surfactants (positive charge), (Ghosh *et al*., 2011). At higher concentration of AHCl, (0.5,0.6, and 1.0mM), the values of C^{SYS} decreases up to 308.1 K and increases again at elevated temperature.

The values of the counter ion binding to the micellar surface also experienced a similar pattern. The interaction between the monomeric CTABr and AHCl was favourable as all the C^{SYS} values obtained were lower than the values obtained when the system contained 0.0 mM AHCl (Table 1). The stepwise increase in the C^{SYS} with increase in temperature can be attributed to a number of factors such as the hydration of the hydrophobic group, an increase in the kinetic energy of the system and the disruption of the micellar palisade layer of the aggregated surfactant + drug micelles (monomers ⇋ micelles), (*Ali et al*., 2014; Chauhan *et al*., 2014). The representative plot of variation of $\ln\chi C^{SYS}$(C^{SYS}expressed in mole fraction ratio) with temperature using Equation (5) has a characteristic U-shape, this type of behaviour is one of the distinguishing features of ionic surfactants (Chauhan *et al*., 2014). In this work the best fit was obtained at 0.6 mM, and was graphically presented in Figure 2.

Table 2: Critical micelle concentration (C^{SYS})and the counter-ion binding (β) of micellization for CTABr containing different concentration of AHCl in aqueous medium

System	Temperature (K)	$C^{SYS}(mM)$	β
CTABr +AHCl (0.1) mM	298.1	0.822	0.731
	303.1	0.833	0.708
	308.1	0.844	0.709
	313.1	0.875	0.703
	318.1	0.901	0.765
CTABr +AHCl (0.3) mM	298.1	0.769	0.764
	303.1	0.797	0.757
	308.1	0.809	0.738
	313.1	0.814	0.747
	318.1	0.877	0.740
CTABr +AHCl (0.5) mM	298.1	0.779	0.731
	303.1	0.665	0.767
	308.1	0.696	0.752
	313.1	0.805	0.753
	318.1	0.873	0.671
CTABr +AHCl (0.6) mM	298.1	0.805	0.744
	303.1	0.809	0.753
	308.1	0.782	0.745
	313.1	0.851	0.749
	318.1	0.882	0.739
CTABr+AHCl (1.0) mM	298.1	0.7355	0.724
	303.1	0.7326	0.736
	308.1	0.7248	0.752
	313.1	0.8211	0.709
	318.1	0.8475	0.753

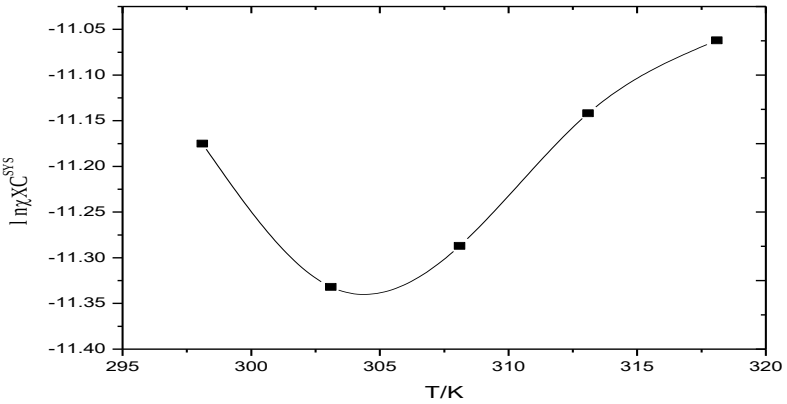

Figure 2: Representative plot of $\ln\chi C^{SYS}$against Temperature at 0.6 mM AHCl

Thermodynamic Parameters of CTABr + AHCl System

Temperature has a definite impact on the micellization process and the dependence of C^{SYS} on temperature can be used to evaluate the energetics of the micellization process. The thermodynamic parameters were obtained with the aid of Equations 2 - 8 and the results were presented in Table 3.

The change in Gibbs free energy (ΔG) of the system was obtained from equation (2) in agreement with the pseudo- phase separation model, (Owoyomi *et al*., 2011):

$$\Delta G_{SYS} = (2-\alpha)RT\ln\chi C^{SYS} \qquad (2)$$

where $\ln\chi C^{SYS}$ is the C^{SYS} calculated on a mole fraction ratio, and α is the degree of counter-ion dissociation from the micellar surface.

Similarly, the enthalpy change (ΔH) was calculated using the Helmholtz and an adjusted

Van't Hoff equation represented as equation 3, (Ali and Ansari 2010).

$$\Delta H_{SYS} = -RT^2[(2-\alpha)\left(\frac{\delta \ln \chi C^{SYS}}{\delta T}\right) - \ln \chi C^{SYS}\left(\frac{\delta \alpha}{\delta T}\right) \quad (3)$$

The change in the degree of counter ion binding was usually small for cationic surfactants and this was also the trend observed in this study, hence the last part of the equation (3) can be ignored, and the equation is reduced to:

$$\Delta H_{SYS} = -RT^2(2-\alpha)\left(\frac{\delta ln \chi C^{SYS}}{\delta T}\right) \quad (4)$$

The last parameter in equation (4) was obtained by plotting $ln\chi C^{SYS}$ against different temperatures with the aid of the appropriate order of derivative (Owoyomi *et al*., 2011), and fittings using equation (5).

$$ln\chi C^{SYS} = A_0 + A_1 lnT + \frac{A_2}{T} \quad (5)$$

The entropy change (ΔS)was obtained (Olubunmi *et al*.2020) using equation (6) as follows:

$$\Delta S_{sys} = \frac{\Delta H_{SYS} - \Delta G_{SYS}}{T} \quad (6)$$

Table 3: Thermodynamic parameters of the micellization for CTABr containing different concentrations of AHCl in aqueous medium

System	Temperature (K)	$-\Delta G_{SYS}$ ($kJmol^{-1}$)	$-\Delta H_{SYS}$ ($kJmol^{-1}$)	ΔS_{SYS} ($Jmol^{-1}K^{-1}$)	$\Delta_{sys}C_P$) ($kJmol^{-1}$)
	298.1	47.710	1.733	154.235	
	303.1	47.835	4.038	144.496	-478.96
CTABr + AHCl (0.1) mM	308.1	48.577	6.366	137.004	
	313.1	49.209	8.694	129.404	
	318.1	51.479	11.372	126.060	
	298.1	48.513	2.476	155.775	
	303.1	49.377	5.247	145.593	-549.3
CTABr + AHCl (0.3) mM	308.1	49.577	7.942	135.135	
	313.1	50.615	10.764	127.278	
	318.1	50.877	13.452	117.65	
	298.1	47.942	-3.555	172.752	
	303.1	50.415	4.724	150.745	-1458.9
CTABr + AHCl (0.5) mM	308.1	50.683	12.078	125.301	
	313.1	50.843	19.431	100.328	
	318.1	50.349	26.351	75.442	
	298.1	48.992	-7.943	190.992	
	303.1	49.193	-0.573	164.192	-1450.9
CTABr + AHCl (0.6) mM	308.1	49.938	5.991	142.639	
	313.1	50.477	13.956	116.646	
	318.1	50.825	21.067	93.549	
	298.1	47.996	-6.548	182.669	
	303.1	49.154	2.229	154.817	-1750.9
CTABr + AHCl (1.0) mM	308.1	50.475	11.075	127.878	
	313.1	49.519	19.403	96.186	
	318.1	51.419	28.728	71.333	

Similarly, the values of the change in Gibbs free energy of the system were negative when the system contained 0.1 mM, and it increases as the temperature increases. The process become more spontaneous as the concentration of AHCl was increased to 0.3 mM with the ΔG_{SYS} values ranging between48.513 and 50.877 $kJmol^{-1}$. However, at 0.5 AHCl, the system was highly spontaneous up to 313 K but the degree of the spontaneity decreased at 318.1K with a value of 50.349 $kJmol^{-1}$ as shown in Table 3. The behaviour of the system at the 0.6 mM AHCl addition is similar to the trend observed for the 0.3 mM AHCl. A negative ΔG values were obtained at all the temperatures of interest. In general, the trend of results obtained for ΔG_{SYS} was similar to that for C^{SYS} and the degree

of counter-ion (Br^-) binding (β) as both the $C^{SYS}(\chi^{SYS})$ and β are the major components of Gibb's free energy. The results obtained indicated that the interactions between the monomers of the surfactant and that of the drug are thermodynamically favourable as earlier reported in the literature, (Akhtar *et al*., 2008).

The values of the change in the enthalpy (ΔH_{SYS}) of CTABr at 0.1 and 0.3 mM AHCl showed that the micellization process was exothermic and the values become more negative at elevated temperatures (Table 3). On the contrary, the system becomes endothermic at lower temperature when the concentration of AHCl was increased to 0.5 and at1.0 mM. Similarly, the system was exothermic at elevated temperatures and only endothermic at 298.1 and 303.1 K for 0.6 mM. The change from exothermic to endothermic is characteristic of ionic surfactant, (Zieliński 2001), and has been linked to the formation of temporary dipole due to hydrophobic interactions. Such systems have been reported, (Chauhan *et al*., 2014) to be enthalpy-controlled at low temperatures. The plot of variation of ΔH_{SYS} with temperature at all investigated concentrations was graphically depicted in Figure 3.

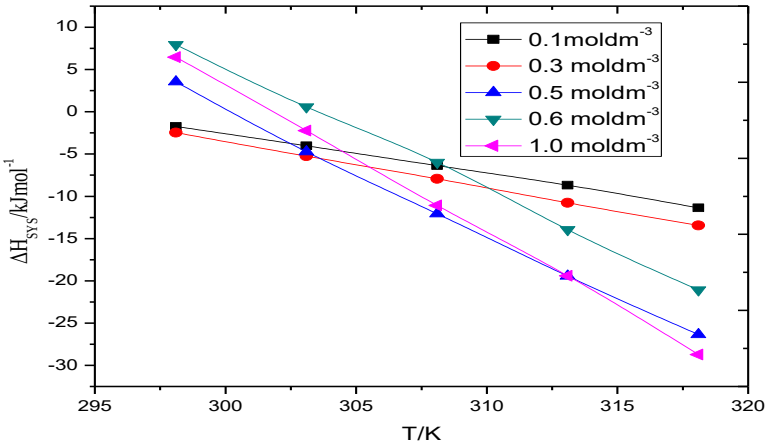

Figure 3: Plot of ΔH_{SYS} against Temperature for micellization of CTABr+AHCl

The entropy of the system was also calculated with the aid of Equation 6 and the variation of ΔS_{SYS} against temperature is depicted in Figure 4. It was discovered that the values were positive at all the investigated temperatures. At a given concentration of AHCl, the entropy values decreased at elevated temperature (T > 298.1 K). The trend of the entropy results corroborated the values of the C^{SYS} and it indicateed that electrostatic repulsion was stronger and more significant at higher temperatures. Consequently, at all the temperatures of interest, the degree of orderliness was increasing as the temperature was increasing, as presented in Table 3. Hence, the results indicated that the system was entropy controlled at high temperature and entropy driven at higher concentration of AHCl as previously reported in the literature (Akhtar *et al*., 2008).

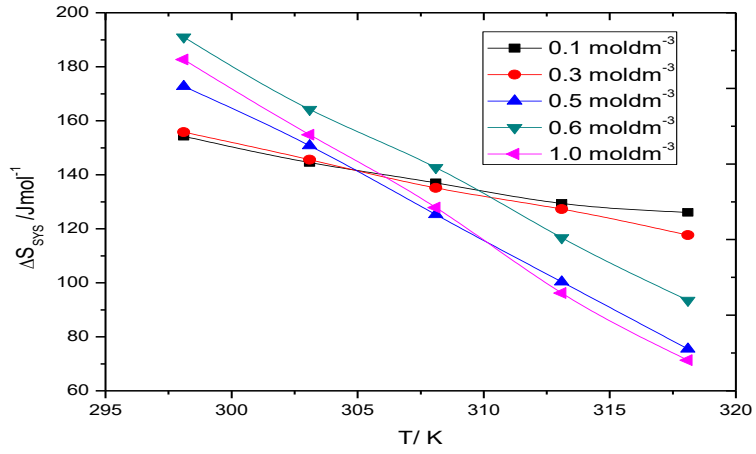

Figure 4: The plot of ΔS_{SYS} against Temperature for micellization of CTABr+AHCl

Information concerning the sequence of structural changes of protein upon binding different ligands can be deduced from the molar heat capacity ($\Delta_{sys}C_P$) of the system through equation 7, (Shelar *et al*., 2020):

$$\Delta_{sys}C_P = \left(\frac{\delta H_{SYS}}{\delta T}\right)p \qquad (7)$$

The change in molar heat capacity ($\Delta_{sys}C_P$)for the surfactant mediated drug was obtained from the slopes of the plot of ΔH_{SYS} against temperature using Equation (7) and was negative at all temperatures of interest. The results as presented in Table 3 further showed that the values become more negative as the concentration of AHCl was increasing. The negative values obtained for the change in the heat capacity of the system was in agreement with the results obtained for the enthalpy of the system. The trend of the results for the molar heat capacity of surfactant + AHCl could be ascribed to the conformational changes and the diminution of the degrees of freedom as a result of motional restriction at higher concentration of AHCl due to the bulkiness of the AHCl, (Hossain and Hoque 2014).

Determination of enthalpy–entropy compensation

The micelle of CTABr + AHCl was further examined to evaluate the enthalpy- entropy compensation of the system and the possibility of a linear relationship (Figure 5) between the change in enthalpy and entropy in accordance with Equation (8).

$$\Delta H_{SYS} = T_c \Delta S_{SYS} + \Delta H^* \qquad (8)$$

The values of the compensation temperature (T_c) and the intrinsic enthalpy gain (ΔH^*) were obtained from the slope and intercept of the graph respectively and the results are presented in Table 4.

Table 4: Enthalpy-entropy compensation parameters for CTABr containing different concentration of AHCl

System	T_c (K)	$-\Delta H^*_{SYS}$ (kJmol^{-1}	R^2
CTABr + AHCl (0.1) mM	325.65	51.460	0.967
CTABr + AHCl (0.3) mM	289.8	47.472	0.957
CTABr + AHCl (0.5) mM	303.7	49.745	0.997
CTABr + AHCl (0.6) mM	299.13	48.857	0.999
CTABr + AHCl (1.0) mM	310.77	50.331	0.998

The T_c parameter which characterized the composition phenomenon as a result of desolvation of the tail group of the surfactant (Di Michele *et al*., 2011), had values that ranged from 289.8 to 325.65 K. These values were in the range of the values for a protein solution (250 to 350 K) as reported in the literature (Di Michele *et al*., 2011). The values of ΔH^* which was associated with interactions between solute-solute and micellar formation (Diamant and Andelman 1996), were all negative with a slight variation as the concentration of AHCl was increasing as presented in Table 4. Furthermore, the values of ΔH^*correspond to the zero entropy gain (Owoyomi *et al*., 2011), ($\Delta S_{sys} = 0$), hence, the results showed that the system was increasingly stable as the concentration of the drug was increasing at the investigated temperatures.

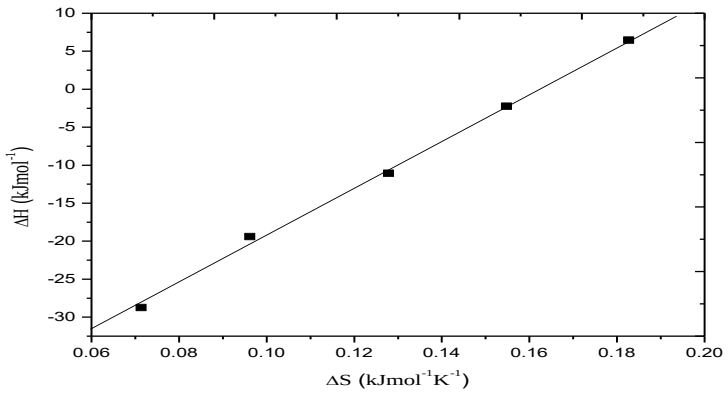

Figure 5: Representative plot for enthalpy-entropy compensation for 0.6 mM AHCl

From the results of ΔH^* (Table 4), it showed that micellar drug aggregate was thermodynamically stable at the investigated temperatures, (Diamant and Andelman 1996).

CONCLUSION

The interaction of linear alkyl ammonium Bromide, cetyltrimethylammonium bromide (CTABr) with amphiphilic drug, amitriptyline hydrochloride (AHCl) was studied in aqueous medium. The results obtained showed that the ability of the micelles of CTABr to interact favourably with the AHCl drug increases with an increase in the concentration of AHCl at all investigated temperatures. The high negative values recorded for the micelle encapsulated drug showed that the system was thermodynamically spontaneous. Furthermore, the system is exothermic on the overall and entropy driven especially at low temperature. The results of the change in heat capacity ($\Delta_{sys}C_P$) of the system indicated a favorable response in the binding pattern, and the aggregation process was shown to be favored even when the disorderliness was not temperature inclined. Consequently, the CTABr micelles can be used for improved solubilization, and bio-distribution (carriers) of antidepressant drugs such as amitriptyline hydrochloride (AHCl) at the concentration and temperatures studied.

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