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CMC determination and thermodynamic changes of the mixture of non-steroidal anti-inflammatory drug (mefenamic acid) with anionic surfactant (SDS), and cationic surfactant (CTAB) in aqueous solution

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***Abstract*---**Surface tension was measured using a platinum plate of the tensiometer for aqueous solutions of non-steroidal anti-inflammatory drugs (NSAIDs) such as mefenamic acid in concentrations of (10^{-3},10^{-2},10^{-10} M) to study the effect of adding surfactants on the drug solubility, which are anionic surfactant such as sodium dodecyl sulfate (SDS) and cationic surfactant such as cetyltriamonium bromide (CTAB) concentrations within range ($1x10^{-3}$ -$1x10^{-1}$ M). The effect of temperature at (313,303,293,283 K) on these aqueous solutions with Mefenamic acid has also been studied. From the plot of the concentration of aqueous solutions of surfactants with drug versus surface tension (ɣ) were obtained the critical micelle concentration (CMC). As well, the values of the Gibbs surface excess concentration (Γmax), minimum area occupied per molecule (Amin.), surface pressure at CMC (Πcmc) were determined on basis of the standard Gibbs free energy of adsorption ($\Delta G°_{ads}$) and the thermodynamic constants (ΔH_m, ΔS_m, ΔG_m, ΔG_{ads}) were found at CMC for aqueous solutions. Free energy values of the micelle formation process ΔGm and the free energy values of adsorption ΔGads were used as an indicator of the spontaneously of micelle formation to improve the solubility of drugs in aqueous solutions where the values of ΔGm ranged of (-6.2 to -0.2) KJ/mol, the values of ΔGads ranged from (-19.2 to -10.7) KJ/mol, and the values of positive entropy ΔS

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ranging from (2.2 to 48.2) JK^{-1} mol^{-1} that indicates an increase in entropy of the process of micellular formation which increases with increasing temperature, and it has been shown that the values of enthalpy or heat of reaction ΔH was negative for the active aqueous solutions of surfactant. From the study of physiological values of buffer solution at pH 1.0,5.8,6.4,7.4 of measured aqueous solutions, it was found that there is no noticeable effect of acidity function on CMC values and thermodynamic functions.

Keywords---NSAIDs, mefenamic acid, surface tension, critical micelle concentration, thermodynamic parameters.

Introduction

Surface active agents or surfactants defined as substances that minimize the contact angle of water-air layer and water surface tension, which composed of high molar mass compound with a head of polar region recognized as water-liking or hydrophilic and tail of non-polar region recognized as water-hating or hydrophobic on its chemical structure [1]. Surfactants possess a wide application in detergents and in pharmaceutical products such as emulsifying agents, solubilizing agents [2]. The advantages of using surfactant due to its ability of micelle formation at a certain range of surfactant concentration, hence it called as critical micelle concentration (CMC) [1-3]. In pharmacologically, micelles used to carry out the drug molecules to the organs of target, act as drug delivery system, because of their ability to improve the solubility of many poorly water- soluble drug by increasing the rate of drug dissolution and wetting then increased the drug bioavailability [4,5].

In addition to the drug wettability, the surfactant used in pharmaceutics, dosage form formulation of drug, by lowering drug toxicity [6]. Non-steroidal anti-inflammatory drugs (NSAIDs) are widely used as antipyretic, analgesic, for pain and inflammation treatment especially for arthritis [6,7,8]. NSAIDs solubility and its dissolution rate is very low in gastric juices, and thus, its bioavailability is also low. Hence, its poor solubility causes an increased local concentration of the drug. This, in turn, can result in adverse effects, such as irritation and ulceration of the stomach mucosa, and even perforation of the gastric wall. Therefore, a number of studies focused on the search for effective NSAIDs with reduced adverse gastrointestinal reactions [9]. Surfactant as anionic surfactant (SDS), and cationic surfactant (CTAB) can form spherical micelles at concentration called critical micelle concentration (CMC) and if the concentration of surfactant is increased above CMC, then the shape of aggregate is changed from spherical to lamellar. Mefenamic acid is a non-steroidal anti-inflammatory drug (NSAIDs) and widely used as an antipyretic analgesic and anti- rheumatic drug, its slightly soluble in water.

Since the powder of mefenamic acid can stick to any type of surface, and its not easy to handle into granulation and tablet process. Hence, to improved solubility and then its dissolution, many studies were used surfactant. The effect of docusate sodium (DOSS) on the nucleation of mefenamic acid was studied in different dimethylacetamide (DMA)–water mixtures. Evaluating the results by the classical nucleation theory reveals that the pre-exponential factor (*A*) increases by approximately 50% while the interfacial energy is essentially uninfluenced, It is also found that the crystal growth rate becomes higher in the presence of DOSS.

Thus hypothesized that transport and desolvation of mefenamic acid molecules are facilitated in the presence of DOSS [10]. On the other hand, the enhancement of its solubility in water using surfactant systems has not been explored. Therefore, we have investigated the interaction between this drug and anionic (SDS, SDBS, DTAB, CTAB, TTAB) surfactants as well as non-ionic (Tween 20, Tween 40, Tween 60, Tween 80, Brij 30, Brij 35,Brij 56 and Brij 58) surfactants. The results show that, irrespective of the surfactant type, the solubility of Mefenamic acid increases with increase in concentration of a surfactant, leading to the conclusion that there is an association between the drug and the surfactants. The molar solubilization ratio, micelle–water partition coefficient (K_M), binding constant (K) and the Gibbs energy of solubilization, ($\Delta G^o s$), of the drug in the micelles were determined to yield a model to correlate the solubility with the structure of the surfactant used.

An outcome of the results is that the order of solubility of this drug in non-ionic and ionic surfactants is Tween 80 > Tween 60 > Tween 40 > Tween 20 and, in the case of the Brij series, is Brij56 > Brij58 > Brij35 > Brij30, while in cationic and anionic surfactants the order is CTAB > TTAB > DTAB and SDBS > SDS [11-13]. The CMC and thermodynamic parameters such as $\Delta G°m$, $\Delta H°m$, and $\Delta S°m$ for micellization process have been investigated [14]. The purpose of this study was to determined the thermodynamic parameters at adsorption of micellization of Mefenamic acid as NSAIDs which interact with surfactant as SDS and CTAB based on surface tension analysis at different temperature.

Experimental

Materials and Methods

All chemicals and solvents used were obtained from Sigma-Aldrich Germany & Fluka Switzerland company. Mefenamic, showed in figure 1, was supplied by the state enterprise for drug industries and medical appliances in Samarra, Iraq. Mefenamic acid based on IUPAC name is N-2,3-xylylanthranilic acid, showed in figure 1. SDS sodium dodecyl sulfate, and CTAB cetyltriamonium bromide are supplied by Sigma-Aldrich Germany company, their chemical structure showed in figure 2. Automatic Surface Tensiometer; Type: BZY-101(BZY-A), apparatus supplied by Shanghai Fangrui Instrument Co., Ltd., China. Technical parameters of measuring range is 0-400 mN/m and minimum resolution is 0.1-0.01 mN/m .

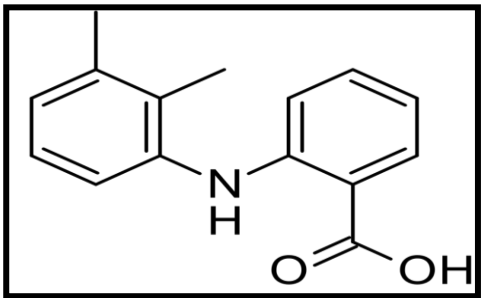
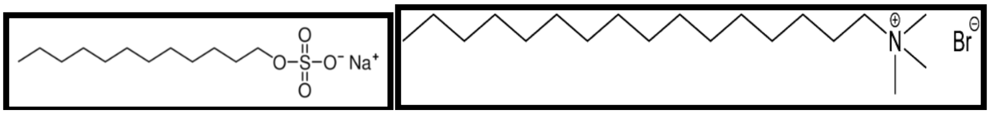


Figure 1. Chemical structure of Mefenamic acid

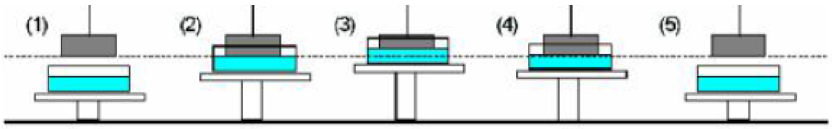


SDS CTAB

Figure 2. Chemical structure of SDS & CTAB

Procedure

Stock solution of SDS and CTAB were prepared of (10^{-1} M) in distilled water. Aqueous solutions of Mefenamic acid were prepared of 10^{-1}, 10^{-2} , 10^{-3} M in SDS and in CTAB. Surface tension were measured for each solution as follow:



Start the test, manually turn the knob slowly, raise the sample table.	Platinum plate has contact with the surface of measured sample.	When the ripple appears on the liquid level, the lifting table stops rising.	Dynamically measuring the surface tension value.	After the measuring has been finished, manually turn the knob to lower the sample table.

The CMC were determined by means of measuring the surface tension of surfactant (SDS and CTAB) of varying concentration with drug. The CMC results from the plot of surface tension against series concentration. It was detected from the intersection between the regression straight line of the linearly dependent region and straight line passing through the plateau.

Results and Discussion

The surface tension of aqueous solution of pure Mefenamic was measured as a function of varying concentration of SDS and CTAB. Figure 4,5,6, and 7,8,9 showed the plots of surface tension against the concentration of surfactant at different temperatures with different concentration of Mefenamic with SDS and

CTAB, respectively, at different temperature to evaluated the CMC at sharp break point for each plot [17].

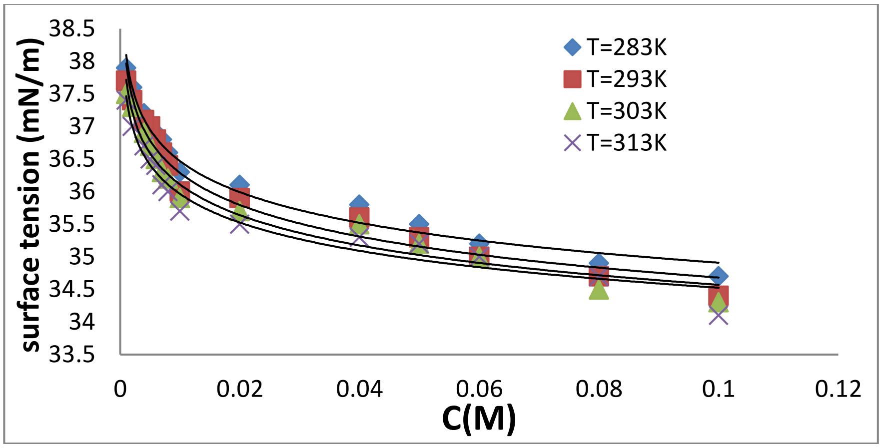


Figure 4. Plot of the surface tension of Mefenamic (10^{-3} M) against varying concentration of SDS

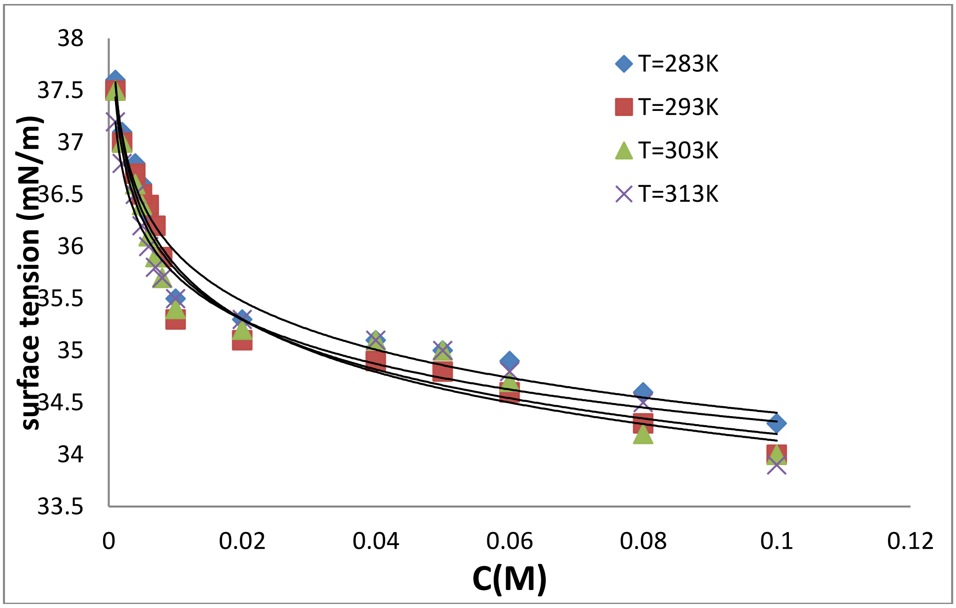


Figure 5. Plot of the surface tension of Mefenamic (10^{-2}M) against varying concentration of SDS

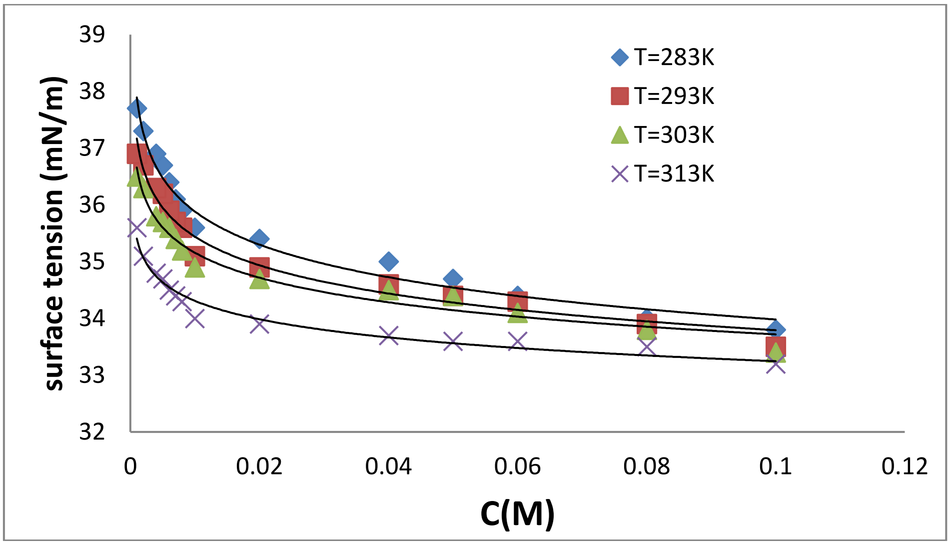


Figure 6. Plot of the surface tension of Mefenamic (10^{-1}M) against varying concentration of SDS

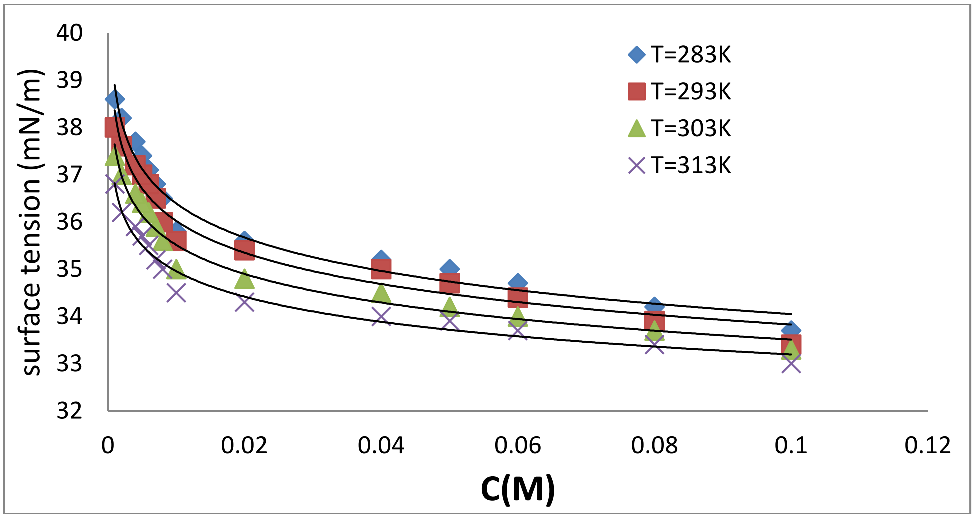


Figure 7. Plot of the surface tension Mefenamic (10^{-3}M) against varying concentration of CTAB

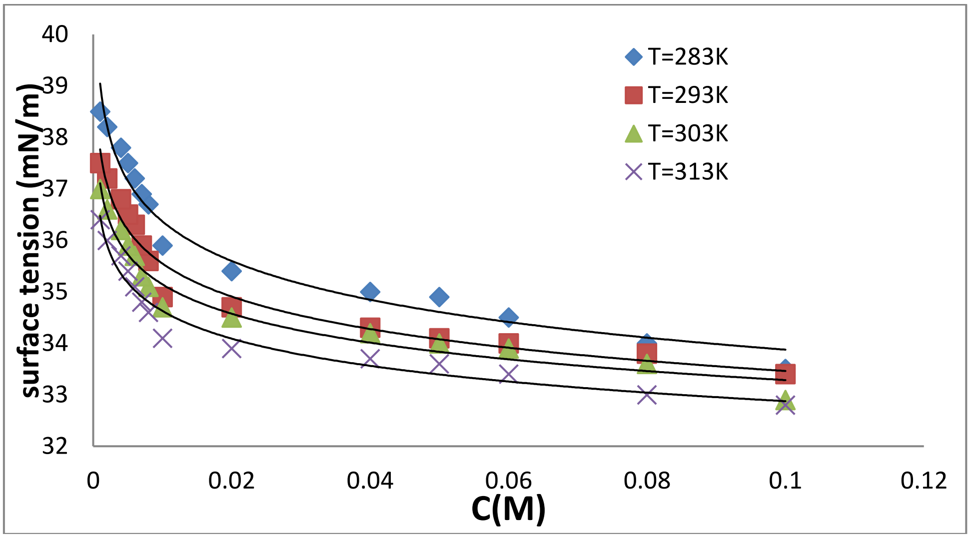


Figure 8. Plot of the surface tension Mefenamic (10^{-2}M) against varying concentration of CTAB

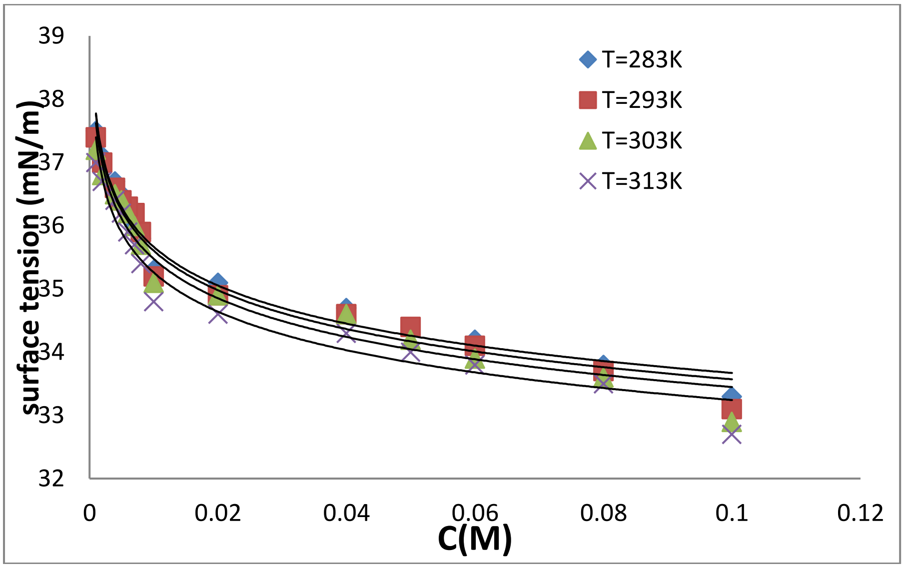


Figure 9. Plot of the surface tension Mefenamic (10^{-1}M) against varying concentration of CTAB

The concentration of maximum surface excess and the minimum area occupied per molecule were calculated by using eq.1 and eq.2, respectively [18,19].

$$\Gamma max = \frac{(\partial \gamma / lnC\ )cmc}{RT} \qquad \text{..........1}$$

$$Amin = \frac{1}{NA\ \Gamma max} \qquad \text{.........2}$$

Where N_A referred to Avogadro number and ($\partial\gamma/ \partial \ln C$) is evaluated from the slope of γ versus lnC plotting which illustrated in Figure 8 as a typical form. The surface pressure (Πcmc) at CMC, was determined from the equation 3:

$$\prod cmc = \text{ɣ} - \text{ɣ}cmc \qquad ....3$$

Where γ and γ_{cmc} denote the surface tensions of the water solvent and of the drug-surfactant micelle at CMC, respectively. The standard free energy of drug adsorption (ΔG°ads) was obtained using equation 4.

$$\Delta G°ads = \Delta G°m - \frac{\Pi cmc}{\Gamma max} \qquad ....4$$

Where ΔG°m is the standard Gibbs free energy of micellization.

Table 2,3,4, and 5 were listed CMC values with corresponding values of their values of the Gibbs surface excess concentration(Γmax), minimum area occupied per molecule(Amin.), surface pressure at CMC (Πcmc) was determined on basis of the standard Gibbs free energy of adsorption (ΔG°ads).

$$\Delta G°m = RT \ln Xcmc \qquad ....5$$

Where XCMC is the mole fraction of surfactant at the CMC.
The enthalpy of micellization ΔH˚m was obtained by applying the Gibbs-Helmholtz equation to the equation above :

$$\Delta H°m = -RT^2(\partial \; lnXcmc/\partial \; T\,) \qquad ....6$$

ΔH˚m was evaluated from the slope of the plot of ln Xcmc versus temperature.

$$\Delta G°m = \Delta H°m - T\Delta S°m \qquad ....7$$

ΔG˚m, ΔH˚m and ΔS˚m that completed by applying the above equations for the span 20 and for different concentration of Mefenamic-SDS reported in Table 2,3,4 and Mefenamic-CTAB in Table 5,6,7 respectively, at different tremperature.

Table 2
Thermodynamic parameters of SDS with Mefenamic acid (10^{-3}M)

T (K)	CMC (M)	$\prod_{cmc}$ (mN/m)	Γ_{max} x10^{-3} (mmol/m^2)	A_{min} x 10^{-23} (A^2/molecule)	ΔG_{ads} (KJ/mol)	ΔG_m (KJ/mol)	ΔH_m (KJ/mol)	ΔS_m (JK⁻¹mol⁻¹)
283	0.013	35.6	3.562	46.63	-16.2028	-6.2093	-12.518	22.2926
293	0.01	36	3.209	51.763	-17.0595	-5.8412	-13.418	25.8607
303	0.008	36.2	2.943	56.437	-17.8342	-5.5351	-14.35	29.0921
313	0.007	36.4	2.757	60.249	-18.6136	-5.4112	-15.312	31.6344

Table 3
Thermodynamic parameters of SDS with Mefenamic acid (10^{-2}M)

T (K)	CMC (M)	$\prod_{cmc}$ (mN/m)	Γ_{max} x10^{-3} (mmol/m²)	A_{min} x 10^{-23} (A²/molecule)	ΔG_{ads} (KJ/mol)	ΔG_m (KJ/mol)	ΔH_m (KJ/mol)	ΔS_m (JK $^{-1}$mol $^{-1}$)
283	0.012	36.5	3.411	48.693	-12.5546	-1.85513	-12.5182	37.6785
293	0.01	36.7	3.146	52.79	-13.3516	-1.68851	-13.4185	40.0342
303	0.009	36.8	2.966	55.999	-14.0228	-1.61692	-14.35	42.0234
313	0.008	37	2.785	59.632	-14.8122	-1.52959	-15.3129	44.0360

Table 4
Thermodynamic parameters of SDS with Mefenamic acid (10^{-1}M)

	CMC (M)	$\prod_{cmc}$ (mN/m)	Γ_{max} x10^{-3} (mmol/m²)	A_{min} x 10^{-23} (A²/molecule)	ΔG_{ads} (KJ/mol)	ΔG_m (KJ/mol)	ΔH_m (KJ/mol)	ΔS_m (JK $^{-1}$mol $^{-1}$)
283	0.013	36.5	3.474	47.812	-10.7934	-0.28756	-12.5182	43.2176
293	0.01	36.9	3.128	53.09	-12.0257	-0.23218	-13.4185	45.0044
303	0.009	37.2	2.932	56.643	-12.902	-0.21709	-14.35	46.6433
313	0.008	37.8	2.721	61.027	-14.0875	-0.20027	-15.3129	48.2830

Table 5
Thermodynamic parameters of CTAB with Mefenamic acid (10^{-3}M)

T (K)	CMC (M)	$\prod_{cmc}$ (mN/m)	Γ_{max} x10^{-3} (mmol/m²)	A_{min} x 10^{-23} (A²/molecule)	ΔG_{ads} (KJ/mol)	ΔG_m (KJ/mol)	ΔH_m (KJ/mol)	ΔS_m (JK $^{-1}$mol $^{-1}$)
283	0.012	36.1	3.449	48.151	-16.4993	-6.0349	-7.9903	6.9093
293	0.01	36.3	3.182	52.198	-17.248	-5.8412	-8.5649	9.29592
303	0.009	37	2.949	56.319	-18.3451	-5.8005	-9.1596	11.0860
313	0.008	37.4	2.753	60.322	-19.2992	-5.717	-9.7741	12.9596

Table 6
Thermodynamic parameters of CTAB with Mefenamic acid (10^{-2}M)

T (K)	CMC (M)	$\prod_{cmc}$ (mN/m)	Γ_{max} x10^{-3} (mmol/m²)	A_{min} x 10^{-23} (A²/molecule)	ΔG_{ads} (KJ/mol)	ΔG_m (KJ/mol)	ΔH_m (KJ/mol)	ΔS_m (JK $^{-1}$mol $^{-1}$)
283	0.014	36	3.584	46.343	-12.1035	-2.0598	-4.0617	7.07381
293	0.01	36.9	3.128	53.09	-13.482	-1.6885	-4.3538	9.09678
303	0.009	37.2	2.932	56.643	-14.3018	-1.6169	-4.6561	10.0303
313	0.008	37.8	2.721	61.02	-15.4168	-1.5295	-4.9685	10.9870

Table 7
Thermodynamic parameters of CTAB with Mefenamic (10^{-1}M)

T (K)	CMC (M)	$\prod_{cmc}$ (mN/m)	Γ_{max} x10^{-3} (mmol/m²)	A_{min} x 10^{-23} (A²/molecule)	ΔG_{ads} (KJ/mol)	ΔG_m (KJ/mol)	ΔH_m (KJ/mol)	ΔS_m (JK $^{-1}$mol $^{-1}$)
283	0.013	36.6	3.464	47.947	-10.852	-0.2875	-0.9322	2.2778
293	0.01	36.8	3.137	52.94	-11.9603	-0.2321	-0.9992	2.6179
303	0.009	37	2.949	56.319	-12.7617	-0.2170	-1.0686	2.81031
313	0.008	37.2	2.769	59.975	-13.6314	-0.2002	-1.1403	3.00334

In Table 2 data of surface pressure ($\prod_{cmc}$) showed an increasing from (35.6 to 36.4) for SDS+Mefenamic10^{-3} solution ,from (35.5 to 35) for SDS+Mefenamic10^{-2} solution ,and (34.2 to 35.5) for SDS+Mefenamic10^{-1} solution with increased temperature .It was noted through the results reduced in surface tension with increased concentration of the surfactant substance ,as well as lower CMC values with increased temperature for aqueous solutions for SDS with the drug .Since the change in temperature has an important role in increasing or decreasing the CMC values of surfactants ,when the temperature increases ,the CMC values decrease due to the breakdown of hydrogen bonds between hydrophilic groups ,and due to the SDS compound is water-loving because it contains a short chain of hydrocarbon[20].

When the active substance is superficially dissolved in the solution ,it requires some kind of adjustment to reduce its occupancy throughout the solution ,which in turn reduces the interaction between the hydrophobic tails of non-polar groups and thus shows a significant value for the concentration of the critical tail CMC at low temperature[21]. Negative values of ΔGads indicate an adsorption of the surface tension in the air interface [22]. As well as ΔGm values being negative indicate that the process of configuring the micelles is automatic .The data also showed that the values of ΔHm are negative so the process of formation of micelles is a heat-emitting reaction and decreases with the increase in temperature ,while the positive ΔSm values increase by increasing the temperature per CMC ,and the increase in entropy of the process of formation of micelles in an aqueous medium can be explained to The formation of the structural shape of the water molecules surrounding the molecules of the surfactant substance increases the order of the system and the process of decomposition by removing the molecules of the surfactant from the aqueous medium so that the process of formation of the micelles will increase the entropy of the system ,due to the rupture of this structure . The degree of freedom of rotation of the hydrophobic chain of molecules of the surfactant substance in the non-polar inner part of the tail is much greater than that of the aqueous medium ,i.e .the entropy of the hydrophobic chain of molecules of the surfactant substance increases when the molecules of the surfactant are removed from the aqueous medium of the micelle[23].

Conclusion

It was concluded, that the results showed that increasing in temperature leads to a decrease in surface tension ,as well, CMC values of mefenamic acid in aqueous solution of surface-active substances of SDS and CTAB decreased with an increasing temperature .It has also been observed that increasing the concentration of the surfactant substance regardless of its type leads to a decrease in the surface tension of all measured solutions .Thermodynamic values such as free energy for the process of modulation formation Δ G m, and free energy for adsorption Δ G ads for all measured aqueous solutions are negative which indicates the spontaneously of micelle formation as well as adsorption ,while entropy values ΔS are positive for all concentrations of solutions and increased by increasing temperatur. Mefenamic has been shown to give the best result to the values of Δ G ads and Δ G m at a concentration of 10^{-3}M compared to the rest of the concentrations used (10^{-2},10^{-1})M of Mefenamic and the highest negative value of ΔG ads and ΔG m with the surgically active substances positive charge CTAB .

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