

How to Cite:

Mohammed, A. A., & Yahya, N. M. (2022). CMC determination and thermodynamic changes of the mixture of mefenamic acid drug with surfactant (Tween 60, Tween 80, And TritonX-100) in aqueous solution. *International Journal of Health Sciences*, 6(S8), 4399–4412. <https://doi.org/10.53730/ijhs.v6nS8.13184>

CMC determination and thermodynamic changes of the mixture of mefenamic acid drug with surfactant (Tween 60, Tween 80, And TritonX-100) in aqueous solution

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Abstract---Surface tension of non-steroidal anti-inflammatory drugs (NSAIDs) such as mefenamic acid was measured at concentrations (10^{-1} , 10^{-2} , 10^{-3} , 2×10^{-3} M) carrying the surfactant active agent such as sorbitan monostearate (Tween 60) and Oxyethylene (20) sorbitan mononuclear (Tween 80) as well as with (Triton X-100) at concentrations from 10^{-1} M to 10^{-4} M using a plate-type tensiometer, as well, the effect of temperatures at (323, 313, 303, 293) K were studied. The critical micelle concentration (CMC) was evaluated from the plot of surface tension with the concentrations, and the thermodynamic constants were estimated at CMC such as the change in enthalpy heat content (ΔH°_m), the change in the free energy of adsorption (ΔG°_{ads}) and the change in free energy for the formation of micelles (ΔG°_m) as well as the change in entropy (ΔS°_m), It was found from the values of the change in the free energy of the micelle formation process (ΔG°_m) and the values of the change in the free energy of adsorption (ΔG°_{ads}) all negative values indicate the spontaneity of micelle formation as the values of (ΔG°_m) ranged from -2.68 to -10.16 (KJ/mol) for Tween 60, from -2.68 to -9.91 (KJ/mol) for the Tween 80, and from -2.68 to -9.7 (KJ/mol) for the Triton X -100, and these values increase with increasing temperature. The results indicated that CMC increased with increasing temperature for Tween 60, Tween 80 and Triton X-100, as well as the presence of the drug (mefenamic acid) with all the surfactants. The effectiveness of the surfactant and surfactant reducing agents of the drug was evaluated using Change of concentration at CMC at different temperatures. The values of the

surface concentration of the surfactant (Γ_{\max}), the area occupied by the surfactant molecule on the surface of the solution with air (A_{\min}), and the surface pressure (Π_{cmc}) were calculated.

Keywords---NSAIDs, mefenamic, 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-loving 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 pharmaceuticals, 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 nonionic surfactant (Tween 60, Tween 80, and TritonX-100) 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, (ΔG°_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 ΔG°_m , ΔH°_m , and ΔS°_m for micellization process have been investigated [14]. The purpose of this study was to determine the thermodynamic parameters at adsorption of micellization of Mefenamic acid as NSAIDs which interact with Tween 60, Tween 80, and Triton X-100 as surfactant based on surface tension analysis at different temperature [14-19].

Experimental

Materials and Methods

All chemicals and solvents used were obtained from Sigma-Aldrich Germany & Fluka Switzerland company. Mefenamic acid, 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 2-(2,3-dimethyl phenyl) amino benzoic acid, showed in figure 1. Tween60, Tween80 and TritonX-100 are supplied by Sigma-Aldrich Germany company, their chemical structure showed in figure 2, 3, 4. 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.

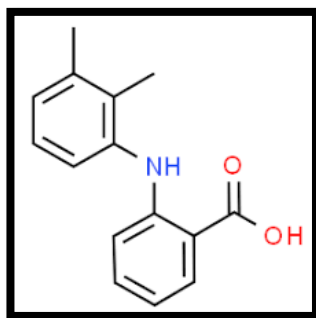


Figure 1: Chemical structure of Mefenamic acid

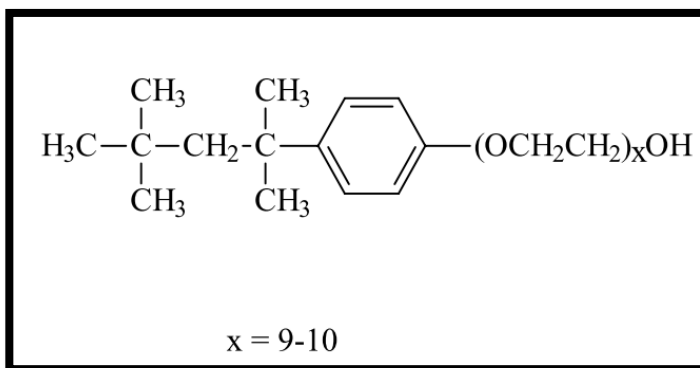


Figure 2: Chemical structure of Triton X-100

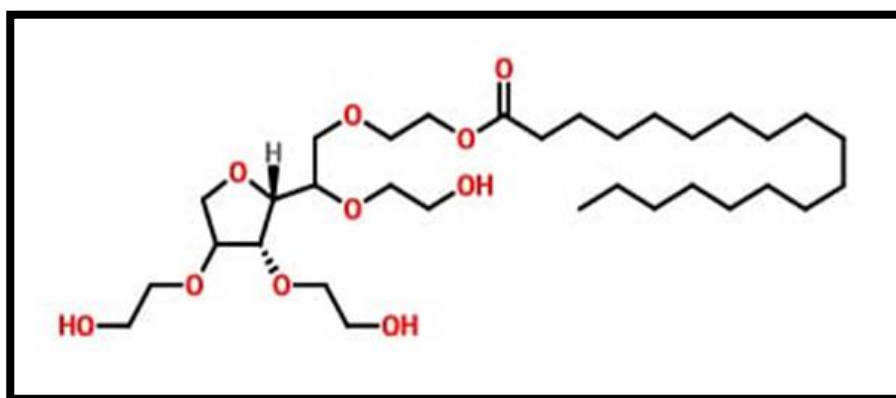


Figure 3: Chemical structure of Tween 60

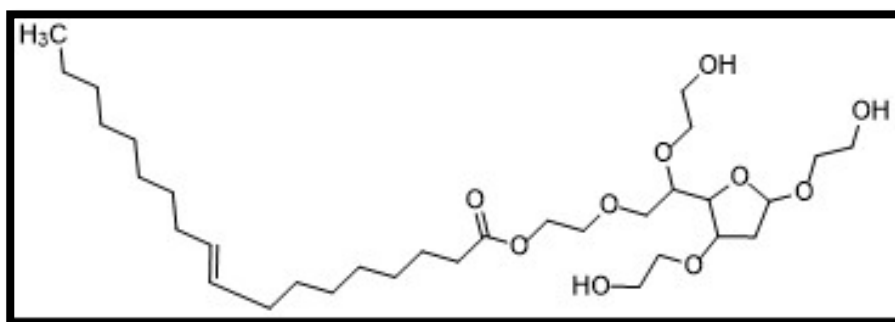
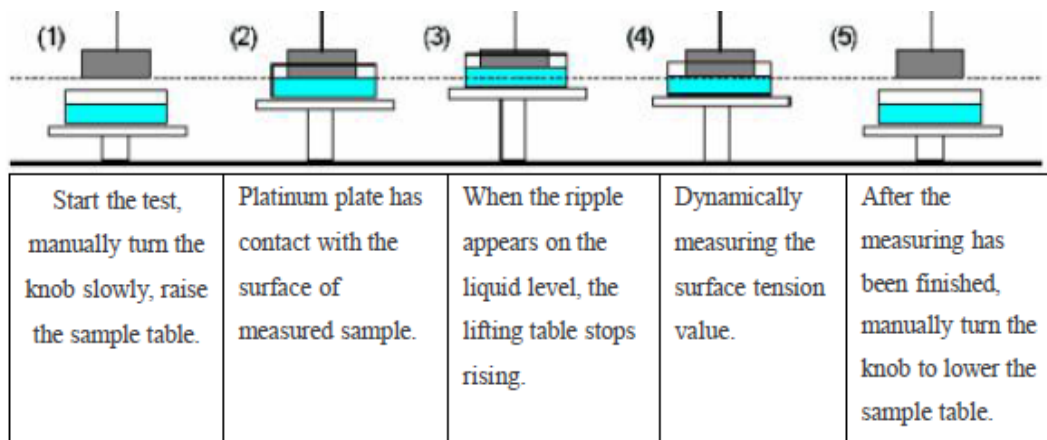


Figure 4: Chemical structure of Tween 80

Procedure

Stock solution of Tween 60 and Tween 80 and Triton X-100 were prepared of (10^{-1} M) in distilled water. Aqueous solutions of Mefenamic acid was prepared of 10^{-1} , 10^{-2} , 10^{-3} M in Tween 60 and in Tween 80 and Triton X-100. Surface tension were measured for each solution as follow:



The CMC were determined by means of measuring the surface tension of surfactant (Tween 60 and Tween 80 and Triton X-100) of varying concentration with drug. The CMC results from the plot of surface tension against series concentration. It were 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 the aqueous solution of pure mefenamic acid was measured as a function of varying concentration of surfactant. Figure 5,6,7,8,9,10,11,12,13,14 and 15 show the plots of surfactant versus surfactant concentration at different temperatures with different concentration of mefenamic acid, respectively, at different temperatures to assess the CMC at the acute breaking point of each plot [17].

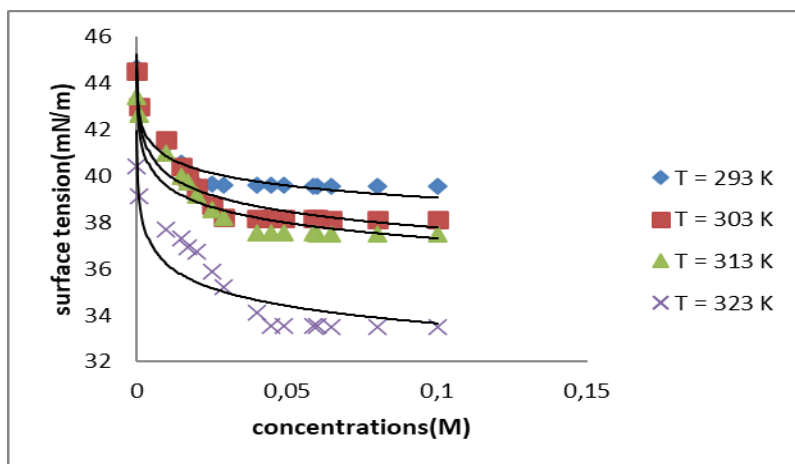


Figure 5: Plot of the surface tension Mefenamic acid (10^{-1}) against varying concentration of Tween 60

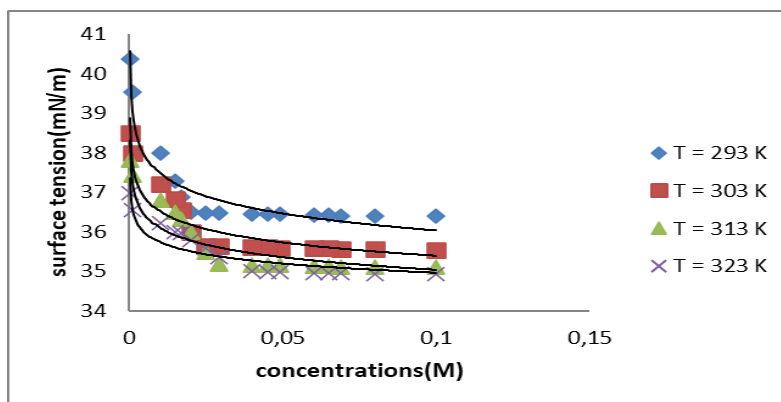


Figure 6: Plot of the surface tension Mefenamic acid (10^{-2}) against varying concentration of Tween 60

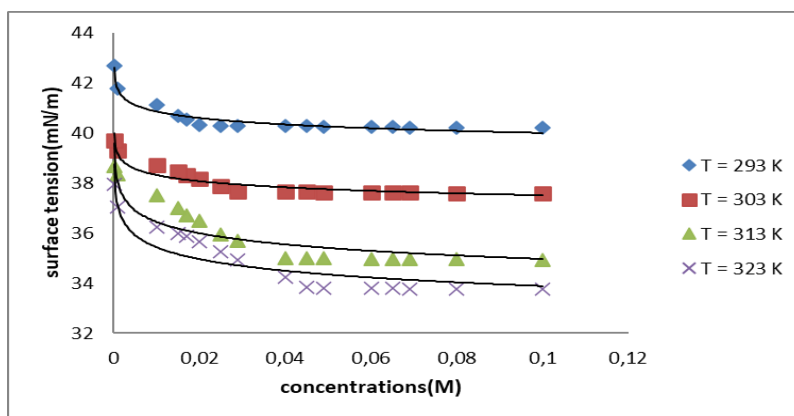


Figure 7: Plot of the surface tension Mefenamic acid (10^{-3}) against varying concentration of Tween 60

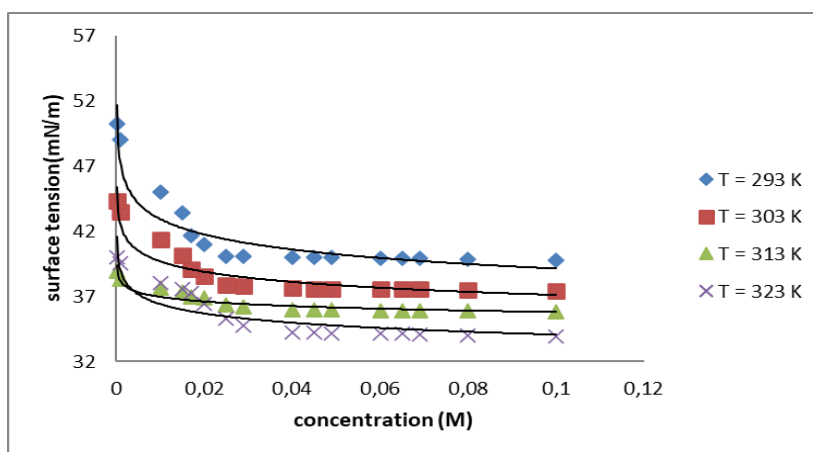


Figure 8: Plot of the surface tension against varying concentration of Tween 80

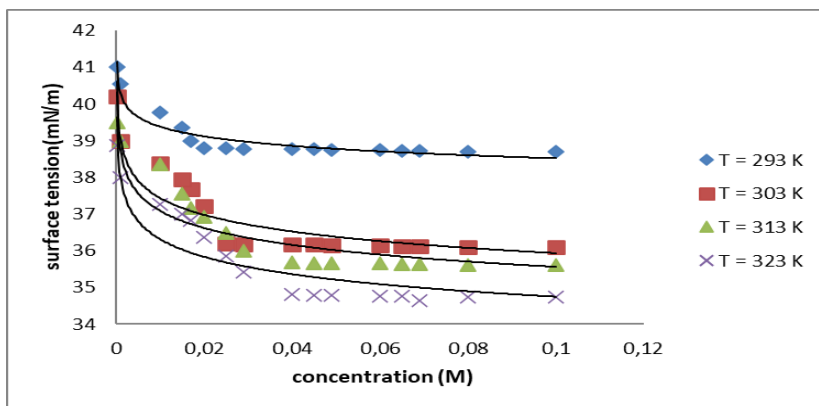


Figure 9: Plot of the surface tension Mefenamic acid (10^{-2}) against varying concentration of Tween 80

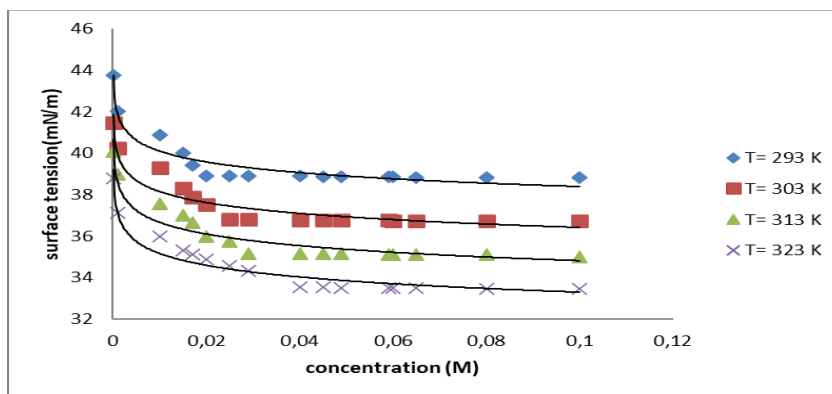


Figure 10: Plot of the surface tension Mefenamic acid (2×10^{-3}) against varying concentration of Tween 80

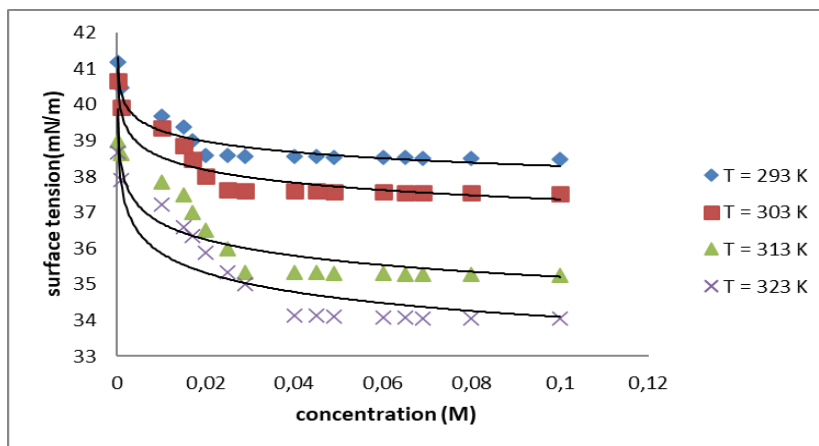


Figure 11: Plot of the surface tension Mefenamic acid (10^{-3}) against varying concentration of Tween 80

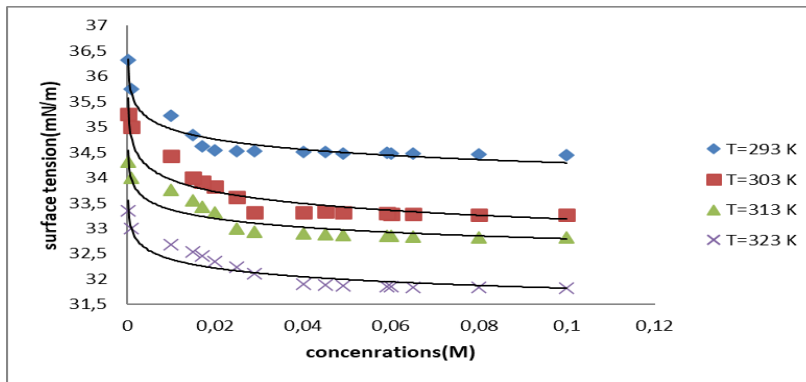


Figure 12: Plot of the surface tension against varying concentration of Triton X-100

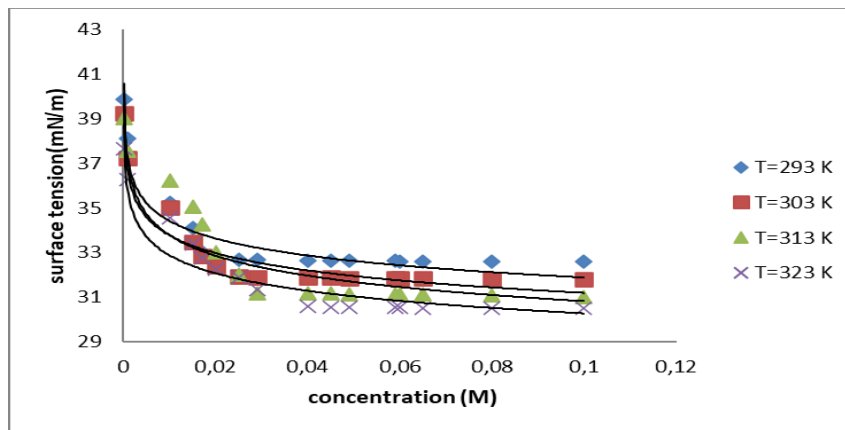


Figure 13: Plot of the surface tension Mefenamic acid (10^{-2}) against varying concentration of Triton X-100

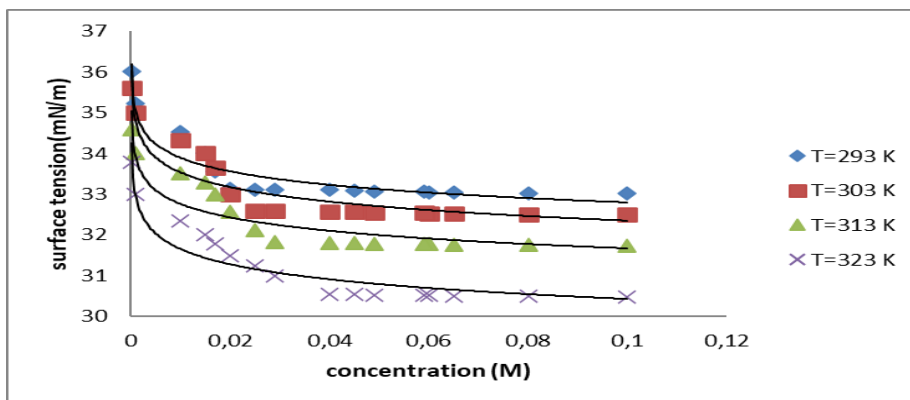


Figure 14: Plot of the surface tension Mefenamic acid (10^{-3}) against varying concentration of Triton X-100

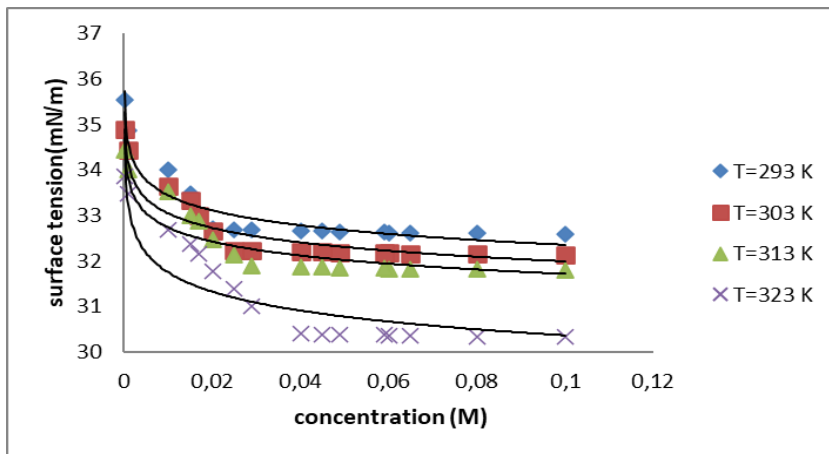


Figure 15: Plot of the surface tension Mefenamic acid (2×10^{-3}) against varying concentration of Triton X-100

The concentration of maximum surface excess and the minimum area occupied per molecule were calculated by using eq.1 and eq.2, respectively [17,18].

$$\Gamma_{max} = \frac{(\partial\gamma/\partial \ln C)_{cmc}}{RT} \quad \dots\dots\dots 1$$

$$A_{min} = \frac{1}{N_A \Gamma_{max}} \quad \dots\dots\dots 2$$

Where N_A referred to Avogadro number and $(\partial\gamma/\partial \ln C)$ is evaluated from the slope of γ versus $\ln C$ plotting which illustrated in Figure 17 as a typical form.

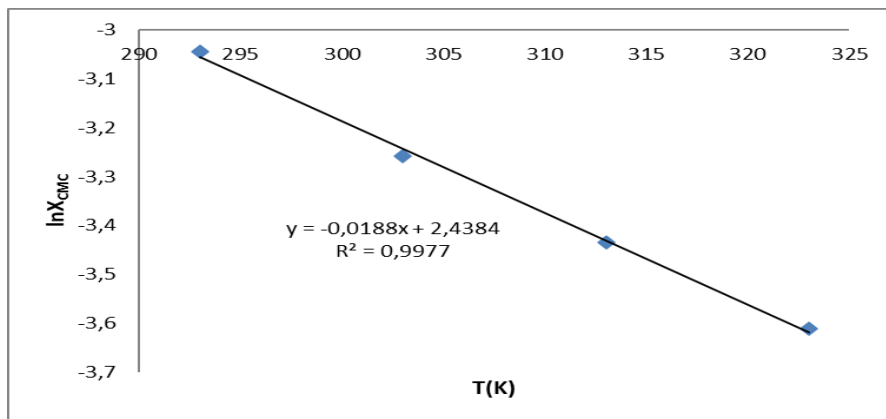


Figure 17: A typical plot of $\ln X_{CMC}$ versus temperature for Mefenamic acid (10^{-3}) against varying concentration of Triton X-100

The surface pressure (Π_{cmc}) at CMC, was determined from the equation 3:

$$\Pi_{cmc} = \gamma - \gamma_{cmc} \quad \dots\dots\dots 3$$

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 ($\Delta G^{\circ}_{\text{ads}}$) was obtained using equation 4.

$$\Delta G^{\circ}_{\text{ads}} = \Delta G^{\circ}_{\text{m}} - \frac{\Pi_{\text{cmc}}}{\Gamma_{\text{max}}} \quad \dots\dots\dots 4$$

Where $\Delta G^{\circ}_{\text{m}}$ is the standard Gibbs free energy of micellization.

Table 1,2,3,4,5,6,7,8 and 9 were listed CMC values with corresponding values of their values of the Gibbs surface excess concentration (Γ_{max}), minimum area occupied per molecule (A_{min}), surface pressure at CMC (Π_{cmc}) was determined on basis of the standard Gibbs free energy of adsorption ($\Delta G^{\circ}_{\text{ads}}$).

$$\Delta G^{\circ}_{\text{m}} = RT \ln X_{\text{cmc}} \quad \dots\dots\dots 5$$

Where X_{CMC} is the mole fraction of surfactant at the CMC.

The enthalpy of micellization $\Delta H^{\circ}_{\text{m}}$ was obtained by applying the Gibbs-Helmholtz equation to the equation above :

$$\Delta H^{\circ}_{\text{m}} = -RT^2 (\partial \ln X_{\text{cmc}} / \partial T) \quad \dots\dots\dots 6$$

$\Delta H^{\circ}_{\text{m}}$ was evaluated from the slope of the plot of $\ln X_{\text{cmc}}$ versus temperature.

$$\Delta G^{\circ}_{\text{m}} = \Delta H^{\circ}_{\text{m}} - T \Delta S^{\circ}_{\text{m}} \quad \dots\dots\dots 7$$

$\Delta G^{\circ}_{\text{m}}$, H°_{m} and S°_{m} which were completed by applying the above equations for surfactants and for different concentration of mefenamic acid mentioned in Table 1 and Table 2 , 3, 4, 5, 6, 7 , 8 , 9 , respectively, at different temperatures.

Table 1: Thermodynamic parameters of Tween 60 with Mefenamic acid (10^{-1}M)

T(K)	CMC (M)	Π_{cmc} (mN/m)	$\Gamma_{\text{max}} \times 10^{-7}$ (mmol/m ²)	ΔG_{m} (KJ/mol)	ΔG_{ads} (KJ/mol)	$A_{\text{min}} \times 10^{-22}$ (Å ² /molecule)	ΔH_{m} (KJ/mol)	ΔS_{m} (JK ⁻¹ mol ⁻¹)
293	0.021	32.3	42.19	-4.64351577	-8.12103	3.94	3.711493	14.25203
303	0.029	33.8	42.83	-6.41479907	-8.53309	3.88	3.96916	15.21663
313	0.031	34.5	41.48	-7.02686759	-9.01923	4	4.235474	15.77687
323	0.043	38.5	39.65	-9.60506821	-10.671	4.19	4.510435	16.9379

Table 2: Thermodynamic parameters of Tween 60 with Mefenamic acid (10^{-2}M)

T(K)	CMC (M)	Π_{cmc} (mN/m)	$\Gamma_{\text{max}} \times 10^{-7}$ (mmol/m ²)	ΔG_{m} (KJ/mol)	ΔG_{ads} (KJ/mol)	$A_{\text{min}} \times 10^{-22}$ (Å ² /molecule)	ΔH_{m} (KJ/mol)	ΔS_{m} (JK ⁻¹ mol ⁻¹)
293	0.02	35.5	38.3	-2.67622173	-11.9448	4.33	10.99173	46.64829
303	0.025	36.4	38.31	-3.15588781	-12.6575	4.33	11.75482	49.21026
313	0.03	36.8	38.58	-3.6072886	-13.1474	4.3	12.54352	51.60079
323	0.038	37	39.86	-4.2123957	-13.496	4.17	13.35783	54.39697

Table 3: Thermodynamic parameters of Tween 60 with Mefenamic acid (10^{-3}M)

T(K)	CMC (M)	γ_{cmc} (mN/m)	$\Gamma_{max} \times 10^{-4}$ (mmol/m ²)	ΔG_m (KJ/mol)	ΔG_{ads} (KJ/mol)	$A_{min} \times 10^{-22}$ (Å ² /molecule)	ΔH_m (KJ/mol)	ΔS_m (JK ⁻¹ mol ⁻¹)
293	0.02	31.6	42.39	-7.41646275	-14.8704	3.91638	17.27272	84.26341
303	0.03	34.3	42.68	-8.65070139	-16.6876	3.89027	18.47186	89.51341
313	0.037	37	40.8	-9.46602499	-18.5356	4.06978	19.71125	93.21812
323	0.043	37.2	41.18	-10.1621461	-19.1947	4.0314	20.99087	96.44897

Table 4: Thermodynamic parameters of Tween 80 with Mefenamic acid (10^{-2}M)

T(K)	CMC (M)	γ_{cmc} (mN/m)	$\Gamma_{max} \times 10^{-4}$ (mmol/m ²)	ΔG_m (KJ/mol)	ΔG_{ads} (KJ/mol)	$A_{min} \times 10^{-22}$ (Å ² /molecule)	ΔH_m (KJ/mol)	ΔS_m (JK ⁻¹ mol ⁻¹)
293	0.02	33.3	40.16	-2.67622173	-10.8762	4.08842	9.635606	42.01989
303	0.03	35.9	40.87	-3.49227235	-12.2769	4.06269	10.30455	45.53407
313	0.033	36.4	40.1	-3.79572762	-12.8722	4.14004	10.99594	47.25773
323	0.036	36.2	40.1	-4.09810517	-13.1248	4.14008	11.70978	48.94083

Table 5: Thermodynamic parameters of Tween 80 with Mefenamic acid ($2 \times 10^{-3}\text{M}$)

T(K)	CMC (M)	γ_{cmc} (mN/m)	$\Gamma_{max} \times 10^{-4}$ (mmol/m ²)	ΔG_m (KJ/mol)	ΔG_{ads} (KJ/mol)	$A_{min} \times 10^{-22}$ (Å ² /molecule)	ΔH_m (KJ/mol)	ΔS_m (JK ⁻¹ mol ⁻¹)
293	0.021	33.1	41.34	-5.94956226	-13.9572	4.01667	12.84747	64.15371
303	0.025	35.2	39.6	-6.5565449	-15.4453	4.19263	13.7394	66.98332
313	0.029	36.9	38.1	-7.1324387	-16.8182	4.35807	14.66126	69.62842
323	0.038	38.6	38.03	-8.04480535	-18.1938	4.36539	15.61304	73.24411

Table 6: Thermodynamic parameters of Tween 80 with Mefenamic acid (10^{-3}M)

T(K)	CMC (M)	γ_{cmc} (mN/m)	$\Gamma_{max} \times 10^{-4}$ (mmol/m ²)	ΔG_m (KJ/mol)	ΔG_{ads} (KJ/mol)	$A_{min} \times 10^{-22}$ (Å ² /molecule)	ΔH_m (KJ/mol)	ΔS_m (JK ⁻¹ mol ⁻¹)
293	0.021	33.4	41.02	-7.5297856	-15.6728	4.04789	14.06085	73.68817
303	0.025	34.4	40.46	-8.20760783	-16.7095	4.10342	15.03701	76.71491
313	0.03	36.6	38.79	-8.9362031	-18.3706	4.27976	16.04593	79.81513

323	0.039	37.9	39.14	-	-19.5891	4.24182		
				9.90619804			17.08761	83.57216

Table 7: Thermodynamic parameters of Triton X-100 with Mefenamic acid ($10^{-2}M$)

T(K)	CMC (M)	γ_{cmc} (mN/m)	$\Gamma_{max} \times 10^{-4}$ (mmol/m ²)	ΔG_m (KJ/mol)	ΔG_{ads} (KJ/mol)	$A_{min} \times 10^{-22}$ (Å ² /molecule)	ΔH_m (KJ/mol)	ΔS_m (JK ⁻¹ mol ⁻¹)
293	0.02	40.2	33.37	-	-14.7232	4.97553		
				2.67622173			9.278732	40.80189
303	0.022	40.6	32.66	-	-15.3621	5.08393		
				2.93014206			9.9229	42.41928
313	0.03	41.4	33.53	-3.6075289	-15.9532	4.95109	10.58869	45.35532
323	0.033	42.3	32.42	-	-16.964	5.12102		
				3.91699687			11.27609	47.03741

Table 8: Thermodynamic parameters of Triton X-100 with Mefenamic acid ($2 \times 10^{-3}M$)

T(K)	CMC (M)	γ_{cmc} (mN/m)	$\Gamma_{max} \times 10^{-4}$ (mmol/m ²)	ΔG_m (KJ/mol)	ΔG_{ads} (KJ/mol)	$A_{min} \times 10^{-22}$ (Å ² /molecule)	ΔH_m (KJ/mol)	ΔS_m (JK ⁻¹ mol ⁻¹)
293	0.021	39.4	34.64	-	-17.3234	4.7929		
				5.94956226			12.27648	62.20491
303	0.026	39.7	35.13	-	-17.9485	4.72595		
				6.64816016			13.12876	65.27037
313	0.03	39.2	35.94	-7.2150577	-18.1206	4.61901	14.00965	67.81055
323	0.037	41.6	34.34	-	-20.092	4.8353		
				7.97681635			14.91913	70.88528

Table 9: Thermodynamic parameters of Triton X-100 with Mefenamic acid ($10^{-3}M$)

T(K)	CMC (M)	γ_{cmc} (mN/m)	$\Gamma_{max} \times 10^{-4}$ (mmol/m ²)	ΔG_m (KJ/mol)	ΔG_{ads} (KJ/mol)	$A_{min} \times 10^{-22}$ (Å ² /molecule)	ΔH_m (KJ/mol)	ΔS_m (JK ⁻¹ mol ⁻¹)
293	0.02	38.9	34.73	-	-18.616	4.78011		
				7.41646275			13.41847	71.109
303	0.025	39.4	35.08	-	-19.4388	4.73278		
				8.20760783			14.35004	74.44768
313	0.03	40.2	34.85	-8.9362031	-20.4716	4.76426	15.31287	77.47307
323	0.036	41.4	34.28	-9.6968384	-21.7745	4.84362	16.30696	80.50711

Tables (5,6,7,8,9,10) shown that the surface tension decreases from 38.7 to 35.8 for a solution (Tween 80+mefenamic acid $10^{-2} M$), as well as from 38.9 to 33.4 for a solution (Tween 80+mefenamic acid $2 \times 10^{-3} M$), and from 38.6 to 34.1 for a solution (Tween 80 + Mefenamic Acid $10^{-3}M$), and from 39.7 to 33.5 for a solution (Tween 60 + Mefenamic Acid $10^{-1}M$), and from 36.5 to 35 for a solution (Tween 60 + Mefenamic Acid $10^{-2}M$), and from 40.4 to 34.8 for a solution (Tween 60 +

Mefenamic Acid 10^{-3}M), and from 31.8 to 29.7 for a solution (Triton X-100 + Mefenamic Acid 10^{-2}M), and from 32.6 to 30.4 for a solution (Triton X-100 + Mefenamic Acid $2 \times 10^{-3}\text{M}$), and from 33.1 to 30.6 for a solution (Triton X-100 + Mefenamic Acid 10^{-3}M). This is due to the fact that the temperature reduces the forces of attraction between the molecules, resulting in the formation of an increase in CMC values in the composition of micelles for aqueous solutions of surfactant with the drug and in different concentrations ($10^{-1}, 10^{-2}, 10^{-3}, 2 \times 10^{-3}$) of drugs (Mefenamic acid) with increased temperature. The addition of the addition of the surfactant active substance leads to a decrease in the surface tension of surfactant solutions with drug in the range mentioned above due to the adsorption between air and water, and the reason for this is because the water-loving groups associated with the force of attraction to the surface in turn the hydrophobic chains are directed in parallel subjects, which reduces the interaction with aqueous solutions and thus leads to a decrease in surface tension values with an increase in the concentration of active substances.

Conclusion

It was concluded that the values of ΔH_m appeared with positive values and that is why the heat absorption reaction leads to the process of formation of micelles and the value of ΔH_m increases with increasing temperature, in addition, negative ΔG_m values indicate that the formation of micelles is spontaneous. It increases with increasing temperature, and that the values increase by ΔS_m with increasing temperature and are positive values at each CMC, which means an increase in the randomness of the system and this is an indication that it is spontaneous activation of the formation of micelles in the solution. It is ΔS more than ΔH , in addition to an increase in CMC with an increase temperature, due to the type of non-ionic surfactant. The results obtained during the measurement showed an increase in temperature leads to a decrease in the value of the surface tension, and that the CMC values of surfactants such as Tween 60, Tween 80 and Triton X-100 increase with increasing temperature because they are non-ionic. It was also found that the higher the concentration of the surfactant, a lower the value of the surface tension of the aqueous solution.

Acknowledgements

Authors would like to thank the University of Mosul, College of Education for Girls, Chemistry Department, management and staff for all the support during the experimental work stage.

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