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# Thermodynamic parameters of ibuprofen micellization with tween 60 at different temperature

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**Abstract**---Surfactant micellization of Non-steroidal anti-inflammatory drugs (NSAIDs) such as Ibuprofen carrying by surface active agent as polyethylene glycol sorbitan monostearate (Tween 60) was determined by measuring the surface tension as a function of molar concentration in aqueous solution at different temperature ranged from 20°C to 50°C to investigate the critical micelle concentration (CMC). The values of the Gibbs surface excess concentration ( $\Gamma_{max}$ ), minimum area occupied per molecule ( $A_{min}$ ), surface pressure at CMC ( $\Pi_{cmc}$ ) was determined on basis of the standard Gibbs free energy of adsorption ( $\Delta G^{\circ}_{ads}$ ). The results indicated that CMC increased by temperature increasing for Tween 60, and inversely for micelle of Ibuprofen with Tween 60. The thermodynamic parameters as standard Gibbs free energy ( $\Delta G^{\circ}$ ), enthalpy ( $\Delta H^{\circ}$ ), and the entropy ( $\Delta S^{\circ}$ ) of drug-surfactant of micellization were evaluated using changing of CMC at different temperature. The results based on thermodynamic parameters investigated the spontaneously of micelle formation and that increase the possibility to predict the wettability of Ibuprofen.

**Keywords**---NSAIDs, ibuprofen, surface tension, critical micelle concentration, thermodynamic parameters.

**Introduction**

Surfactant or surface active agents are defined as substance that reduces the contact angle of water-air layer and surface tension of water, which consists of

high molar mass compound a head of polar region referred as water- liking or hydrophilic and tail of non-polar region referred as water-hating or hydrophobic on its chemical structure [1]. At a certain range of surfactant concentration, the micelles are formed by surfactant, hence it called as critical micelle concentration (CMC) [1,2]. Surfactants play an important role in many application as emulsifying agents, solubilizing agents, and in detergents, cosmetic as well in pharmaceutical preparations [3]. 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]. Polysorbates surfactant such as Tween 20, 40, 60, and 80 possessed four poly-oxyethylene chain which is a hydrocarbon chain linked to poly-oxyethylene one and to a hetro-cyclic ring. According to that, the adsorption and aggregation properties of Tweens are probably different. Hence, Gibbs surface excess concentration in the water-air monolayer investigated different values, and also obtained different CMC [9,10]. On the basis of the values of surface tension, the thermodynamic analysis of the adsorption of micellization process of Tweens at different temperatures was performed [11]. Using of the surfactant micellization as NSAIDs of Ibuprofen carrying by anionic micelles [12]; naproxen and diclofenac in the type of cationic micelles [13]; indomethacin in both anionic and cationic micellar aggregation [14] as well of ibuprofen in amphiphilic polymers [15]. The CMC and thermodynamic parameters such as  $\Delta G^{\circ m}$ ,  $\Delta H^{\circ m}$ , and  $\Delta S^{\circ m}$  for micellization process have been investigated [16]. The purpose of this study was to determined the thermodynamic parameters at adsorption of micellization of Ibuprofen as NSAIDs which interact with Tween 60 as surfactant 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. Ibuprofen, showed in figure 1, was supplied by the state enterprise for drug industries and medical appliances in Samarra, Iraq. Ibuprofen based on IUPAC name is S-2-(4- isobutyl phenyl) propanoic acid (IBP), showed in figure 1. Polysorbate 60 or Tween 60 ( amphipathic surfactant) is polyethylene glycol sorbitan monostearate supplied by Sigma-Aldrich Germany company, its 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 and composition of surface tensiometer showed in Technical indexes in Figure 3.

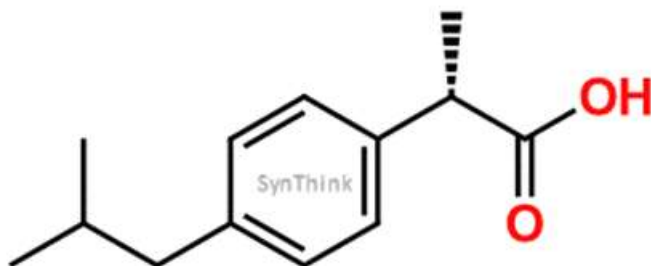


Figure 1: Chemical structure of Ibuprofen

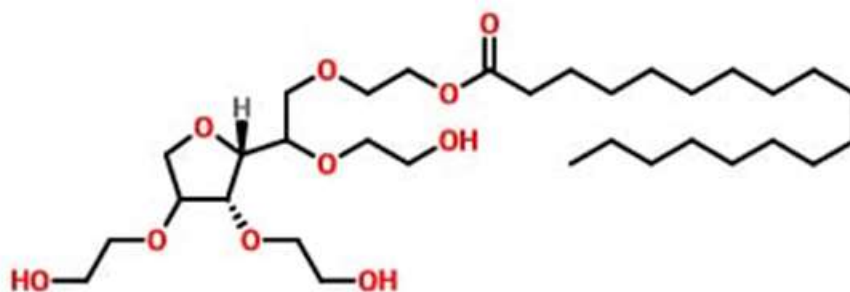


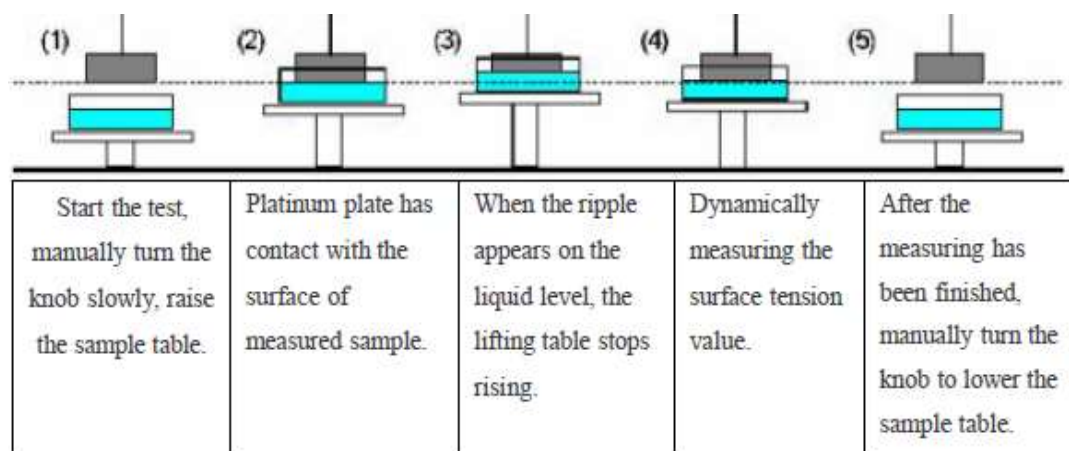
Figure 2: Chemical structure of Tween 60

Table 1: Technical indexes of tensiometer

Measurement method	BZY-101、BZY-201 platinum plate method BZY-102、BZY-202 platinum ring method BZY-103、BZY-203 platinum plate and platinum ring method
Measuring range	0-600mN/m, 0-400mN/m Note: 1mN/m=1dyne/cm
Minimum resolution	0.1mN/m, 0.01mN/m
Standard deviation	±0.1mN/m, ±0.05mN/m ( the second distilled water at 20℃)
Display mode	LCD display
Best time of reading value	Generally it is 3-5 seconds. If the sample for testing has larger viscosity or contains surface active agent, different sampling time can be adopted according to the requirements of customer.
Supply voltage	AC220V
Control mode	CNC key

### Procedure

Ibuprofen was prepared of  $10^{-1}$ ,  $10^{-2}$ ,  $10^{-3}$  M in SAA. Stock solution of Tween 60 was prepared of  $10^{-3}$ M in distilled water. Surface tension were measured for each solution as follow:



The CMC were determined by means of measuring the surface tension of surfactant(Tween 60) of varying concentration without and 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 aqueous solution of pure Ibuprofen was measured as a function of varying concentration of Tween 60. Figure 4,5,6, and 7 showed the plots of surface tension against the concentration of surfactant at different temperatures without and with different concentration of Ibuprofen, respectively, at different temperature to evaluated the CMC at sharp break point for each plot [17].

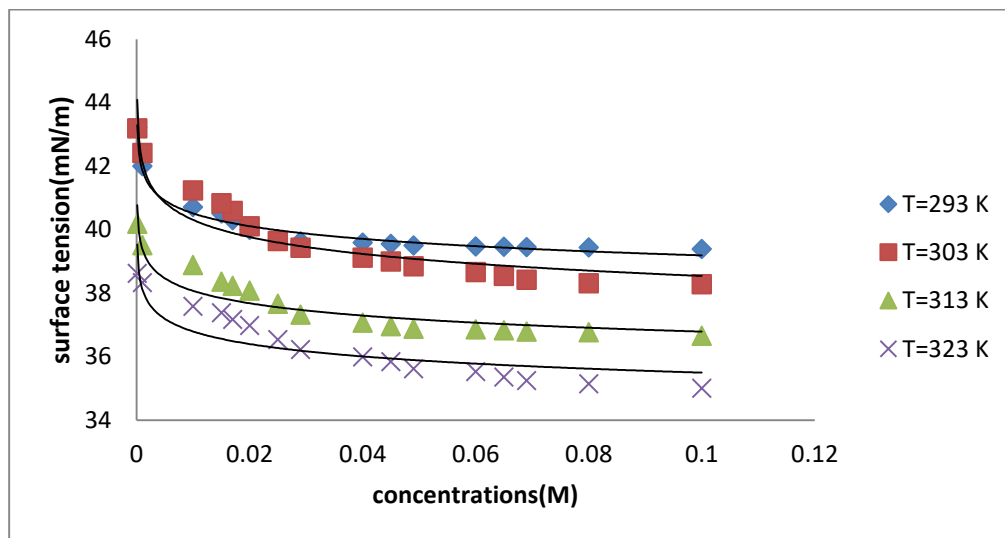


Figure 4: Plot of the surface tension against varying concentration of Tween 60

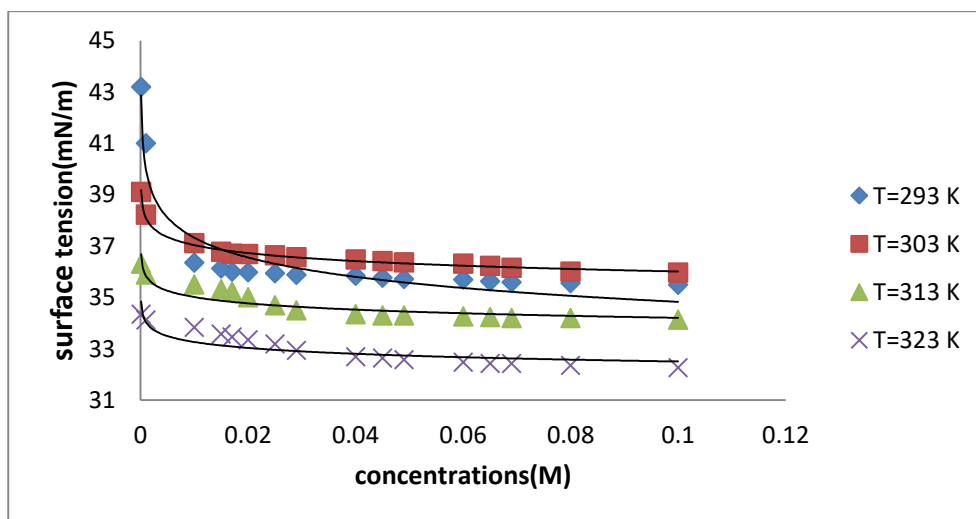


Figure 5: Plot of the surface tension Ibuprofen (10<sup>-2</sup>M) against varying concentration of Tween 60

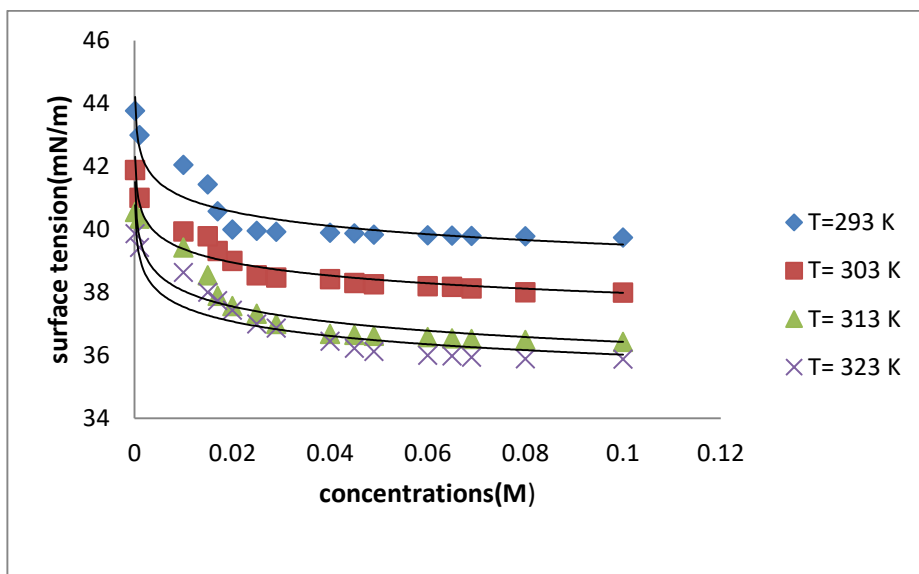


Figure 6: Plot of the surface tension Ibuprofen ( $2 \times 10^{-3}M$ ) against varying concentration of Tween 60

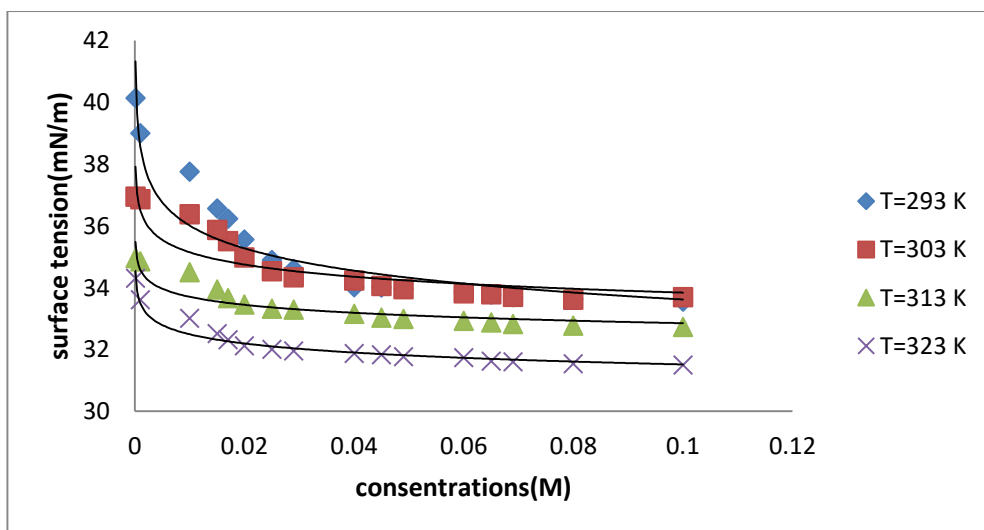


Figure 7: Plot of the surface tension Ibuprofen ( $10^{-3}M$ ) against varying concentration of Tween 60

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].

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

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

Where  $N_A$  referred to Avogadro number and  $(\partial\gamma/\partial\ln C)$  is evaluated from the slope of  $\gamma$  versus  $\ln C$  plotting which illustrated in Figure 8 as a typical form.

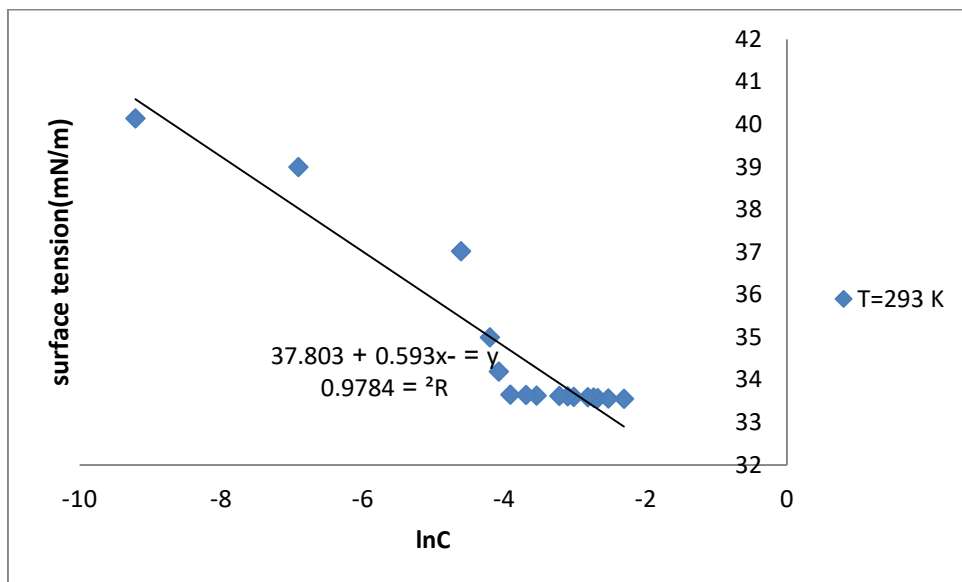


Figure 8: Typical plot of surface tension versus  $\ln C$  at 293K of Tween 60

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

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

Where  $\gamma$  and  $\gamma_{cmc}$  denote the surface tensions of the water solvent and of the drug-surfactant micelle at CMC, respectively. The standard free energy of drug adsorption ( $\Delta G^{\circ}_{ads}$ ) was obtained using equation 4.

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

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

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

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

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

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

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

$\Delta G^{\circ}_m$ ,  $\Delta H^{\circ}_m$  and  $\Delta S^{\circ}_m$  that completed by applying the above equations for the span 20 and for different concentration Ibuprofen -Tween 60 reported in Table 2 and in Table 3,4,5, respectively, at different temperature.

Where  $\Delta G^{\circ}_m$  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 ( $\Gamma_{max}$ ), minimum area occupied per molecule ( $A_{min}$ ), surface pressure at CMC ( $\Pi_{cmc}$ ) was determined on basis of the standard Gibbs free energy of adsorption ( $\Delta G^{\circ}_{ads}$ ).

Table 2: Thermodynamic parameters of pure Tween 60

T(K)	CMC (M)	$\Pi_{cmc}$ (mN/m)	$\Gamma_{max} \cdot 10^{-4}$ (mmol/m <sup>2</sup> )	$\Delta G_m$ (KJ/mol)	$\Delta G_{ads}$ (KJ/mol)	$A_{min} \cdot 10^{-22}$ (Å <sup>2</sup> /molecule)	$\Delta H_m$ (KJ/mol)	$\Delta S_m$ (JK <sup>-1</sup> mol <sup>-1</sup> )
293	0.025	32.3	44.18	-8.98612	-17.6065	3.75804	8.595674	60.00612

303	0.035	33	46.18	-8.55419	-16.8339	3.59528	9.192422	58.20994
313	0.036	35	42.77	-8.6506	-15.5911	3.88193	9.809195	58.97698
323	0.037	35.8	40.9	-8.8534	-16.2971	4.05942	10.44599	59.75044

Table 3: Thermodynamic parameters of Tween 60 with Ibuprofen ( $10^{-2}M$ )

T(K)	CMC (M)	$\gamma_{cmc}$ (mN/m)	$\Gamma_{max} \cdot 10^{-4}$ (mmol/m <sup>2</sup> )	$\Delta G_m$ (KJ/mol)	$\Delta G_{ads}$ (KJ/mol)	$A_{min} \cdot 10^{-22}$ (Å <sup>2</sup> /molecule)	$\Delta H_m$ (KJ/mol)	$\Delta S_m$ (JK <sup>-1</sup> mol <sup>-1</sup> )
293	0.01	35.8	32.27	-11.6011	-22.695	5.14503	34.42624	157.0898
303	0.015	35.3	34.69	-10.5797	-20.7558	4.78625	36.81625	156.4221
313	0.034	37.6	39.09	-8.79934	-18.4172	4.24695	39.28647	153.6288
323	0.038	39.3	37.24	-8.78178	-19.3361	4.45886	41.83688	156.7141

Table 4: Thermodynamic parameters of Tween 60 with Ibuprofen ( $2 \times 10^{-3}M$ )

T(K)	CMC (M)	$\gamma_{cmc}$ (mN/m)	$\Gamma_{max} \cdot 10^{-4}$ (mmol/m <sup>2</sup> )	$\Delta G_m$ (KJ/mol)	$\Delta G_{ads}$ (KJ/mol)	$A_{min} \cdot 10^{-22}$ (Å <sup>2</sup> /molecule)	$\Delta H_m$ (KJ/mol)	$\Delta S_m$ (JK <sup>-1</sup> mol <sup>-1</sup> )
293	0.021	32.1	41.9	9.5297	-17.1908	3.96254	13.75893	79.48337
303	0.03	33.5	42.7	-9.00732	-16.8528	3.8883	14.71413	78.28863
313	0.031	35.2	41.46	-8.87703	-17.3671	4.00459	15.70139	78.5253
323	0.038	35.6	40.78	-8.92698	-17.6567	4.07136	16.7207	79.40458

Table 5: Thermodynamic parameters of Tween 60 with Ibuprofen ( $10^{-3}M$ )

T(K)	CMC (M)	$\gamma_{cmc}$ (mN/m)	$\Gamma_{max} \cdot 10^{-4}$ (mmol/m <sup>2</sup> )	$\Delta G_m$ (KJ/mol)	$\Delta G_{ads}$ (KJ/mol)	$A_{min} \cdot 10^{-22}$ (Å <sup>2</sup> /molecule)	$\Delta H_m$ (KJ/mol)	$\Delta S_m$ (JK <sup>-1</sup> mol <sup>-1</sup> )
293	0.01	38.4	35.7	-9.41084	-20.1661	4.65025	1.555584	-37.4281
303	0.015	38.2	38.26	-8.83352	-18.817	4.33914	1.663579	-34.6439
313	0.034	39.25	36.23	-9.03972	-19.8736	4.5828	1.775198	-34.5525
323	0.038	40.43	35.95	-8.78178	-20.0281	4.61844	1.890441	-33.0409

In Table 2 data showed that the CMC increased as temperature increasing of Tween 60. In contrast, the data in Table 3, 4, and 5 showed due to the wettability of Ibuprofen at micelle formation; the hydrophobic group of the hydrocarbon chain of the Tween 60 interacts with the nonpolar group of Ibuprofen. Also the temperature increasing caused an increasing of structure breakdown of water surrounding the hydrophobic group which results an decreasing of CMC at micelle formation of Ibuprofen-Tween 60. Therefore, the data showed the positive values of the  $\Delta H^{\circ}_m$ , for these reason the micellization process were endothermic reaction and increased with temperature increasing. Moreover, the  $\Delta G^{\circ}_m$  found to have negative values referred to spontaneous process of micellization which enhance the solubility of Ibuprofen in the presence of surfactant. As well the magnitude of the positive values of entropy encouraged the micelle formation.

## Conclusion

As a conclusion, an investigation of micelle formation of Ibuprofen-Tween60 as a function of drug delivery system of ibuprofen at temperature of 293K, 303K, 313K, and 323K. Based on data reported, the CMC was decreased as temperature

increased that means the aggregation of micelle was affected by temperature increased and reduced the solubility of insoluble drug of ibuprofen. So that, a spontaneous of ibuprofen solubility confirmed at high temperature indicated by negative values of Gibbs free energy at micellization ( $\Delta G^\circ_m$ ) along the concentration of ibuprofen in this study, especially at 0.01 M of ibuprofen with high values of the corresponding entropy ( $\Delta S^\circ_m$ ). It is recommended the micelle obtained from Ibuprofen (0.01M)- Tween 60 as a best concentration to the hydrophobic portion of Ibuprofen drug.

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