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Thermodynamic Parameters of Meloxicam Micellization with Span20 at Different Temperature

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Abstract

Surfactant micellization of Non-steroidal anti-inflammatory drugs (NSAIDs) such as Meloxicam carrying by surface active agent as polyethylene glycol sorbitan monostearate (Span 20) 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(Γmax), minimum area occupied per molecule(Amin.), surface pressure at CMC (Πcmc) was determined on basis of the standard Gibbs free energy of adsorption ($\Delta G°_{ads}$). The results indicated that CMC increased by temperature increasing for Span 20, and inversely for micelle of Meloxicam with Span 20. The thermodynamic parameters as standard Gibbs free energy(ΔG°), enthalpy(ΔH°), and the entropy(ΔS°) 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 Meloxicam.

Keywords: NSAIDs, Meloxicam, 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 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]. Meloxicam 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]. Esterification of primary alcohol of sorbitan with lauric acid (10°C) gives sorbitan mono laurate (Span 20)[10]. Surfactant as span 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

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to lamellar 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 Meloxicam carrying by anionic micelles [12]; naproxen and diclofenac in the type of cationic micelles [13]; indomethacin in both anionic and cationic micellar aggregation [14-16] as well of Meloxicam in amphiphilic polymers [17,18]. The CMC and thermodynamic parameters such as ΔG°m, ΔH°m, and ΔS°m for micellization process have been investigated [19-21]. The purpose of this study was to determined the thermodynamic parameters at adsorption of micellization of Meloxicam as NSAIDs which interact with Span 20 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. Meloxicam, showed in figure 1, was supplied by the state enterprise for drug industries and medical appliances in Samarra, Iraq. Meloxicam based on IUPAC name is 4-hydroxy-2-methyl-N-(5-methyl-2-thiazoyl)-2H-1, 2-benzothiazine-3-carboxamide-1, 1-dioxide), showed in figure 1. Polysorbate 60 or Span 20 (amphipathic surfactant) is sorbitan monolaurate 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 Table 1.

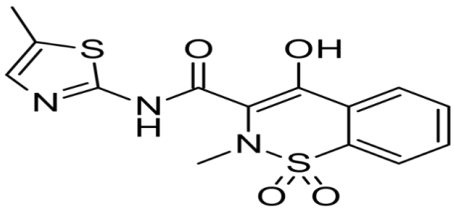


Fig.1. Chemical structure of Meloxicam.

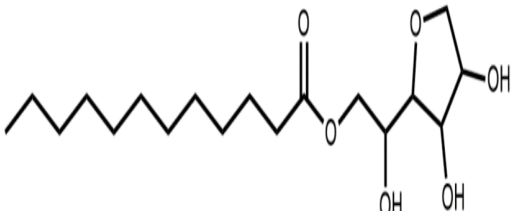


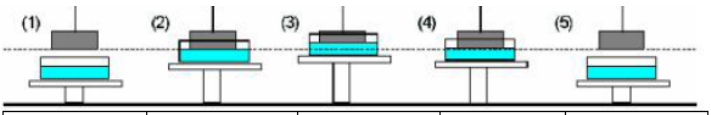
Fig.2. Chemical structure of Span 20.

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

Meloxicam was prepared of 10-1, 10-2 , 10-3 M in aqueous solution of SAA(Surface Active Agent). Stock solution of Span 20 was prepared of ($8x10^{-1}$M) in distilled water. 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(Span 20) 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 Meloxicam were measured as a function of varying concentration of Span 20. 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 Meloxicam, respectively, at different temperature to evaluated the CMC at sharp break point for each plot [22]. As shown, the surface tension of span 20 decreased as its concentration increased due to the sparingly soluble of Meloxicam adding. Its also indicated that the surface tension decreased of span 20 and the mixture of span 20- Meloxicam solution at all concentrations as temperature increasing, i.e. an increase of kinetic energy of the molecules caused diminishing in surface tension to overcome poorly solubility of Meloxicam.

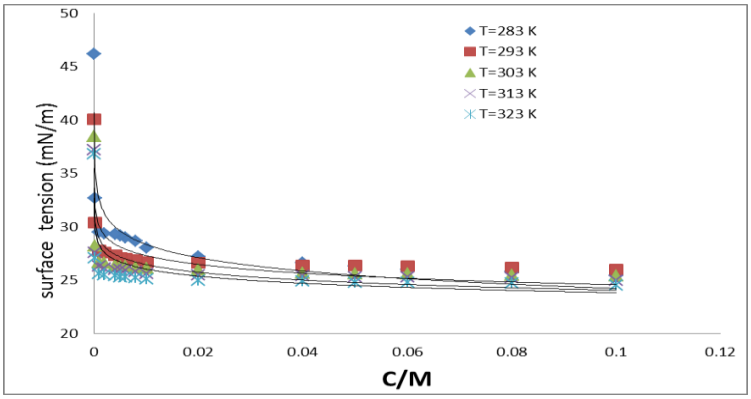


Fig.4. Plot of the surface tension against varying concentration of Span 20.

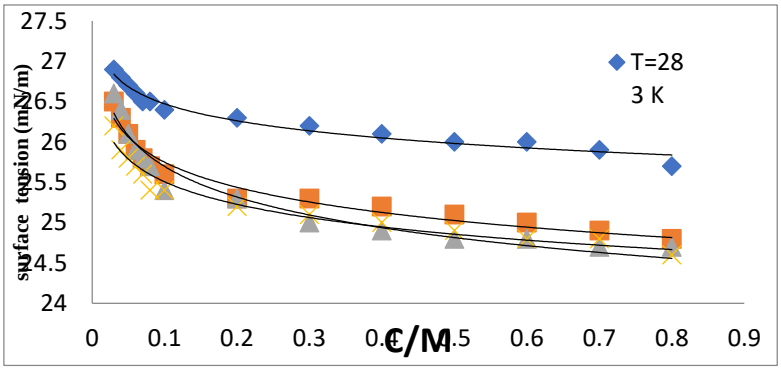


Fig.5. Plot of the surface tension of Meloxicam (10^{-1}M) against varying concentration of Span 20.

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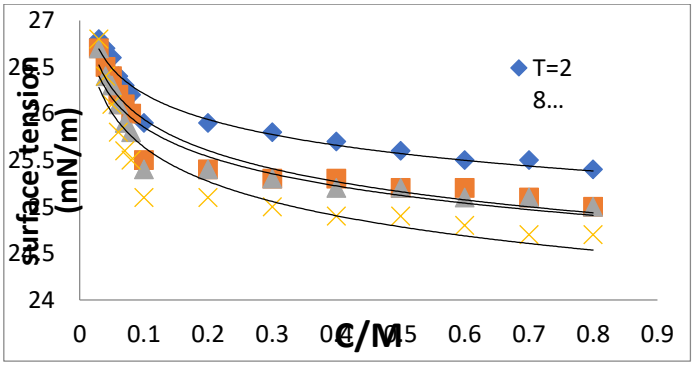

Fig.6. Plot of the surface tension of Meloxicam (10^{-2}M) against varying concentration of Span 20.

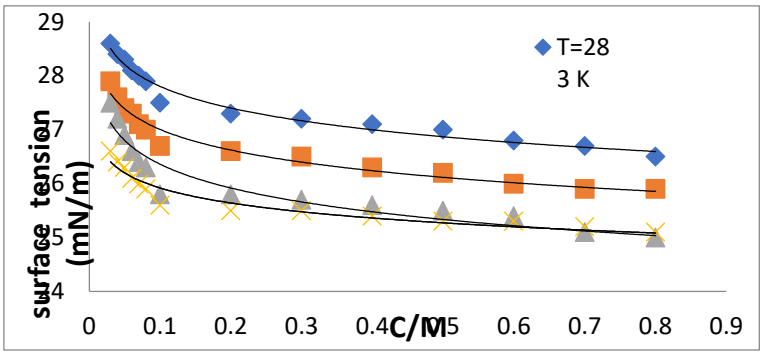

Fig.7. Plot of the surface tension of Meloxicam (10^{-3}M) against varying concentration of Span 20.

The concentration of maximum surface excess and the minimum area occupied per molecule were calculated by using eq.1 and eq.2, respectively [23,24].

$$\Gamma max = \frac{(\partial \gamma / lnC)cmc}{RT} \quad \ldots\ldots\ldots 1$$

$$Amin = \frac{1}{NA\,\Gamma max} \quad \ldots\ldots\ldots 2$$

Where N_A referred to Avogadro number and ($\partial\gamma/\partial$lnC) is evaluated from the slope of γ versus lnC plotting, according to equation 1, which illustrated in Figure 8 as a typical form.

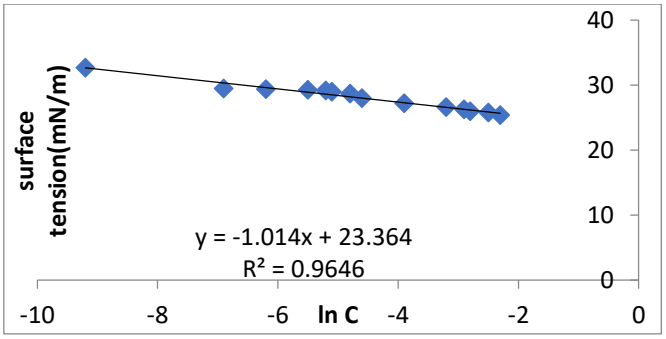

Fig.8. Typical plot of surface tension versus lnC at 283K of Span 20.

The surface pressure (Πcmc) at CMC, was determined from the equation 3:

$$\prod cmc = \gamma - \gamma cmc \quad \ldots\ldots 3$$

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.

$$\Delta G°ads = \Delta G°m - \frac{\prod cmc}{\Gamma max} \quad \ldots\ldots\ldots 4$$

Where ΔG°m is the standard Gibbs free energy of micellization[25-28].

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).

$$\Delta G°m = RT \ln Xcmc \ldots\ldots 5$$

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 :

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

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

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

ΔG˚m, ΔH˚m and ΔS˚m that completed by applying the above equations for the pure span 20 reported in Table 2, at different temperature.

ΔG˚m, ΔH˚m and ΔS˚m that completed by applying the above equations for the different concentration of Meloxicam-span20 reported in Table 3,4,5, respectively, at different temperature.

Table 2: Thermodynamic parameters of pure span20.

T (K)	CMC (M)	∏cmc (mN/m)	Γmax*10⁻³ (mmol/m²)	Amin * 10^{-23} (A²/molecule)	ΔG°ads (KJ/mol)	ΔG°m (KJ/mol)	ΔH°m (KJ/mol)	ΔS°m (JK⁻¹mol⁻¹)
283	0.009	45	2.43	68.493	-29.602	-11.084	8.589	69.519
293	0.01	45.3	2.38	69.93	-30.251	-11.217	9.207	69.71
303	0.012	46	2.33	71.428	-30.882	-11.139	9.846	69.261
313	0.013	46.4	2.226	73.529	-31.83	-11.299	10.507	69.668
323	0.015	46.9	2.222	74.85	-32.402	-11.276	11.189	69.552

Table 3: Thermodynamic parameters of span20 with meloxicam (10^{-3}M)

T (K)	CMC (M)	∏cmc (mN/m)	Γmax*10⁻³ (mmol/m²)	Amin * 10^{-23} (A²/molecule)	ΔG°ads (KJ/mol)	ΔG°m (KJ/mol)	ΔH°m (KJ/mol)	ΔS°m (JK⁻¹mol⁻¹)
283	0.09	44.5	4.85	34.364	-14.338	-5.663	6.392	42.599
293	0.1	45.3	4.76	34.965	-15.124	-5.607	6.851	42.524
303	0.11	46.2	4.64	35.971	-15.516	-5.559	7.327	42.532
313	0.12	46.5	4.62	36.213	-15.581	-5.516	7.819	42.607

Table 4: Thermodynamic parameters of span20 with meloxicam (10^{-2}M)

T (K)	CMC (M)	∏cmc (mN/m)	Γmax*10⁻³ (mmol/m²)	Amin * 10^{-23} (A²/molecule)	ΔG°ads (KJ/mol)	ΔG°m (KJ/mol)	ΔH°m (KJ/mol)	ΔS°m (JK⁻¹mol⁻¹)
283	0.1	46	4.8	34.722	-14.999	-5.416	5.792	39.608
293	0.11	46.5	4.74	35.087	-15.427	-5.617	6.209	40.364
303	0.12	46.6	4.75	35.087	-15.151	-5.34	6.64	39.542
313	0.13	47	4.7	35.46	-15.308	-5.308	7.086	39.6

Table 5: Thermodynamic parameters of span20 with meloxicam (10^{-1}M)

T (K)	CMC (M)	∏cmc (mN/m)	Γmax*10⁻³ (mmol/m²)	Amin * 10^{-23} (A²/molecule)	ΔG°ads (KJ/mol)	ΔG°m (KJ/mol)	ΔH°m (KJ/mol)	ΔS°m (JK⁻¹mol⁻¹)
283	0.08	45.6	28.33	5.882	-7.552	-5.94	8.789	52.05
293	0.09	46.6	25.09	6.666	-7.727	-5.863	9.421	52.167
303	0.1	46.8	23.02	7.246	-7.833	-5.799	10.075	52.391
313	0.12	46.9	4.54	37.037	-15.939	-5.516	10.751	51.31

In Table 2 data showed that the CMC increased as temperature increasing of Span 20. Also, the data in Table 3,4, and 5 characterized the same behavior due to the wettability of Meloxicam at micelle formation; the hydrophobic group of the hydrocarbon chain of the Span 20 interacts with the nonpolar group of Meloxicam. The data of CMC for pure span 20 and for its solution with Meloxicam, in the study range of temperature, indicate an increasing of CMC by increasing of temperature. Therefore, the temperature increasing caused an decreasing of structure breakdown of water surrounding the hydrophobic

group which results an increasing of CMC at micelle formation of Meloxicam-Span 20. Therefore, the data showed the positive values of the ΔH°m, for these reason the micellization process were endothermic reaction and increased with temperature increasing, and having the minimum values at low temperature of 283K. In addition, ΔS°m is almost increasing as temperature increased for each micelle concentration. Moreover, the ΔG°m found to have negative values referred to spontaneous process of micellization which enhance the solubility of Meloxicam in the presence of surfactant. As well the magnitude of the positive values of entropy encouraged the spontaneous of micelle formation (TΔS > ΔH).

Conclusion:

It was concluded, that the evaluation of the interaction of Meloxicam-Span20 has an important role as a function of micellization formation for drug delivery system. At low temperature, the CMC was the best value along the varying of Meloxicam concentration. Enhancement of micelle formation confirmed by negative magnitude of Gibbs free energy at micellization. Thus, the mixture showed a spontaneous reaction due to ΔG°m and that means good solubility. It is recommended the micelle obtained from Meloxicam (0.1M)-Span20 as a best concentration to the hydrophobic portion of Meloxicam drug.

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