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Study of Micellar Behavior of a Tween 80 Surfactant in Aqueous Media Containing Diphenhydramine Hydrochloride

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Abstract

The surface properties of mixtures of a nonionic surfactant Tween 80 (Tw 80) and a cationic drug, diphenhydramine HCl (DPH**)** have been investigated. This was done by calculating the surface excess concentration (Γ_{max}), minimum molecular area (A_{min}), surface pressure at the CMC (π_{cmc}), Gibbs Free Energy of adsorption ($\Delta G°_{ads}$), Gibbs free energy of micellization ($\Delta G°_{m}$), the standard enthalpy of micellization ($\Delta H°_{m}$), and the standard entropy of micellization ($\Delta S°_{m}$). The calculation was performed using the surface tension in the temperature range of 293-323 K with the variation of surfactant concentration to determine the critical micelle concentration (cmc) of the system studied. The variation of cmc values of drug concentration (DPH) with temperature was used to calculate the parameters above. The results indicate that the cmc values of Tw 80 increased when the (DPH) was added and when the temperature increased at the whole temperature studied. The results obtained for interfacial properties show that Γ_{max} decreases with the addition of DPH and decreases with DPH concentration increase from 10^{-5} to 10^{-4}M and decreases with temperature increases. The results of thermodynamic properties indicate that the micellization and adsorption at the interface are spontaneous and the $\Delta \mathring{G}_{ads}$ are more negative than $\Delta \mathring{G}_{m}$ at all temperatures.

Keywords: Tween 80, diphenhydramine HCl, critical micelle concentration, interfacial properties.

دراسة تصرف تكوين المايسل للمادة الفعالة سطحيا Tween 80 في الوسط المائي الحاوي على Diphenhydramine Hydrochloride

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الخلاصة

تم استقصاء صفات السطح لمزيج المادة الفعالة سطحيا اللايونية (Tween 80 [TW 80]) والدواء الكاتيوني . (diphenhydramine HCl [DPH]) تم ذلك من خلال حساب الدوال (Γmax, Amin, πcmc ومزيجها مع (TW 80) لكل من المادة الفعالة سطحيا منفردة (ΔG°ads, ΔG°m, ΔH°m, and ΔS°m) الدواء (DPH) بتركيزين (1 (10−4×1و ((10−5×مولاري. تم اجراء الحسابات باستخدام الشد السطحي

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ضمن مدى من درجات الحرارة (293−323 (K مع تغير تركيز المادة الفعالة سطحيا لايجاد التركيز الحرج لتكوين المايسل (cmc) لكل الانظمة التي تم دراستها. استخدم تغير (cmc) مع تركيز الدواء (DPH) ودرجة الحرارة لحساب الدوال اعلاه. دلت النتائج ان التركيز الحرج لتكوين المايسل للمادة الفعالة سطحيا (TW 80) يزداد عند اضافة (DPH) وكذلك عند زيادة درجة الحرارة في المدى من درجات الحرارة تحت الدراسة. اظهرت النتائج التي حصلنا عليها للصفات عند السطوح البينية بان (Γmax) تقل عند اضافة (DPH) وتقل اكبر عندما تركيز (DPH) يزداد من (10−5 (Mالى (10−4 (Mوتقل مع زيادة درجة الحرارة. ودلت نتائج الصفات الثرموديناميكية ان تكوين المايسل والامتزاز عند السطوح البينية كانت تلقائية وان (ΔG̊ads) هي اكثر سالبية من (ΔG̊m) عند كل درجات الحرارة.

1. Inoduction

The low solubility properties of drugs are already decreasing their bioavailability and therapeutic activity and increasing consumption, while a surplus of doses of drug leads to side effects [1,2]. Because of that, research on drugs that have water solubility and encapsulation performance is wanted to increase drug absorption, bioavailability, and decrease drug doses [3-5]. Different methods have been studied to improve the drug solubility, such as the use of nanocarrier drugs in formulations, self-emulsifying formulations, and using polymers soluble in water in the formulations [6-8].

Non-ionic surfactants have a lot of interest in medicinal areas because of their action in enveloping both amphiphilic (hydrophilic and hydrophobic) drugs. This discovery is that the aggregates of these surfactants can increase the drugs' bioavailability and can be used as a new way for delivering different therapeutic reagents. For example, drugs, proteins, and genes, with low side effects, and toxicity [9].

In this work, the interaction of diphenhydramine hydrochloride drug with a Tween 80 (Tw 80) surfactant was studied using surface tension measurements in the temperature range of 293 to 323 K. The cmc value of a surfactant was determined from the plots of surface tension versus concentration. It was then used to calculate various parameters of interfacial and thermodynamic properties.

2- Experimental

2.1- Materials

The nonionic surfactant Tween 80 (Tw 80) (polyoxyethylene-20 sorbitan-monooleate contains 18 carbon atoms and only one double bond) was supplied from Fluka, Switzerland and used without additional purification. Deionized water (specific conductivity = 2×10^{-6} $s.cm^{-1}$), 2-(diphenylmethoxy)-*N*,*N*-dimethylethylamine hydrochloride (≥98%), which is also named diphenhydramine HCl was purchased from Tokyo Chemical Industry Co. Ltd. (Tokyo, Japan). It is a poorly water-soluble drug, and its structure is depicted in Figure 1:

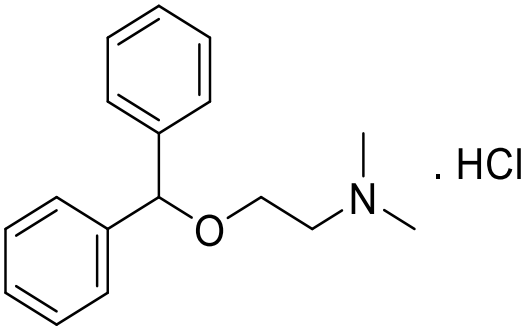

Figure 1 - Chemical structure of diphenhydramine HCl

2.2 Methods

Surface tension measurements were made using a platinum ring tensiometer (model DST 30 M, Surface and Electro Optics (SEO) Company- Korea). For every series of experiments, the ring was cleaned out by immersing it in a HNO_3 solution (0.1 M). Each measurement was repeated three times to ensure the reproducibility of the results. The value of surface tension (γ) was exactly within 0.1 mN m^{-1}.

3. Theory

3.1. Interfacial parameters

Some surface properties were calculated in this study, such as Γ_{max} and A_{min} ($Å^2$/molecule), which were calculated by the Gibbs adsorption equations below [10]:

$$\Gamma_{max} = -\frac{\left(\frac{d\gamma}{dlnC}\right)}{nRT} \quad (1)$$

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

Where γ = the surface tension (mN m^{-1}), T = the absolute temperature (K), R = 8.314 J $mol^{-1}K^{-1}$ (gas constant value), C = the molar concentration of the surfactant. While n is the number of species constituting the surfactant, for the nonionic surfactant n = 1 [11], and N = Avogadro's number. ($\partial\gamma$ /∂ln C) are determined from the plots of γ versus ln C.

Π_{cmc}(surface pressure at the CMC) values were determined using the following equation:

$$\Pi_{cmc} = \gamma_0 - \gamma_{cmc} \quad (3)$$

Where γ_{cmc} = the solution surface tension at cmc and γ_0 = the pure solvent surface tension (water). γ_{cmc} value was used to measure the effectiveness of the surfactant to lower the value of water surface tension [12].

3.2. Thermodynamics

The energy of micellization of an individual surfactant and its mixtures was evaluated by calculating some thermodynamic parameters of micellization. For example, ΔG°_m (the standard Gibbs free energy), and ΔH°_m (the standard enthalpy) by the following equations:

$$\Delta G^{\circ}_m = RTlnX_{cmc} \quad (4)$$

$$\Delta H^{\circ}_m = -RT^2\left[\frac{dlnX_{cmc}}{dT}\right] \quad (5)$$

Where X_{cmc} = surfactant mole fraction at the cmc, which was calculated *via* the following equation [13]:

$$X_{cmc} = \frac{cmc}{cmc + 55.4} \quad (6)$$

(∂lnX_{cmc}/∂T) is evaluated using the plot of lnX_{cmc} against temperature.

The standard entropy values of micelle formation ($\Delta S^{\circ}m$) values were determined using the following equation [13]:

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

ΔG°_{ad} at the air/water interface was calculated by the following equation:

$$\Delta G^{\circ}_{ads} = \Delta G^{\circ}_m - \left(\frac{\Pi_{cmc}}{\Gamma_{max}}\right) \quad (8)$$

4. Results and Discussion

Surface properties at the air/liquid interface and in the micelles have been evaluated in aqueous solutions of pure surfactants and for mixtures containing (10^{-5} and 10^{-4} M) DPH drugs using the surface tension technique in a temperature range of 293-323 K. The variations of surface tension values versus molar concentration of Tw 80 for the Tw 80-DPH systems are depicted in Figure 2.

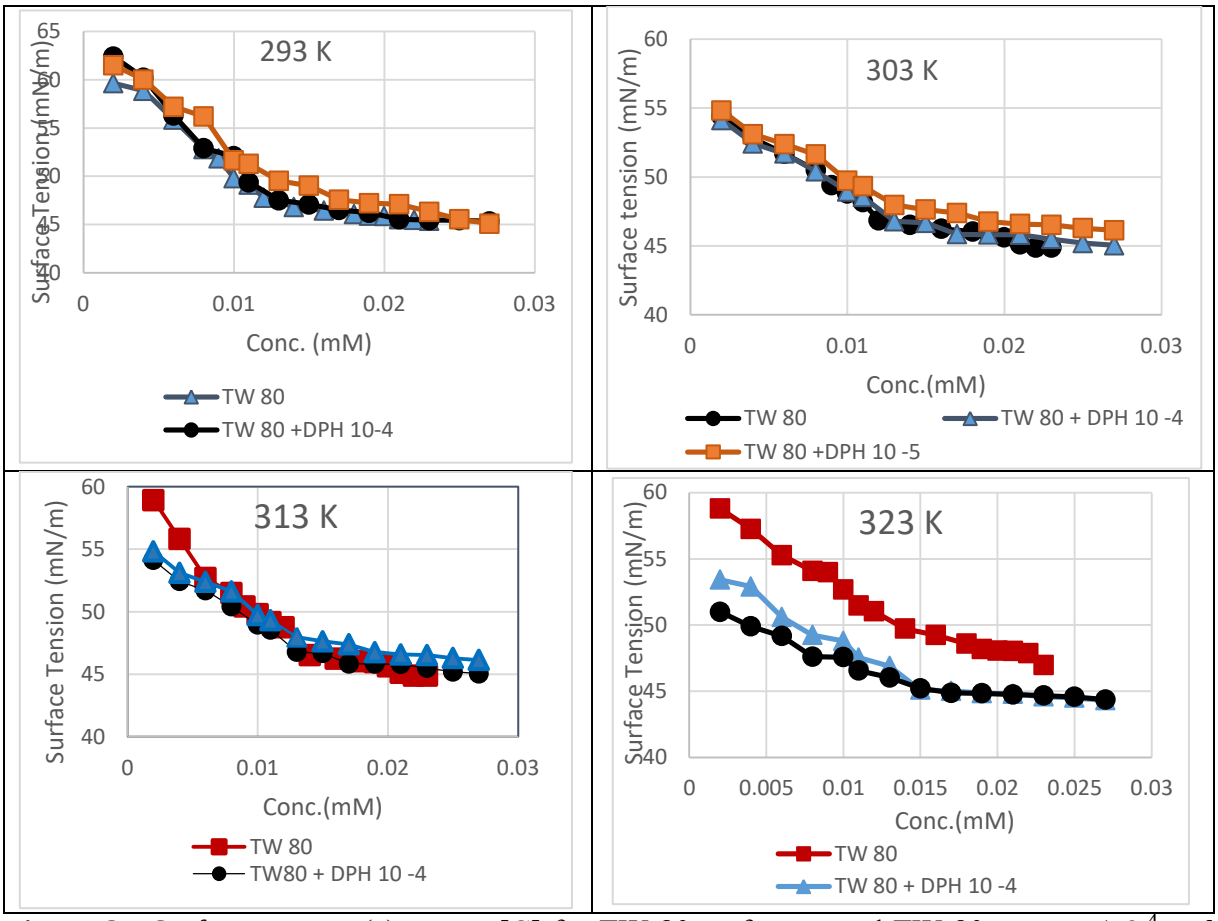

Figure 2 - Surface tension (γ) versus [C] for TW 80 surfactant and TW 80 + DPH (10^{-4} and 10^{-5} M) drug systems at different temperatures

The cmc values obtained from the intersection between the two linear lines for the individual surfactants are 0.00125, 0.00130, 0.00133, and 0.00139 M at 293, 303, 313, and 323 K, respectively. These results are within the range of those reported in the literature [14-16]. After adding DPH, the cmc values are vary depending on the DPH concentration, which can be shown in Table 1.

Table 1- Interfacial and thermodynamic parameters for Tw 80 surfactant and Tw 80 + DPH (10^{-4} and 10^{-5} M) drug systems at different temperatures

	T (K)	cmc/mM	Π_{cmc} mN/m	$\Gamma_{max}.10^{-6}$ mol/m2	A_{min} Å^2/molecule	$-\Delta G°_{ad}$ kJ/mol	$-\Delta G°_{m}$ kJ/mol	$-\Delta H°_{m}$ kJ/mol	$\Delta S°_{m}$ J/mol.K
Tw 80	293	0.00125	23.987	2.836	58.67	51.351	42.893	2.283	138.600
	303	0.00130	24.087	2.310	71.88	61.090	44.258	2.442	138.006
	313	0.00133	24.187	2.135	77.77	56.987	45.659	2.606	137.549
	323	0.00139	21.287	1.594	104.17	60.354	47.000	2.775	136.919
TW 80 + DPH 10^{-5}	293	0.0130	21.687	2.707	61.343	45.200	37.190	3.069	116.453
	303	0.0137	23.287	1.376	120.681	55.250	38.327	3.282	115.660

	313	0.0142	24.287	1.161	143.029	60.418	39.499	3.502	115.006
	323	0.0148	25.787	0.990	167.582	66.672	40.649	3.729	114.303
TW 80 + DPH 10^{-4}	293	0.0130	23.987	3.313	50.123	44.430	37.190	3.925	113.532
	303	0.0139	24.487	1.453	114.286	55.142	38.290	4.198	112.514
	313	0.0148	25.187	1.375	120.769	57.708	39.391	4.479	111.539
	323	0.0153	25.987	1.368	121.387	59.556	40.560	4.770	110.804

The cmc values obtained for the Tw 80 and DPH systems increased compared with the pure Tw 80 surfactant, and the magnitude increased when the molar concentration of DPH was raised from 10^{-5} to 10^{-4} M. This means that the Tw 80 surfactant creates a greater effect on the solubility of the DPH drug; therefore, the micellization was delayed [17]. Furthermore, the rise in the cmc values indicates that the micelle formation (micellization) in the molecules of the DPH drug was executed the micelle formed by Tw 80. This phenomenon is based on the nature and polarity of the micelle core of drug molecules [18].

From experimental observations, the solubility becomes greater for polar drugs in aqueous solution, resulting in the stabilization of monomeric surfactants. This causes restrictions on micelle formation. Thus, when the temperature is elevated, an increase in the value of cmc is seen, so that the values of cmc for Tw 80 in the mixture system (Tw 80 + DPH) become greater when the temperature rises.

At high temperatures, the arrangement of molecular structures in terms of the hydrogen bonding between DPH and head groups of Tw 80 molecules is broken down, and disfavoring micellization increases the Tw 80 cmc value. Furthermore, with the formation of a palisade layer of developing micelles, thermal motion is increased at higher temperatures. Because of the surfactant's instability, its cmc values increase. This is because the surfactant monomers become more stable as the temperature rises due to the high solubility of hydrocarbons. Therefore, the formation of micelles is hampered, leading to an increase in the Tw 80 cmc values [19, 20].

The calculated interfacial and thermodynamic parameters for the Tw 80 surfactant in aqueous solution and in the two concentrations of DPH are listed in Table 1.

Table 1 shows that when the DPH drug was added to the TW 80 surfactant, the cmc values did not follow any trend. Γ_{max} decreased and A_{min} increased compared with the individual nonionic surfactant TW 80 when DPH was added [21]. This decrease in Γ_{max} or increase in A_{min} may be due to two reasons; drug molecule interaction with the surfactant head, and the occurrence of drug molecules behind surfactant molecules at the air/water interface [22]. The existence of DPH molecules around the hydrophilic head of the amphiphile will therefore increase repulsion and reduce Γ_{max}.

ΔG°_{m} values are lower than pure surfactant and they are negative at all inspected temperatures and become more negative with a rise in temperature. This means that the micelle formation is spontaneous thermodynamically [23]. ΔG°_{ads} values are negative and slightly lower than Tw 80 alone at the temperatures of 293 and 303K. The results also show that the observed ΔG°_{ads} values are more than ΔG°_{m} values (with their sign), which indicate that the Tween 80 first adsorbs at the interface and then forms the micelle in the bulk solution [24]. The values

obtained show that the ΔS°_{m} are positive at all temperature ranges studied, and the values decrease when the temperature increases. This is due to the reduction in the hydrophilic hydration of the surfactant head group and the hydrophilic portion of the DPH, which promotes the electrostatic interaction of the loaded portion of surfactants and drugs [25,26]. Additionally, the negative values of the standard enthalpy of micellization (ΔH°_{m}) point out the exothermic nature of the micellization process [27].

5. Conclusion

The interaction of Tw 80 and DPH drugs was studied by measuring the variation of surface tension with surfactant molar concentration for individual surfactants and for mixtures at two concentrations of DPH (10^{-5} and 10^{-4} M) and four temperatures ranging from 293 to 323 K. The results indicate that Tw 80 and DPH systems have a better surface activity than the pure Tw 80 surfactant. The cmc values of Tw 80 increased when the DPH drug was added to the Tw 80 solution, and the magnitude increased as the concentration of the IBU drug increased from 10^{-5} to 10^{-4} M. Also, the values of cmc show that it is hardly dependent on temperature and that it reduces with temperature increase. Thermodynamics parameter values and signs indicate that the micellization and adsorption in the interface processes are spontaneous. The micellization process is exothermic, and the randomness in the micelle core increases.

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