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 ($\Gamma_{\text{max}}$), minimum molecular area ($A_{\text{min}}$), surface pressure at the CMC ($\Pi_{\text{cmc}}$), Gibbs Free Energy of adsorption ($\Delta G_{\text{ads}}^\circ$), Gibbs free energy of micellization ($\Delta G_{\text{m}}^\circ$), the standard enthalpy of micellization ($\Delta H_{\text{m}}^\circ$), and the standard entropy of micellization ($\Delta S_{\text{m}}^\circ$). 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 $\Gamma_{\text{max}}$ 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 $\Delta G_{\text{ads}}$ are more negative than $\Delta G_{\text{m}}$ at all temperatures.

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

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

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الخلاصة

تم استقراء صفات السطح لمزيج المادة الفعالة سطحيا اللايوني (80) ودواء الكاتيوني (diphenhydramine HCl [DPH]) من خلال حساب الدوال ($\Gamma_{\text{max}}, A_{\text{min}}, \Pi_{\text{cmc}}, \Delta G_{\text{ads}}^\circ, \Delta G_{\text{m}}^\circ, \Delta H_{\text{m}}^\circ, \Delta S_{\text{m}}^\circ$) لكل من المادة الفعالة سطحيا متفردة (80) ومزجها مع الدواء (DPH) بتركزين (1-5×10^{-4} M). تؤثر أعمال البحث على استخدام الشد السطحي

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1. Introduction

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 = 2x10^{-6} s.cm^{-1}), 2-(diphenylmethoxy)-N,N-dimethylamino 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](image-url)
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 HNO₃ 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 (Å²/molecule), which were calculated by the Gibbs adsorption equations below [10]:

\[ \Gamma_{\text{max}} = -\frac{\left(\frac{d\gamma}{d\ln C}\right)}{nRT} \]  
\[ A_{\text{min}} = \frac{1}{N_A\Gamma_{\text{max}}} \]  

Where γ = the surface tension (mN m⁻¹), T = the absolute temperature (K), R = 8.314 J mol⁻¹K⁻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. (dγ / dln C) are determined from the plots of γ versus ln C.

\[ \Pi_{\text{cmc}} \] (surface pressure at the CMC) values were determined using the following equation:

\[ \Pi_{\text{cmc}} = \gamma_0 - \gamma_{\text{cmc}} \]  

Where \( \gamma_{\text{cmc}} \) = the solution surface tension at cmc and \( \gamma_0 \) = the pure solvent surface tension (water). \( \gamma_{\text{cmc}} \) 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, \( \Delta G_m^\circ \) (the standard Gibbs free energy), and \( \Delta H_m^\circ \) (the standard enthalpy) by the following equations:

\[ \Delta G_m^\circ = RT\ln X_{\text{cmc}} \]  
\[ \Delta H_m^\circ = -RT^2 \frac{d\ln X_{\text{cmc}}}{dT} \]  

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

\[ X_{\text{cmc}} = \frac{c_{\text{cmc}}}{c_{\text{cmc}} + 55.4} \]  

\( (d\ln X_{\text{cmc}}/dT) \) is evaluated using the plot of \( \ln X_{\text{cmc}} \) against temperature.

The standard entropy values of micelle formation (\( \Delta S_m^\circ \)) values were determined using the following equation [13]:

\[ T\Delta S_m^\circ = \Delta H_m^\circ - \Delta G_m^\circ \]  

\( \Delta G_m^\circ \) at the air/water interface was calculated by the following equation:

\[ \Delta G_m^\circ_{\text{ads}} = \Delta G_m^\circ - \left(\frac{\Pi_{\text{cmc}}}{\Gamma_{\text{max}}}\right) \]  

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.
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

<table>
<thead>
<tr>
<th></th>
<th>T (K)</th>
<th>cmc/mM</th>
<th>Π_{i} \text{mN/m}</th>
<th>Φ_{i} \text{mN/m}</th>
<th>Α_{i} \text{mN/m}</th>
<th>Α_{i} \text{mN/m}</th>
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<th>Α_{i} \text{mN/m}</th>
<th>Α_{i} \text{mN/m}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tw 80</td>
<td>293</td>
<td>0.00125</td>
<td>23.987</td>
<td>2.836</td>
<td>58.67</td>
<td>51.351</td>
<td>42.893</td>
<td>2.283</td>
<td>138.600</td>
<td></td>
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<tr>
<td></td>
<td>303</td>
<td>0.00130</td>
<td>24.087</td>
<td>2.310</td>
<td>71.88</td>
<td>61.090</td>
<td>44.258</td>
<td>2.442</td>
<td>138.006</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>313</td>
<td>0.00133</td>
<td>24.187</td>
<td>2.135</td>
<td>77.77</td>
<td>56.987</td>
<td>45.659</td>
<td>2.606</td>
<td>137.549</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>323</td>
<td>0.00139</td>
<td>21.287</td>
<td>1.594</td>
<td>104.17</td>
<td>60.354</td>
<td>47.000</td>
<td>2.775</td>
<td>136.919</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>TW 80 + DPH 10⁻⁴</td>
<td>293</td>
<td>0.0130</td>
<td>21.687</td>
<td>2.707</td>
<td>61.343</td>
<td>45.200</td>
<td>37.190</td>
<td>3.069</td>
<td>116.453</td>
<td></td>
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<tr>
<td></td>
<td>303</td>
<td>0.0137</td>
<td>23.287</td>
<td>1.376</td>
<td>120.681</td>
<td>55.250</td>
<td>38.327</td>
<td>3.282</td>
<td>115.660</td>
<td></td>
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</tbody>
</table>

**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 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. $\Gamma_{\text{max}}$ decreased and $A_{\text{min}}$ increased compared with the individual nonionic surfactant Tw 80 when DPH was added [21]. This decrease in $\Gamma_{\text{max}}$ or increase in $A_{\text{min}}$ 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 $\Gamma_{\text{max}}$.

$\Delta G_{\text{m}}$ 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]. $\Delta G_{\text{ads}}$ values are negative and slightly lower than Tw 80 alone at the temperatures of 293 and 303K. The results also show that the observed $\Delta G_{\text{ads}}$ values are more than $\Delta G_{\text{m}}$ 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 $\Delta S_m^*$ 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 ($\Delta H_m^*$) 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.

References


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