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Self-association and thermodynamic behavior of etilefrine hydrochloride in aqueous electrolyte solution

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ABSTRACT

The self-association (micellization) behavior of etilefrine HCl, an amphiphilic drug, in aqueous electrolyte solution has been investigated as a function of temperature and sodium chloride (NaCl) concentration by conductivity and ^{1}H NMR measurements. The critical micelle concentration (CMC) was calculated from the inflection in the data obtained from both techniques. The CMC and the degree of ionization (α) values were determined over the temperature range (298.15 to 313.15) K in water and in presence of different concentrations of NaCl. The thermodynamic parameters of micellization for etilefrine HCl i.e. the standard Gibbs free energy change ΔG°_m, the standard enthalpy change, ΔH°_m, and the standard entropy change, ΔS°_m, were evaluated according to the pseudo-phase model. The obtained CMC values, in presence and absence of electrolyte, showed an inverted U-shaped behavior. While the degree of micelle ionization (α) showed a linear response to the increase in temperature in absence of electrolyte, addition of NaCl did not cause a specific response.

1. Introduction

Amphiphilic molecules including some drugs undergo self-association in aqueous solutions to form micelles with a small number of aggregates [1–10]. Association usually takes place above a certain concentration known as the critical micelle concentration (CMC) [11]. The self-association of these molecules is usually accompanied with a change in the physical properties of the amphiphile solution including conductivity, viscosity, surface tension of the solution, NMR chemical shift or light scattering [11–14]. When these surface active drugs self-associate, they behave like detergents. The process starts with binding of self-associated molecules to plasma membrane causing their disruption and solubilization and hence an improved penetration of drug molecules into the target membranes [15]. Conductivity [2–5,16,17] and ^{1}H NMR [6–10] are among the techniques that have been widely applied to study the self-association of amphiphilic drugs in aqueous solutions and also to detect the CMC.

Self-association or micellization is affected by different factors such as temperature, solvent, additive, pressure, pH and ionic strength [13].

Etilefrine HCl, chemically recognized as (1*RS*)-2-(Ethyl amino)-1-(3-hydroxyphenyl) ethanol hydrochloride [18], is a sympathomimetic amine with β_1-agonist and some α- and β_2-agonist actions. Etilefrine is commonly used in treating orthostatic hypotension of neurological, cardiovascular, endocrine or metabolic origin [19]. The widespread use of etilefrine HCl (alone or in combination with salt), especially as an OTC antihypotensive in Egypt and the Middle East was motivating to conduct the current investigation. To the best of our knowledge, the self-association of etilefrine HCl has not been reported before. The aim of the present work is to determine the CMC at which the association of etilefrine HCl aqueous solutions occurs in absence and presence of NaCl and to understand the effect of the presence of NaCl on the thermodynamics of association employing conductivity and ^{1}H NMR measurements.

2. Experimental

2.1. Materials and methods

2.1.1. Materials and reagents

All employed chemicals were of analytical grade and doubly distilled water was used throughout the study. Etilefrine HCl (purity >98%) was provided by CID Co., Egypt. Sodium chloride (purity 99.5%) was of Analar grade. Deuterium oxide D_2O (99.9% D) was purchased from Cambridge Isotope Laboratories, Inc., USA. The used chemicals were used as received without any further purification. The suppliers and purity of the used chemicals are provided in table 1.

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2.1.2. Conductivity measurements

The conductance was measured by using a HANNA Conductivity/TDS Meter (HI 8033), with a HANNA Conductivity Probe (HI 76301W). The conductivity cell was calibrated using standard KCl solution at $T = 298.15$ K (specific conductivity 1413 μS/cm). The temperature control was attained by means of a thermostated water bath with a precision of ±0.01 °C. All conductivity measurements were done using direct current (DC) method and the uncertainty of the electrical conductivity measurements κ was ±1.0%.

2.1.3. ^{1}H NMR measurements

All NMR measurements were done on JEOL ECA 500 MHz NMR spectrometer, Japan. Samples were measured in Deuterium oxide D_2O (99.9% D).

2.1.4. General procedure

Etilefrine HCl (0.07 mol · kg^{-1} ± 0.02) solution was prepared in 100 ml of doubly distilled water and then the solution was transferred into the conductivity measuring cell. The measuring cell was immersed in a thermostated water bath, maintaining the temperature constant (at 298.15, 303.15, 308.15, and 313.15 K). One - two ml of the solution was removed and an equal volume of pure doubly distilled water maintained at the same temperature of the test solution was added to the measuring cell. The conductivity data of the diluted solution was collected after stabilization of the display on the instrument scale. The previous steps were repeated till the solution concentration is 0.01 mol · kg^{-1}.

The whole procedure was repeated for preparing a 0.07 mol · kg^{-1} solution of etilefrine HCl in different concentrations of NaCl (0.025, 0.05, 0.075 and 0.1) mol · kg^{-1} ± 0.005. The conductance was measured at different drug concentrations by removing 1 or 2 ml from the solution and the addition of the same volume of NaCl solution.

For ^{1}H NMR measurements, different concentrations (0.01, 0.03, 0.05, 0.07, 0.1, and 0.2) mol · kg^{-1} were prepared in D_2O and measured by NMR at $T = 298.15$ K.

3. Results and discussion

3.1. Conductivity measurements

The conductivity of etilefrine HCl in water was measured as a function of etilefrine HCl concentration at different temperatures i.e. 298.15–313.15 K. Figure 1 shows the specific conductivity κ as a function of the molal concentration of etilefrine HCl in aqueous solution and in different NaCl concentrations at

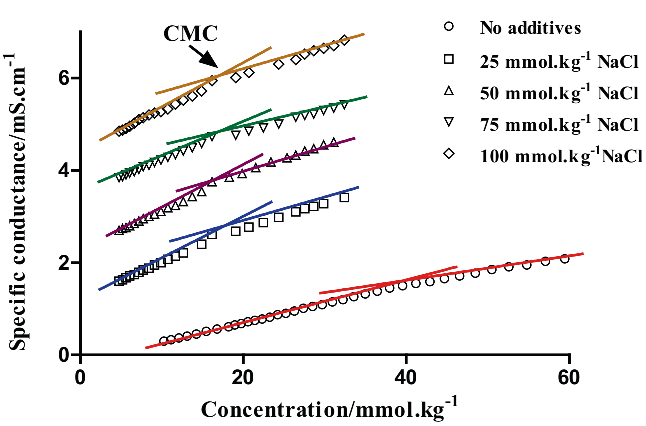

FIGURE 1. Specific conductance/mS · cm^{-1} vs. concentration/mmol · kg^{-1} plots of (etilefrine HCl + NaCl) systems at $T = 298.15$ K.

TABLE 1
Specification and mass fraction purity of the chemicals.

Compound	Supplier	Mass fraction purity[a]	Purification method
Etilefrine HCl	CID Co.	>0.980	Used as received
Sodium chloride	Analar Normapur	0.995	Used as received
Deuterium oxide	Cambridge Isotope Lab.	0.999	Used as received

[a] Declared by supplier.

$T = 298.15$ K. Similar plots (not shown) were obtained at the investigated temperatures. The specific conductivity values for different (etilefrine HCl + NaCl) systems at $T = 298.15$ K were represented in table 2.

The molal concentration versus conductivity plots are presented in figure 1. The inflections in these plots can be attributed to the commencement of the micelle formation. According to Williams method [20] the values of the critical micelle concentrations, CMC, were estimated from the intercepts of the two straight lines drawn above and below the inflection point. One inflection point is observed for each plot at which the CMC is recorded. The calculated CMC values at different concentrations of NaCl and at different temperature are represented in table 3.

3.1.1. Effect of temperature on CMC

Generally, the CMC of ionic amphiphiles decreases by increasing the temperature and then increases (U-shaped behavior). This can be justified in accordance to two opposing factors:

(1) The increase in temperature leads to a decrease in the hydration (i.e. increase the dehydration) of the hydrophilic head groups of the amphiphile, an issue that would result in increased hydrophobicity characters of the molecules. This behavior encourages the micellization, which in turn, occurs at low concentration and the CMC decreases.
(2) On the other hand, the increase in temperature leads to an increase the thermal solubility of amphiphile in water due to the disruption of the structure of water molecules around the hydrophobic tail of the amphiphile so micellization occurs at high concentration and the CMC increases.

In case of etilefrine HCl, and despite of being cationic, plotting the CMC values that against temperature show an inverted U-shaped behavior [first increase with increasing the temperature till a certain temperature at which CMC is maximum (T_{max}) and then decrease with further increase in temperature] as illustrated in figure 2. The behavior of etilefrine HCl can be explicated as follows: Below T_{max}, the thermal solubility effect predominates over the dehydration effect. The increase in the solubility of the amphiphile hinders its aggregation and fewer head groups would aggregate at high concentration of amphiphile so the CMC increases. Above T_{max}, the dehydration effect predominates over the thermal solubility effect and so the CMC values start to decrease. The same behavior was reported in some cases of amphiphilic drugs [5,21].

3.1.2. Degree of ionization

The degree of ionization of the micelles (α) can be determined from the conductance vs. molal concentration plots, where (α) is ratio of the slopes of postmicellar to premicellar plots [22]. The degree of ionization of the micelles (α) was found to increase linearly with temperature in absence of added electrolyte as shown in figure 3. This behavior can be attributed to the increase in thermal activity [5]. The linear dependence of (α) with temperature variation is in accordance with what was reported by