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Volumetric and ultrasonic approach in the investigation of critical micellar phenomenon of amphiphilic drugs in aqueous solutions at different temperatures

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ABSTRACT

The apparent molar volumes (V_ϕ) along with apparent molar isentropic compressibilities (κ_ϕ) of aqueous solutions of the amphiphilic drugs namely amantadine hydrochloride and semicarbazide hydrochloride have been determined from density and ultrasound data at $T =$ (288.15, 293.15, 298.15, 303.15 and 308.15) K. The critical micelle concentration along with the free energy change (ΔG^0_m), enthalpy change (ΔH^0_m) and ($T \cdot \Delta S^0_m$) of micellization was obtained for the aqueous binary mixtures of drugs. The volume changes due to micellization (ΔV^m_ϕ) were also estimated for both the studied drugs at different temperatures. Negative deviation from the Debye–Hückel limiting law of the apparent molal volume was obtained for water + amantadine hydrochloride system while positive deviation was observed in the case of water + semicarbazide hydrochloride system. The aggregation number (n) for the studied drugs in the aqueous environment has been also determined at 298.15 K. The results obtained at different temperatures have been interpreted in terms of drug–water interactions and solute–solute interactions which seem to depend upon the structural features of the solute molecule and also on the surrounding environment of drug molecules.

1. Introduction

Amphiphilic compounds have hydrophobic and hydrophilic domains that are separated by intermediate alkyl chains. The amphiphilic behavior of drugs is important in the biological and membranous activity of these drugs. This membranous activity results into different type of interactions of drug molecules with the environment outside the membrane. The changes in the structural features and the interactions of the drug can also serve as deciding criteria for the selective permeability of the drugs through the membrane and into the interior of the cells and lymph of the organism [1]. Also the accumulation of the drug molecules at certain sites in the body may cause a localized high concentration resulting into aggregation and subsequent changes in biological activity due to decreased transport rates or decreased ability to pass through biological barriers [2]. The amphiphilic drugs also feature the micelle formation which is an important characteristic property of biological importance. The critical concentration for micelle formation can be estimated by the inflections or discontinuity in the physical property such as conductivity, surface tension, light scattering and many more. Essential information can be obtained on the critical micellar concentration and the thermodynamics involved in it to have detailed and thorough approach to understand the dynamics underlying the phenomenon [3]. The thermodynamics of aggregation can be deeply studied by the systematic volumetric and acoustic investigations of the aqueous binary systems of the drugs at different temperatures. Free energy of micellization also holds importance as it gives an estimate of the spontaneity of the process and the energetic of micellization [4]. In the present investigation, two amphiphilic drugs namely Amantadine hydrochloride and Semicarbazide hydrochloride have been studied for their micellization characteristics in the aqueous environment at five different temperatures $T =$ (288.15, 293.15, 298.15, 303.15 and 308.15) K. Amantadine hydrochloride drug is found to possess antiviral properties against influenza with type A virus and also exhibits mild action against Parkinson disease. It also affects the brain in many ways including release of neurotransmitters such as dopamine and norepinephrine from nerve endings [5]. On the other hand, semicarbazide hydrochloride is found to have carcinogenic effects in animals and is highly toxic. It is also used as building block for the carbonyl compounds [6]. Thus, it would be interesting to know the chemical interactions of these molecules with water at temperatures close to our body temperature. This study comprises of the investigations into the solute–solvent interaction (hydrophobic hydration) in pre-micellar concentration and solute–solute association (hydrophobic interaction) in post-micellar concentration region.

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2. Experimental

2.1. Chemicals

Amantadine hydrochloride, semicarbazide hydrochloride and sodium chloride were procured from Sigma-Aldrich with greater than 99% mass fraction purity. The details are provided in Table 1. These compounds were used without further purification. The compounds under the study were stored in desiccator over fused calcium chloride for drying before use. All the solutions were prepared in fresh triple distilled water on molality basis using an electronic balance (Shimadzu AUW220D) having precision of ±0.01 mg for weighing.

2.2. Methods

The density and sound velocity measurements were done by an automated vibrating tube densitometer (Anton Paar DSA 5000 M density and sound velocity meter) at different temperatures i. e. $T = (288.15, 293.15, 298.15, 303.15$ and $308.15)$ K, respectively. The temperature was controlled in a densitometer by Peltier effect with a precision of ±0.001 K. The reliability of the instrument was checked using double distilled water executing a water check and our results agreed well to the literature data [7]. A density check or an air/water adjustment was performed at all the experimental temperatures with ultrapure water sample and with dry air at atmospheric pressure. The densitometer was calibrated with the help of NaCl solution and our density results agreed well to the literature data [8], whereas an inbuilt ultrasound speed analyzer was calibrated using double distilled water [9]. The reproducibility of densities and speeds of sound results were found to be within ±0.05 $kg \cdot m^{-3}$ and ±0.5 $m \cdot s^{-1}$, respectively.

3. Results and discussions

3.1. Volumetric study

The density values of the aqueous solutions of both the drugs at temperatures $T = (288.15, 293.15, 298.15, 303.15$ and $308.15)$ K are listed in Table 2. Density values increases continuously with addition of drug in the aqueous solution at all the studied temperature. From the close scrutiny of the data, it was seen that the density of solution increases linearly with rise in concentration of solution at a given temperature and also the densities of aqueous solutions decrease linearly with rise in temperature as represented in Fig. 1 for aqueous solutions of amantadine hydrochloride. The same has been obtained for semicarbazide hydrochloride drug system.

The apparent molar volume is crucial in the sense that it manifests the behavior of solutes in solution with the change in temperature. The apparent molar volume of the solute in aqueous solution (V_ϕ) has been calculated by using the following equation [10–12]:

$$V_\phi = \frac{M_2}{\rho} + \left[\frac{1000(\rho_0 - \rho)}{m.\rho.\rho_0}\right] \tag{1}$$

where ρ_0 and ρ are the densities of solvent and solution, respectively and m and M_2 are the molality of the solution and molecular mass of the solute, respectively. The apparent molar volumes of aqueous binary mixtures of drugs i.e. amantadine hydrochloride and semicarbazide hydrochloride are given in Table 2. The uncertainty in V_ϕ values by considering the uncertainty in density measurements ±0.05 $kg \cdot m^{-3}$ at lower concentration 0.01 m of both amantadine hydrochloride solution and semicarbazide hydrochloride solution was found to be $\approx 5.10^{-6}$ $m^3 \cdot mol^{-1}$ and for higher concentration 0.1 m was found $\approx 5.10^{-7}$ $m^3 \cdot mol^{-1}$. Fig. 2 shows the variation of apparent molar volume with the molal concentration at 298.15 K for both the drugs. The plot between $V_\phi - A_V \cdot m^{1/2}$ against m resulted reverse sigmoidal curves having two straight lines, corresponding to monomeric drug molecules and drug aggregate zones, respectively; intersection of these lines usually coincides to get critical micelle concentration. It can be seen that the values of $V_\phi - A_V \cdot m^{1/2}$ up to cmc decreases rapidly for water + amantadine hydrochloride system and opposite trend was observed for water + semicarbazide hydrochloride. After critical micelle concentration, the gradient of the plots approach zero at higher drug concentration. This can be thought to be the onset of the aggregation behavior of the solute molecules in water [10]. Assuming the pseudo phase model of micellization, the apparent molar volume [1,13–14] can be written in the form of following equation:

$$V_\phi = V_\phi^m + \frac{cmc}{m}\left[V_\phi^0 - V_\phi^m\right] \tag{2}$$

where V_ϕ^0 is the limiting apparent molar volume of the solute and V_ϕ^{mic} is the apparent molar volume of the solute in the micellar state, respectively. A more exact and appropriate way to determine the limiting apparent molar volume of the solute is to assume that solutions of amphiphilic compounds behave as solutions of 1:1 electrolytes up to the critical concentration. Accordingly, Redlich–Meyer equation was used to determine the limiting apparent molar volume at infinite dilution V_ϕ^0 by smooth extrapolation of $V_\phi - A_V \cdot m^{1/2}$ against m to zero concentration [11,15] as:

$$V_\phi = V_\phi^0 + A_V \cdot m^{1/2} + S_V \cdot m \tag{3}$$

where A_V is the Debye–Hückel limiting slope, S_V is the adjustable parameter related to a pair of interaction and equivalent to the second virial coefficient which measures the deviation from the limiting law due to the non-electrostatic solute–solvent interactions [16–19].

A_V is the Debye–Hückel limiting slope which depends upon valency and temperature and is calculated by the relation,

$$A_V = kw^{3/2} \tag{4}$$

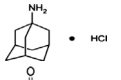
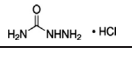
where k is the coefficient which is given by the Redlich–Meyer polynomial equation in terms of temperature T/°C between 0 and 70 [20,21].

$$k = 1.4447 + \left(1.67990 \times 10^{-2} \cdot T\right) - \left(8.4055 \times 10^{-6} \cdot T^2\right) + \left(5.513 \times 10^{-7} \cdot T^3\right) \tag{5}$$

and w is the valency factor which is determined by the relation

$$w = 0.5 \sum v_i \cdot z_i^2 \tag{6}$$

Table 1
Provenance and mass fraction purity of the chemical samples.

Chemical name	Provenance	CAS no.	Mass fraction purity[a]	Structure
Amantadine hydrochloride	Sigma-Aldrich	665-66-7	≥99%	
Semicarbazide hydrochloride	Sigma-Aldrich	563-41-7	≥99%	

[a] Purity as provided by suppliers.